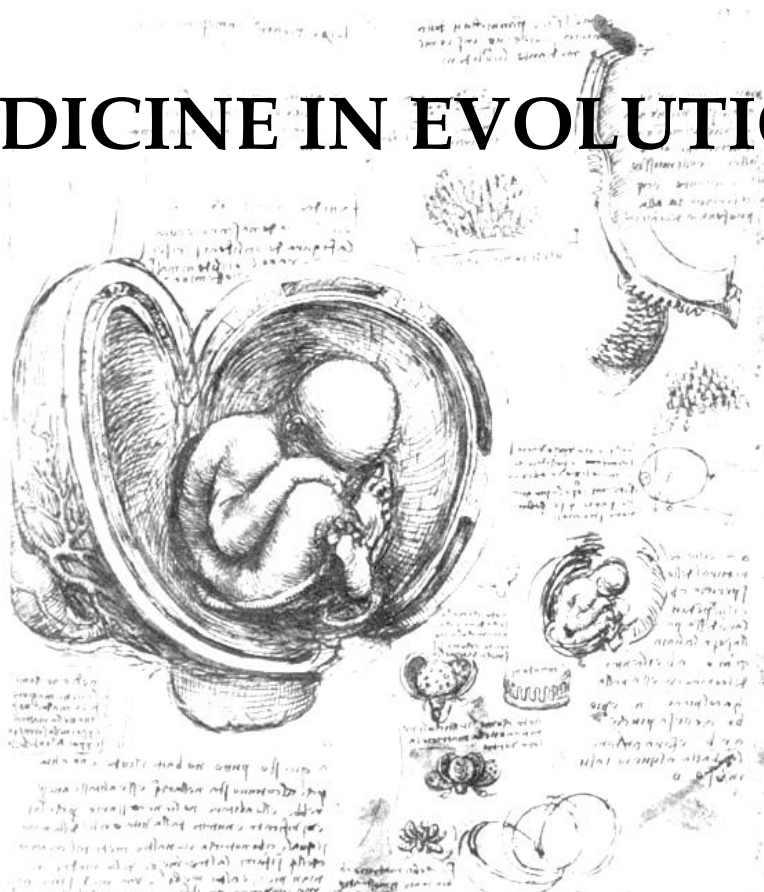


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CONTENTS

ARTICLES

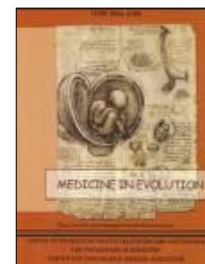
H. Ionescu, A. Bucur, O. Dinca, M. B. Bucur, C. Vladan, R. Boesecke, G. John Kane EVALUATION OF OPTICAL TRACKING SYSTEMS FOR THE IMPLEMENTATION OF COMPUTER NAVIGATED ORTHOGNATHIC SURGERY	228
P. Bicov, D. Nemes, L. Catan, E. Amaricai, D. Popa, S. Cerbu, D. Tanase, G. Puenea, D. Andrei COMPLEX ASSESSMENT OF POST-TRAUMATIC SOFT TISSUE INJURIES OF THE KNEE	236
R. Dumache, M. Puiu, A. Bucur, R. Minciu, B. Bumbacila CLINICAL APPLICATIONS OF TUMORAL BIOMARKERS IN THE DIAGNOSTIC AND PROGNOSTIC OF PROSTATE CANCER	243
R. Albulescu, M. Munteanu POSTOPERATIVE COMPLICATIONS OF DIABETIC CATARACT SURGERY	248
M. M. Delamarian, I. Ionita, H. Ionita MONITORING THE RESPONSE TO TYROSINE KINASE INHIBITORS IN CHRONIC MYELOGENOUS LEUKEMIA	254
A. Istodor, O. Mazilu, D. Iliescu, L. Sima, A. Blidisel, O. Cretu THE COMPLICATIONS OF SURGICAL TREATMENT OF HEPATIC TRAUMA AT POLYTRAUMATIZED PATIENT	262
A. M. David, S. Nastase STUDY OF INTERACTIONS BETWEEN ANTIPSYCHOTICS AND THEIR MEMBRANE RECEPTORS BY QSAR METHODS - TOWARDS NEW ANTIPSYCHOTICS DRUG DESIGN	267
C. Duda-Seiman, A. Isvoran, C. Grigorie, D. Duda-Seiman, S. Avram, C. Puscas, C. Bolcu, S. Mancas, R. Cinca, D. Ciubotaru QSAR STUDY (QUANTITATIVE RELATIONS-STRUCTURE-BIOLOGICAL ACTIVITY) WITHIN CALCIUM CHANNEL BLOCKERS, DIHYDROPYRIDINES TYPE	274
G. Homolka, M. Puschita, C. Popa THE IMPORTANCE OF MODERN MANAGEMENT METHODS IN THE MEDICAL FIELD	282

M. Obreja, M. Mihailescu CORELATIONS BETWEEN TUMOR LOCATION AND SYMPTOMS IN A SERIES OF 65 PATIENTS WITH GIST MEDICAL FIELD	290
L. Catan, P. Bicov, D. Nemes, E. Amaricai, D. Popa, Daniela Tanase, G. Puenea, D. Andrei FUNCTIONING AND QUALITY OF LIFE IN PATIENTS WITH POST-TRAUMATIC SOFT TISSUE INJURIES OF THE KNEE	297
A. Somesan, I. Ungurean, V. Tudorache, N. Bertici, M. Marc, O. Fira Mladinescu, E. T. Tudorache, C. Oancea MUSCLE EVALUATION IN COPD	304
I. Penteridis, Mornos C., A. Ionac, H. Feier, M. Gaspar, St. I. Dragulescu PRE-OPERATIVE TRANSTHORACIC THREE-DIMENSIONAL ECHOCARDIOGRAPHY IN THE ASSESSMENT OF MITRAL STENOSIS: CLINICAL EXPERIENCE	311
L. C. Iordache, E. Amaricai, D. Popa, L. Catan, R. Petroman, D. Andrei, R. Popescu THE COMPLEX APPROACH OF PATIENTS WITH NEUROLOGIC DISORDERS AND OSTEOARTHRITIS	318
V. Nistor, Al. Istodor, O. Mazilu THE MANAGEMENT OF INCISIONAL HERNIA IN AN EASTERN EUROPEAN EMERGENCY CENTER	323
C. C. Diaconu, D. Bartos FREQUENCY OF PULMONARY HYPERTENSION IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION	327
C. Petrescu, A. M. Voiculescu, O. Suci, T. R. Olariu HYGIENE CONDITIONS IN DENTAL OFFICES DURING TREATMENT PROCEDURES AND RELATION WITH PATIENTS` DENTAL HEALTH	331
T. Hamburda, M. Salceanu, C.Topoliceanu, A.Melian, L.Aminov M. Vataman, I. Caruntu ASPECTS REGARDING MODIFICATIONS AT MACROSCOPIC, HISTOPATHOLOGICAL AND RADIOGRAPHIC LEVEL IN INFLAMMATORY ROOT APICAL RESORPTIONS	338
A. N. Valeanu, L. E. Vasile, M. Rivis MORPHOLOGICAL INDICATORS IN THE APPRECIATION OF THE RISK OF MAXILLARY CYSTS RECURRENCE	343

A. Jivanescu, D. Naiche, E. Bratu FIVE YEAR CLINICAL EVALUATION OF PRESSED CERAMIC VENEERS	349
P.Bold, A. Bold AESTHETICS: PERFECTION, NECESSITY OR COMPROMISE	357
S. Gaman, M. C. Bortun, V. Mercut EVALUATION FOR OPTIMIZATIONS AND REOPTIMIZATIONS OF REMOVABLE PARTIAL DENTURES MADE TO PATIENTS IN DOLH COUNTY	361
I. Olariu, A. C. Podariu, R. A. Popovici, O. L. Gag Otilia, T. V. Olariu DENTIST - STUDENT INTERNATIONAL COMMUNICATION STRATEGY	369
C. F. Lazar, A. Babametis, E. Bratu, P. Deutsch, A. Deutsch, M. Papurica MESUREMENT OF DENTAL FEAR AND ASSESING THE NEED OF PHARMACOLOGICAL MANAGEMENT OF PAIN IN DENTISTRY, A SURVEY OF THE POPULATION IN TIMISOARA	374
R. A. Balan, D. C. Bratu, M. Luca, R. Bitu, E. Bratu THE MIOFUNCTIONAL THERAPY USING MYOBRACE IN THE TREATMENT OF CLASS II/2 DENTAL ANOMALY CASE PRESENTATION	382
R. Stanescu, A. C. Didilescu, A. M. Jianu, M. C.Rusu THE TOPOGRAPHY AND SHAPE OF THE MANDIBULAR CANAL IN EDENTULOUS PATIENTS	386
O. A. Velea, D. Onisei, C. Kralev, D. Onisei ODONTO-PERIODONTAL MANIFESTATIONS IN CALCIUM AND VITAMIN D PROLONGED DEFICIENCY	391
T. G. Stanoiu, M. Surpateanu, A. C. Podariu, T. Tirca, R. A. Popovici ADDITION PLASTY-MODERN COMPONENT OF THE COMPLEX MARGINAL PERIODONTAL DISEASE TREATMENT	402
S. Rosu, F. Montanaro A SINGLE SITE, OPEN NON-CONTROLLED STUDY OF EFFICACY AND TOLERABILITY OF TWO FORMULATIONS OF THE MEDICAL DEVICE GENGIGEL ® BABY GEL (0.2% HYALURONIC ACID) IN THE TOPICAL TREATMENT OF TEETHING IN INFANTS	409
C. Zeicu, A. C. Podariu, R. A. Popovici, R. S.-Rosianu, D. Jumanca, R. Oancea, A. Galuscan COMPARATIVE STUDY OF EDUCATIONAL ORAL HEALTH PROGRAMMES ON THE WORLD	416

D. Bei, A. M. Pallag, I. Szabo, A. Honiges BLOOD ANTIOXIDANT STATUS BETA-BLOCKERS TREATMENT	424
E. Stancu, A. E. Taerel REMEDIES REGISTERED IN THE ANNUAL ACCOUNTS BOOK OF A PRIVATE RURAL PHARMACY IN 1928	431
G. Burcea, M. Barca, A. M. Ciobanu, A. Cimpoiesu, D. Popa, C. Baloescu IDENTIFICATION AND ASSAY OF CEFACLOR BY SPECTRALE METHODS FROM CECLODYNE ® CAPSULES OF 250 MG AND 500 MG	435

EVALUATION OF OPTICAL TRACKING SYSTEMS FOR THE IMPLEMENTATION OF COMPUTER NAVIGATED ORTHOGNATHIC SURGERY



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ABSTRACT

One of the major technologies in computer assisted surgery is the computer navigation, based on tracking systems. This study evaluates the up-to-date available tracking systems to identify the best suited for computer navigated oral and maxillofacial surgery, with focus on orthognathic surgical procedures. Surgical navigation is the concept and set of methods needed to track the position of a virtual 3D dataset gathered by computer medical imaging with the real position of the patient.

The goal was to evaluate the accuracy and feasibility for navigated oral and maxillofacial surgery using standard instruments, with focus on orthognathic procedures. We have used a mandibular model onto which we have applied a three-marker DRF on the teeth, using a rigid moulding material. We compared the spatial readings referring to the same coord we compared the readings generated by the Polaris tracking pointer with the ones of the FaroArm. The global positional shift was calculated as the length of the 3D vector between the Polaris and FaroArm determined points. Inate system, using the Polaris tracker and a reference position read using a mechanical arm tracking system.

The surgical navigation in oral and maxillofacial surgery and especially in orthognathic surgery represents a new and major trend, helping to minimize risks through a better visualisation in a complex but dimensionally limited surgical field.

Key words: surgical navigation, maxillofacial surgery.

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INTRODUCTION

Considering the complexity of the head and neck anatomy, oral and maxillofacial surgical procedures require a permanent and detailed awareness of the involved structures in the operated area, despite limited space and visibility. Computer assisted surgery in the maxillofacial field brings a significant contribution to overcome this obstacles and started to be clinically applicable in the 1990s, after years of development for neurosurgical procedures¹.

One of the major technologies in computer assisted surgery is the computer navigation, based on tracking systems. This study evaluates the up-to-date available tracking systems to identify the best suited for computer navigated oral and maxillofacial surgery, with focus on orthognathic surgical procedures.

Principles of surgical navigation

Surgical navigation is the concept and set of methods needed to track the position of a virtual 3D dataset gathered by computer medical imaging with the real position of the patient. It is crucial in computer assisted surgery, in order to insure the virtual reproducibility of the clinical situation during surgery.

Creating a virtual image of the patient - The most important component for surgical navigation is obtaining an accurate three-dimensional model of the patient's anatomy. This can be conducted through a number of medical imaging technologies including CT, MRI, x-rays, ultrasound plus many more. It is also possible to employ a number of scanning methods, with the datasets combined through data fusion techniques. The final objective is the creation of a 3D dataset that

reproduces the exact geometrical situation of the normal and pathological tissues and structures of that region. Of the available 3D scanning methods, the computed tomography (CT) is preferred, because MRI datasets are known to have volumetric deformations that may lead to inaccuracies. Furthermore, for the viscerocranium, the CT permits an easy selection of the bony structures, having highly specific thresholds for various tissue structures, including bone.

After data acquisition, usually further image processing is required, in order to isolate the regions of interest for the surgical procedure. For example, in the case of navigated mandibular surgery, a so-called *segmentation* protocol is applied, in order to have only the mandible visible. This could be achieved through thresholding (based on specific attenuation values for bone on CT datasets - between 400 and 1000 Hounsfield units²) and further through topographic segmentation of the ROI (region of interest).

Stereotaxy and tracking

Another challenge for the surgical navigation technology is maintaining the spatial correspondence between the dataset and the patient. In essence, the goal is to obtain constant, reproducible dimensional constraints between the operated area and a geometric reference system. The options are either to constrain the patient a fixed position to the reference system (the method is called stereotaxy), or to have the reference system moving in real time with the moving anatomical structures, thus keeping the geometric constraints - and of course to be able to track the reference system position (the method is called tracking).

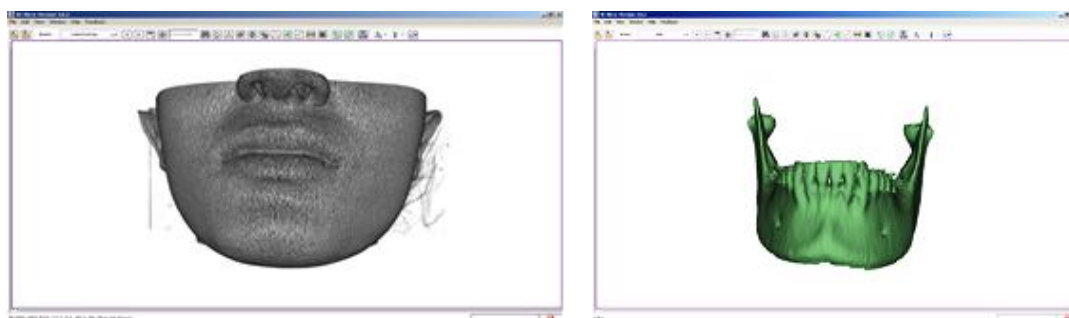


Fig.1. Three-dimensional representation of the same CT dataset: original dataset and isolated mandible after thresholding and topographic ROI segmentation (using 3D Slicer 3.5, National Alliance for Medical Image Computing).

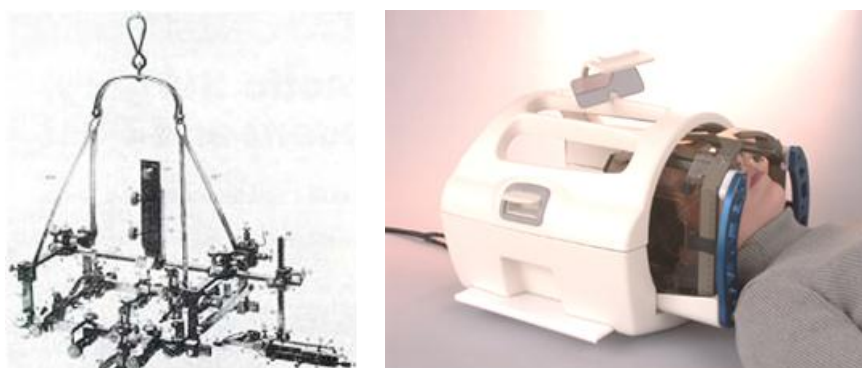


Fig 2. Representation of the original Horsley-Clarke apparatus ⁴ and modern Magmedics ® stereotactic frame positioner.⁵

Stereotaxy is the simplest method, based on the fixation of the anatomical region in a reproducible constraint, both at the time of the imagistic investigation and in the operating room. The method of head fixation has been used for reproducible guidance in neurosurgery since 1908 (the original Horsley-Clarke apparatus)³, using so-called stereotactic fixation devices. An improved method is still in use today, based on stereotactic helmets or masks for computer navigated neuroradiotherapy.

Surgical tracking represents a more technicist solution, but with improved ergonomics. The principle is to have reference markers applied in a geometrically fixed position onto a free-moving patient, and monitor the real time position (or movements) of these reference markers.

Of course, in this case, a determination of the initial geometrical

correspondence between the reference markers and various reproducible anatomical landmarks is needed. This is achieved through a so-called *registration procedure*, right after the fixation of the markers, by indicating predefined anatomical landmarks, under tracking premises. It is assumed that the geometrical position of each anatomical landmark to the reference markers will remain constant as long as the latter remains on the patient.

The same applies to the surgical instruments to be tracked – they receive the same kind of markers on their handles, and in the same manner have to be *calibrated* to define their geometry regarding the markers position under tracking premises.

There are more tracking systems commercially available, based on various physical principles (mostly optical or electromagnetic). Regardless of the operating principle, a

tracking system consists of the following elements:

1. *Fiducial markers* applied onto the patient and the surgical instruments;

2. *The location module* is an electronic device based on positioning sensors, allowing the tracking of the fiducial markers in the real three-dimensional space and communicating them to a computer;

3. *The interface computer* is attached through a serial link to the location module and, through specialised drivers and routines, based on the marker location information, does the real time translational and rotational calculus of the tracked objects to correlate them with the virtual datasets and the object rendering on the screen.

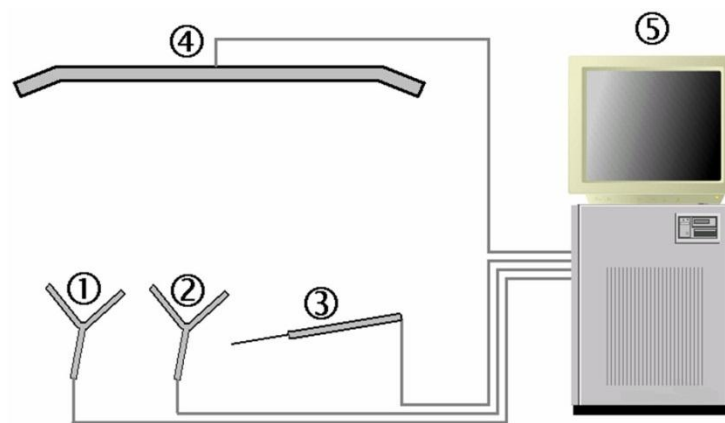


Fig. 3. Representation of the components of a surgical navigation system: 1, 2 – fiducial markers on applied on the patient; 3 – tracked surgical instrument; 4 – location module; 5 – computer.⁶

There are different technologies available for surgical tracking, based on different physical principles:

- optical tracking systems are based on stereophotogrammetric calculation of bright light reflecting or emitting markers. The systems include at least 2 cameras and more fiducial markers, that could be active (light emitting), or passive (reflecting light from a separate source);

- electromagnetic tracking systems are based on measuring electrical currents generated by the motion of small ferromagnetic sensors

in an electromagnetic field (called Foucault currents); the system is not suited to be implemented in a surgical environment with usual metallic instruments, because their movement generate major distortions of the magnetic field and therefore high and unpredictable tracking errors;

- other tracking systems, less suitable for head and neck surgical navigation: mechanical tracking, ultrasound tracking, radiofrequency tracking, inertial (accelerometer based) tracking, image recognition tracking.

MATERIAL AND METHOD

We have analyzed the reliability and the accuracy of a widely available optical tracking system, the NDI Polaris

Spectra (Northern Digital Inc., Waterloo, Canada). The goal was to evaluate the accuracy and feasibility for

navigated oral and maxillofacial surgery using standard instruments, with focus on orthognatic procedures. The literature indicates a spatial accuracy under 1 mm⁷, reaching up to 0,3 mm according to product specifications for newer NDI Polaris Spectra or Polaris Vicra systems⁸. The specific features of such a system are further described.

Fiducial markers. For optical tracking, there is need for at least three fiducial markers for each reference structure. In order to define a tridimensional vector for each reference, a 3D plane should be defined; therefore at least three non-collinear markers will be included. The markers will be rigidly fixed to so-called DRFs (Dynamic Reference Frames) that will be applied onto the

patient and instruments. It is recommended to use more than the geometrically required three makers, in order to increase marker visibility and accuracy through redundancy.

There are passive or active optical fiducial markers. The passive ones reflect infrared light from a lamp on the location module; therefore there is no need for wiring of the patient or instruments. The active markers are infrared LEDs, having a good visibility, but need to be wired to an energy source.

The location module consists of series of CCD cameras – usually two coplanare or three colinear. These register the image of the markers the marker position is calculated through stereofotogrammetric algorithms.

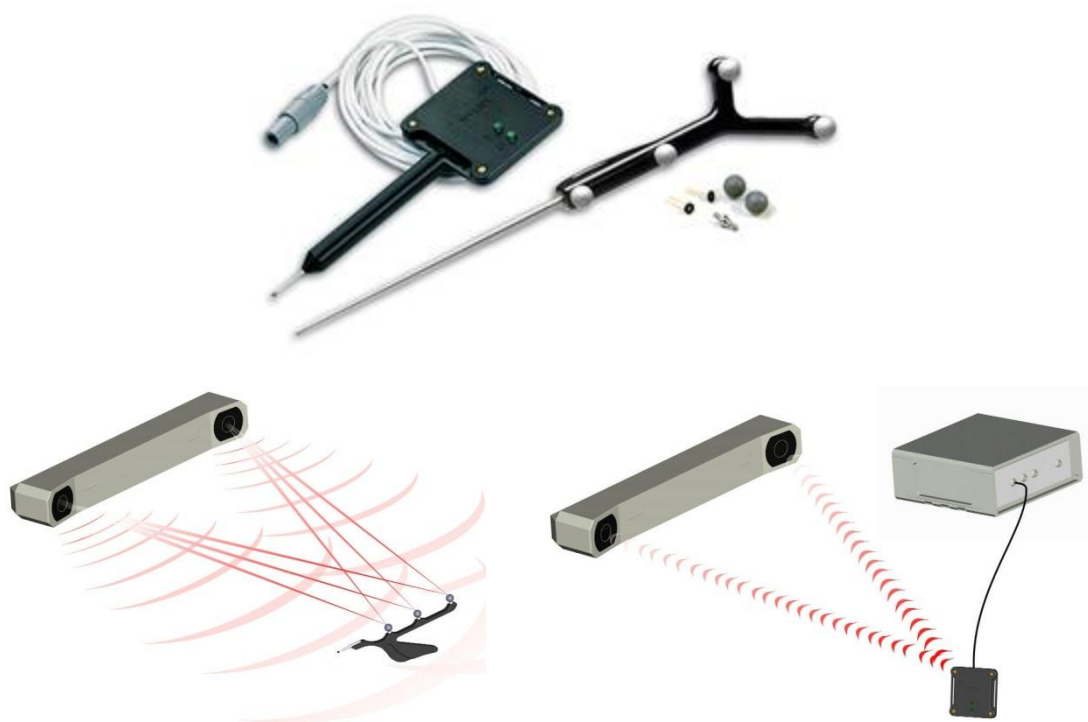


Fig 4. Fiducial markers – active (wired) and passive, mounted on DRFs on tracking pointers (Northern Digital Inc.)⁹; principle of passive, respectively active optical tracking¹⁰.

With the goal of determining the tracking accuracy in real situations, we experimented with a NDI Polaris

Spectra tracking system (Northern Digital Inc., Waterloo, Canada), based on 11 mm diameter reflective passive

optical markers, and a two CCD camera tracking sensor.

We have used a mandibular model onto which we have applied a three-marker DRF on the teeth, using a rigid moulding material. We compared the spatial readings referring to the same coordinate system, using the Polaris tracker and a reference position read using a mechanical arm tracking system.

We developed software routine based on quaternion calculation of the translational or rotational movements of the DRF. This was developed as a routine in Microsoft Visual C++ 2008 Express Edition on a Windows XP platform. The data transfer between the tracker and the computer was based on

a serial RS 232 port and a null-modem cable. The mechanical arm tracking system that we used was a FaroPlatinumArm (FARO Swiss Holding GmbH, Switzerland), a high-end industrial mechanical arm coordinate reading device. He considered it as the reference measurement, based on its accuracy specification of 0.020 mm by measurements nearer as 1,8 m.¹¹

We made 5 sets of measurements of the three-dimensional position of different points on the mandible. These points were the left mandibular foramen and the tip of right coronoid process. For each set of measurements, the actual position of the mandibular model on the table was changed.

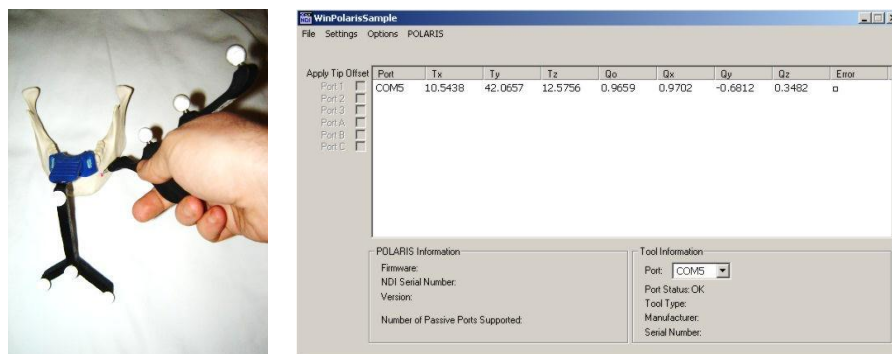


Fig. 5. Position reading on the mandibular model with the mounted DRF, using the optical tracking pointer; sample of the software interface.



Fig. 6. The FaroPlatinumArm system and the laser scanner head.

RESULTS AND DISCUSSIONS

We compared the readings generated by the Polaris tracking pointer with the ones of the FaroArm. The global positional shift was calculated as the length of the 3D vector between the Polaris and FaroArm determined points. The error factor is an euclidian calculated error factor based on Polaris data input,

influenced by the distance between the DRF and the tracking sensor.

Considering also the human error factor in the measurements (precision of the tool tip positioning), we consider the median error value of 0.65 mm as very good and suitable for operative tracking in oral and maxillofacial surgery, and especially for orthognathic interventions.

Table 1 Dimensional differences between Polaris and FaroArm readings

No.	Difference (mm)	Euristic error factor (mm)
1. (left mand. foramen)	0,64	0,052
1'. (right coronoid proc.)	0,87	0,036
2. (left mand. foramen)	0,63	0,032
2'. (right coronoid proc.)	0,67	0,027
3. (left mand. foramen)	0,81	0,029
3'. (right coronoid proc.)	0,91	0,020
4. (left mand. foramen)	0,16	0,031
4'. (right coronoid proc.)	0,60	0,029
5. (left mand. foramen)	0,74	0,028
5'. (right coronoid proc.)	0,54	0,035
Median	0,65	0,026

Passive optical tracking vs. active optical tracking

Starting from the Polaris producer's data (Northern Digital Inc.)¹², we evaluated the optimal choice

of a tracking system for orthognathic surgery. There is to be mentioned that there are no significant accuracy differences between these systems.

Passive optical tracking	Active optical tracking
<ul style="list-style-type: none"> Passive tools use spherical, retro-reflective markers that reflect infrared light emitted by the illuminators on the position sensor Tools are wireless Offers simple tool construction Requires each tool have a unique marker geometry resulting in larger tool sizes Passive spheres need to be replaced after single use Difficult to clean passive spheres intra-operatively 	<ul style="list-style-type: none"> Active tools incorporate infrared-emitting markers that are activated by an electrical current Tools are wired to the system More complex to build than passive tools Tools can be small since the same geometry can be used multiple times Markers have limited life and are not replaceable Markers can be cleaned easily Can incorporate switches and visible LEDs Tool Definition File can be programmed into tool

CONCLUSIONS

The surgical navigation in oral and maxillofacial surgery and especially in orthognathic surgery represents a new and major trend, helping to minimize risks through a better visualisation in a complex but dimensionally limited surgical field.

From various surgical navigation solutions available, we opted out for the passive optical tracking system that confers submillimetrical accuracy and an ergonomically optimal implementation.

REFERENCES

1. Schramm A, Gellrich NC, Schmelzeisen R: Navigational Surgery of the Facial Skeleton. Springer-Verlag Berlin, Heidelberg, 2007
2. Banik S, Rangayyan RM, Boag GS: Landmarking and segmentation of 3D CT images. Morgan&Claypool, 2009
3. Marshall LH, Magoun HW: The Horsley-Clarke Stereotaxic Instrument: The Beginning. Neuroscience History Program Brain Research Institute, University of California, Los Angeles, CA 90024-176118
4. Levy R: A Short History of Stereotactic Neurosurgery. Cyber Museum of Neurosurgery, www.neurosurgery.org/cybermuseum/stereotactichall/stereoarticle.html
5. www.magmedix.com/products/procedures/speciality_coils.html
6. Bucur A, Acero J, Stanciu D, Carreño A, Marmulla R, Popescu M, Dincă O, Ionescu H: Tratamentul chirurgical al anomaliilor dento-maxilare severe. În: Bucur A (ed.), Navarro-Vila C, Lowry J, Acero J (coord.): Compendiu de chirurgie oro-maxilo-facială, Vol. II. Q Med Publishing, București, 2009
7. Cliassal F, Lavallee S: Experimental Protocol of Accuracy Evaluation for Computer-Integrated Surgery: Application to Four Optical Localizers. În Wells W M III, Colchester A, Delp S (Eds.): „Medical Image Computing and Computer-Assisted Intervention - MICCAI 98”, Springer Verlag, Berlin, 1998;277-280
8. NDI Optical Measurement Technology, www.ndigital.com/medical/technology-optical.php
9. NDI InFocus: Active Versus Passive Tracking, 2007. www.ndigital.com/medical/infocus/2007-10/article-6.php
10. NDI Polaris - prospect online. www.ndigital.com/medical/documents/polaris/polaris-howitworks.pdf
11. measuring-arms.faro.com/distri/start/
12. CURAC - Computer- und Roboterassistierte Chirurgie (Computer and Robotically Assisted Surgery), Karlsruhe, Germany, 11-13 Oct. 2007. www.ndigital.com/medical/infocus/2007-10/InFocusOct2007.pdf

COMPLEX ASSESSMENT OF POST-TRAUMATIC SOFT TISSUE INJURIES OF THE KNEE



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ABSTRACT

Aim and objectives: To point out importance of complex assessment of post-traumatic soft tissue injuries of the knee in order to have adequate therapeutic approach.

Material and methods: During a one year period we studied 104 patients diagnosed with different types of soft tissue post-traumatic knee lesions. Patients were divided into 4 groups. Every patient undertook three assessments, namely complex clinical examination, functioning and quality of life assessment by using KOOS and musculoskeletal knee ultrasonography.

Results: We noticed the increase in quality of life in group 2 and 4 patients. The ultrasonography scores were correlated with KOOS scores.

Conclusions: The key for obtaining therapeutic success in treating post-traumatic soft tissue injuries of the knee is represented by an early rehabilitation program that should follow a complex clinical, functional and ultrasonography assessment. Musculoskeletal knee ultrasonography can detect lesions that are not detectable by routine clinical examination.

Key words: ultrasonography, knee, rehabilitation.

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INTRODUCTION

Periarticular injuries of the knee due to different types of traumatism on normal or pathologic anatomic structures have a high incidence in general population with important socioeconomic involvements, but especially with the decrease in functioning and quality of life. The treatment of this pathology is not so much common as the treatment of the knee joint pathology itself.

In the absence of an adequate and complex therapeutic approach that has to be applied early and sustained, after a correct diagnosis and a careful assessment, the evolution of these disorders is unfavourable leading to different degrees of disability. The assessment should contain a rigorous clinical examination, as well as functional and imagistic evaluations of a high degree of precision such as specific X-ray examination, MRI (magnetic resonance imaging), musculoskeletal ultrasonography of the joint and of the soft tissues, electromyography or Doppler ultrasonography¹⁻³. Musculoskeletal ultrasonography can visualise the muscular structures, tendons, bursae,

ligaments, joints and synovia. In the same time it can evaluate the response to a specific treatment. It has become lately one of the most used methods of imaging in medical practice, being in many cases the first intention investigation that can orientate the clinician to a certain diagnosis⁴⁻⁷. The main advantages of musculoskeletal ultrasonography are the following: it is non-invasive, not painful, easy to perform, easy to repeat, accessible, it offers complex morphologic information, it is a real time examination and it does not require a special patient's preparation⁸⁻⁹. Along the time it has proven its efficiency not only from the economic and time consuming points of view. The earnings are multiple and knowing the adequate condition and treatment, together with an active participation in decision making in order to make a therapeutic management can lead the patients suffering from a disabling disease to take decisions that would allow improvements in quality of life, namely in terms of needs, goals and circumstances¹⁰.

AIM AND OBJECTIVES

1. To point out the importance of a complex assessment, including an ultrasonography examination of the post-traumatic soft tissue injuries of the knee joint in order to make the correct therapeutic approach and to follow up its efficiency;
2. The evaluation of the effects of pre-existing rheumatic degenerative or inflammatory lesions on the knee soft tissue structures and that can affect patients' functioning and quality of life;
3. To create an ultrasonography score that can quantify post-traumatic soft tissue injuries of the knee. This score should be correlated with final KOOS score (Knee Injury and Osteoarthritis Outcome Score). KOOS evaluates functioning, daily activities, leisure and sport activities, and last, but not the least, the overall quality of life;
4. To prove the importance of rehabilitation treatment combined with a medical adequate therapy.

MATERIAL AND METHOD

During a 1-year period (between March 2011 and February 2012) we studied a number of 104 patients diagnosed with different types of post-traumatic soft tissue injuries of the knee. The patients were between 15 and 88 years old. 64 of the patients (61.53%) were females and 40 patients (38.46%) were males.

The soft tissue injuries were singular or multiple and were represented by soft tissues edema, quadriceps tendon lesions (tendinitis, partial or complete tear, avulsion), prepatellar or infrapatellar bursitis, bursitis of the pes anserinus, lesions of the patellar retinaculum (elongation, partial or complete tear), lesions of the medial collateral ligament (elongation, partial or total tear), lesions of the iliotibial band (friction syndrome with or without bursitis). These injuries were diagnosed clinically and by using musculoskeletal knee ultrasonography after the recommendation of a rehabilitation or rheumatology specialist. After excluding an osteoarticular disorder caused by injury, in 53 cases (50.96%) it was noticed a pre-existing rheumatic inflammatory or degenerative lesion at the knee level.

The 104 selected patients were divided into four homogenous groups and followed a differentiated treatment. Group 1 was made of 27 patients that had post-traumatic soft tissue injuries on an unaffected knee joint. They followed a complex medical treatment consisting in oral antalgics (Gabapentin 300 mg per day, Ketorolac tromethamine 10 mg per day), oral nonsteroidal anti-inflammatory drugs (Celecoxib 200 mg per day, Diclofenac 150 mg per day or Meloxicam 15 mg per day) and trophic medicines (Regenovex 1 tablet per day, ALAnerv

1 tablet per day, Lenifast ointment twice a day). Group 2 was made of 24 patients that had post-traumatic soft tissue injuries on an unaffected knee joint. They followed the same medical treatment as group 1 combined with an intensive and sustained rehabilitation program. The last one was started in the early stages of the injury and was carried out for one year, consisting at the beginning in 30 daily sessions and continued with 10 sessions (three times a week) every three months. The rehabilitation had the following aims: pain release, prevention or correction of the posture disorders, functioning improvements (increase in range of motion, muscle strengthening, improvement in stability, control, coordination and equilibrium in order to prevent the falls, walking improvement and optimal performing of activities of daily living). Group 3 was made of 28 patients, while group 4 was made of 25 patients. Group 3 and 4 patients had post-traumatic soft tissue injuries on a pathologic knee joint. Group 3 followed the same medical treatment as group 1, while group 4 followed the same medical and rehabilitation treatment as group 2.

In the first month after the traumatic event every patient of the four study groups required a functional knee brace in order to increase knee stability and to prevent deformations.

Each of the patients followed three assessments, initially, after 6 months and finally after one year. Every assessment consisted in a complete clinical examination (see figures 1a and 1b), a functional evaluation and a musculoskeletal ultrasonography of the traumatic knee (see figures 2a and 2b). For assessing functioning the KOOS questionnaire was used. It assesses pain, stiffness,

activities of daily living (functioning, self-care and ability to walk), leisure and sport activities and the quality of life^{11, 12}. We proposed an ultrasonography protocol in order to

quantify the severity of soft tissue injuries of the knee (see table I). The final ultrasonography score should be correlated more easily with the KOOS score.

Table 1 Ultrasonography protocol for assessment of post-traumatic soft tissue injuries of the knee (authors' personal contribution)

KNEE			RIGHT	LEFT
Soft tissue edema/ subcutaneous tissue edema		1		
		2		
KNEE			RIGHT	LEFT
Quadriceps tendon	Tendinitis	1		
	Partial tear, intact sheath	2		
	Total tear, torn sheath, avulsion	3		
KNEE			RIGHT	LEFT
Prepatellar bursitis		Liquid < 15 Mm	1	
		Liquid > 15 Mm	2	
KNEE			RIGHT	LEFT
Patellar retinaculum	Elongation	1		
	Partial tear	2		
	Complete tear	3		
KNEE			RIGHT	LEFT
Infrapatellar bursitis		1		
KNEE			RIGHT	LEFT
Medial collateral ligament	Elongation	1		
	Partial fibrillar tear	2		
	Complete tear	3		
KNEE			RIGHT	LEFT
Pes anserinus		Bursitis	1	
KNEE			RIGHT	LEFT
Iliotibial band	Friction syndrome	1		
	Friction syndrome + Bursitis	2		
KNEE			RIGHT	LEFT
TOTAL SCORE				

Total score:

- 1-3: minor lesions of knee soft tissues;
- 4-7: moderate lesions of knee soft tissues;
- 8-12: severe lesions of knee soft tissues.



Fig. 1 a, b. Post-traumatic knee injuries with soft tissues involvement (authors' personal collection, having the patient's informed consent)

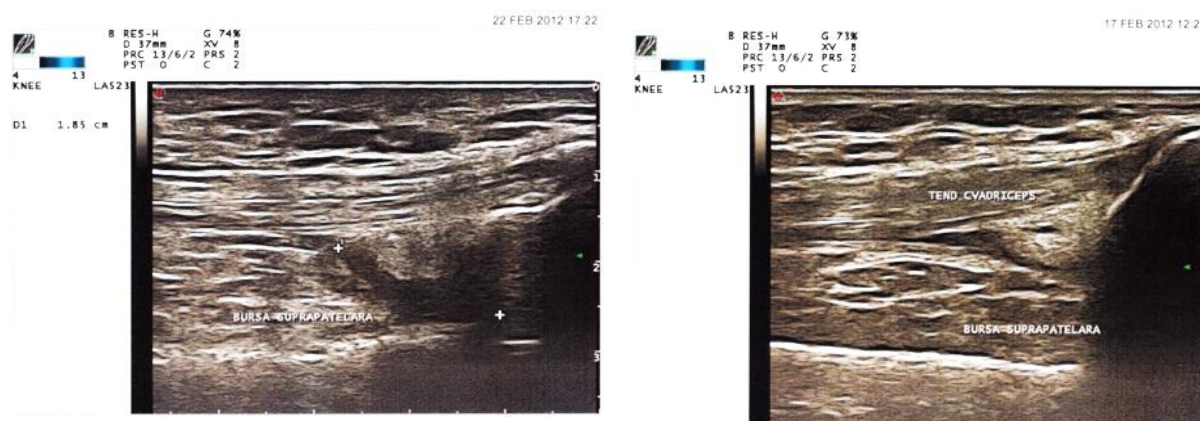


Fig. 2 a, b. Ultrasonography of post-traumatic knee joint (2a- suprapatellar bursitis; 2b- quadriceps tendinitis) (authors' personal collection, having the patient's informed consent)

RESULTS

1. The functional and ultrasonography assessments showed a better evolution in group 2 patients in comparison to group 1, 3 or 4 patients, as well as a better evolution of group 3 patients in comparison to group 4 patients. Although the initial clinical examination and the ultrasonography total score were similar, the above mentioned improvements were noticed both at intermediate assessment (after 6 months) and at the end of the study (see table II and figure 3).
2. The ultrasonography total score obtained by summing the specific elements evaluates objectively the functional outcomes in all four study groups and the efficiency of the therapeutic approaches.
3. The rehabilitation program should be individualised, sustained and started as soon as possible. It has proven its efficiency for the 49 patients of groups 2 and 4. The quality of life of these patients has improved significantly in comparison to the other two groups. The most important outcomes were noticed in those patients who had a pre-traumatic unaffected knee joint and who followed both medical treatment and physical therapy (see table II and figure 3).

Table 2 Progression of ultrasonography total scores in the four study groups

Group	Total US 1 score	Total US 2 score	Total US 3 score
1 (n-27)	6.66	4.88	2.88
2 (n-24)	6.78	3.0	2.2
3 (n-28)	7.5	5.2	5.7
4 (n-25)	7.2	6.0	4.0

n: number of patients; US: ultrasonography

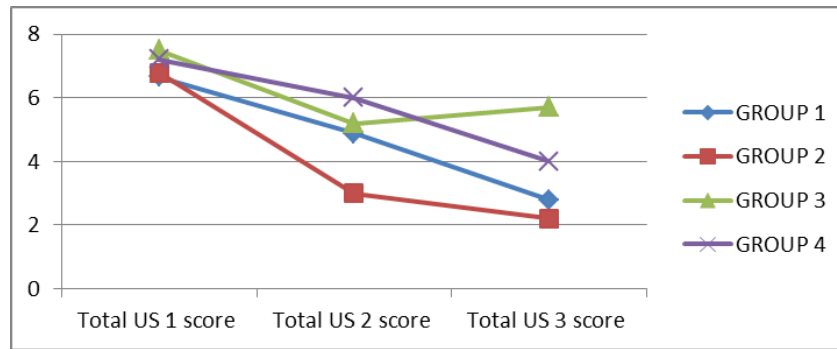


Fig. 3. Graphic representation of the average ultrasonography total scores in the four study groups.

CONCLUSIONS

The key for obtaining a therapeutic success of the post-traumatic soft tissue injuries of the knee is represented by the beginning of an early staged rehabilitation program. This treatment must follow complex clinical, functional and ultrasonography assessments. The results of these evaluations should be correlated before starting the proper therapy. In case of post-traumatic soft tissue injuries of the knee, musculoskeletal ultrasonography can detect lesions that are not detectable by

a routine clinical examination. These disorders have important effects upon patients' functioning and quality of life. Being a diagnostic method with a high degree of confidence and with performances related to the MRI, the musculoskeletal ultrasonography can be used successfully in detecting many of the post-traumatic soft tissue and bone injuries. Its advantages are represented by economic implications, with proven cost effectiveness, as well as by a very good patients' compliance.

REFERENCES

1. Sarraf P, Reginato AM. Periarticular Rheumatic Diseases. In: Bartlett J Susan et all, editors. Clinical Care in the Rheumatic Diseases. Association of Rheumatology Health Professionals, a Division of the American College of Rheumatology, Atlanta, Georgia; 2006, p. 145-51.
2. Pellicci P, McCormack RR. Bursitis and Tendinitis. In: Paget SA et all, editors. Hospital for Special Surgery manual of rheumatology and outpatient orthopedic disorders: diagnosis and treatment 5th Ed, Lippincott Williams & Wilkins; 2006, p. 203-6.
3. Dieppe PA. Recommended methodology for assessing the progression of osteoarthritis of the hip and knee joints. Osteoarthritis Cartilage 1995; 3: 73-7.
4. Siwek CW, Rao JP. Ruptures of the extensor mechanism of the knee joint. J Bone Joint Surg Am 1981; 63(6): 932-7.
5. Yu JS, Petersilge C, Sartoris DJ, Pathria MN, Resnick D. MR imaging of injuries of the extensor mechanism of the knee. Radiographics 1994; 14(3): 541-51.
6. Myllymaki T, Bondestam S, Suramo I, Cederberg A, Peltokallio P. Ultrasonography of jumper's knee. Acta Radiol 1990; 31(2): 147-9.
7. Kaneko K, DeMouy EH, Brunet ME, Benzian J. Radiographic diagnosis of quadriceps tendon rupture: analysis of diagnostic failure. J Emerg Med 1994; 12(2): 225-9.
8. Friedman L, Finlay K, Jurriaans E. Ultrasound of the knee. Skeletal Radiol 2001; 30: 361-77.
9. Grassi W, Lamanna G, Farina A, Cervini C. Sonographic imaging of normal and osteoarthritic cartilage. Semin Arthritis Rheum 1999; 28: 398-403.
10. DeLisa JA. Physical medicine and rehabilitation: principles and practice, fourth edition. Philadelphia: Lippincott Williams & Wilkins Publisher; 2005, p. 721-1204.

11. Aaronson N.K. Quantitative issues in health-related quality of life assessment. *Health Policy* 1988; 10: 217-30.
12. Cella D, Nowinski CJ. Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. *Arch Phys Med Rehab* 2002; 83: 10-7.

CLINICAL APPLICATIONS OF TUMORAL BIOMARKERS IN THE DIAGNOSTIC AND PROGNOSTIC OF PROSTATE CANCER



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ABSTRACT

A biomarker represents an indicator of normal biologic processes, pathogenic processes or pharmacologic response to a therapeutic intervention. It facilitates screening and detecting of cancers, monitoring the progression of the disease and prediction of the prognosis and survival after clinical intervention.

Current advances in molecular techniques have offered new tools regarding the discovery of new biomarkers for prostate cancer.

Key words: prostate cancer, biomarker.

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INTRODUCTION

Epidemiology of prostate cancer (PCa)

In 2009, about 192.280 new cases of prostate cancer were diagnosed among American men ¹. This type of cancer, the second leading cause of cancer-related death among males, is exceeded by lung cancer. It is considered that prostate cancer is mainly a disease of older men.

It has been demonstrated that, the incidence of prostate cancer in afro-americans is 60% higher compared with the occurrences in the White population ². Afro-american men are often diagnosed with more advanced stages of PCa and at an earlier age. In the last 10 years, many studies have been done to search "inside" the molecular mechanisms involved in the development and progression of PCa. Genetics, environmental factors, such as: diet and lifestyle, have been proved to play an important role in PCa development, and may act as determining factors which could explain why some men are at higher risk for developing PCa than others.

Because of these, much effort is made to discover and develop new molecular biomarkers which may detect PCa in an early stage, when it can be cured, and to decrease the rate of mortality from this disease ³.

Molecular biomarkers:

A biomarker is defined by The National Cancer Institute as: a biological molecule which is found in blood, other body fluids, or tissues, that is a sign of a normal or abnormal process ⁴.

Biomarkers that present highly sensitive and specific indicators of some disease pathways are used as substitutes for outcomes in clinical trials where they can predict and

evaluate the clinical risk or benefit of the treatment ⁵.

Biology of the prostate

Androgens regulate the prostate gland as the major stimulus for cell division in the prostatic epithelium ⁶. On the other hand, it is known that androgens contribute to prostatic carcinogenesis. Prostate cancer develops when the rate of cell division surpasses cell death, leading to uncontrolled tumor growth. It has been demonstrated that more than 95% of prostate cancers are adenocarcinomas that arise from prostatic epithelial cells⁷. From these cases, about 70% occur in the peripheral zone, 15-20% occur in the central zone and 10-15% occur in the transitional zone⁸.

Screening for prostate cancer

It is well known that the major techniques which are used for prostate cancer diagnosis in its early stage are: digital rectal examination (DRE), serum prostate-specific antigen (PSA) test, and trans-rectal ultrasound guided biopsy (TRUS)⁹. The management of prostate cancer has undergone some changes due to the evolution of biomarkers used in screening, detecting and prediction of the disease¹⁰.

The PSA test was first used in the forensic field, as a biomarker for human semen¹¹, and it was first purified in the '70s from prostate extracts. The prostate gland produces PSA, and the PSA test measures PSA levels from the serum. Both prostate cancer and benign prostatic conditions (benign prostatic hyperplasia) can present increased levels of serum PSA from a normally low level to an elevated state in serum.

Digital rectal examination (DRE) is regarded as a tool for screening and

early detection of prostate cancer and is estimated to present an accuracy of 59%¹². Its main advantage is that it may detect cancer in men with a normal serum PSA level and the tumors that are small and well differentiated. The main limitation is that most palpable cancers are not early cancers, and important cancers are located in regions of the gland that are distant to digital palpation¹³. Many experts, agreed that based on DRE sensitivity and specificity and its role in the early detection of prostate cancer, its detection is less likely when using digital rectal examination independently, compared with digital rectal examination used in combination with other predictors¹⁴.

The use of PSA for prostate cancer screening has led to an increase in the number of men undergoing trans-rectal ultrasound-guided biopsy (TRUS), which is an invasive procedure in which a probe sends out energy sound waves is inserted into the rectum, against the prostate gland to image the entire gland. The advantage of TRUS is its high sensitivity, but on the other hand, it has a very poor specificity if used independently for screening modality.

Molecular biomarkers used in the diagnosis and prognosis of prostate cancer

Biomarkers for the early detection of cancer indicate the presence of an early cancer, or the fact that that cancer will occur or recurrence with 100% certainty within a short period of time. Biomarkers used in the diagnosis and prognosis of prostate cancer include DNA-based biomarkers, RNA-based biomarkers and protein-based biomarkers. Current advancements in proteomics, tissue microarray, DNA microarray, real-time PCR, and other biotechnologies have increased the

pace at which novel molecular biomarkers are discovered and developed.

1 *α-methylacyl-CoA racemase (AMACR)*: α-methylacyl-CoA racemase (AMACR), is an enzyme involved in the oxidative metabolism and synthesis of branched fatty acids found in dairy products and red meat. The enzyme is encoded by a gene located on chromosome 5p13.3 which contains polymorphisms associated with PCa. Many studies made with microarray demonstrated that AMACR appears over expressed in PCa. Recently it has been shown that decreased AMACR production could have a prognostic value in predicting biochemical recurrence and death due to PCa. Circulating concentrations of AMACR mRNA in serum and urine have been detected by reverse-transcription PCR analysis (RT-PCR)¹⁴. Studies of immunohistochemical staining of AMACR distinguished benign from cancerous prostate tissue with a 97% diagnostic sensitivity and a 92 % specificity¹⁵.

2 *PCA3 (prostate cancer antigen 3)*: PCA3 is a non-coding RNA and the most specific prostate malignancy biomarker described so far. The gene encoding PCA3 is located on chromosome 9q21-22. The PCA3 RNA is highly over-expressed in approximately 95% of tumours when compared to benign or normal prostate tissue¹⁶. As cancerous cells with high levels of PCA3 RNA are shed from the prostate into the urine, the levels of PCA3 RNA can be measured in the urinary sediments after prostatic massage. To perform the test it is necessary to collect about 20-30 ml of voided urine after a digital rectal examination. The assay available, APTIMA® (Gen-Probe) PCA3 test, detects quantitatively the expression of PCA3 RNA in urine and prostatic

fluids using transcription-mediated amplification¹⁷. The PCA3 score is defined as PCA3-RNA/ PSA-mRNA ratio, meaning that PCA3 expression is standardized with the PSA expression, used as a housekeeping gene. The PCA3 score correlates with the likelihood of positive biopsies: the higher the PCA3 score, the greater the probability of a positive biopsy. PCA3 score is not influenced by prostate volume, the number of prior biopsies, and is unaffected by patients' age, and the test is not influenced by the principal causes of PSA elevations: BPH and prostatitis¹⁸. PCA3 being a highly specific PCa test, is very useful for detecting the presence of PCa in men with alternative causes of PSA elevation, including inflammation of the gland and increase of its size.

3 Glutathione-S transferase P1 (GSTP1): The glutathione -S transferase P1 (GSTP1) gene is emerging as one of the most important tumor suppressor genes in PCa. GSTP1 can detoxify environmental electrophilic carcinogens and oxidants and may play a genome caretaker role by preventing oxidant and electrophilic DNA damage¹⁹. Hypermethylation of GSTP1 gene is the most common (>90%) reported epigenetic alteration in PCa. It occurs early in cancer progression and

is a promising biomarker for detecting organ-confined disease²⁰. In a study, Goessl et al demonstrated that gene GSTP1 appears hypermethylated in about 72% of serum, 50% of ejaculates, and 37% of urine samples from patients with PCa, but it was not found in any samples from patients with BPH²¹.

4 TMPRSS2: ERG: Genetic aberrations occur in almost all human malignancies. In the last years many studies have demonstrated that in patients with PCa, gene rearrangements involving androgen regulated gene- TMPRSS2 and ETS transcription factor genes (ERG and ETV) are present. The genes are located on chromosome 21. TMPRSS2 is located at 21q22.3 and ERG at 21q22.2²². TMPRSS2: ERG -fusion represents the most common variant which occurs in 40-70% of patients with PCa. The gene rearrangement occurs exclusively in patients with over-expression of ERG (95%), the gene which is currently considered a key oncogene in PCa²³.

The product of TMPRSS2: ERG fusion is found in about 20% of PIN cases, but it does not appear in benign prostate tissue specimens or proliferative inflammatory atrophy (PIA). TMPRSS2: ERG rearrangement can be detected in urine after DRE²⁴.

CONCLUSIONS

Recent developments in the field of molecular biology have provided new tools that have led to the discovery of many promising biomarkers for PCa. These biomarkers may be instrumental

in the development of new screening tests that have a high specificity in the diagnostic gray zone and as such are able to reduce the number of unnecessary biopsies.

REFERENCES

1. Parekh DJ, Ankerst DP, Troyer D et al. Biomarkers for prostate cancer detection. J Urol 2007;178:2252-2259
2. McDavid K, Lee J, Fulton JP, et al. Prostate cancer incidence and mortality rates and trends in the United States and Canada. Public Health Rep 2004; 119: 174-86

3. Jamal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008; 58: 71-96
4. Chodak G. Prostate cancer: epidemiology, screening, and biomarkers. *Rev Urol* 2006; 8 Suppl 2:S2-S3
5. Roobol MJ, Zappa M, Maattanen L et al. The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC). *Prostate* 2007; 67: 439-446
6. Jemal A, Tiwari RC, Murray et al. Cancer statistics, 2004. *CA Cancer J. Clin.* 2004; 54:8-29
7. Hessels D, Klein Gunnewiek JM, Van OI Karthaus HF, et al. DD3 (PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. *Eur Urol* 2003;44: 8-15
8. Deras IL, Aubin SM, Blasé A et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol* 2008;179:1587-1592
9. Van Glis MP, Hessels D, Jannink SA et al. The time-resolved fluorescence based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. *Clin Cancer Res* 2007; 13: 939-943
10. Mitelman F, Johansson B, Mertens F. The impact of translocations and gene fusions on cancer causation. *Nat Rev Cancer* 2007;7:233-245
11. Perner S, Mosquera JM, Demichelis F, et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. *Am J Surg Pathol* 2007; 31: 882-888
12. Demichelis F, Fall K, Perner S, et al. TMPRSS2: ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort. *Oncogene* 2007;26:4596-4599
13. Hessels D, Smith FP, Verhaegh GW, et al. Detection of TMPRSS2: ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer. *Clin Cancer Res* 2007;13:5103-5108
14. Zehenter BK, Secrist H, Zhang X, et al. Detection of α -methylacyl-coenzyme-A racemase transcripts in blood and urine samples of prostate cancer patients. *Mol Diagn Ther* 2006;10:397-403
15. Rubin MA, Bismar TA, Andren O, et al. Decreased α -methylacyl CoA racemase expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-specific death. *Cancer Epidemiol Biomarkers Prev* 2005;14:1424-32.
16. Shariat SF, Lamb DJ, Kattan MW, et al. Association of preoperative plasma levels of insulin-like growth factor 1 and insulin-like growth factor binding proteins-2 and 3 with prostate cancer invasion, progression, and metastasis. *J Clin Oncol* 2002;20:833-41
17. Harman SM, Metter EJ, Blackman MR et al. Serum levels of insulin-like growth factor1 (IGF-I) IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. *J Clin Endocrinol Metab* 2000;85:4258-65
18. Duffy MJ, Napieralski R, Martens JW, et al. Methylated genes as new cancer biomarkers. *Eur J Cancer* 2009;45:335-346
19. Bryzgunova OE, Morozkin ES, Yarmoschuk SV et al. Methylation-specific sequencing of GSTP1 gene promoter in circulating/extracellular DNA from blood and urine of healthy donors and prostate cancer patients. *Ann N Y Acad Sci* 2008;1137:222-225
20. Goessl C, Muller M, Straub B et al. DNA alterations in body fluids as molecular tumor markers for urological malignancies. *Eur Urol* 2002;41:668-676
21. Committee on Developing Biomarker-Based Tools for Cancer Screening, Diagnosis and Treatment. *Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment*. Washington DC: National Academic Press, 2007
22. National Cancer Institute. Dictionary of Cancer Terms. <http://www.cancer.gov/dictionary/?searchTxt=biomarker>
23. Tricoli JV, Schoenfeldt M, Conley BA. Detection of prostate cancer and predicting progression: current and future diagnostic markers. *Clin Cancer Res* 2004; 10:3943-53
24. Theodorescu D, Krupski T. Prostate Cancer- Biology, Diagnosis, Pathology, Staging, and Natural History. <http://www.emedicine.com>

POSTOPERATIVE COMPLICATIONS OF DIABETIC CATARACT SURGERY



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ABSTRACT

Diabetic cataract surgery is a procedure with higher risk than senile cataract surgery, considering that the postoperative complications in first are more frequent than senile cataract surgery complications. Cataract extraction in patients with diabetes may worsen the evolution of diabetic retinopathy. Functional results of cataract surgery are related to the prevention of diabetic complications and its proper and timely treatment.

Key words: *diabetic cataract, postoperative complications*

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INTRODUCTION

Diabetes mellitus is one of the most widespread endocrine disorders; every ten years, the morbidity induced by this disorder increases by approximately 100% ¹. The spread, frequency and severity of the associated complications have attributed diabetes mellitus the definition of social disease. The eye disease in patients with diabetes mellitus is one of the major causes of blindness among the individuals from the world's developed countries ^{2, 3}. According to the studies performed by the World Health Organization, more than 15 million people among diabetic patients lose their eyesight every year ⁴.

The cataract surgery in diabetic patients is a high-risk procedure. The

intra- and postoperative complications of cataract removal surgery in diabetic patients are more numerous, by comparison with the complications in the senile cataract surgery and they should be known by the ophthalmic surgeon in order to be quickly and correctly prevented and treated ^{5, 6}. Cataract removal in patients with diabetes mellitus may adversely affect the development of diabetic retinopathy which requires, if allowed by the crystalline lens opacification, the preoperative treatment of diabetic retinopathy by laser photocoagulation and the close postoperative monitoring of the changes in the retina, especially macular changes.

METHODS AND MATERIALS

The paper presents the analysis of postoperative complications in 1071 cases of diabetic cataract operated on between 2007 and 2011 at the Ophthalmology Clinic from Timisoara.

The surgical technique used for the study patients has been the extra-capsular cataract extraction with posterior chamber intraocular lens implantation: ECCE+IOL (PC) using the "mini-nuc" technique or phacoemulsification.

The complications occurred after the operation on patients with diabetic cataract have been immediately identified and treated during hospitalization: inflammatory reaction, corneal edema, cystoid macular edema, as well as later complications monitored in the out-patient clinic, represented by the posterior capsular opacification and the aggravation of the diabetic retinopathy.

1. Inflammatory reaction:

According to its severity, three inflammatory stages have been observed: low inflammatory reaction, mild inflammatory reaction and severe inflammatory reaction. The patients with low inflammatory reaction (implant precipitates, Tyndall +) represented 35% of the cases.

The cases of mild inflammatory reaction amounted to 14%. In 3% of the cases, the patients developed a severe fibrinous reaction.

The inflammatory reaction is most probably a consequence of a rupture in the hemato-ocular barrier induced by the alteration in the capillary wall (7).

The treatment of the inflammatory reaction consisted in the administration of topic medicines (corticosteroids, nonsteroidal anti-inflammatory agents) and peribulbar injections of corticosteroids in variable quantities according to the severity of the

inflammatory reaction. The inflammatory reaction has left no sequelae and, in 4.7% of the cases, an

ocular hypertonia was observed; however, remission was achieved with adequate topic treatment.

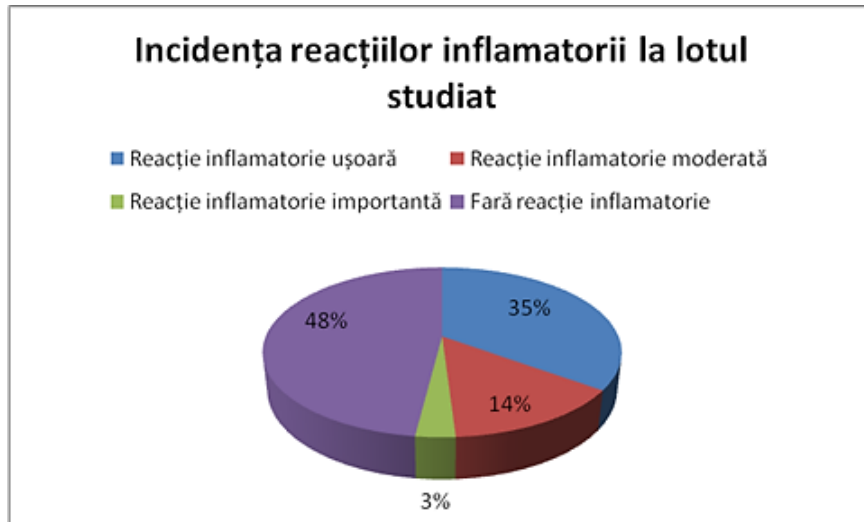


Fig.1. Reprezentarea procentuală a reacțiilor inflamatorii aparute post-operator

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2. Corneal edema

An important factor in the occurrence of corneal edema is considered to be mechanical trauma of the eye. The irrigating solutions used during the surgical procedure and even the viscoelastic substances introduced in the anterior chamber may prove

toxic to the corneal endothelium. The miotic and mydriatic substances used during the procedure may have an iatrogenic effect on the corneal endothelium ^{7, 8}. We have encountered a postoperative corneal edema in 7.2% of the cases, especially in diabetic patients with a precarious metabolic balance. Two of the studied cases presented a chronic corneal edema, with a 70% and 80% decrease in their visual acuity.

3. Cystoid macular edema (CME)

Literature reports that cystoid macular edema occurs in percentages between 4.5% up to 11% of the patients with diabetes mellitus ^{7, 8} while occurring in much fewer cases (1%) in the general population. In approximately 5% of the cases, we have noticed the persistence of the postoperative cystoid macular edema for up to 5 months ^{8,9}.

In our study group, 6.2% of the diabetic patients developed cystoid

macular edema. A year after the surgical procedure, the cystoid macular edema was noted in 0.7% of the cases, accompanied by decreased visual acuity. Similarly to the inflammatory reaction, the cystoid macular edema is caused by the rupture in the hemato-ocular barrier induced by the alteration of the capillary wall ^{8, 9}. The cystoid macular edema affecting the study patients improved and even disappeared completely after a sustained topical treatment with nonsteroidal anti-inflammatory agents.

4. Posterior capsular opacification

In patients with diabetic cataract we have noted the fact that the posterior capsular opacification is more frequent and it occurs earlier than in patients with senile cataract ^{10, 11}. In our study group we have noted posterior capsular opacification in 69% of the cases, which occurred 6 months to one year after the surgical procedure. The posterior capsular opacification was treated with YAG laser and the vision was restored in 95% of the cases.

5. The aggravation of the diabetic retinopathy

In patients without diabetic retinopathy, we have noticed the occurrence of diabetic retinopathy in the first 6 months after the surgical procedure in 0.1% of the cases; 12 months after the surgical procedure, the number of cases of incipient diabetic retinopathy had increased to 1.5%, and 24 months later the percentage was 1.9%. In patients with incipient diabetic retinopathy, the occurrence of the nonproliferative diabetic retinopathy in the first 6 months after the surgery was noticed in 6% of the cases, while 12 months after the surgery the nonproliferative diabetic retinopathy was noticed in 6.5% of the study patients, and 24 months later we noticed an increase up to 7.2% of the occurrences.

The aggravation of the diabetic retinopathy in the first 6 months after the surgery was noticed in 3.8% of the cases, while 12 months after the surgery the percentage had increased to 4.3%, and 24 months later the percentage was 5.2%.

The occurrence of proliferative diabetic retinopathy in patients with nonproliferative diabetic retinopathy was noticed in 9.5% of the cases.

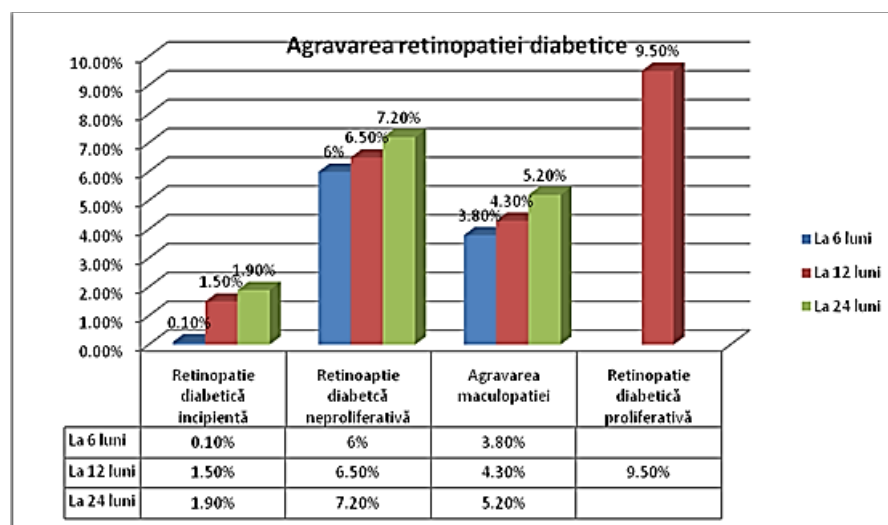


Fig.2. Reprezentarea grafica a pacientilor care au dezvoltat agravarea retinopatiei diabetice dupa operatia de cataracta.

RESULTS

The functional results of cataract surgery in diabetic patients vary according to the stages of diabetic retinopathy, being in accordance with the results reported in the literature ^{12, 13}. In patients with incipient diabetic retinopathy (30% of the study patients), visual acuity between 8/10 and 10/10 was restored in 98% of the cases.

In patients with nonproliferative diabetic retinopathy (20% of the study group), visual acuity between 5/10 and 8/10 was restored in 88% of the cases.

In patients with nonproliferative diabetic retinopathy accompanied by maculopathy (20% of the study patients), visual acuity between 5/10 and 8/10 was restored in 69% of the study cases. In patients with proliferative diabetic retinopathy accompanied by maculopathy - the stage of severe diabetic retinopathy (5% of the study patients), visual acuity between 5/10 and 1/10 was restored in 4% of the cases.

DISCUSSIONS

The following aspects have resulted from the study performed:

52% of the patients have developed an inflammatory reaction after the surgical procedure, with various degrees of severity: the highest number of patients have developed a low inflammatory reaction (approximately one third), followed by the patients who have developed a mild inflammatory reaction; the number of patients who have developed a severe inflammatory reaction was very low (3% of the cases).

The occurrence of cystoid macular edema was noticed in a higher percentage in patients with diabetes mellitus (6.2%), as compared with patients who did not have diabetes (1%). The occurrence of cystoid macular edema impacts the visual acuity and causes dissatisfaction in the patient operated on; therefore, it is necessary to discover the occurrences of cystoid macular edema during the postoperative period. Following surgical treatment, the risk of persistent cystoid macular edema was of 1%.

In the study patients with diabetic cataract we have noticed that the

posterior lens capsular opacification after the surgical procedure occurs in 69% of the cases; however, it can be treated with YAG laser and the visual acuity is restored - in our study, visual acuity was restored in 95% of the cases.

It is important to implant the IOL in the capsule, in order to avoid ciliary irritation and the formation of secondary cataract.

The aggravation of the diabetic retinopathy following the surgical procedure performed on patients with diabetic cataract was closely related to the initial stage of the retinopathy; the following aspects were noticed: the occurrence of incipient diabetic retinopathy in patients without diabetic retinopathy 6 months after the surgical procedure (0.1% of the cases); the patients with incipient diabetic retinopathy have developed nonproliferative diabetic retinopathy 6 months after the surgical procedure (6% of the cases); in patients with nonproliferative diabetic retinopathy we have noticed the occurrence of proliferative diabetic retinopathy 12 months after the surgical procedure (9.5% of the cases), while in patients

with maculopathy we have noticed its aggravation 6 months after the surgical procedure (3.8% of the cases).

Implants with a diameter of 6 mm or larger have been used, in order to perform the laser photocoagulation.

Posterior capsular tear should be avoided, as this increases the incidence of retinal complications;

The surgical procedure should be performed in diabetic patients with a good metabolic balance, as this is a factor which determines a good functional result;

A close postoperative monitoring should be performed, in order to avoid the aggravation of the diabetic retinopathy.

CONCLUSIONS

Following the performed study, a series of aspects need to be pointed out:

- The surgical procedure for cataract removal should be performed in diabetic patients with the best possible metabolic balance;
- The diabetic retinopathy should be assessed before the surgery and laser therapy should be used; also, the diabetic retinopathy should be monitored after the surgery and

laser therapy should be used, as necessary;

- The surgical procedure should be attentively performed and the postoperative complications should be treated as early and as intensively as possible;
- The early treatment of postoperative complications should be instituted, especially in the cases of cystoid macular edema, impacting visual acuity.

REFERENCES

1. P. Cernea, C. Vladutiu, *Tratat de oftalmologie clinică*, ed.II, Editura Medicala Bucuresti, 2002
2. Ileana Zolog, Cristina Mazilu-, *Retinopatia diabetica*- in V. Serban: *Tratat roman de boli metabolice*. Editura Brumar 2011, pg. 63-75.
3. B. N. Mukesh, A. Le, P. N. Dimitrov, S. Ahmed, H. R. Taylor, and C. A. McCarty, "Development of cataract and associated risk factors: the Visual Impairment Project," *Archives of Ophthalmology*, vol. 124, no. 1, pp. 79-85, 2006.
4. Clarke LC, Fraser SG. Hospital episode statistics and trends in ophthalmic surgery 1998-2004. *BMC Ophthalmol* 2006;6:37
5. Tomkins. C Over 120 years of defending ophthalmologists. *Br.J Ophthalmol* 2006;90:1084-5
6. Ali N. A decade of clinical negligence in ophthalmology. *BMC Ophthalmol* 2007;7:20
7. Bhan A, Dave D, Vernon SA, et al. Risk management strategies following analysis of cataract negligence claims. *Eye* 2005;19:264-8
8. Endophthalmitis Study Group, European society of Cataract& Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of the risk factors. *J Cataract Refract Surg* 2007;33:978-88
9. Mavroforou A, Michalodimitrakis E. Physicians liability in ophthalmology practice. *Acta Ophthalmol Scand* 2003;81:321-5
10. Lu M, Taylor A, Chylack LT Jr, Rogers G, Hankinson SE, Willett WC, et al. Dietary fat intake and early age related lens opacities. *Am J Clin Nutr.* Apr 2005;81(4):773-9
11. Johns KJ, Feder RS, Rosenfeld SI, et al. Lens and cataract. In: *American Academy of Ophthalmology Basic and Clinical Science Course*. Vol 11 1999-2000.
12. Kanski J-Clinical Ophthalmology, fourth edition- Butterworth Heinemann ed.2000
13. Yanoff M., Duker J.S- *Ophthalmology*, second editions, ed. Mosby 2006

MONITORING THE RESPONSE TO TYROSINE KINASE INHIBITORS IN CHRONIC MYELOGENOUS LEUKEMIA



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ABSTRACT

Chronic myelogenous leukemia (CML) is a myeloproliferative disease characterized by a specific chromosome aberration i.e. the Philadelphia chromosome (Ph). The Ph chromosome is the result of a reciprocal translocation between the long arms of chromosomes 9 and 22 t(9;22) (q34;q11). This translocation results in the formation of the BCR-ABL fusion gene. The abnormal gene is transcribed in a hybrid mRNA which will eventually lead to the synthesis of a Bcr-Abl chimeric protein with a high tyrosine kinase activity.

Imatinib mesylate, regarded as the golden standard of first line CML treatment, is a tyrosine kinase selective inhibitor. The response to Imatinib is assessed hematologically, cytogenetically and at molecular level.

The prognosis of CML patients has considerably improved during the last few years due to increasingly effective therapeutic options, thus the appropriate monitoring of these patients becomes increasingly important. The studies on CML patients had the end point of reaching the major molecular response (MMR) in patients with complete cytogenetic response (CCyR).

The use of RT-Q-PCR enables us to define the molecular response as being optimal/suboptimal and identifies the category of patients with a favourable prognosis. It may be a predictive factor for CCyR and also for rebound, progressive disease or kinase mutations.

Key words: *chronic myelogenous leukemia (CML), major molecular response (MMR), complete cytogenetic response (CCyR), imatinib, monitoring.*

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DEFINITION

Chronic myelogenous leukemia (CML) is a clonal disease of the pluripotent hematopoietic stem cell, characterized by the presence of the Ph chromosome and/or the BCR/ABL rearrangement with demonstrated

pathogenetic role. It is the first malignant disease in which a characteristic cytogenetic abnormality has been described and the first disease for which a molecular targeted treatment has been applied.

EPIDEMIOLOGY

CML accounts for around 20% of the adult leukemia cases. The incidence is of 1 - 2 new cases/year in 100.000 adults, with no major geographical differences. It is more frequent in men

(1.4:1). The mean age at the moment of diagnosis is 60 years. The disease is rare in children (5% of childhood leukemia cases).

ETIOLOGY

It is not known in most cases. The disease may occur with an increased frequency after exposure to ionizing radiation: the survivors of atomic bombardments, radiologists, patients

treated with ionizing radiations for benign (ankylopoietic spondylitis) or malignant diseases. No geographic, ethnic, hereditary or economic factors are known to be associated with CML.

EPIDEMIOLOGY

The diagnosis is based upon blood cell counts: leukocytosis (frequently associated with thrombocytosis) with left shift of the formula from metamyelocyte to myeloblast and basophilia. Splenomegaly is present in over 50% of CML cases during the initial chronic phase (CP) with around 50% of asymptomatic patients.

The diagnostic proof is given by demonstrating the presence of the Ph chromosome (22q-) resulting from the

t(9;22)(q34;q11) balanced translocation and/or BCR/ABL rearrangement detected in the peripheral blood or in the hematopoietic bone marrow. In approximately 5% of cases the Ph chromosome cannot be detected, the confirmation of the diagnosis being accomplished by molecular genetics techniques such as fluorescent in situ hybridization (FISH) or by reverse-transcriptase polymerase chain reaction (RT-PCR).^{1,2}

STAGING AND PROGNOSIS

The common clinical evolution includes three phases: the chronic phase (CP), the accelerated phase (AP) and the blastic phase (BP) or blastic crisis (BC).

During the pre-imatinib era, prognostic factors were based upon age, size of the spleen, number and differentiation degree of the hematopoietic cells; these may still

determine classification into risk groups with different prognosis, with various response rates (RR) with progression free survival (PFS), event free survival (EFS) and overall survival (OS) in Imatinib treated patients.

The hematologic, cytogenetic and molecular responses offer important prognostic information in terms of time dependent variables. The importance of the complete cytogenetic response (CCyR) has been confirmed.^{2, 3}

TREATMENT

Medication is superior to allogeneic stem cell transplant as first line therapy in CML when transplant related mortality is considered.

Based upon the randomized trial with Imatinib, ABL selective tyrosine kinase inhibitor, versus alpha Interferon and low doses of Cytarabin (the IRIS Study), Imatinib 400 mg/day has been established as standard first line therapy for all CML-CP patients.⁴

The success of tyrosine kinase inhibitors (TKI) treatment in patients with Ph-positive CML fundamentally changed the prognosis of this disease. In case of treatment with imatinib mesylate the estimated 7-10 years survival is 80-85%, and 90-93%, respectively, considering CML associated deaths^{5,6}.

Nilotinib and dasatinib are second generation TKI with improved efficacy in the treatment of CML in cases of imatinib failure^{7, 8}. In randomized studies with first line CML treatment, nilotinib and dasatinib, as compared to imatinib, showed significantly higher CCyR and MMR after 12 to 18 months, decreased incidence of progression to accelerated and blastic phases and a better tolerance^{9, 10}. Nilotinib (300 mg twice a day) and dasatinib (100 mg a day) have been recently approved as first line therapy in CML patients. The stress on MMR as main objective in the treatment of CML and the existence of three TKIs in the treatment of CML raises questions on chronic phase CML management.

Cytogenetic response (% Ph-1 positive mitosis)

Complete CCyR: 0

Major MCyR: ≤35%

Minor mCyR: 35-95%

No response NCyR: 100%

MMR is defined by the decrease of BCR-ABL level by at least 3 log from a standardized baseline

Initial therapeutic objectives of the cp cml treatment

The accomplishment of CCyR has been associated to increased survival both in previous treatment regimens and in the case of imatinib. Obtaining a MMR as oposed to the absence of MMR after 12 months has been associated to a better EFS, but not with an increased

survival.¹¹ This conclusion has not been confirmed. Other studies showed that the accomplishment of MMR versus the absence of MMR at 18 months (not at 12 months) was not associated with a better EFS.^{3,5,11}

The major objective of CML treatment is the eradication of the malignant clone with progression free

survival. The assessment of therapeutic options in CML depends on obtaining the hematologic, cytogenetic and/or molecular response, as well as on PFS.

The cytogenetic response may be complete (CCyR), major (MCyR) or minor (mCyR) and, in some cases, the treatment does not lead to a cytogenetic response (NCyR). Obtaining the CCyR represent the premise for a long progression free survival.

Patients who obtain MMR have a better evolution as compared to those who do not, the latter being a heterogenous group including patients with CCyR without MMR and other

patients (those with complete hematologic response without CCyR). This heterogenous group is compared to patients with MMR, suggesting that MMR causes a better long term result.

The reason for CCyR becoming the golden standard of favourable response to treatment in CML is the demonstration of its association with a survival advantage.^{3,12} Obtaining the CCyR remains the objective of the TKI treatment in CML, even though additional MMR represents a protective factor against the probability of events and of accelerated or blastic transformation.

Tabel 1 Recommendations for monitoring in chronic myelogenous leukemia

Parameter	ELN 2006	Strategy of CML experts
Objective	Frequency	Frequency
Hematologic	Every 2 weeks to CHR and then every 3 months or whenever needed	Similar to ELN recommendations
Cytogenetic	At the moment of diagnosis, after 3 and 6 months, then every 6 months to CCyR, then at least every 12 months, if molecular monitoring cannot be performed; always in case of treatment failure or inexplicable cytopenia 0	Every 6 months to CCyR; then bone marrow CG examination every 2-3 years in cases of stable CCyR (this should not be required in the future, in cases of longer follow up periods); bone marrow CG examination every 6 months only in the case of CG abnormalities in Ph-negative cells; monitoring of stable CCyR cases according to Table 2, by FISH and QPCR performed every 6 months; at the moment of treatment failure and in cases of inexplicable cytopenia
Molecular	Molecular every 3 months until the MMR is confirmed, then every 6 months	Every 6 months (Table 2)
FISH	In case of insufficient metaphases or if bone marrow cannot be harvested	Every 6 months (Table 2)
Mutations	In case of failure or suboptimal response; always necessary before changing the treatment	In case of failure (decision to change the treatment)
Abbreviations: ELN, <i>European Leukemia Nef</i> , CHR, complete hematologic response; CG, cytogenetic; QPCR, quantitative gene amplification (<i>quantitative polymerase chain reaction</i>).		

Monitoring the response to tki treatment

Monitoring is essential for optimizing the treatment and for cost-

effectiveness analysis. At the beginning of the treatment and during the first three months, clinical, biochemical and hematologic monitoring are

recommended every 2 weeks in order to ascertain patient compliance. Starting with the 3rd month of treatment, the cytogenetic examination (chromosomal banding) is recommended at least every 6 months until the CCyR is confirmed.^{2,3,12}

RT-Q-PCR (BCR-ABL: ABL%, in blood cells) is recommended every 3 months until MMR is confirmed. Once the CCyR and MMR have been achieved, cytogenetic examination every 12 months and RT-Q-PCR every 6 months may be performed.

If the patient has an increased Sokal risk or in case of suboptimal response, more frequent monitoring is recommended. Screening for BCR-ABL kinase mutations is only recommended in cases of failure or suboptimal response.

Measuring the peripheral blood Imatinib concentration is recommended in cases of suboptimal

response, failure, dose related toxicity or side effects.

CML^{2,3,13,14,15} and ELN¹⁶ experts (Table 1) have proposed many monitoring strategies. Outpatient onco-hematologic practice is oriented towards molecular analysis based monitoring, even though this is not necessarily recommended by CML experts. Table 2¹⁵ presents a proposed monitoring strategy in patients with persistent CCyR (after 12 to 18 months of treatment, when the concordance between CCyR and the BCR-ABL ratio improves). This strategy proposes to supplement the molecular analysis by FISH, as well as to verify the concordance, especially in patients in whom the MMR is not achieved.

Bone marrow examination for monitoring treatment response has been replaced by tests performed from the peripheral blood.

Tabel 2 Proposed monitoring by FISH and molecular studies in patients with persistent complete cytogenetic response

FISH	BCR-ABL ratio International Standard (%)	Interpretation
Negative	≤0.1	Excellent response; follow up at 6 months
Negative	0.1-1	Follow up every 6 months, follow up after 3 months if there is a 3 log increase of the BCR-ABL ratio; compliance assessment
Positive	≤0.1	False positive or false negative FISH or molecular tests; repeated after 3 months
Negative	>1	False positive or false negative FISH or molecular tests; repeated after 3 months
Positive	>1	Bone marrow and cytogenetic examination are performed; possible rebounds; compliance assessment

RT-Q-PCR (BCR-ABL: ABL%, in blood cells) is recommended every 3 months until MMR is confirmed. Once the CCyR and MMR have been achieved, cytogenetic examination

every 12 months and RT-Q-PCR every 6 months may be performed.

The bone marrow examination before treatment initiation is indispensable for accurate disease staging (in order to evaluate the

proportion of blastic and basophilic cells), as well as for detecting the clonal evolution;^{3,13} it may also help in avoiding diagnostic errors associated to false positive or false negative FISH and BCR-ABL studies in peripheral blood.

In clinical studies, the bone marrow cytogenetic analysis may be needed at 6 and 12 months for baseline assessments of the therapeutic response, even though it is being argued that negative FISH results at 6 or at 12 months might remove the need for bone marrow analysis. A high concordance rate has been reported between the CCyR as demonstrated by cytogenetic examination and a negative FISH test. Thus, FISH analysis may be used to monitor the CCyR.^[17]

In patients with a stable CCyR (after 2 years of treatment), the evolution of CML is predictable. Sudden blastic transformation phenomena are rare, most of them occurring during the first 2 years, usually in younger patients who develop lymphoid blastic transformation. After the second year of evolution, CML transformation in patients under first line TKI treatment is rare (under 1% yearly). This is the basis for the recommended monitoring every 6 months and not every 3 months, by use of FISH/PCR in patients with stable CCyR.

Bone marrow examinations are only necessary in patients with stable CCyR when chromosomal abnormalities in Ph-negative cells are observed, this being an alarm sign which requires follow up bone marrow studies every 6-12 months.¹⁸

Mutation analysis is not useful before initializing TKI treatment in recently diagnosed CML patients and its value is limited in patients responding to TKI treatment. The exception is represented by the patient

with increasing values of the BCR-ABL ratio, in whom mutation studies detect an unfavourable mutation.

It has been stated that monitoring blood levels of imatinib can optimize its administration. This aspect has been erroneously interpreted as a possibility to adjust imatinib dose according to individual blood levels (low blood imatinib levels accompanying a suboptimal response lead to an increase of the imatinib dose, and high imatinib levels associated to clinical toxicity phenomena determine the decrease of the dose). At present, blood levels of imatinib are not useful in monitoring or adjusting the treatment.

Long term objectives of tki treatment in cml-cp patients

The response to second generation TKI is usually rapid, and, in 6 months, decision to continue with Imatinib, second generation TKI or stem cell transplantation in eligible patients can be made.

Presently, eligibility criteria for stem cell transplantation have been extended by using the reduced intensity conditioning regimens or by non-myeloablative procedures, as well as due to the availability of alternative stem cells (cord-blood cells).^{2,3}

In case of suboptimal response to Imatinib, which frequently represents a transitory state, the best treatment option is still being discussed; the patient may continue with the same dose or with a higher dose of Imatinib, being also eligible for study with second generation TKI.^{3,16}

Once the patient has progressed to the AP, BP/BC, the treatment depends on the previous regimen and may include other TKI, different from those used in the CP, other target experimental agents: homocetaxine or cytotoxic chemotherapy with the recommendation for allogeneic stem

cell transplantation whenever possible.
2,19

In the future, the choice of first line TKI treatment will depend on the final data regarding the long term objectives. In the case of imatinib treatment, the estimated 7-10 years survival may be over 85%.^{1,3} Demonstrating a significant survival benefit for second generation TKI will require a high number of patients observed over long periods in randomized studies.

Studies such as: Evaluating Nilotinib Efficacy and Safety in Clinical

Trials-Newly Diagnosed Patients (ENESTnd),¹⁰ Dasatinib Versus Imatinib Study in Treatment- Naive LMC Patients (DASISION),⁹ as well as those of MD Anderson,¹² have demonstrated corresponding 5-year PFS/EFS rates of 96%, 90%, 89% and 81%, respectively, for various definitions applied in the same patients. This aspect reveals the importance of elaborating uniform criteria for defining results, if PFS and EFS are to become valuable criteria for selecting first line TKI treatment.

CONCLUSIONS

The favourable therapeutic results, as well as the availability of more TKI and various monitoring methods used to evaluate initial and late surrogate objectives of therapeutic benefit and prognosis, require the knowledge of therapeutic objectives and monitoring procedures, as well as their benefits and limitations. Achieving the CCyR remains the main

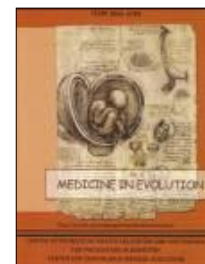
treatment objective, even though the MMR may offer additional protection against the increased risk of disease progression. Various monitoring methods are available, but these may be confusing in certain circumstances. A better definition of long term objectives is needed in order to guide the selection of TKI treatments with increased effectiveness.

REFERENCES

1. Cortes J, Silver R, Kantarjian H. Chronic myeloid leukemia, in Hong W, Bast R, Hait W, et al (eds): Cancer Medicine (ed 8). Shelton, CT, People's Medical Publishing House, 2010, pp 1582-1590.
2. Baccarani M., Dreyling M. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2010;5:165-167.
3. Kantarjian H., Cortes J. Considerations in the Management of Patients With Philadelphia Chromosome-Positive Chronic Myeloid Leukemia Receiving Tyrosine Kinase Inhibitor Therapy. *J of Clin Oncol* 2011;29:1512-1516.
4. O'Brien SG, Guilhot F, Larson Ra, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 348:994-1004, 2003
5. Druker B, Guilhot F, O'Brien S, et al: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355:2408-2417, 2006
6. Kantarjian H, Talpaz M, O'Brien S, et al: Survival benefit with imatinib mesylate versus interferon-based regimens in newly diagnosed chronic-phase chronic myelogenous leukemia. *Blood* 108:1835-1840, 2006
7. Kantarjian HM, Giles F, Gattermann N, et al: Nilotinib (formerly amn107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 110:3540- 3546, 2007
8. Hochhaus A, Kantarjian H, Baccarani M, et al: Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 109:2303-2309, 2007
9. Kantarjian H, Shah NP, Hochhaus A, et al: Dasatinib versus imatinib in newly diagnosed

- chronic-phase chronic myeloid leukemia. *N Engl J Med* 362: 2260-2270, 2010
10. Saglio G, Kim DW, Issaragrisil S, et al: Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 362:2251-2259, 2010
 11. Hughes TP, Kaeda J, Branford S, et al: Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 349:1423-1432, 2003
 12. Kantarjian H, Shan J, Jones D, et al: Significance of Increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *J Clin Oncol* 27:3659-3663, 2009
 13. Press R, Love Z, Tronnes A, et al: BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. *Blood* 107:4250-4256, 2006
 14. Kantarjian H, Schiffer C, Jones D, et al: Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine kinase inhibitors: Practical advice on the use and interpretation of monitoring methods. *Blood* 111:1774-1780, 2008
 15. Hughes TP, Hochhaus A, Branford S, et al: Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: An analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood* 116:3758-3765, 2010
 16. Baccarani M, Saglio G, Goldman J, et al: Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 108:1809-1820, 2006
 17. Testoni N, Marzocchi G, Luatti S, et al: Chronic myeloid leukemia: A prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: A study of the GIMEMA CML WP. *Blood* 114:4939-4943, 2009
 18. Jabbour E, Kantarjian H, Abruzzo L, et al: Chromosomal abnormalities in Philadelphia chromosome-negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Blood* 110:2991-2995, 2007
 19. Hehlmann R, Berger U, Pffirmann M et al: Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia *Blood* 2007; 109 4686-4692.

THE COMPLICATIONS OF SURGICAL TREATMENT OF HEPATIC TRAUMA AT POLYTRAUMATIZED PATIENT



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ABSTRACT

Introduction: Severe hepatic lesions pose some of the most redoubtable problems regarding diagnosis and, above all, conduct within the framework of abdominal trauma. Therefore, the most important problem, upon hospitalization or after resuscitation of the patient, is deciding on surgical intervention. Decisive factors for this are the severity of the lesions detected with computed tomography (CT) (1, 2) and the patient's hemodynamic state ^{3, 4}.

The method: We present the case of a 33 year old patient, victim of a road accident, for which the dynamic abdominal ultrasound shows presence of intraperitoneal perihepatic effusion, which increases quantitatively during the patient's evolution. The abdominal CT exam confirms it and also shows a hepatic contusion with posttraumatic rupture of the right lobe of the liver.

Results: During the surgical intervention we discover hemoperitoneum, third degree posttraumatic rupture in segments VII and VIII of the liver, cecum depolish. We apply hepatic packing, peritoneal toilet, multiple drainage. In the fourth day, during another surgical intervention, the insulations from the hepatic cavity are extracted. The subsequent evolution was lagging, with septic fever and development of an interhepato-diaphragmatic collection which increases dynamically. Another surgery, using right sub-costal incision, is performed and a bilious collection blocked suprahepatically is found. The collection is removed and postoperative we detect a biliary fistula on the suprahepatic drain tubes with progressive flow decrease.

Conclusions: The biloma appears normally during the conservative treatment of the hepatic traumatic lesions, but it can appear also postoperative if therapeutic procedures like hemostatic packing, hepatic packing and other local treatments are used. Usually, these fistulae are a consequence of hepatic lacerations affecting some biliary passages of small caliber and, consequently, with insignificant flow and self-limiting development.

Key words: hepatic trauma, damage control surgery, hepatic packing, biloma, biliary fistula.

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INTRODUCTION

Severe hepatic lesions pose some of the most redoubtable problems regarding diagnosis and, above all, conduct within the framework of abdominal trauma. Therefore, the most important problem, upon hospitalization or after resuscitation of the patient, is deciding on surgical intervention. Decisive factors for this are the severity of the lesions detected with computed tomography (CT) ^{1, 2} and the patient's hemodynamic state ^{3, 4}. Consequently, CT scan is mandatory for all patients with abdominal trauma and suspected liver lesions. Hemodynamically unstable patients require immediate surgery but even in these cases, current studies recommend limited interventions, with reduced operational impact.

Currently, hepatic packing is essential when using damage control surgery, which can be applied to the hepatic polytraumatized patient, especially when associated with other traumatic lesions ⁶.

Accomplished progress and the reintroduction of this procedure revealed a series of unquestionable advantages of hepatic packing, specifically: packing by itself proves to be a sufficient procedure for approximate 50% of the patients on which is used, while for the other cases it gives time for correcting hemorrhagic anemia, coagulopathy, hypothermia and acidosis.

The disadvantages of hepatic packing are related to the risk of perihepatic abscesses, hepatic parenchymal necrosis, or development of abdominal compartment syndrome ⁷. Therefore, efficient antibiotic treatment and continuous clinical and biological monitoring of these patients are absolutely mandatory ¹¹. Furthermore, the risk of bleeding

during unpacking is real for approximate 50% of the patients, which require repacking or another hepatic hemostasis procedure (resection, ligation of hepatic artery, etc.).

Repacking is usually recommended when, during unpacking, the bleeding is so intense that any other hemostasis procedure is highly risky. Removal of packing is usually done 2-3 days after and takes place during a scheduled intervention with the whole surgical team and after the efficient stabilization of the patient. If repacking is decided, a new intervention will be scheduled at least 5 days after the second packing. Moreover, the main shortcoming of the method seems to be the necessity of a new surgical intervention in the first postoperative days, which ensures the removal of used fields and checks the hemostasis achieved by these.

Biliary fistulae occur usually during the conservative treatment of hepatic traumatic lesions but they can occur also postoperative, if hemostatic packing or another kind of local tamponment procedure was applied. Generally, these fistulae are a consequence of the hepatic lacerations affecting some biliary passages of small caliber and, as such, with insignificant flow and self-limiting development ⁸.

Hematomelia manifest as hemorrhagic lesions at level of the biliary tree, the blood which reaches the duodenum being eliminated as upper digestive bleeding.

Nowadays, it is considered that hepatic trauma is the main cause of hematomelia. Regarding abdominal trauma, hematomelia represents 3% of the serious hepatic trauma ^{9, 10}, while the iatrogenic lesions are causing 40 to 60% of the diagnosed hematomelia. The biloma is a complication subsequent to the formation of a hepatic intra-

parenchymatous post-trauma. The formation can have expansive character, especially in the case of lesions of biliary ductus of greater caliber, and its diagnosis is done

mainly through tomography. The CT image for these situations is represented by a hypodense, well-delimited formation, sometimes strained, in the hepatic parenchyma.

AIM

Exposing a case of hepatic trauma for a poly-traumatized patient treated

surgical and who presents biloma and biliary fistula in his evolution.

MATERIAL AND METHODS

33 year old patient PR, victim of a road accident by falling from the motorcycle.

Upon hospitalization, the patient presents pain at the level of the right hemithorax, right lomb and right hypochondrium, pain and functional impotence of the left coxofemoral joint, pain at the level of the left shoulder, hemodynamically stable (TA=120/75 mmHg) and respiratory. The abdominal ultrasound carried urgently does not show presence of intra-peritoneal fluid retention.

The radiologic explorations reveal the presence of a fracture of the right costal arch C X, right hemithorax which is drained with aspiration; low left coxofemoral luxation for which orthopedic reduction is done.

Further dynamic abdominal ultrasounds reveal the appearance of intra-peritoneal perihepatic fluid retention, which increases during its evolution and is confirmed by the abdominal CT, which also shows a hepatic contusion with posttraumatic rupture at the LHD level (see Figure 1).



Fig.1 Abdominal CT.

Surgical intervention takes place and during the operation we find hemoperitoneum, third degree posttraumatic rupture in segments VII

and VIII of the liver, cecum depolish. We apply hepatic packing with three insulations (two suprahepatic and one subhepatic), suture of the cecum

depolish, Kocher manoeuvre on the duodenum, peritoneal toilet, multiple drainage. Right pleurotomy is done with evacuation of the right hemopneumothorax. Postoperative evolution is favorable, marked by phenomena of acute respiratory insufficiency. The thoracic ultrasound shows massive intrapleural fluid retention, for which the drain tube is repositioned.

In the fourth day, during another surgical intervention, the insulations from the hepatic cavity are extracted and peritoneal toilet and drainage is done. Postoperative evolution is favorable, with resumption of the intestinal transit and alimentation.

Abdominal CT done for the 10 days postoperative control poses the suspicion of a VCI thrombosis with extension on the left common iliac vein, which is not confirmed by the abdominal echo Doppler exam.

The subsequent evolution was lagging, with septic fever and development of a interhepato-diaphragmatic collection which increases dynamically.

18 days after the first surgery, another one is performed using right sub-costal incision and a bilious collection blocked suprahepatically is found and removed.

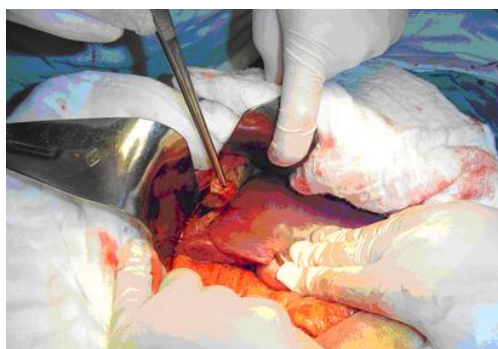


Fig.2



Fig.3

Postoperative we discover a biliary fistula on the suprahepatic drain tubes with progressive flow decrease, from approximate 600ml/24h until

disappearance, when we remove the drain tubes, 25 days after the last surgical intervention. The patient is discharged surgically cured.

DISCUSSION

Nowadays, most of the authors agree that severe hepatic trauma require surgery. Decision on surgery and the procedure to use depend on the gravity of the lesions, established initially through computer tomography and later during surgery, but also on the patient's status.

Hepatic packing for severe and complex hepatic trauma represents an

efficient method for controlling bleeding in over 80% of cases, but sepsis, continuation of bleeding or multiple organ insufficiency are classical complications of this kind of intervention. Moreover, the main drawback of the method is represented by the necessity of a new surgical intervention in the first postoperative days, which ensures the removal of the

used fields and checks the hemostasis accomplished by these, as well as the postoperative complications of this second intervention. The main problems are biliary fistulae, hematobilia, bleeding recurrence, intra-abdominal abscesses, sepsis and wound suppurative complications.

For fistulae with greater flow, the progressive complications which can occur are represented by biliary peritonitis, bilemia or biloma, their incidence being between 2.3 and 7.4%^{8, 12}.

CONCLUSIONS

Hepatic trauma represents an invariant in surgical services and severe hepatic lesions have as chosen indication packing of the hepatic cavity. However, the development may be burdened by progressive complications like biliary fistula or biloma.

Biliary fistula show up as a consequence of hepatic parenchyma lacerations trauma with involvement of some biliary ducts of variable caliber. In the case of fistula with low flow, the evolution is usually favorable, with progressive recovery.

REFERENCES

1. Cogbill TH, Moore EE, Jurkovich GJ et al. Severe hepatic trauma: a multicentric experience with 1355 liver injuries. *J Trauma* 1988, 28: 1433-1438.
2. Asesio JA, Roldan G, Petrone P et al. Operative management and outcomes in 103 AAST_OIS grades IV and V complex hepatic injuries: trauma surgeons still need to operate, but angioembolization helps. *J Trauma* 2003, 54: 647-654.
3. Croce MA, Fabian TC, Menke PG et al. Nonoperative management of blunt hepatic trauma in the treatment of choice for hemodynamically stable patients. Results of a prospective trial. *Ann Surg* 1995, 221: 744-753.
4. Krige JE, Borman PC, Terblanche J. Therapeutic perihepatic packing in the complex liver trauma. *Br J Surg* 1992, 79: 43-46.
5. Beckingham IJ, Krige JE. Liver and pancreatic trauma. *BMJ* 2001, 322: 783-785.
6. Rotondo MF, Schwab CW, Gonigal MD et al. Damage control - an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993, 35: 375-382.
7. Moore FA, Moore EE, Seagroves A. On resectional management of major hepatic trauma. An evolving concept. *Am J Surg* 1985, 150: 725-729.
8. Carrillo EH, Spain DA, Wolhetman CD et al. Interventional techniques are useful adjuncts in nonoperative management of hepatic injuries. *J Trauma* 1999, 46: 619-622.
9. Backer De, Fierens A, Schepper DH et al. Diagnosis and nonsurgical management of bile leak complicated by biloma after blunt liver injury. Report of two cases. *Eur Radiol* 1998, 8: 1619-1622.
10. Basile KE, Sivitt CJ, Sachs PP et al. Hepatic arterial pseudoaneurysm: a rare complication of blunt abdominal trauma in children. *Pediatr Radiol* 1999, 29: 306-308.
11. Fang JF, Chen RJ, Lin BC et al. Blunt hepatic injury: minimal intervention is the policy. *J Trauma* 2000, 49: 722-728.
12. Pachter HL, Hostteter SR. The current status of nonoperative management of adult hepatic injuries. *Am J Surg* 1995, 169: 442-454.

STUDY OF INTERACTIONS BETWEEN ANTIPSYCHOTICS AND THEIR MEMBRANE RECEPTORS BY QSAR METHODS - TOWARDS NEW ANTIPSYCHOTICS DRUG DESIGN



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ABSTRACT

Affinity of typical and atypical antipsychotic drugs to dopaminergic D2 and serotonergic 5HT1A membrane receptors have been studied using quantitative structure activity relationship (QSAR) analysis. Using computational chemistry the antipsychotics affinities expressed as (-log Ki) to dopaminergic D2 and serotonergic 5-HT1A were correlated with pharmacokinetic descriptors namely: the Solvent Accessible Surface Area (SASA), molecular volume (V), globularity (G), Octanol/water partition coefficient (logP), solubility (S), dipole moment, polarizability, and most important, the Blood/Brain barrier permeability. The statistical results indicated that the simultaneous contribution of logP, molecular volume and solvent accessible surface, polarizability and dipole moment are important for antipsychotics activity. The best correlation between predicted and experimental biological activities of antipsychotics was recorded when interaction between antipsychotics and membrane receptor D2 was analyzed.

Key words: QSAR, antipsychotics, schizophrenia, membrane receptors

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INTRODUCTION

Schizophrenia is described as a major mental disease which affects 1% of the general population. The patients experience severe symptoms such as: psychosis, apathy and social withdrawal, all of these leading to an important disturbance of professional skills, severe decrease of hygiene, less independent life or bad interpersonal relationships. It was also shown that patients suffering of alcoholism or drug dependence, and recently, of infectious diseases or post-traumatic stress disorder present a higher risk of schizophrenia. The schizophrenia etiology included the genetic and the environmental factors which play major roles ¹. It has been found that the genetic risks are increased to nearly 50% when both parents are affected and to 60–84% when a monozygotic twin is affected. The environmental risks for schizophrenia include biological and, also, psychosocial factors ².

Drugs used against schizophrenia are typical and atypical antipsychotics. All typical antipsychotics present a high affinity for dopamine D2 receptors and a strong correlation between therapeutic doses and their binding affinity to D2 receptor has been noticed ^{3, 4}. The high efficacy of antipsychotics against schizophrenia and their high affinity to D2 dopamine receptors have led to the "dopamine hypothesis" of schizophrenia, which assumes "an over-activity of the dopamine neurons". Specific dopamine receptor binding techniques show that the positive

symptoms of schizophrenia are induced by the dopamine D2 receptor blockage. Typical antipsychotics also induce the blockage of muscarinic M1, alpha 1 adrenergic, histaminergic H1 and serotonergic receptors with specific side effects. The atypical antipsychotics are able to improve cognition, affection, suicidal behavior and social functions. Other important properties of the atypical antipsychotics are represented by fewer extrapyramidal symptoms (EPS) and the less tardive dyskinesia (TD). Similarly to typical antipsychotics, the atypical ones inhibit the D2 dopaminergic receptors. Some of them (clozapine, olanzapine) also have a higher cholinergic activity, while risperidone, ziprazidone, clozapine and olanzapine strongly inhibit serotonergic and noradrenergic receptors.

Many typical and atypical antipsychotics are very efficient against the positive, but not against the negative symptoms. To increase the efficiency of known antipsychotics, many research efforts have recently focused on the development of new strategies for new antipsychotics drug design. For this reason it was necessary to apply very fast and precise techniques, such as QSAR (Quantitative Structure-Activity Relationships) which is capable to analyze and predict the biological activity for these structures, taking into account the possible changes of molecular structures.

COMPUTATIONAL STRATEGY

The typical and atypical antipsychotic molecular modeling and their minimum energy evaluation.

The binding constants of 21 antipsychotics as active compounds, against serotonin 5-HT1A and

dopaminergic D2 receptors were compiled from literature ⁵. Compounds affinity for membrane receptors, expressed as the inhibition constant K_i , was originally determined in nanomolar values, but here it was

converted to experimental pK_i by calculating $\text{Log}(1/K_i)$. Pharmaceutical nomenclature of compounds, and also their experimental and predicted biological activities as pK_i are presented in Table 1.

Table 1 Experimental affinities (pK_i) of antipsychotics at 5HT1A and D2 active site [reference]

Antipsychotics	Experimental affinities (pK_i) of antipsychotics at 5HT1A active site	Experimental affinities (pK_i) of antipsychotics at D2 active site
aripiprazole	8.25	9.18
clozapine	-	6.59
flufenazine	6.83	9.26
flupentixol	-	8.82
haloperidol	5.92	8.39
loxapine	5.6	7.92
mesoridazid	-	7.72
molindone	5.42	7.2
olanzapine	5.68	7.46
perphenazine	6.37	8.85
pimozide	-	9.18
promazine	4.92	6.79
quetiapine	6.36	-
risperidone	6.37	8.18
sertindole	6.55	8.04
thiothixene	6.39	9.2
tioridazide	6.75	7.95
trifluoperazine	6.02	8.88
prochlorperazine	5.22	8.76
ziprazidone	7.11	8.01

A wide range of the observed inhibition constant K_i values (pK_i from 5.22 to 9.26), favorable pharmacokinetic properties covering the interactions with dopamine and serotonin receptors, various substituents, covering as many chemical classes of compounds as possible were the selection criteria for the compounds considered in this study.

Three dimensional structures of studied compounds were obtained using the build module from Sybyl 7 software. In the first step, 2D structures of the antipsychotics that were

automatically changed into 3D structures were saved in Sybyl specific files .mol2 (Figure 1). In this study, the conformation of the antipsychotics with the minimum potential energy was established using the Maxim 2 minimization routine in Sybyl 7, with Tripos force field, conjugate-gradient algorithm and convergence 0.01 without constraint. After energy minimization, the Gasteiger-Marsili partial charges of the compounds were loaded on the chemical structures from the Sybyl 7 dictionary.

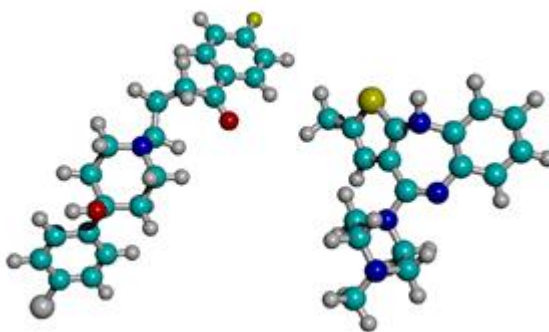


Fig.1 Spatial structures (3D) of haloperidol (left) and olanzapine (right)

2. QSAR strategy

Quantitative structure–activity relationship (QSAR) is a very useful tool in contemporary drug design in medical chemistry. The study of interactions between membrane receptors and antipsychotics are very important not only for psychiatry but, also, for many scientific fields like: chemistry, pharmacology, or biochemistry. Because many membrane receptors are involved, it is necessary to apply very fast and precise techniques, capable to analyze and predict the biological activity for new antipsychotics, which should be able to moderate the dopamine endogenous flow.

Basically, all QSAR methods consider that the macroscopic properties (e.g. biological activity) are induced by the molecular structure and every change into molecular structure leads to modification of these properties. Differences among QSAR methods consist in the way they describe the structural properties of compounds and in the quantitative relationships found between these properties and activities. A QSAR generally takes the form of a linear equation:

$$\text{Biological Activity } (\log 1/K_i) = \text{const} + (c_1 p_1) + (c_2 p_2) + (c_3 p_3) + \dots$$

where the parameters p_1 through p_n are: molecular volume, dipole moment, etc and are computed for each molecule in the series and the coefficients c_1 through c_n are calculated by fitting variations in the parameters and the biological activity.

The descriptors used in our study were: (i) Polarizability (P) which measures the dipole moment of a molecule induced by an electric field; (ii) Octanol-water partition coefficient ($\log P$) which represents a concentration of the chemical structure into octanol layer/Concentration of chemical structure into water layer; (iii) Blood-Brain barrier permeability (BB) computed as the concentration of chemical structure into brain versus concentration of chemical structure into blood; (iv) Dipole moment (DM) is defined as the product of the total amount of positive or negative charge and the distance between their centroids; (v) Molecular Volume (V) and Solvent Accessible Surface Area (SASA) are defined as dimensional steric parameters represented and (vi) Globularity (G) which is a 3D molecular descriptor which depend on

the structure connectivity and conformation.

Statistic validation of QSAR is performed by correlation coefficient r^2

(appropriate value higher than 0.60) and standard error estimate (appropriate value less than 0.50).

RESULTS and DISCUSSION

The 2D-QSAR D2 model predicted antagonist potency of 19 compounds by MLR (multi linear regression) analysis running led to a fitted correlation coefficient r^2 of 0.90 and standard error estimate of 0.31. When the antagonist potency of compounds

referred were studied to the serotonin 5HT_{1A} receptor, a second QSAR model was obtained and the statistic parameters fitted correlation coefficient r^2 of 0.64 and standard error estimate of 0.54.

Table 2 Experimental and predicted affinities (pK_i) of antidepressants and antipsychotics at 5-HT_{1A} and D2 active site and difference between them (residual value).

Neuroleptics	pK _i predicted D ₂	Residual values D ₂	pK _i predicted 5HT _{1A}	Residual values 5HT _{1A}
aripiprazole	8.6	0.6	7.5	0.7
clozapine	6.6	0	-	-
flufenazine	8.6	0.7	6.7	0.1
flupentixole	8.3	0.5	-	-
haloperidole	7.7	0.7	6.4	-0.5
loxapine	7.7	0.2	5.4	0.2
mesoridazide	7.7	0	-	-
molindone	6.7	0.5	5.5	-0.1
olanzapine	7.1	0.4	5.1	0.6
perphenazine	8.9	0	6.3	0.1
pimozide	8.8	0.4	-	-
promazine	6.5	0.3	5.4	-0.5
quetiapine	-	-	6.3	0
risperidone	8.3	-0.1	6.6	-0.2
sertindole	7.9	0.1	6.9	-0.4
thiothixene	8.6	0.6	6.7	-0.3
tioridazide	7.6	0.4	6.6	0.1
trifluoperazine	8.2	0.7	5.7	0.3
compazine	8.5	0.3	6.0	-0.8
ziprazidone	7.6	0.4	6.1	1

Analysis of the contribution of the molecular descriptors of antipsychotics in interaction with D2 showed that the significant statistical fitted correlation coefficient r^2 parameters and standard error estimate were obtained when the descriptors hydrophobicity (LogP), dipole moment (DM), globularity (G),

surface (SAAS), polarizability (P) and blood barrier BB were considered. Analysis of the contribution of the molecular descriptors of antipsychotics in interaction with 5HT_{1A} showed that the significant statistical fitted correlation coefficient r^2 parameters and standard error estimate were

obtained when the descriptors logP, V, G, SAAS, P, BB were considered.

In our study, good correlations between the observed and predicted antagonist potency of the compounds to the dopamine D2 receptor were obtained (Table 3). The best correlation between predicted antagonist potency was found in the case of clozapine (pKi observed - pKi predicted = 0.00), mesoridazide (pKi observed - pKi predicted = 0.00) and perphenazine (pKi observed - pKi predicted = 0.00). This result is confirmed by clinical practice, where clozapine is used in cases of treatment resistant schizophrenia, being a very potent antipsychotic. The

observed and predicted antagonist potency of serotonin 5HT1A receptor is also shown in Table 2. In case of this receptor the best correlation was found in the case of quetiapine (pKi observed - pKi predicted = 0.00), molindone (pKi observed - pKi predicted = 0.01). This result is confirmed by clinical practice, where quetiapine is used in the cases of depression, besides its use in psychosis.

The data in Table 2 are supported by the correlations between experimental and predicted antagonistic activities of psychiatric drugs. Figure 2a and 2b show the correlation for the robust QSAR models D2 and 5HT1A.

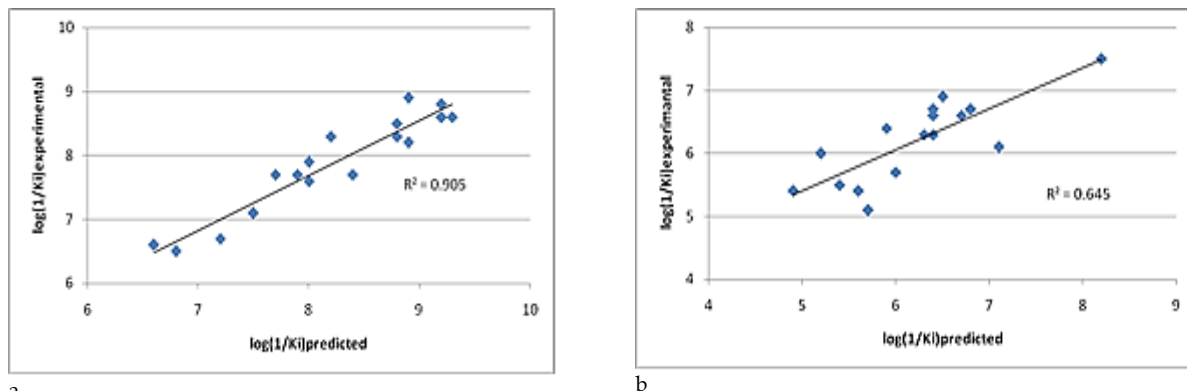


Fig. 2. Correlation between experimental and predicted pKi of antidepressants and antipsychotics: (a) QSAR model D2 (coefficient of correlation between pKi_{observed}/pKi_{predicted} = 0.91), (b) QSAR model 5HT1A (coefficient of correlation between pKi_{observed}/pKi_{predicted} = 0.64)

CONCLUSIONS

In this QSAR study, the goal was the quantitative correlation of molecular structure with the binding constant of antipsychotics already used in clinical practice. The models were used to elucidate the most important physico-chemical properties responsible for the antagonist potency of the chemical structures to dopamine D2 and serotonin 5HT1A receptors. Good predicted biological activities of

the typical and atypical antipsychotics were obtained when their interactions with serotonergic 5HT1A and dopaminergic D2 receptors were considered. Including the steric parameters - molecular volume and solvent accessible surface - the electrostatic parameters - dipole moment and polarizability - or the conformational descriptor: globularity, into monoparametric linear correlation,

good correlations between predicted and observed biological activity were noticed. Thus, judicious modulation of the physico-chemical properties, particularly hydrogen bond

acceptor/donor and hydrophobic properties may be very useful for the design of new chemical structures as possible antagonists of D2 and 5HT1A receptors.

REFERENCES

1. Kroeze W.K., Hufeisen S.J., Popadak B.A., Renock S.M., Steinberg S., Ernsberger P. 2002 H1-Histamine Receptor Affinity Predicts Short-Term Weight Gain for Typical and Atypical Antipsychotic Drugs. *Neuropsychopharmacology* 2002: 1-8.
2. Saxena A., Ram S., Saxena M., Singh N., Prathipati P., Jain P., Singh H., Anand, N. 2003
3. QSAR studies in substituted 1,2,3,4,6,7,12,12a-octa-hydropyrazino[2',1':6,1]pyrido[3,4-b]indoles-a potent class of neuroleptics. *Bioorganic & Medicinal Chemistry* 11:2085-2090
4. Bostrom J., Bohm M., Gundertofte K., Klebe G. 2003 A 3D QSAR study on a set of dopamine D4 receptor antagonists. *J Chem Inf Comput Sci*, 43 (4): 1020-1027.
5. Liégeois J.F., Eyrolles L., Ellenbroek B.A., Lejeune C., Carato P., Bruhwyler J., Géczy J., Damas J., Delarge J. 2002 New pyridobenzodiazepine derivatives: modifications of the basic side chain differentially modulate binding to dopamine (D4.2, D2L) and serotonin (5HT2A) receptors. *J. Med. Chem.* 45 (23): 5136-5149.
6. Campiani G., Butini S., Fattorusso C., Catalanotti B. et al. 2004. Pyrrolo [1,3] benzothiazepine-based serotonin and dopamine receptor antagonists. Molecular modeling, further structure activity relationship studies, and identification of novel atypical antipsychotic agents *J. Med. Chem.* 47, 143-157.

QSAR STUDY (QUANTITATIVE RELATIONS-STRUCTURE-BIOLOGICAL ACTIVITY) WITHIN CALCIUM CHANNEL BLOCKERS, DIHYDROPYRIDINES TYPE



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ABSTRACT

The objectives of the present study consist in evaluating quantitative relations structure-biological activity of calcium channels blockers (CCBs), dihydropyridines (DHP) type.

Materials and methods: We purposed to investigate some quanto-chemical parameters and their influences on the biological activity of a series of DHPs. Using the HyperChem package program we represented the charge density and electrostatic potential of the most and least active molecules from the studied DHP series.

Results: Correlating quanto-chemical parameters of the compounds within the studied DHP series with their biological activity, essential information was depicted about structural requirements of DHPs in order to improve their biological effect with less as possible secondary effects.

Conclusion: *After correlating biological activity with calculated quanto-chemical parameters (multi-parameter correlations) in a series of DHPs, hydrating energy, log P, polarizability are essential to define an improved biological activity.*

Key words: *calcium channel blockers, dihydropyridines, QSAR analysis.*

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INTRODUCTION

Calcium channels blockers were introduced in therapy at the end of 1600 year as anti-anginos and anti-arrhythmic drugs. Further, their antihypertensive action was established because of their capacity of reducing the vascular tonus, producing vasodilatation and reducing the peripheral vascular resistance.¹

The three main structural classes of CCBs are: phenylalkylamines, 1,4-dihydropyridines and benzothiazepines, whose representative prototypes are verapamil, nifedipine and diltiazem, respective. CCBs act mainly upon membranal slow calcium channels (so called L-type), inhibiting the movement of calcium ions across cell membranes, by means of calcium influx.² L-type channels are located in the myocardium, in the smooth and skeletal muscles and they are highly sensitive to DHPs.³

CCBs are a group of drugs showing a high selectivity. This selectivity results from a variety of factors, such as: pharmacokinetics (absorbtion, distribution and metabolism), the mobilization way of calcium ions (closed chain tension, intracellular storages or other sources), modulatory tension class and subclass of calcium channels, according to interaction possibility (the dependence to frequency and voltage) and the pathological state. CCBs act at different levels of the calcium channel and they posses both tissue selectivity and different final hemodynamic effects.

Since the "accidental" discovery of molecules with coronarodilatatory features via calcium channels inhibition (prenylamine and verapamil)⁴, significant progress was made to synthesize CCBs with valuable biological efficiency and high safety profile.

AIM and OBJECTIVES

The aim of this study is to analyze a series of CCBs - DHPs, dihydropyridines type, by means of

quantitative structure - biological activities relations (QSAR).

MATERIAL and METHODS

Scientific research regarding the relations chemical structure-reactivity has known a fast and efficient development over the past years. The way in which the structural effects influence the reactivity and physical properties of organic compounds were modeled quantitatively for the first time by Hammett⁵, who obtained the same named equation. Hansen⁶ tried to apply the Hammett equation in the study of biological activities, while

Zahradnik⁷ suggested the use of a similar equation.

In this study we approach main chemical structure parametrization and quantification techniques of electronic, steric, topologic and hydrophobic effects with applicability in QSAR models. (Eq. 1). We will give a particular regard to the way of development and utilization of the QSAR relation (Eq. 1) and also to the necessity this equation to be

statistically valid across the proposed correlation analysis models.⁸

$$A_x = a + b_1 t_x + b_2 t_x^2 + b_3 \sigma_{I,x} + b_4 \sigma_{D,x} + b_5 S$$

A represents bioactivity, t is a transport parameter, σ_I and σ_D express localized electronic effects (field and/or inductive), respectively delocalized (resonance) and S measures steric effects. Bioactivity, A , is usually given by $\log(1/C)$, C being the molar concentration which determines a constant biological answer.

The correlation equation¹ or other relations derived from it, statistically validated, is called quantitative structure-biological activity relation (or QSAR). If there are grafted many X substitutes on the molecular structure of L effectors, the effects of those may be treated additive or, opposite, each substitute may be treated separately.

The first stage in any QSAR study is the selection of a calculus technique suitable for the determination of geometry and drug molecules conformation.

The second stage aims to identify the low energy conformation and optimization of those conformations for the selected derivatives for the analysis.

The identification of low energy conformation certifies the obtaining of comparable data for all molecules.

The third stage of the quantitative analysis structure-activity aims to develop a quantitative model structure-activity using descriptors obtained from AM_1 calculations, graph theory calculations and estimates of the physical and chemical properties. These calculated descriptors may be divided in four groups: geometrical, electronic, topological, physico-chemical.

- Geometrical descriptors reflect the molecular dimensions and include

values such as bond lengths, angles and interatomic distances.

- Electronic descriptors represent properties of electronic distribution and include values such as: charge density on atoms and molecular ionization potential, being derived also from semiempiric calculations.
- Topological descriptors refer to the molecular complexity and ramifications, using indices determined from graph theory.
- Physico-chemical descriptors describe the molecule ability to penetrate biological membranes; they are determined by empiric calculations.

The electrostatic potential (MEP) representations serve to identify the main electrostatic characteristics of CCB molecules.

The regions with negative electrostatic potential are usually associated with pairs of non-participating electrons. A high negative electrostatic potential indicates that that group is more alkaline, acting as acceptant in hydrogen bonds.

Positive electrostatic potential is always associated with the atomic framework of molecule, so the identification of positive electrostatic potential is trivial.

The molecular electrostatic potential representations may offer complementary information to those determined from QSAR analysis.

The electrostatic potential provides a description of electrostatic topology conditions around the drug molecule. It is based on electronic density and on atomic nucleus position and may be generated through quantum mechanics semiempirical techniques.

One of the new trends in molecular pharmacology is to build the actions of a drug based on substitute constants

derived from organic and physique models.

The regional analysis which using these parameters indicates that the stereo-electronic factor associated with a molecule determines its selectivity at the action site, and hydroalkalinity constant log P plays an important role in pharmacokinetics.

The relative evaluation of steric and hydrophobic factors in quantitative prediction of molecular and pharmacological drug properties is essential for a QSAR study.

A series of CCBs, dihydropyridines type, with the general structure⁹ presented in figure 1 was considered in this study.

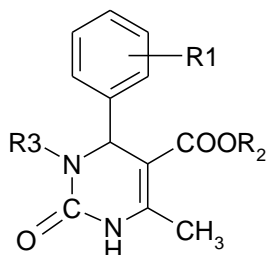


Fig.1 General structure of dihydropyridines.

Table 1 Biological activities, quonto-chemical parameters of the series.

No.	R1	R2	R3	¹ χ ^v _{R2} a)	D _{R2} b)	¹ χ ^v _{R3} c)	Log(1/IC ₅₀) d)
1.	3-NO ₂	iPr	CON(Me)2	1.55	0.0	1.80	7.16
2.	3-NO ₂	iPr	CONHMe	1.18	0.0	1.80	6.90
3.	3-NO ₂	iPr	CONH2	0.72	1.0	1.80	7.56
4.	3-NO ₂	iPr	H	0.00	0.0	1.80	6.08
5.	3-NO ₂	Et	CONH2	0.72	1.0	1.40	7.00
6.	3-NO ₂	Me	CONH2	0.72	1.0	0.81	6.21
7.	3-NO ₂	iPr	CONHEt	1.74	0.0	1.80	7.29
8.	3-NO ₂	iPr	CONHiPr	1.86	0.0	1.80	7.38
9.	3-NO ₂	iPr	CONHCH2Ph	3.30	0.0	1.80	8.38
10.	3-NO ₂	iPr	CH2CH2N(Me)Bn	4.16	0.0	1.80	8.98
11.	3-NO ₂	iPr	CONH2	0.72	1.0	1.80	7.53
12.	3-CF ₃	iPr	CONH2	0.72	1.0	1.80	7.53
13.	2-CF ₃	iPr	CONH2	0.72	1.0	1.80	7.53
14.	3-Cl	iPr	CONH2	0.72	1.0	1.80	7.53
15.	2-Cl	iPr	CONH2	0.72	1.0	1.80	7.53
16.	3-Br	iPr	CONH2	0.72	1.0	1.80	7.53
17.	2-Br	iPr	CONH2	0.72	1.0	1.80	7.53
18.	2,6-Cl ₂	iPr	CONH2	0.72	1.0	1.80	7.53
19.	2,3-Cl ₂	iPr	CONH2	0.76	1.0	1.80	7.53

a) Connectivity index for R2

b) Specific parameter for R2

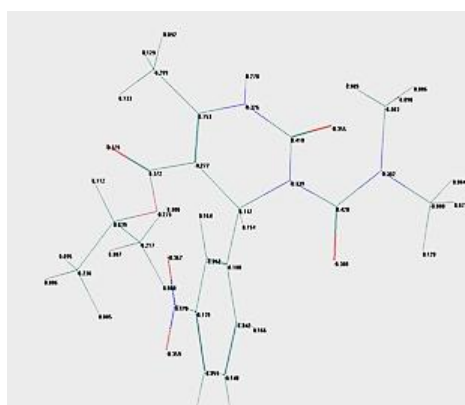
c) Connectivity index for R3

d) Biological activity

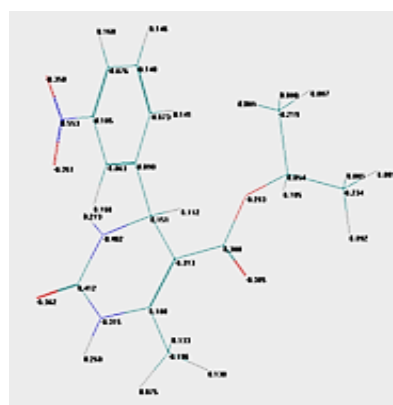
Charge density and electrostatic potential – Using the HyperChem 7.0 program package (licensed to West University of Timisoara and Romanian Academy – Chemistry Institute Timisoara), the charge density and electrostatic potential of two of the most active molecules from the studied DHPs series were represented (figure 2, 3). The analysis of potential areas may offer particularly valuable information

upon the interactions nature that a given ligand can take part.

A suggestive image on the electric charge distribution in the studied molecules is offered by the map which describes the electrostatic potential: in violet were represented negative electrostatic potentials, and in green the positive ones.

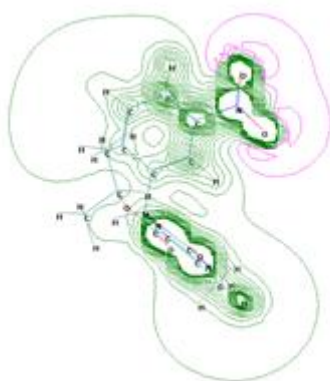


a) compound 2 (A=6.90)

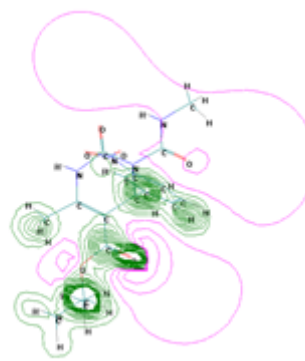


b) compound 4 (A=6.08)

Fig. 2. (a,b) Charge density of the most three active molecules.



a) compound 4 (A=6.08)



b) compound 2 (A=6.90)

Fig. 3. Electrostatic potential representation (3D) for the most active molecules.

RESULTS

Using quantitative structure-biological activity relations studies (QSAR) we investigated quanto-chemical parameters calculated with

HyperChem 7.0 program package (licensed to West University of Timisoara and Romanian Academy – Chemistry Institute Timisoara)

establishing their influence on the biological activity of considered DHPs.

The studied series comprises 19 compounds with calcium channel blocking properties, being classified as DHPs.

The biological activity of the 19 derivatives was taken from literature⁹ and it is expressed as $\log (1/IC_{50})$, where

IC_{50} represents the vaso-relaxing activity of the compounds and it refers to the minimum inhibitory concentration which determines the biological effect in 50% of experimental animals. Following parameters were also taken from literature⁹: connectivity index $^1\chi^v_R$ and D_R parameter which is specific to $CONH_2$ group.

Table 2 The correlational analysis of biological activity with determined quonto-chemical parameters in studied DHP series.

Compound	Parameters							
	Hydrating energy (Kcal/ mol)	Log P	Polarizability (Å ³)	Refractivity (Å ³)	Volume (Å ³)	Surface area (Å ²)	Surface area (grid) (Å ²)	Weight (u.a.m)
1.	-7.69	-0.38	38.28	104.24	1028.85	545.63	588.81	390.4
2.	-10.26	-0.63	36.44	99.35	1001.66	545.12	588.01	376.37
3.	-12.86	-0.87	34.61	94.45	922.82	459.80	529.05	362.34
4.	-9.81	-0.60	31.33	86.21	855.18	450.30	503.90	319.32
5.	-13.20	-1.29	32.77	90.03	888.17	453.67	523.66	342.32
6.	-13.65	-1.63	30.94	85.28	844.50	431.69	505.17	334.29
7.	-9.27	-0.28	38.28	104.10	1025.98	528.21	580.34	390.4
8.	-8.78	0.13	40.11	108.51	1078.14	562.36	609.02	404.42
9.	-10.30	1.15	46.10	123.96	1158.96	528.00	636.98	452.47
10.	-5.77	0.83	45.53	123.00	1239.70	695.24	701.99	432.52
11.	-9.11	-0.87	34.61	94.45	923.02	431.22	536.12	362.34
12.	-7.28	0.51	34.33	93.45	963.60	503.15	565.68	385.34
13.	-6.56	0.51	34.33	93.45	915.77	401.68	522.59	385.34
14.	-6.38	-0.28	34.69	92.95	927.97	480.10	547.71	351.79
15.	-7.18	-0.28	34.69	92.95	905.45	422.35	517.85	351.79
16.	-7.45	-0.01	35.39	95.77	948.38	487.52	558.15	396.24
17.	-7.34	-0.01	35.39	95.77	933.36	482.22	540.62	396.24
18.	-6.62	-0.50	36.62	97.66	945.35	458.70	544.09	386.23
19.	-6.92	-0.50	36.62	97.66	641.91	456.98	537.01	386.23

Using the HyperChem 7.0 program package (licensed to West University of Timisoara and Romanian Academy - Chemistry Institute Timisoara) following quonto-chemical parameters were calculated:

- log p – partition coefficient octanol-water
- hydrating energy (kcal/mol)

- polarizability (Å³)
- refractivity (Å³)
- volume (Å³)
- surface area (Å²)
- surface area (grid) (Å²)
- weight (u.a.m)

The correlation of these parameters with the studied DHPs' biological

activity expressed as $\log(1/IC_{50})$ (taken from literature⁹) emphasized essential structural requirements for the studied DHPs to have an improved biological effect.

In table 2 calculated parameters with HyperChem 7.0 program package (licensed to West University of Timisoara and Romanian Academy – Chemistry Institute Timisoara) are shown.

The best QSAR model was obtained after considering six parameters to intervene in the biological activity determinism of considered DHPs. The obtained equation is:

$$A = 3,742 (\pm 2,007) + 0,071 \text{ energ} (\pm 0,248) + 0,115 \log P (\pm 0,312) + 3,431 \text{ pol} (\pm 2,890) + (- 3,120) \text{ refract} (\pm 3,001) + 0,148 \text{ vol} (\pm 0,301) + 0,275 \text{ masa} (\pm 0,409)$$

$$t = 1,864 \quad t = 0,289 \quad t = 0,368$$

$$t = 1,186 \quad t = -1,039 \quad t = 0,493$$

$$t = 0,672$$

$$r = 0,861 \quad r^2_{\text{adj}} = 0,614$$

$$\text{see} = 0,394 \quad F = 5,773$$

Correlations between biological activity of the considered DHP series and calculated quanto-chemical parameters led to following results:

- the parameters with importance in the increase of biological activity

($r=0.84-0.86$, values obtained after triparametrical, tetraparametrical, respectively pentaparametrical correlations) are:

- hydrating energy, $\log P$ and polarizability
- hydrating energy, polarizability and refractivity
- hydrating energy, polarizability and weight
- $\log P$, polarizability and refractivity
- hydrating energy, polarizability, refractivity and weight
- hydrating energy, $\log P$, polarizability and refractivity
- hydrating energy, $\log P$, polarizability and weight
- $\log P$, polarizability, refractivity and volume
- $\log P$, polarizability, refractivity and weight
- polarizability, refractivity, volume and weight
- hydrating energy, $\log P$, polarizability, refractivity and weight
- $\log P$, polarizability, refractivity, volume and weight
- hydrating energy, $\log P$, polarizability, volume and weight
- hydrating energy, $\log P$, polarizability, volume, weight and refractivity.

CONCLUSIONS

The QSAR study upon the considered CCB – DHP series with 19 compounds shows that quanto-

chemical parameters contribute to the determinism of the inhibitory activity, in a synergistic manner.

REFERENCES

1. Rodica Cinca, Marinela Popovici, V. Dumitraşcu, D. Ana, Adelina Chevereşan, Ioana Ana, Simona Şipoş, N. Şuta, Ioana Maliţa, Beatrice Barac, Dana Lengyel. Curs de Farmacologie. Editura Mirton, Timişoara, 2006, ISBN 973 661 796 3.
2. McDonagh MS, Eden KB, Peterson K. Drug class review on calcium channel blockers. Final report. Oregon Health & Science University Portland, 2005.
3. Yousef WM, Omar AH, Morsy MD, Abd-El Wahed MM, Ghanayem NM. The mechanism of

- action of calcium channel blockers in the treatment of diabetic nephropathy. *Int J Diabetes & Metabolism*. 2005; 13:76-82.
4. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers and vascular smooth muscle. *Annu Rev Pharmacol Toxicol*. 1977; 17:149-166.
 5. Hammett LP. The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. *J Amer Chem Soc*. 1937; 59:96-103.
 6. Hansen OR. Hammett Series with Biological Activity. *Acta Chem Scand*. 1962; 16:1593-1600.
 7. Zahradnik R. Influence of the structure of aliphatic substituents on the magnitude of the biological effect of substances. *Arch Int Pharmacodyn Ther*. 1962; 135:311-329.
 8. Ebert K, Ederer H, Isenhour TL. *Computer Applications in Chemistry*. VCH, Weinheim, 1989. ISBN 3-527-27807-9.
 9. Atwal KS, Rovnyak GC, Kimball SD, Floyd DM, Moreland S, Swanson BN, Gougoutas JZ, Schwartz J, Smillie KM, Malley MF. Dihydropyrimidine calcium channel blockers. II. 3-Substituted-4-aryl-1, 4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. *J Med Chem*. 1990; 33:2629-2635.

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THE IMPORTANCE OF MODERN MANAGEMENT METHODS IN THE MEDICAL FIELD



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ABSTRACT

Introduction: Health insurance is considered to be an essential objective of a health system. Management is a professional function which means driving in a given context, a group of people who have to achieve a common goal, in accordance with the aims of the organization they belong to. The professional function is a practical professional activity that requires for its use specific, technical and relational knowledge and skills. A primary goal in providing health is to achieve a high level of health and equitable distribution of healthcare services. Another goal is equitable financing, the costs reflecting the ability to pay, and not necessarily the risk of illness.

Material and method: The hospital is a sanitary unit with beds, which provides curative complete care and recovery, preventive care to hospitalized patients; in addition the hospital provides specialized medical assistance. The hospital must be present in the community in order to bring the services it needs. The factors influencing hospitalization indicators are: economic development, living standards and the effects of pollution, age structure of population, environmental quality and effective treatment of patients in the ambulatory system.

Results and discussions: The management into a hospital is based on targets and budgets in order to increase the number of services, the quality of provided services, and the complexity of cases treated by attracting and efficient use of financial, material and human resources. Management methods and techniques in a hospital are: diagnosis, delegation, meeting, dashboard, management by budgets. Their sizing involves specifying parameters such as number of decided beds, the index of bed use, number of accounting days of hospitalization, number of patients admitted / discharged, the case-mix index, the price realized per case solved.

Conclusions: Making an analysis of the distinctive characteristics of health care assessments, where the needed resources are expressed into costs, and the obtained results are expressed as health effects, we conclude that it is necessary to change the conceptual issues regarding health care financing. The proposed objectives results of setting the following priorities: improving the clinical standards and the practice patterns in order to increase the degree of patient satisfaction; monitoring and evaluation of the medical activities performed in the hospital in order to increase the professional performance and the efficient use of allocated resources; developing the project of the hospital acquisitions plan in the estimated budget limit; and strengthening of economic and financial discipline.

Key words: management, chronic patients, cardiovascular disease, cost-saving, budget.

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INTRODUCTION

Peter F. Drucker said: "Management means, ultimately, replacing muscle and strength with the power of thought, customs and superstitions with the knowledge and aggression with cooperation. It means that responsibility replaces obedience to rank and authority performance takes the place of function authority. "



Health insurance is considered an essential objective of a health system. A primary goal is to achieve a high level of health and equitable distribution of healthcare services. Also, a healthcare system should correspond to people's expectations, which implies respect for the individual (autonomy and confidentiality) and the client orientation (prompt service and quality equipment). Another goal is equitable financing, the costs reflecting the ability to pay, and not necessarily the risk of illness.

Management is a professional function which means driving in a given context, a group of people who have to achieve a common goal, in accordance with the aims of the organization they belong to. The professional function is a practical professional activity that requires for its use specific, technical and relational knowledge and skills.

The hospital is a sanitary unit with beds, which provides curative complete

care and recovery, preventive care to hospitalized patients; in addition the hospital provides specialized medical assistance. The hospital must be present in the community in order to bring the services it needs. To work, this institution needs financial, human and material resources. The sources of funding of the hospital institution are: health insurance through the County Health Insurance House, C.A.S.T., transfers from the Department of Public Health budget, direct payment services to uninsured patients or for services provided on request, donations and sponsorships.

The factors influencing the hospitalization indicators are: economic development, living standards and the effects of pollution, age structure of population, environmental quality and effective treatment of patients in the ambulatory system. The basic elements that influence the efficiency of medical services into the hospital activity are: technical equipment and qualified staff. To highlight the important role of the financial system in medicine and the necessity to know from where the funds are coming and which are the expenditures of a chronic section into a hospital we have chosen the theme analysis about income and expenses allocated to this institution, that will help to a better division of the budget. To substantiate the costs will be considered: physical indicators with which can appreciate the financial effort (number of employees, number of discharged cases, number of beds, number of days of hospitalization); the evolution of costs the last 2-3 years, in order to observe a tendency to increase or reduce costs; and rules and regulations regarding the expenditures (food allowances, repairs).

MATERIAL AND METHODS

To highlight the important role of the financial system in medicine and the necessity to know from where the funds are coming and which are the expenditures of a chronic section within a hospital we have chosen the theme analysis about income and expenses allocated to this institution, that will help to a better division of the budget. The main motivation is to achieve the best results with lowest costs. Health services provided under the above mentioned conditions must be qualitative and can be measured and improved if necessary.

To achieve the objectives we study a lot which will include a total of 1,200 patients admitted to Medical Department, Cardiovascular profile, in Arad County Hospital. It will be analyzed statistically: incidence of cardiovascular disease in the group, repetitive admissions, the need for consumption of drugs and investigations, cost estimates for the periods of hospitalization and specific diseases.



The medical department of cardiovascular disease is a specialized healthcare unit in which runs activities of patient care with cardiovascular diseases and activity of education, medical research, guidance and coordination of methodological work on its field.

Cardiovascular risk factors are divided into two large categories:

modifiable and non-modifiable. Usually a person has one or more risk factors for heart disease and a person who has one risk factor, but much modified, is considered having a lower cardiovascular risk than one who has many moderate risk factors modified. (Example: a man of 45 years, nonsmoker, with no high blood pressure, which has only increased plasma cholesterol (280 mg/dl), the cardiovascular risk is lower than the same old man, smoker (10 cigarettes / day, 20 years), glucose = 110 mg/dl, total cholesterol 240 mg/dl.). On the basis of the risk scores (Framingham, Heart Score), a person could be included in a light, medium, high and very high risk group, and in a certain subgroups of patients the cardiovascular risk may be wrong estimated, even based on scores risk, for example young patients is often overestimated and patients with diabetes and those with familial dyslipidemia are having automatically an increased risk.

Modifiable risk factors are: hypertension, increased total plasma cholesterol, increased LDL cholesterol (bad cholesterol), decreased HDL cholesterol (good cholesterol), increased plasma triglycerides, increased plasma glucose and obesity.

Non-modifiable risk factors are: age, sex, cardiovascular disease in first degree relatives (parents, brothers, sisters) and at younger ages, under 55 years in men and under 65 years in women, heart disease or valvular heart disease in personal history. Lifestyle also contributes to increased cardiovascular risk: smoking, physical inactivity, excess alcohol consumption, rich diet in saturated fat and cholesterol.

Total cardiovascular risk estimated the probability of dying by heart disease over the next 10 years. The diagnostic steps are: risk assessment, setting goals to achieve, establish means and methods that achieve the proposed objectives. The diagnostic procedures involved in assessing cardiovascular risk, such as cardiologycal consultations, biological tests, echocardiography and vascular ultrasound (echography) can define the parameters for calculating risk. Lifestyle changes and appropriate drug therapy to each risk factor separately may lower the risk of cardiovascular events in each individual treated.

In our country, the health insurance system was introduced by Law nr.145/1997, adopting the health system based on Bismarck Health Insurance. The system involves obtaining income from obligatory contributions and specific ways of redistribution and allocation of funds in the health system. Law no. 145/1997 of health insurance had many changes after its adoption, was then abrogated by the Government Emergency Ordinance no. 150/2002 on organization and functioning of social health insurance. Currently, the health insurance is regulated by Title VIII of Law. 95/2006 on healthcare reform, law that was Ordinance no. 150/2002 repealed. According to article 208 of Law no. 95/2006, health insurance represent the main financing system of population health care, which provides access to a basic package for insurance patients, this system aims to protect the insured against medical costs in case of illness or accident and providing insured protection universally, fairly and without discrimination. Social protection systems have an important role in the European Union, as in all European Union countries the question of budgets resizing health services, an

attempt to find solutions that ensure universal access to care by reducing costs without reducing the quality of services and access to them. The communication of European Commission in 2001 on the future of healthcare and medical services for the elderly has focused on three main objectives that can ensure the accessibility, quality and financial support of the systems: improving effectiveness and efficiency of health systems, ensuring the access for all members of society to health services of high quality and focused attention to disease prevention and health protection.

The Organization for Economic Co-operation and Development (OECD) indicators show that cardiovascular disease costs the European Union amounted to 169 billion, of which: 105 billion to treat and 64 billion from lost productivity and from the informal care costs. The costing calculation is based on the tracking the indicators costs of each department in a hospital ward: cost / day of hospitalization, cost / per hospitalized patient, cost / on the bed, cost / per patient discharged, medication cost / patient, cost drugs / day of hospitalization, medical supplies cost / per hospitalized patient, sanitary materials cost / day of hospitalization.

To substantiate the costs will be considered:

a) physical indicators with which can appreciate the financial effort (number of employees, number of discharged cases, number of beds, number of days of hospitalization);

b) the evolution of costs the last 2-3 years, in order to observe a tendency to increase or reduce costs;

d) rules and regulations regarding the expenditures (food allowances, repairs).

The management into a hospital is based on targets and budgets in order

to increase the number of services, the quality of provided services, and the complexity of cases treated by attracting and efficient use of financial, material and human resources. Management methods and techniques in a hospital are: diagnosis, delegation, meeting, dashboard, management by budgets. Their sizing involves specifying parameters such as number of decided beds, the index of bed use, number of accounting days of hospitalization, number of patients admitted / discharged, the case-mix index, the price realized per case solved. These parameters underlying design, substantiation and realization of each sections income, under contracts concluded with CJAS. On each cost center the direct costs have been identified on the budget classification structure (personnel costs, costs with assets and services, capital expenditure), detailed on articles and paragraph.

To establishing basic objectives are proposed:

- Increasing income by 2%
- Reduce costs by 3%
- Case mix index increased to 1.6
- Reduce mortality by 0.5%.

The establishing other categories of objectives are limited to:

Writing and implementation of clinical practice protocols in all sections and in all chapters of pathology: compliance of indications, selection of cases and thus the improve the quality and the results;

- Preparation of monthly evidence of the results at the sections level, analysis of mortality and causes of mortality;

Signing private partnerships under the law and purchase of equipment's in rates system, leasing, rental (cardiac echo, Holter TA), in order to allow diversification and improved performance of offered benefits, leading to increased addressability.

RESULTS

The classification system in groups of diagnoses (Diagnosis Related Groups - DRG) is a scheme of patient classification based on the diagnosis. This system is similar to the international classification system diseases (International Classification of Diseases - ICD), in which diagnoses are classified into classes and subclasses. In contrast, to the DRG system is used a supplementary criterion for classification, namely the cost of the used resources for the patient care. Thus, through the DRG system, patients can be classified simultaneously by both pathology and after care costs, which allows it to associate the types of patients with hospital expenses incurred. The DRG system is a patient classification system

based on the diagnosis, procedures and other clinical information about the patient, which allows correlating the type of patients that the hospital treats (index of complexity of the case or case-mix) with costs of the hospital.

When DRG's are used as the basis for funding hospitals, other data are needed to establish a price or charge for each DRG. Through diagnostic groups (DRG) is analyzed each patient characteristics discharged of the hospital, and according to these characteristics, the patients are grouped into a separate category.

In order to classify each patient discharged in a diagnostic group is required:

- Obtaining / registration of clinical data on patients discharged;

- Coding necessary data (diagnoses and procedures) in order to use a standardized language for these variables and to be used more easily;

- Collection of such data in electronic form;

- Automatic sending of each patient in a diagnostic group (using a group computer application - "grouper").

After grouping the patients into DRGs for financing hospitals, another two steps are required:

- Establishment of charges for each diagnostic group (or relative values of tariffs), they are based on adjacent costs of patients in each group of diagnoses that can be imported with a grouper or can be developed locally; once these costs are calculated, are converted into tariffs and used for all participating hospitals in the financing scheme.

- The budget for hospital assistance must be allocate to hospitals care, starting from the number and type of discharged patients (case-mix of each hospital) and price list (or relative values) for each DRG.

The payment arrangements for hospital medical services, contracted with health insurance offices are established by rules and can be, as appropriate:

- a) price per case resolved: DRG system or average price per specialties case resolved;

- b) budget established by title, expenditure articles and paragraph based on specific indicators set

- by rules for hospitals / clinics;

- c) the medical service fee.

Revenue growth at the hospital level aims to:

- Improving the structure and equipment of the hospitals by increasing their revenue, hospitals will be able to improve provision of equipment and devices and in this way can provide more diversified and quality services;

- The possibility of increasing the revenue staff, going from revenues realized they could develop appropriate payment mechanisms for the medical personnel, this will be stimulated in increasing quality of services;

- Subsidizing through private resources of underfunded public services, by making its own funds outside the public system.

Some public hospitals will be able to continue to provide further services under obligatory insurance, even if reimbursement for these services will be insufficient, also, the hospitals can cover in this way and the services provided for the uninsured patients, which public hospitals are obliged to ensure some minimum services or emergency medical services. Overall, the hospitals are stimulated to keep costs at a lower price for each type of patient, in order to save resources and use them for different purposes.

Expected outcome is to improve the health of the population on medium and long term by modifying the cardiovascular specific health indicators, namely: prevention of cardiac death, decreased incidence of acute myocardial infarction, decreased hypertension and cardiovascular risk factors by a healthy lifestyle.

CONCLUSIONS

Making an analysis of the distinctive characteristics of health care assessments, where the needed resources are expressed into costs, and

the obtained results are expressed as health effects, we conclude that it is necessary to change the conceptual issues regarding health care financing.

We want to use management by objectives as:

- Printing of feature order, discipline and rigor of the led field, as premise of its effectiveness and efficiency;

- Exercise a prevision, anticipatory management, supported by foundation and development of objectives;

- Responsible managers of the management centers (heads of department, laboratories) and their components. Management centers have a high decisional and operational autonomy, and the value of the centers is conditioned by their competent leaders;

- Amplifying the motivational dimension of the management, providing moral spiritual and material rewards / sanctions and it is conditioned by the degree of achievement of individual objectives, management centers, as well as the level of involvement in their realization.

The proposed objectives results of setting the following priorities:

- improving the clinical standards and the practice patterns in order to increase the degree of patient satisfaction;

- monitoring and evaluation of the medical activities performed in the hospital in order to increase the professional performance and the efficient use of allocated resources;

- developing the project of the hospital acquisitions plan in the estimated budget limit;

- strengthening of economic and financial discipline.



"In addition to your juggling, what other background do you have in medical management?"

This paper suggests the importance of the modern management methods in the medical field and might be a reference for professionals in the medical sector, for medical managers, of medical equipment and medication distribution, for hospital practitioners doctors and hospital managers in particular, respectively leaders of the medical sections.

The management methods represent all means and procedures by which the management influences the system elements action he leads to achieve the established objectives. The management of contemporary organizations cannot be conceived without the use of some scientific methods to enable knowledge and effective application of objective economic laws, rational and efficient use of resources, stimulating and creative use of staff employed and managers, accurately assess the obtained results, the decision process optimization and all the management functions, integration of technical dimensions, and economic, social, political and human of the organizations.

REFERENCES

1. Baum F: "The New Public Health", Oxford University Press, New York, 2003.
2. Batrancea, I.: "Analiza financiara", editura "Dacia", Cluj-Napoca, 2000.

3. Beaglehole R, Bonita R: "Basic Epidemiology", World Health Organization, Geneva, 2003.
4. Beaglehole R, Deters R, Holland WW: "Oxford Textbook of Public Health", Oxford University Press, New York, 2004.
5. Beaglehole R: "Global Public Health- A New Era", Oxford University Press, New York, 2003.
6. Beju, V.: "Buget, contabilitate si audit la institutiile publice", editura "Casa Cartii de Stiinta", Cluj-Napoca, 2007.
7. Beju, V.: "Contabilitate bugetara", editura „Dimitrie Cantemir”, Targu- Mures, 2004.
8. Brezeanu, P.: "Audit si control financiar", editura "ASE", Bucuresti, 2001.
9. Cassens B: "Preventive medicine and Public Health", Harwal Publishing Company, Malvern, Pensilvania, USA, 1992.
10. Chobanian AV, Bakris HR et al: "The seventh report of the Joins National Comitte on Prevention." JAMMA 2003; 289, 19: 2560 – 2572.
11. Dragomir Manuela, Ghelase M, Dinescu S: "Sanatate publica - Demografie si Epidemiologie", editura medicala universitara Craiova, 2005.
12. Drugus L. "Managementul Sanatatii." Ed. Sedcom Libris, Iasi 2003.
13. Enachescu D, Zarcovic G., "Probleme privind politicile de sanatate in tarile Europei Centrale si de Rasarit.", Ed.Infomedica, Bucuresti 1998.
14. Enachescu D., Marcu M, „Sanatate publica si management sanitar.", Ed.All, 2000.
15. Fourmier A, Andreja KM, Tribouilloz C,Lesbre JP: „Examen d'un malade hypertendu. In: Hypertension arterielle." Ed Hermann, Editeurs des sciences et des arts. Paris 1998: 161 – 163.
16. Greceanu-Cocos, "Practica auditului la institutiile publice." Societatea Adevarul, Bucuresti, 2000.
17. Leal J et al. "Economic Burden of Cardiovascular Diseases in the enlarged European Union." Euro Heart J 2006; 27:1610-19.
18. Legea nr. 426/16.05.2002 privind auditul intern si controlul financiar preventiv, publicata in Monitorul Oficial nr.339/22.05.2002.
19. Legea nr. 500/11.07.2002 privind finantele publice, in Monitorul Oficial nr. 597/17.08.2002.
20. Legea nr. 95/2006 privind reforma in domeniul sanatatii. Vladescu C, Managementul serviciilor de sanatate, Ed.Expert, Bucuresti, 2000.
21. Levenson JW et al. "Reducing the global burden of cardiovascular disease: the role of risk factors." Preventative Cardiology 2002; 5:188–99.
22. Management pe baza centrelor de responsabilitate Editura Economica, Bucuresti, 2002.
23. Managementul proiectelor. Asociatia Project Management Romania, Editura Economica, Bucuresti, 2002.
24. Management public, Editura Economica, Bucuresti 2001
25. Marcu M, Minca Dana: "Sanatate Publica si Management sanitar.", editura universitara Carol Davila, Bucuresti, 2003
26. Marinescu P. "Managementul institutiilor publice." Editura Universitatii, Bucuresti, 2003.
27. Margulescu, D. "Analiza economico-financiara." editura "Romcart", Bucuresti, 1994.
28. Nica P., Iftimescu C. "Management.", Editura SedcomLibris, Iasi 2004.
29. Nicolaescu O, Verboncu I. "Fundamentele managementului organizatiei." editura Tribuna Economica, 2001.
30. Ordonanta Guvernului nr.119/1999 privind controlul intern si controlul financiar preventiv, republicata, (Monitorul Oficial al Romaniei, Partea I, nr.799/12.XI.2003).
31. Popa I. "Management general." editura ASE, 2005.
32. Popa I. "Management strategic." editura Economica, 2005
33. Pop O, Nistor F: "Epidemiologie generala." editura Helicon, Timisoara, 1995.
34. Profiroiu M. "Managementul organizatiilor publice." Editura Economica, Bucuresti, 2001.
35. Scoala Nationala de Sanatate Publica si Management Sanitar "Managementul spitalului." editura Public H Press, 2006, Bucuresti.
36. Stanciu S., Mihailescu L., Cornescu V. "Managementul organizatiei." Editura All Beck, Bucuresti 2003.
37. Stoica Constantin, Ana Constantin "Managementul resurselor umane."Editura Institutului European, 2002.
38. Thom T et al. "Heart disease and stroke statistics – 2006 update." Circulation 2006; 113:e85-e151.
39. Vladescu C. "Politica de Reforma a sistemului de Sanatate din Romania." Ed. Infomedica, Bucuresti 1999.
40. Verdinas Verginia, "Statutul functionarului public." Editura Nemira, Bucuresti, 1998.
41. Wood D, De Backer G. "Clinician's Manual on Total Risk Management, A guide to prevention of Coronary Heart Disease." Science Press And the European Society of Cardiology, 2001.
42. Zanoschi G. "Sanatate publica si Management sanitar." Ed. DAN, Iasi 2003.

CORELATIONS BETWEEN TUMOR LOCATION AND SYMPTOMS IN A SERIES OF 65 PATIENTS WITH GIST MEDICAL FIELD



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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, which originate from interstitial cell of Cajal. GISTs can arise anywhere along the gastrointestinal tract but are most common in the stomach and small intestine. The most common clinical presentation of these tumors is gastrointestinal bleeding; otherwise they may cause intestinal obstruction, abdominal pain, a palpable mass, or can be incidentally detected during surgery or endoscopic/radiological procedures.

Aim – Primary aim of this study was to report our experience regarding GIST patients, correlating symptoms at presentation with tumor localization.

Patients and methods – 65 consecutive patients undergone to surgical resection for GISTs were enrolled in a prospective study from January 2002 to December 2011. Patient's clinical and pathological features were collected and analysed.

Results – The most common symptom in our experience was upper gastrointestinal bleeding (37,87%), followed by intestinal obstruction or subocclusive events (19,69%) and epigastric pain (15,15%). Bleeding in the digestive tract and abdominal pain were more common in gastric GIST, acute abdominal symptoms were more frequent in jejunal and ileal GIST.

Conclusion – According with our findings symptoms correlate to tumor location; however we cannot conclude that symptoms are per se predictive of survival or patient's outcome.

Keywords: GIST, diagnosis, neurofibromatosis type 1, paediatric, immunohistochemistry, gastric.

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BACKGROUND

Two main criteria were set for a tumor to be labeled as GIST that is the main tumor and the presence of mutant c-KIT gene and CD117. These tumors usually occur in adults, with an average age of 55-60 years and an incidence of 10-20 new cases per million / year ¹. GIST represents 80% of gastrointestinal mesenchymal tumors and 0,1-3% of all gastrointestinal malignancies ²⁻⁷. GIST have specific immunohistochemical markers: 95% are positive for CD-117, 70-80% are CD34 positive, and 20-30% are positive for SMA, desmina is positive in less than 5% of GIST ¹⁻¹². GIST can occur at all levels of the gastrointestinal tract: 50-70% in the stomach, 25-30% in the small intestine, 5-10% in the colon and rectum, 5% in the esophagus, the rest may appear in the omentum or peritoneal layers (EGISTs) ¹². Familial

forms are very rare, 5% of tumors occur in patients with neurofibromatosis type 1 and Carney triad (gastric GIST, paraganglioma, lung condroma) ¹. Most common clinical presentation of these tumors is gastrointestinal bleeding, gastrointestinal obstruction, abdominal pain, weight loss or as a palpable mass, or may be detected incidentally during surgery or other laboratory examinations ⁶. Prognosis is related to tumor size and mitotic rate: tumors larger than 10 cm or mitotic rate greater than 5/50 HPF has a higher risk of recurrence and metastasis is associated with a poor prognosis. Other prognostic factors are tumor location, tumor persistence of residues within the surgical resection, tumor rupture and c-kit mutation. Modern treatment of GIST is: surgery and targeted molecular therapy.

MATERIAL AND METHODS

Sixty-five patients with GIST were enrolled in a prospective observational study: Twenty-five patients (from January 2002 to December 2011) from C.F. Hospital Cluj Napoca, and forty patients (from January 2002 to December 2011) from Cancer Institute "Ion Chiricuță" Cluj Napoca.

Inclusion Criteria

- patients admitted in the Surgical Department of University Hospital C.F. Cluj-Napoca and the Oncology Institute "Ion Chiricuță" Cluj during January 2002 - December 2011
- diagnosis of GIST confirmed histopathologically and immunohistochemically (by analysis of piece resection or intraoperative biopsy)- patients with localized primary GIST (no

loco-regional invasion): clinical and paraclinical GIST diagnosed and who required surgery for GIST found accidentally during surgery for other pathologies or during medical investigations for other diseases

- patients with extensive disease (loco-regional invasion there): operable, inoperable metastases at diagnosis.
- patients who were evaluated postoperatively for more than six months

Exclusion Criteria

- incomplete relationships on evolution and survival
- patients with benign tumors of the digestive tract that raised the differential diagnosis of GIST with

<p>low risk of malignancy: a lipoma, a schwannoma and a leiomyoma.</p> <p>– patients with malignant tumors of the digestive tract that raised the differential diagnosis of GIST with</p>	<p>increased risk of malignancy: two leiomyosarcomas.</p> <p>– patients in whom surgical intervention was not done (because of increased surgical risk or refusal of the patient)</p>
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RESULTS

Based on these criteria in our study were included 65 patients diagnosed with GIST in the two surgical wards mentioned above, in the period January 2002 - December 2011. All patients were evaluated before treatment by clinical examination and laboratory investigations. Subsequently clinical and imaging data were confronted with histopathological and immunohistochemical results. Total number of patients hospitalized with a diagnosis of GIST in the Department of Surgery, University Hospital CF Cluj-Napoca and the Oncology Institute "Ion Chiricuță" Cluj during January 2002 - December 2011 was 65. The 65 patients amounted to a total of 494 days of hospitalization, on average 7,48 days.

Patients were classified into two groups at the same time: the group of patients diagnosed with localized disease (group I) and the group of patients diagnosed with extensive disease (group II). Were diagnosed on average 2 to 12 patients per year with an average of 6,1 patients per year. The increase in the number of diagnosed patients has been observed in recent years of observation of this study most likely attributed to the increase in diagnostic quality of these tumors. Thus out of 65 patients diagnosed with GIST in the two surgical sections, 44 patients (67,69%) had localized disease and were included in group I and 21 patients (32,30%) had extensive disease and were included in group II.

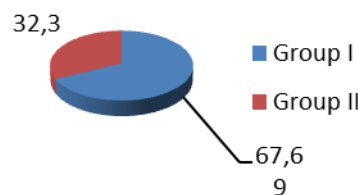


Fig.1 Percentage distribution of GIST in the two groups.

Depending upon discovery the two groups have some peculiarities, namely:

- in the group I, four GIST (9,09% of all patients in group I and 6,15% of the total 65 patients) were discovered by accident when checking for surgery for other pathologies (one gastric GIST was discovered during surgery for gallbladder cancer, another gastric

GIST during a surgical cure of a diaphragmatic hernia, one jejunal GIST in a subumbilical eventration and the last one was ileal and was discovered during an appendectomy)

- within group I, three GIST (6,81% of all patients in group I and 4,61% of the total 65 patients) were associated with other malignancies in which two were gastric and one pancreatic. So seven GIST in Group I

(15,9% of all tumors in group I) were discovered accidentally during surgery for other pathologies.

- one GIST was found incidentally during a paraclinical examination for other pathology (2,27% of all patients in

group I and 1,53% of the total 65 patients), colonoscopy performed for sigmoid cancer showed one GIST of the left colic flexure. We have no information about the existence of GIST discovered after necropsies.

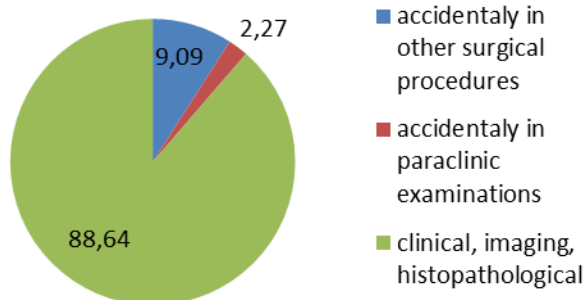


Fig.2 GIST distribution within the group I depending on when discovered.

In the group II of 21 patients with extensive disease, 15 patients had metastatic disease (71,42% in group II and 23,07% of the total 65 patients) and the remaining 6 had loco-regional invasion (28,57% in group II and 9,23% of the total 65 patients). In the 15 patients with metastatic disease six patients had single or multiple liver metastases (40% of all patients in group II and 9,23% of the total 65 patients), 5 patients had peritoneal metastases (23,8% of group II and 7,69% of the total 65 patients), 3 patients had mesenteric metastasis (14,28% of all patients in group II and 4,61% of the total 65 patients) and one patient had lymph nodes metastases (4,76% of all patients in group II and 1,53% of the total 65 patients).

GIST can occur at any level of the digestive tract, the most common forms are exophytique (develop outside the digestive tract) and endophytic (growing to the inside of the digestive tract). In our study seven of 65 tumors were endophytic forms (10,76%) the remaining 59 were exophytique forms (90,76%). Of the 7 endophytic GIST four were gastric, two ileals and one jejunal. In our study 32 of 65 GIST

tumors had gastric location (49,23%), 2 at duodenal level (3,07%), 13 jejunal (20%), 4 ileal (6,15%), 3 colon (4,61%), 1 transverse colon (1,53%), 1 descending colon (1,53%), 3 sigmoid (4,61%), 5 rectum (7,69%), 1 esophagus (1,53%). In case of group I we have 27 gastric GIST (61,36% of 44 tumors in group I), 1 duodenal (2,27%), 10 jejunal (22,72%), 3 ileal (6,81%), 2 sigmoid (4,54%) and 1 descending colon (2,72%). If the group II we have 5 gastric GIST (23,8% of 21 tumors in group II), 1 duodenal (4,76%), 3 jejunal (14,28%), 1 ileal (4,76%), 1 colon transverse (4,76%), 3 ascending colon (14,28%), 1 sigmoid (4,76%), 5 rectum (23,8%) and 1 esophagus (4,76%). The most common location is the stomach in both groups followed by the jejunal location and the rarest being the esophageal and colonic. Symptoms and signs of this disease become clinically evident up to 72% of cases and vary according to location, growth and tumor diameter. Gastrointestinal stromal tumors can be asymptomatic until the tumor volume increased in size or may manifest nonspecific.

Symptoms are related to tumor mass (abdominal pain, discomfort,

fullness, palpable abdominal mass, occlusive syndrome) or anemia (as a result of the gastrointestinal bleeding caused by ulcers, occult or manifest particularly in large tumors). Over 25% of patients are suffering from acute

bleeding in the intestinal tract or peritoneal cavity from tumor rupture. Submucosa location of the tumor can cause obstruction or perforation, especially in locations like esophagus or small intestine.

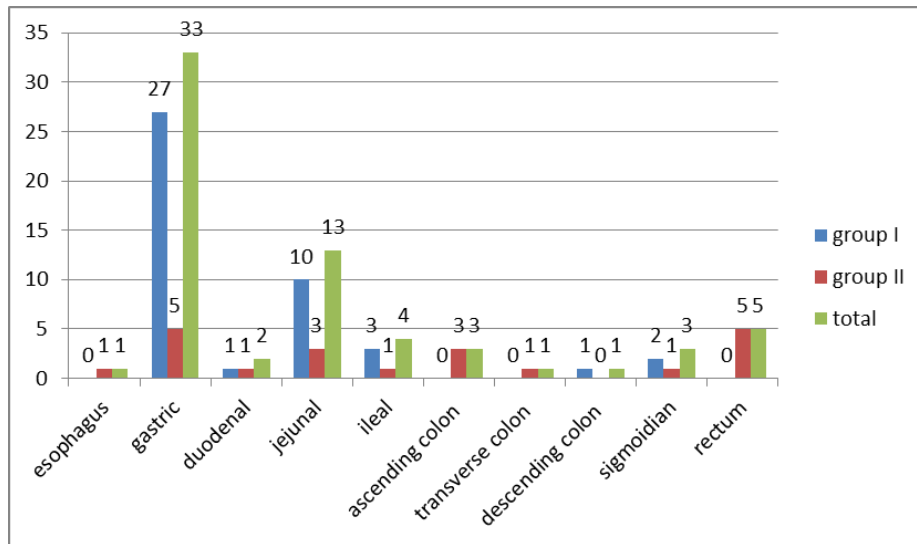


Fig.3 Distribution of digestive localization in patients with GIST in the two groups.

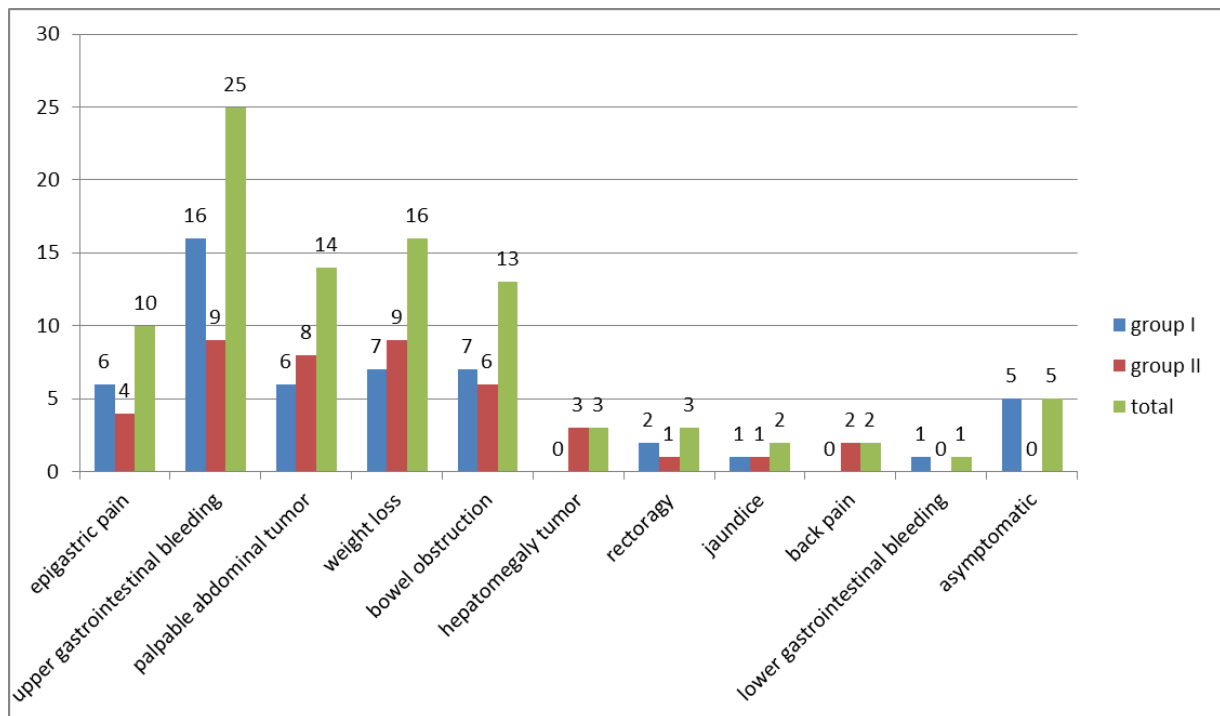


Fig.4 Distribution of signs and symptoms in patients with GIST in the two groups.

Results:

- 10 patients had epigastric pain (15,15%);
- 25 patients had upper gastrointestinal bleeding (37,87%);
- 14 patients had palpable abdominal tumor (7,57%);
- 16 patients experienced weight loss (24,24%);
- 13 patients had bowel obstruction or subocclusive symptoms (19,69%);
- 3 patients had hepatomegaly tumor (4,54%);
- 3 patients had rectoragy (4,54%);
- 2 patients had jaundice (3,03%);
- 2 patients experienced back pain (3,1%);
- 1 patient had lower gastrointestinal bleeding (1,51%);
- 5 patients were asyptomatic (7,57%).

DISCUSSION

GIST usually affects both sexes, with the same rate; however we have reported a slight prevalence in women, with an index F: M of 1.2. We noted an increased incidence of disease in the sixth decade of life. The clinical presentation is usually related to tumor location, biology and spread of disease. De Matteo reported a median duration of symptoms of 6 months before diagnosis. The most common symptoms are: abdominal pain, primarily epigastric pain (usually a late symptom caused by compression of the neighboring organs) and gastrointestinal bleeding caused by submucosal tumors that cause compression ischemia, or infiltration of adjacent mucosa ⁸. The most common symptom in our experience was upper gastrointestinal bleeding (37,87%),

followed by intestinal obstruction or subocclusive events (19,69%) and epigastric pain (15,15%). Palpable abdominal mass is usually reported in gastric GIST tumors and large jejunal ones: we reported nine patients (13,84%) with palpable tumors of these three tumor showed hepatomegaly. 16 patients experienced weight loss (24,24%) and 5 patients were asymptomatic (7,57%). Upper gastrointestinal bleeding and epigastric pain were more frequent in group I and palpable tumor and weight loss in group II, remaining symptoms are represented evenly in both groups. The most common location is the stomach in both groups followed by jejunal location and the rarest is the esophageal and colonic.

CONCLUSIONS

Our study shows that symptoms correlate with tumor location. However, because of the small number of patients investigated, we can not

conclude that the symptoms per se are predictors of patient survival or prognosis.

REFERENCES

1. Miettinen M, Lasota J. Gastrointestinal Stromal Tumors. Review on Morphology, Molecular pathology, Prognosis, and Differential Diagnosis. Arch Pathol Lab Med. 2006;130(10):1466-78.

2. Miettinen M, Lasota J. Gastrointestinal Stromal Tumors - definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001;438:1-12. doi: 10.1007/s004280000338.
3. Nilsson B, Bumming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era - a population-based study in western Sweden. *Cancer.* 2005; 103:821-829. doi: 10.1002/cncr.20862.
4. Burkill GJ, Badran M, Al-Muderis O, Meirion Thomas J, Judson IR, Fisher C, Moskovic EC. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. *Radiology.* 2003; 226:527-532. doi: 10.1148/radiol.2262011880.
5. Duffaud F, Blay JY. Gastrointestinal stromal tumors: biology and treatment. *Oncology.* 2003; 65:187-197. doi: 10.1159/000074470.
6. De Matteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors. Recurrence patterns and prognostic factors for survival. *Ann Surg.* 2000;231:51-58. doi: 10.1097/00000658-200001000-00008.
7. Lewis JJ, Brennan MF. Soft tissue sarcomas. *Curr Probl Surg.* 1996;33:817-872. doi: 10.1016/S0011-3840(96)80013-X.
8. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 1998; 279:577-580. doi: 10.1126/science.279.5350.577.
9. Kitamura Y, Hirota S. Kit as a human oncogenic tyrosine kinase. *Cell Mol Life Sci.* 2004; 61:2924-2931. doi: 10.1007/s00018-004-4273-y.
10. Pawson T. Regulation and targets of receptor tyrosine kinases. *Eur J Cancer.* 2002; 38(Suppl 5):S3-S10. doi: 10.1016/S0959-8049(02)80597-4.
11. Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, Hibbard MK, Chen CJ, Xiao S, Tuveson DA, Demetri GD, Fletcher CD, Fletcher JA. KIT activation is ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res.* 2001; 61:8118-8121.
12. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrintestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. *Mod Pathol.* 2000; 13:577-585. doi: 10.1038/modpathol.3880099.

FUNCTIONING AND QUALITY OF LIFE IN PATIENTS WITH POST-TRAUMATIC SOFT TISSUE INJURIES OF THE KNEE



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ABSTRACT

Aim and objectives: To point out the importance of complex treatment of post-traumatic soft tissue injuries of the knee in order to increase functioning and quality of life.

Material and methods: During one year period we studied 80 patients with different post-traumatic soft tissue injuries of the knee. The patients were divided into four groups and followed a differentiated medical with or without a rehabilitation therapy. Every patient undertook three assessments by using clinical examination and KOOS (Knee Injury and Osteoarthritis Outcome Score) questionnaire.

Results: We noticed the increase in functioning and quality of life in group 2 and 4 patients. **Conclusions:** In order to obtain therapeutic success in treating post-traumatic soft tissue injuries of the knee an early and complex medical and rehabilitation treatment should be initiated after assessing functioning and quality of life of these patients.

Key words: post-traumatic knee, soft tissue injuries, assessment, quality of life.

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INTRODUCTION

The knee joint is one of the biggest and most important joint of the human body. Due to its position, its role in static and dynamic biomechanics of the lower limb, as well as due to its weak soft tissues protection, the knee is highly predisposed and vulnerable to direct and indirect traumatism¹⁻³.

Post-traumatic soft tissue injuries of the knee were considered less important than the knee joint pathology itself. In spite of that fact, the soft tissue lesions are disorders with a high risk of disability, having the potential to affect functioning and quality of life causing thus important socioeconomic implications. That is why an early diagnosis, a correct assessment and an adequate therapeutic approach are extremely important for the progression of this pathology⁴⁻⁶. The soft tissue injuries can be caused by direct or indirect traumatic mechanisms on an unaffected knee or on a pathologic knee joint. The last one can be a rheumatic degenerative joint (knee osteoarthritis) or an inflammatory

rheumatic pathology (rheumatoid arthritis or type III ankylosing spondylitis). In both cases there is the need of a complex clinical, functional and quality of life assessment, as well as the need to start as soon as possible the most appropriate therapy.

The pre-existing disorders of the knee joint, such as the rheumatic ones (degenerative or inflammatory) have a disabling potential, not only by the presence of pain and the decrease in range of motion, but also through the instability of the knee while performing many of the activities of daily living. Knee instability during walking or usual daily activities can increase the risk of developing a traumatic event⁷⁻⁹.

The subjective assessment permits the functional assessment of the knee joint by using evaluation scales as questionnaires that are completed by the patients themselves. These questionnaires evaluate symptomatology, functioning and quality of life in patients suffering from traumatic soft tissue injuries of the knee¹⁰.

AIM AND OBJECTIVES

1. To point the importance of the complex medical and rehabilitation treatment for improving functioning and quality of life in patients diagnosed with post-traumatic soft tissue injuries of the knee;
2. To assess from the clinical and functional point of views the way in which an early specific physical

- therapy program can influence quality of life, functioning and treatment compliance in patients with post-traumatic soft tissue injuries of the knee;
3. To appreciate the impact of the pre-existing rheumatic knee disorders (degenerative or inflammatory) upon the soft tissues of the knee joint.

MATERIAL AND METHODS

During a 1-year period (between January and December 2011) we

studied a number of 80 patients diagnosed with different types of post-

traumatic soft tissue injuries of the knee. The patients were between 17 and 88 years old. 49 of the patients (61.25%) were women and 31 of the patients (38.75%) were men. The soft tissue injuries were singular or multiple and were represented by soft tissues edema, quadriceps tendon lesions (tendinitis, partial or complete tear, avulsion), prepatellar or infrapatellar bursitis, bursitis of the pes anserinus, lesions of the patellar retinaculum (elongation, partial or complete tear), lesions of the medial collateral ligament (elongation, partial or total tear) or lesions of the iliotibial band (friction syndrome with or without bursitis).

The diagnosis of post-traumatic soft tissue injury of the knee joint was made on clinical basis, as well as by using musculoskeletal knee ultrasonography after the recommendation of a rehabilitation or rheumatology specialist. After excluding an osteoarticular disorder caused by the injury itself, in 39 cases (48.75%) it was noticed a pre-existing rheumatic inflammatory or degenerative lesion at the knee level. In 30 cases (76.92%) the patients were suffering from knee osteoarthritis, while in 9 cases (23.08%) patients were suffering from a rheumatic inflammatory disease (7 cases of rheumatoid arthritis and 2 cases of type III ankylosing spondylitis). All of the patients diagnosed with inflammatory rheumatism were in the chronic inactive phase of the disease.

All of the 80 patients had given their informed consent for participation in the study and for using the results of the study, as well as photo and video materials exclusively for scientific purposes. The patients were divided into four homogenous groups and followed a differentiated treatment.

Group 1 was made of 20 patients that had post-traumatic soft tissue injuries on an unaffected knee joint. They followed a complex medical treatment consisting in oral antalgics (Gabapentin 300 mg per day, Ketorolac tromethamine 10 mg per day), oral nonsteroidal anti-inflammatory drugs (Celecoxib 200 mg per day, Diclofenac 150 mg per day or Meloxicam 15 mg per day) and trophic medicines (Regenovex 1 tablet per day, ALAnerv 1 tablet per day, Lenifast ointment twice a day). Group 2 was made of 21 patients that had post-traumatic soft tissue injuries on an unaffected knee joint. They followed the same medical treatment as group 1 associated with an intensive and sustained rehabilitation program. The last one was started in the early stages of the soft tissue injury and was carried out for one year, consisting at the beginning in 30 daily sessions and continued with 10 sessions (three times a week) every three months. The rehabilitation had the following aims: pain release, prevention or correction of the posture disorders, functioning improvements (increase in range of motion, muscle strengthening, improvement in stability, control, coordination and equilibrium in order to prevent the falls, walking improvement and optimal performing of activities of daily living) (see figure 1).

Group 3 was made of 20 patients who suffered post-traumatic soft tissue injuries on a pathologic knee joint. 14 patients had knee osteoarthritis, 5 patients had rheumatoid arthritis and 1 patient had ankylosing spondylitis. Group 3 followed the same medical treatment as group 1. Group 4 was made of 19 patients who suffered post-traumatic soft tissue injuries on a pathologic knee joint. 16 patients had knee osteoarthritis, 2 patients had rheumatoid arthritis and 1 patient had

ankylosing spondylitis. Group 4 followed the same medical treatment as group 2. In the first month after the traumatic event every patient of the four study groups required a functional knee brace in order to increase knee stability and to prevent deformations.

Each of the patients followed three assessments, initially, after 6 months and finally after one year. Every assessment consisted in a complete clinical examination and a functional/activities of daily living evaluation by using the KOOS (Knee Injury and Osteoarthritis Outcome Score) questionnaire. This scale assesses pain,

stiffness, activities of daily living (functioning, self-care and ability to walk), sports and recreational activities and the quality of life¹⁰⁻¹².

The qualifiers given by patients at each of the KOOS questionnaire section were converted into numerical scores that quantify each of the scale parameters and that make the statistical analysis more accurate. Thus, there were used five different ratings for every question starting from 1 (excellent, ideal, no pain or stiffness) to 5 (unsatisfying, extreme pain or stiffness, total disability). Finally, a total KOOS score was calculated.



Fig. 1. Images during the physical therapy program performed in group 2 and group 4 patients (electrotherapy, massage and kinesitherapy) (authors' personal collection, having the patient's informed consent).

RESULTS

1. The assessments showed better improvements in group 2 patients in comparison to group 1, 3 or 4 patients. Also, there were noticed better results in group 3 patients than in group 4 patients. These results were noticed both at intermediate evaluation (after 6 months) and at final evaluation (after 12 months), although initially the clinical examination, KOOS parameters and total KOOS scores were similarly (see tables I and II, and figure 2).
2. The individualised and sustained rehabilitation treatment started as early as possible after the traumatic event showed its efficiency in 40 patients of group 2 and 4. The quality of life of these patients has improved significantly compared to group 1 and 3 patients. The best evolution was seen in those patients who suffered a traumatic event on an pre-existing unaffected knee joint and who followed both a complex medical treatment and physical therapy (see tables I and II, and figure 2).

Table 1 Progression of the average total KOOS scores in the four study groups

Group	Total KOOS 1	Total KOOS 2	Total KOOS 3
1 (n-20)	4.1	3.1	1.9
2 (n-21)	4.3	2.1	1.3
3 (n-20)	4.4	3.7	3.2
4 (n-19)	4.6	2.8	2.2

n: number of patients; KOOS: Knee Injury and Osteoarthritis Outcome Score

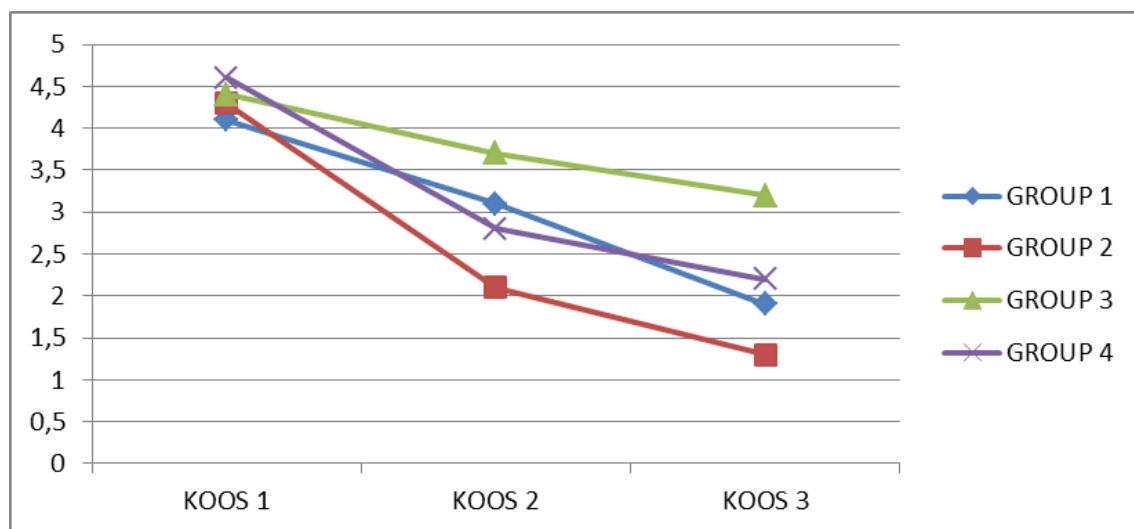


Fig. 2. Graphic representation of the average total KOOS scores in the four study groups.

Table 2 Progression of the average total KOOS scores in the four study groups at the initial, intermediate and final assessments

KOOS parameters	Group 1 (n-20)	Group 2 (n-21)	Group 3 (n-20)	Group 4 (n-19)
KOOS-S 1	4.1	4.6	4.5	4.5
KOOS-S 2	3.0	2.0	4.0	2.5
KOOS-S 3	1.4	1.2	3.2	2.0
KOOS-St 1	4.0	4.0	4.3	4.5
KOOS-St 2	3.2	2.0	4.0	3.0
KOOS-St 3	1.5	1.0	3.5	2.0
KOOS-P 1	4.0	4.2	4.5	4.5
KOOS-P 2	3.2	2.1	4.0	3.0
KOOS-P 3	2.0	1.0	3.2	2.0
KOOS-ADL 1	4.0	4.3	4.3	4.7
KOOS-ADL 2	3.0	1.8	3.5	2.5
KOOS-ADL 3	2.0	1.5	3.0	2.0
KOOS- SP 1	4.5	4.5	4.5	5.0
KOOS-SP 2	3.2	2.2	3.5	3.0
KOOS-SP 3	2,5	2.0	3.3	2.5
KOOS-QOL 1	4.0	4.2	4.3	4.4
KOOS-QOL 2	3.0	2.5	3.2	2.8
KOOS-QOL 3	2.0	1.1	3.0	2.7

DISCUSSION

The post-traumatic soft tissue injuries of the knee are disorders with a high risk of disability in the absence of an adequate therapeutic approach. These lesions can affect in many ways patients' functioning and quality of life, causing thus important social and economic effects.

The key for obtaining a therapeutic success in treating the post-traumatic soft tissue injuries of the knee is represented by the starting of an

early and staged rehabilitation program. This treatment must follow complex assessments of patients' functioning and quality of life. The physical therapy is absolutely necessary as soon as local inflammatory processes have been resolved taking into account that the "time" factor is essential for regaining the everyday activities and normal walking.

REFERENCES

1. American College of Rheumatology (ACR). Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on osteoarthritis Guidelines. *Arthritis Rheum.* 2000; 43: 1905-15.

2. American College of Rheumatology. Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum.* 2002; 46: 328-46.
3. OARSI recommendations for management of hip and knee osteoarthritis. Part I and II based expert consensus guidelines. *Osteoarthr Cartilage.* 2008; 16: 137-62.
4. Pellicci P, McCormack RR. Bursitis and Tendinitis. In: Paget SA. et al, editors. *Hospital for Special Surgery manual of rheumatology and outpatient orthopedic disorders: diagnosis and treatment*, 5th Ed. Lippincott Williams & Wilkins; 2006, p. 203-6.
5. Dieppe PA. Recommended methodology for assessing the progression of osteoarthritis of the hip and knee joints. *Osteoarthr Cartilage.* 1995; 3: 73-7.
6. Webb J, Corry I. Injuries of the sporting knee, epidemiology of knee injuries: diagnosis and triage. *Brit J Sport Med.* 2000; 34: 227-8.
7. Fitzgerald GK, Piva SR, Irgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. *Arthritis Rheum.* 2004; 51 (6): 941-6.
8. Felson DT, Niu J, MC Clennan C. Knee Buckling: Prevalence, Risk Factors, and Associated Limitation in Function. *Ann Intern Med.* 2007; 147: 534-40.
9. Wada M, Imura S, Baba H. Knee laxity in patients with osteoarthritis and rheumatoid arthritis. *Brit J Rheumatol.* 1996; 35: 560-3.
10. Garratt AM, Brealey S, Gillespie WJ. Patient-assessed health instruments for the knee: a structured review. *Rheumatology.* 2004; 43: 1414-23.
11. Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)- validation of a Swedish version. *Scand J Med Sci Spor.* 1998; 8: 439-48.
12. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)- development of a self-administered outcome measure. *J Orthop Sport Phys.* 1998; 28: 88-96.

MUSCLE EVALUATION IN COPD



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ABSTRACT

Muscle dysfunction represents a pathophysiological feature of chronic obstructive pulmonary disease (COPD). Muscle impairment contributes to decreased effort capacity in these patients at least in the same proportion as pulmonary function limitation. Our study was oriented towards the identification of new methods and correlations that would identify peripheral muscular dysfunction. The peripheral muscular dysfunction represents an important factor which leads to increases in the level of dyspnea in patients with COPD and consequently the level of sedentariness. Computed tomography (CT) of the chest showed important data concerning the extension of the pulmonary lesions, but, at the same time the CT taken at the 1/3 level of the upper rib, together with the 6 minutes walking test (6MWT), the spirometry and lean body weight (LBW) can help us find the level of the muscular dysfunction. The rib CT can represent a true marker in the combined evaluation of the respiratory dysfunction and the external muscular dysfunction.

Key words: COPD, muscles evaluation, computed tomography

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INTRODUCTION

COPD is characterised by pregressive, irreversible airway obstruction that is associated with a continuous inflammatory answer. Airways obstruction is due to a combination of inflammatory lesions of the airways and pulmonary parenchyma.¹

The dominant symptomatology in patients with COPD is represented by dyspnea, decreased effort compliance and the alteration in the quality of life. Recently, it was observed that the peripheral muscle disfunction is an important factor for increasing the level of sedentarism in patients with COPD. The importance of skeletal muscle disfunction in reduction of the capacity of performing exercises in patients with COPD was suggested, first, by Killian and co.² They observed that many patients with COPD complained of fatigability at the level of the inferior parts of the body during the maximum effort test, but without reporting dyspnea as limiting factor of performance.

Since the pulmonary function of patients with COPD can be easily improved by medical therapy, respiratory rehabilitation plays an important part in increasing the effort compliance by improving the muscular function and therefor reducing the sensation of dyspnea and improving the quality of life.³

Generally, the physical exercise is associated to more significant improvements in the quality of life and functional capacity. Currently, there are a large number of useful therapies in the rehabilitation process of people with COPD. Among them, the following therapies could be mentioned: oxygen therapy, resistive exercises, the suplimentation with

anabolic steroids, the suplimantation with creatine and the electric neuromuscular stimulation.⁴ Nevertheless, there is evidence that the physical exercise is the most efficient procedure regarding the pulmonary rehabilitation. Associated with any other type of therapy, the physical exercise can significantly increase the physical capacity and the quality of life in patients with COPD.

Dourado and co.⁵ found a significant correlation between the performance of the six-minute-walking test and the „activity“ and „impact“ domains, in the SGRQ questionnaire regarding the quality of life related to respiratory diseases. Compared to other types of treatment, such as bronchodilator agents and oral teofiline, physical exercise is associated with more significant improvements in the quality of life and functional capacity.

Peripheral muscle abnormalities in COPD patients include atrophy, weakness, morphological modification and also altered metabolic capacity. Bernard and col.⁶ found a 30% decrease in the average cross-sectional thigh in patients with COPD in stages III and IV (according to GOLD guidelines), compared to healthy subjects of similar age.

The loss of muscle mass was associated with fatigue, quadriceps muscle strength ratio of hip to mid thigh cross section being reduced. An example of morpho-pathological changes in these patients was the reduction in muscle fiber type 1 with an increase in type 2b fibers, the changes being correlated with the degree of fatigue occurred during the exercises.^{7,8}

AIMS

Considering the fact that one of the major factors of the occurrence of dyspnea in COPD is represented by peripheral muscle dysfunction (quadriceps muscle being of the largest

peripheral muscle group), we want to quantify the degradation of peripheral muscle in legs in terms of patients with COPD.

MATERIAL AND METHODS

In the study entered 9 patients with COPD IV (GOLD stage - according guidelines) and 4 healthy subjects. All subjects were men. Both patients with COPD and healthy subjects had similar demographic data (see Table 1). Patients were diagnosed with COPD after about 3 years. Both patients with COPD and anormal subjects had a moderate ADL and presented no major differences in diet. The study was conducted in accordance with good clinical practice. All the subjects were invited to complete an informed consent.

Tests - A *spirometer* Jaeger (Wuerzburg, Germany) with shutter module for analysis of muscular respiratory pressures was used. The obtained values were expressed as percentages from ideal values. The force of respiratory muscles may be evaluated using the static measurements (MIP, MEP), or it may result from dynamic maneuvers (MVV - voluntary maximal ventilation). MIP represents the highest subatmospheric pressure that can be generated during an inspiration against a blocked airway (Muller maneuver). MEP is the highest pressure that can be achieved during a high expiratory effort against a blocked airway (Valsalva maneuver). The method is usually used by starting the maneuver from the residual volume for MIP determination and from the maximal capacity for MEP

determination. There are just a few contraindications for these exploratory maneuvers: aneurysm, uncontrolled hypertension, urinary infection, recent abdominal or thoracic surgery.⁹

In order to determine *body composition* a 310e Biodynamics impedance meter was used (Body Composition Analyzer, USA), that is able to provide data concerning: lean body weight (LBW; total weight without fat); fat body weight (FBW, mass of body fat); and percentage of body fat (%BF). Although FBW and %BF may vary (heart disease, salt diet, etc), LBW represents a more stable and specific parameter than BMI or anthropometric parameters in assessing muscle mass.⁹

Hand muscle strength was recorded with a *dynamometer* (Dynatest, Jungingen, Germany). The record was achieved after the following procedure: the subject takes the dynamometer in his hand and squeezes it as hard as possible, without further movement. Two recordings are required and only the highest values obtained on the pressure scale of the dynamometer measured in kilograms force were taken into consideration. The procedure was performed with the dominant hand. Obtained values are expressed in kgF.⁹

The *6MWT* was performed according to the American Thoracic Society and the European Respiratory Society (ATS/ERS) standard on a 30-m

long and 1.5-m wide, flat corridor inside the hospital. The patients were asked to walk the maximal distance they could for 6 minutes. They were monitored by a doctor who assisted them, periodically encouraged them, and informed them about the remaining time and the possibility that some adverse clinical signs might appear. O₂ saturation was assessed using a Nonin (Onys, USA) pulse oximeter and was recorded at 3 minutes at the beginning of the testing and at 6 minutes at the end of the testing. Cardiac parameters (blood pressure [BP] and heart rate [HR]) were continuously monitored during the test and the dyspnea score on the Borg scale was also assessed. The test was performed twice at an interval of 60 minutes and we chose the best value.⁹

Computed tomography: we used a Philips CT Aura monospyral model, 3.5 MHU tube, slices 474,881 to 1.5.L3 software. Thigh native examination was performed in patients using an artroscaner type protocol with 2 mm sections, centered on the third medium of the thigh, caudo-cranial scanning 15

cm superior to the knee articulation with technical execution parameters 140 kV, 140 mAs. At photo analysis and processing it was used the same optical resolution and it was taken into account the largest muscle diameter revealed in the third upper right thigh.

Statistical analysis

Statistical analysis and graphic representation of the data were performed using the software programs Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and SPSS 15.0 (Statistical Package for the Social Sciences IBM SPSS Data Collection). Presented data are expressed as mean \pm standard deviation and graphic representation as mean \pm standard error. Statistical comparison of the data from all groups was performed by means of analysis of variance tests (ANOVA). Statistical significance was considered when $p < 0.05$. We used the scale of assessment by Beaglehole (1997), regardless of the purpose of the association: strong ($r > 0.70$), moderate ($r: 0.40-0.70$), weak ($r: 0.20-0.40$), and absent ($r < 0.20$).

RESULTS

Table 1 shows the data of the studied subjects. It may be noted that although BMI was within normal limits

in both groups there was a significant difference in loss of muscle mass (LBW).

Table 1 Characteristic data of COPD patients and control group.

	Normal subjects	COPD patients (GOLD IV)	p
Subject no.	4	9	-
Age (years)	56 \pm 3	58 \pm 5	-
BMI	23 \pm 1.9	21 \pm 1.7	-
LBW (kg)	63.2 \pm 8	54.49 \pm 9.79	$p < 0.05$
FEV1 (%pred)	96.76 \pm 8.66	25.84 \pm 3.24	$p < 0.05$
FEV1/FVC	91.38 \pm 4.8	52.47 \pm 4.43	$p < 0.05$
Dynamometry(kgF)	0.71 \pm 0.6	0.41 \pm 0.07	$p < 0.05$
PImax (kPa)	7.9 \pm 1.4	4.24 \pm 2.17	$p < 0.01$
PEmax (kPa)	10.84 \pm 2.76	8.32 \pm 3.19	$p < 0.01$
6MWT (meters)	564 \pm 67	390 \pm 49	$p < 0.01$
CT (thigh diameter - cm)	58 \pm 1.7	49 \pm 2.7	-

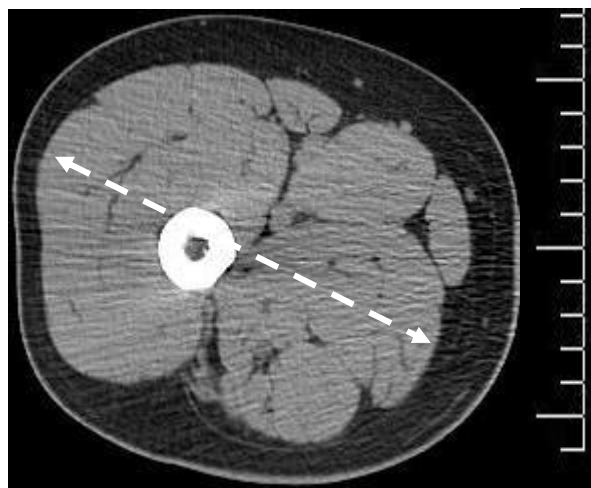


Fig. 1. Normal subject

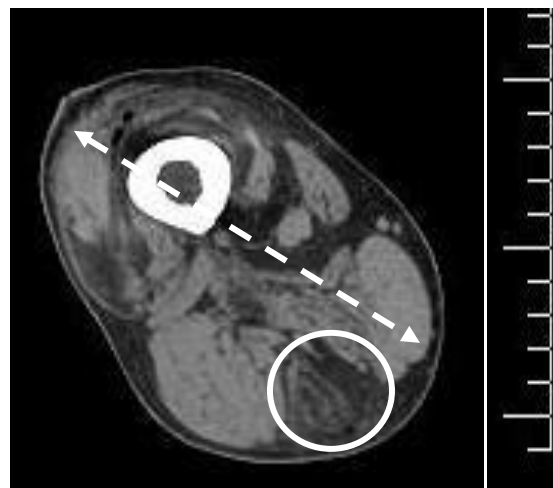


Fig. 2. COPD patient

The registered CT images highlight in healthy subjects in the control group (Fig. 1) a normal aspect of thigh (normal aspect of quadriceps musculature), without any changes in the adjacent soft parts. In patients with COPD (Fig. 2) we found a reducing in the sectional muscle area in 1/3 upper right thigh with a decrease in the thickness of muscular groups that are components of the quadriceps (vastus lateralis, medial and intermediate as well as right hip) and emphasize of the

fatty perimuscular components. Data processing revealed a weak correlation between the decreased thigh diameter (in COPD) and the distance performed in the walking test ($r = 0.31$). A weak correlation was recorded between respiratory muscle pressure drop and the distance carried out in the walking test ($r = 0.28$). We found a reduction in diameter of the thigh in patients with COPD by approximately 15% versus the control group subjects.

DISCUSSION

The decreased effort tolerance is one of the main complaints of patients with COPD, which is not explained only by ventilation limitations or low capacity of alveolar diffusion. Peripheral muscle abnormalities in COPD patients include atrophy, weakness and therefore morphological changes in muscle fibers in numerous studies being observed that patients with moderate / severe COPD have in average, a 30% decrease of the cross-sectional of the thigh compared to healthy subjects.^{10,11}

A decrease in diameter (on CT) of about 15% in patients with COPD have been registered in our study but in the

near future the loss of LBW should more precisely be quantified at this level.

It was proved that not all the muscles are equally affected, so the muscles power in the upper limbs was relatively preserved compared to the lower extremities. Also in our study we had no correlation between decreasing diameter in thigh and the decreased muscle force in the upper limb. In addition there were no statistically significant differences registered concerning the upper limb muscle strength in patients with COPD and the normal subjects.

The results of the studies published in the literature on muscle function are difficult to compare due to the following reasons: low number of compliant patients, relatively high cost of analysis, follow-up of the patient, etc.^{12,13} The effort tolerance in patients with COPD is in continuous decrease, compared to that of healthy subjects, the reasons are complex and involve both changes in the lung kinetics and in the cardiovascular function, impairing of the central reflexes and decreased peripheral skeletal muscle performance.

Due to mechanical limitations, it is not surprising that patients with COPD show a decreased effort capacity compared to healthy ones,^{15,16} the main reason the patients stopped the walking test was increased fatigue in

the legs area and thus the degree of dyspnea compared to healthy subjects that only accused a slight fatigue in the foot area. Data from our study show a poor correlation between respiratory muscle strength and the walked distance.

This finding emphasizes the importance of not relying on body weight or BMI of the patient. The most useful marker that can be used is LBW registered with a relatively simple instrument (bioimpedance).

Although patients with COPD had a relatively normal BMI it has been shown a loss in the muscle mass demonstrated by the LBW reduced and the lower transverse diameter of the thigh and the reduction of the distance covered during the walking test.

Limitation of study

Increased costs of investigations have been a major impediment to enrolling more patients. A larger number of patients would have also led to more accurate in statistic processing. Some correlations (that are in early stages) are possible to be more powerful if more subjects would have been enrolled.

REFERENCES

1. GOLD-Global Strategy for the Diagnosis, Management and Prevention of Chronic obstructive Pulmonary Disease - updated version 2008;
2. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJM. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992; 146:935-940.
3. Baarends EM, Schols AMWJ, Mostert R, et al. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10:2807-2813
4. Schols AMWJ, Mostert R, Soeters PB, et al. Body composition and exercise performance in patients with obstructive pulmonary disease. *Thorax* 1991; 46:695-699
5. Dourado VZ, Antunes LCO, Carvalho LR, Godoy I. Influência de características gerais na qualidade de vida de pacientes com doença pulmonar obstrutiva crônica. *J Bras Pneumol* 2004; 30:207-14.
6. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:896-01.
7. American Thoracic Society - ERS. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:S1-S28.
8. Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2000; 20:353-60.
9. Tudorache V, Oancea C, Fira-Mladinescu O. Clinical relevance of maximal inspiratory pressure: determination in COPD exacerbation *International Journal of Chronic Obstructive Pulmonary Disease* 2010; 5 119-123
10. Maltais F, Simard A, Simard C, Jobin J, Desgagnés P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996; 153:288-93.
11. Debigaré R, Côté CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease - Clinical relevance and mechanisms. *Am J Respir Crit Care Med* 2001;164:1712-7.

12. Nery LE, Wasserman K, Andrews JD, et al. Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J Appl Physiol* 1982; 53:1594–1602
13. Palange P, Galassetti P, Mannix ET, et al. Oxygen effect on O₂ deficit and Vo₂ kinetics during exercise in obstructive pulmonary disease. *J Appl Physiol* 1995; 78:2228-2234
14. Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991; 143:9–18
15. Rochester DF, Braun NMT, Arora NS. Respiratory muscle strength in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1979; 119:151–154
16. Ramirez-Sarmiento A, Orozco-Levi M, Barreiro E. Expiratory muscle endurance in chronic obstructive pulmonary disease. *Thorax* 2002; 57:132–136

PRE-OPERATIVE TRANSTHORACIC THREE-DIMENSIONAL ECHOCARDIOGRAPHY IN THE ASSESSMENT OF MITRAL STENOSIS: CLINICAL EXPERIENCE



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ABSTRACT

We investigated three-dimensional (3D) transthoracic echocardiography (TTE) in the assessment of mitral stenosis. Bidimensional (2D) TTE and 3DTTE was performed in 42 patients with mitral stenosis concomitant with cardiac catheterisation, prior to valve surgery. Using a surgical scoring protocol for recognition of the valvular segments, 2D and 3D methods were compared. Adequate echocardiographic visualization of the mitral segments was more frequently obtained by 3DTTE than by 2DTTE. Total 3DTTE score were significantly better than 2DTTE score. Using surgical classification as gold standard, the sensibility and specificity were 93% and 87 % for 3DTTE, and 86% and 79% for 2DTTE. The opening area determined by 3DTTE showed better linear association with the area determined intraoperative or invasively by Gorlin formula compared with 2DTTE. In conclusions, 3DTTE was superior to 2DTTE for the analysis of mitral stenosis and could be used for the accurate identification of the severity.

Key words: mitral valve stenosis, mitral valve area, three-dimensional transthoracic echocardiography, bidimensional transthoracic echocardiography, Gorlin formula.

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INTRODUCTION

Rheumatic mitral valve stenosis still remains an important public health concern, and the assessment of the severity of mitral valve stenosis requires accurate measurements of the mitral valve orifice area. Direct measurement of the mitral valve area (MVA) can be performed by planimetry using two-dimensional (2D) echocardiography¹. However, planimetry by 2-D echo requires significant experience and operator skill to define the correct image plane that displays the true mitral valve orifice¹⁻³. Some studies suggest that adding three-dimensional (3D) imaging

to standard 2D echocardiography could be helpful in the quantification of valvular diseases^{4,5}.

The aim of this prospective study was to evaluate three aspects of 3D transthoracic echocardiography (3DTTE): (i) the accuracy of the method (vs. surgical inspection) in patients undergoing surgery for mitral stenosis; (ii) to compare the accuracy of 3DTTE with 2DTTE; (iii) to compare the valvular area measured 3DTTE and 2DTTE with the area determined by Gorlin method and intraoperative area in patients with mitral stenosis.

MATERIAL AND METHODS

Forty-two consecutive patients with mitral stenosis referred to surgery were evaluated by 2DTTE and 3DTTE. A complete TTE study was obtained prior to or following the invasive study, in a time gap <48 h; surgery was done in the next 7 days. The TTE study was performed in all patients using Vivid 9 GE echocardiographic system. Exclusion criteria were represented by inadequate echocardiographic images, movement artifacts, difficulty with ECG registering, and equipment failure. Two-dimensional TTE views of the mitral valve was obtained from the parasternal window; the planimetry was also performed. Three cardiac cycles for patients in sinus rhythm and five for patients in atrial fibrillation were recorded, and their results averaged for every patient. The 3D examination was done after a routine diagnostic. Three-dimensional acquisition and reconstruction times were measured in each patient. A single echocardiographer acquired and measured the 2D and 3D echo studies.

Three-dimensional and 2D data were compared with invasive and, then with surgical data. The Carpentier nomenclature was applied to the mitral leaflets². The fusion of the commissures and vegetations were also noted. Gross etiology was classified.

Invasive hemodynamic evaluation was performed within 48 h of the echocardiographic recordings. Using the catheter-based data and the Gorlin's equation, the mitral valve area was obtained⁶.

The surgeon described the anatomy of the mitral valve and measured the opening area. He was aware of the 2D findings, but not of the 3D analysis. The Carpentier classification was used. The 2D and 3D images (figure 1a and 1b) were analysed off-line separately and blinded to the surgical findings. Segments considered inadequate were not included for the analysis. Valvular morphology data described by the operating surgeon was used as gold standard. He described the anatomy of

the valve using the same proforma like for echocardiographic analysis.

Segments were counted as accurately imaged if they matched surgical findings precisely in terms of pathology description and correct location (score = 1). The segments that were not adequately recognised (score = 0) were coded as inaccurate. The local ethics committee approved the study. Informed consent was obtained from all patients.

Statistical analysis

The sensitivity and specificity of the echocardiographic evaluation were calculated with surgical data as a reference. Variables are expressed as

proportions, mean, and standard deviation. The chi-squared test and the student t-test with subsequent two-tailed t-tests were used to compare differences between groups. Correlation between planimetry measured by 2D and 3DTTE and invasive or intraoperative area were evaluated by Pearson's correlation coefficient.

Differences were considered statistically significant at the two-sided $P < 0.05$ level.

All computations were carried out with the software SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

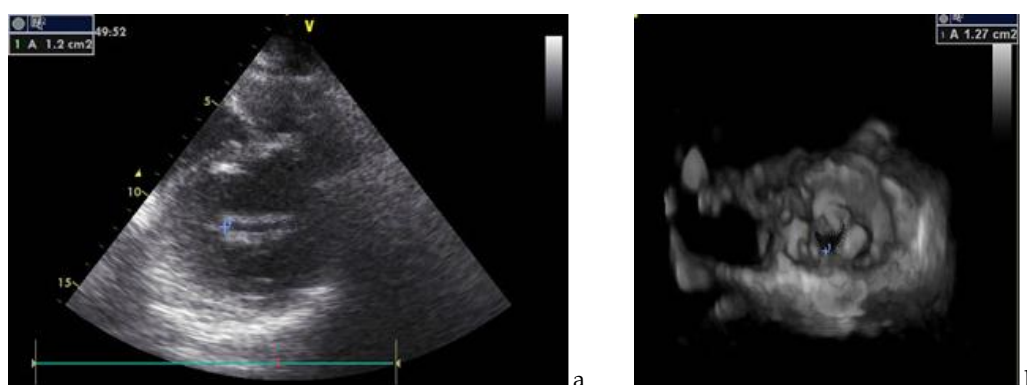


Fig. 1. Mitral opening area determined by bidimensional and three-dimensional transthoracic echocardiographic study in a patient with mitral stenosis.

RESULTS

From 52 patients with mitral stenosis screened between January 2010 and June 2011, 42 (29 women) were enrolled in the study. Mean age was 44 ± 16 years. Characteristics of the patients study group are presented in Table 1.

For each patient, 1-3 acquisitions were realized and the best one chosen for imaging and quantification. Acquisition time ranged between 32 s and 1 min 52 s, depending on the basal heart rate and rhythm disturbances.

Mean processing time was 2 min 18 s. Adequate echocardiographic visualization of the valve segments was more frequently obtained by 3DTTE than by 2DTTE imaging (316/336 by 3DTTE and 284/336 by 2DTTE, $p < 0.05$). The valve leaflets segments were more clearly identified by 3DTTE than by 2DTTE (237/252 by 3DTTE and 210/252 by 2DTTE, $p < 0.05$). For adjacent commissures the results were similar by the two methods (79/84 by 3DTTE and 74/84 by 2DTTE, $p > 0.05$).

Table 1 Progression of the average total KOOS scores in the four study groups

Characteristics	Date
Number of patients	42
Age, years	44 ± 16
Woman/Male	29 (69%) / 13 (31%)
Body mass index, kg/m ²	25.4 ± 4.2
Heart rate, beats/min	79 ± 12
Atrial Fibrillation	14 (33%)
Mean blood pressure, mmHg	95.2 ± 14.5
New York Heart Association class	2.8 ± 0.8
LV ejection fraction, %	59 ± 11
PSAP, mmHg	48.2 ± 14.8

LV = left ventricle; PSAP = pulmonary systolic artery pressure.

Total 3DTTE score for the mitral valve was significantly better than 2DTTE score (mean score 7.41 ± 0.58 by 3DTTE vs 6.18 ± 0.75 by 2DTTE, $p < 0.05$). This superiority of 3DTTE was irrespective of rhythm ($p < 0.05$ for both, sinus rhythm and atrial fibrillation). Using surgical classification as gold standard, the sensibility and specificity were 93% and 87% for 3DTTE and 86% and 79% for 2DTTE, respectively. The main cause of mitral stenosis was represented by rheumatic fever in all patients (100%).

The valvular opening area determined by 3DTTE (figure 2a) showed better linear association with

the area determined invasively by Gorlin formula ($r = 0.97$, $p < 0.001$) compared with 2DTTE ($r = 0.88$, $p < 0.001$) (figure 2b), respectively.

If we consider the area determined by the surgeon, the correlation with the valvular opening area determined by 3DTTE (figure 3a) was better ($r = 0.95$, $p < 0.001$) compared with the area determined by 2DTTE ($r = 0.88$, $p < 0.001$) (figure 3b), respectively. Areas determined by 3D echo were on average slightly smaller (1.16 ± 0.23) than those by 2DTTE (1.24 ± 0.19 , $p < 0.05$) if we consider as standard the area determined by Gorlin formula 1.15 ± 0.22 .

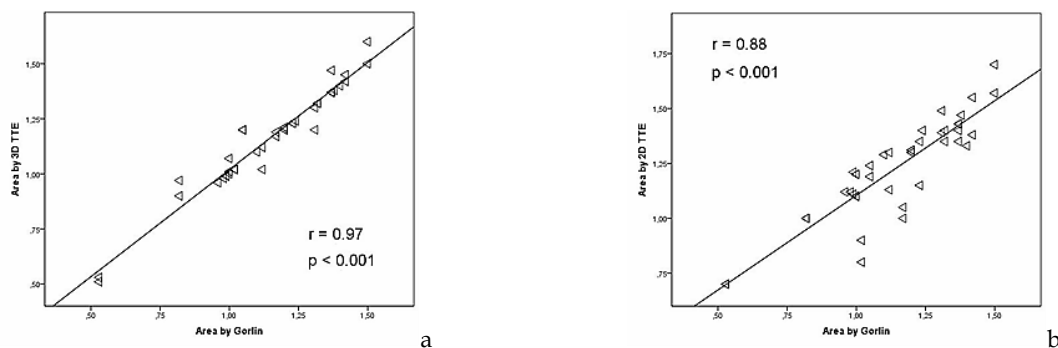


Fig 2. Scatter plots with linear regression fit for valvular opening area determined by 3D transthoracic echocardiography and area determined invasively by Gorlin formula (a) and for the area determined by 2D transthoracic echocardiography planimetry and that determined by Gorlin formula (b), in patients with valvular stenosis. The unit for all valvular areas is cm².

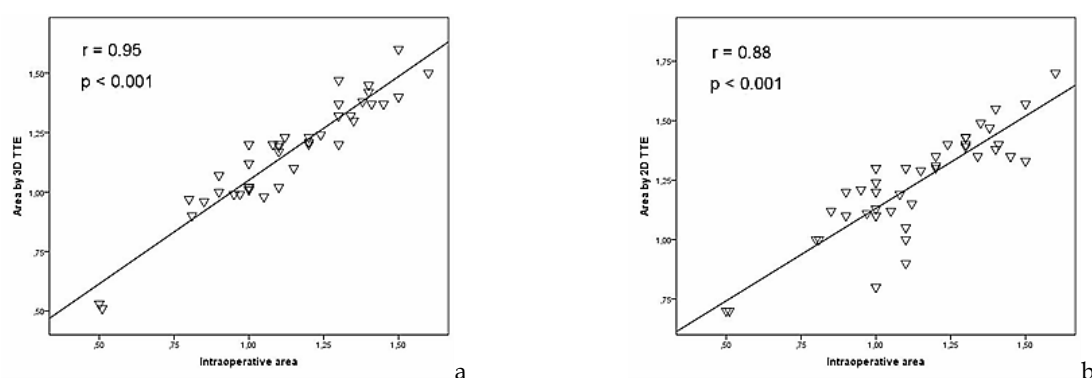


Fig 3. Scatter plots with linear regression fit for valvular opening area determined by 3D transthoracic echocardiography and area determined intraoperatively (a) and for the area determined by 2D transthoracic echocardiography planimetry and that determined intraoperatively (b), in patients with valvular stenosis. The unit for all valvular areas is cm^2 .

DISCUSSION

The results of this study fully validate 3DTTE as an accurate tool for mitral stenosis evaluation and clinical decision-making. We studied an unselected cohort of patients with mitral stenosis undergoing surgery, irrespective of heart rhythm, with a representative array of etiologies typically encountered at a surgical centre and we observed a valuable incremental role of 3DTTE over 2DTTE in the complete and accurate evaluation of mitral valve morphology prior to valve surgery. This study demonstrates also that 3DTTE is an accurate tool for area calculation and clinical decision-making in patients with mitral stenosis.

Conventional 2DTTE can diagnose valvular diseases, but can not show *en face* views of the leaflets, which can lead to difficulty defining the exact location of defect, and may result in difficulties communicating with surgeons. The detection of valvular lesion location in 2D examination may be influenced by the change of blood pressure². As shown in our study, 2DTTE is limited in its ability to completely visualize the mitral valve, in particular the leaflets.

New generation 3D technology reduces the acquisition and reconstruction time to few minutes and facilitates the visualization of the aortic and mitral valves⁵. In the majority of cases in our study, imaging quality was good or optimal and permitted 3D reconstruction. Using surgical classification as gold standard, we found a sensibility of 93% and a specificity of 87% for the identification of valvular pathology using 3DTTE, a percentage comparable to previous studies^{2,4}. Interestingly, in our patients with adequate echographic window, 3DTTE was not different to 2DTTE in the identification of commissural pathologies, but was significantly superior in the evaluation of leaflet segments. There are several studies that showed similar results^{1,2}; in contrast, some authors reported that 3D method was excellent in identifying the commissures morphology of mitral valve, in particular if the transesophageal echocardiography was used^{4,5}.

Our study has also demonstrated additional value for determination of maximal opening area of mitral valve.

Planimetry of the valve orifice is the only direct measurement in 2D echocardiography. The success rate of mitral valve planimetry in 2D echocardiography has been reported to be as low as 75% depending on the study population². A major limitation of this method is the difficulty of defining the correct image plane that displays the true valve orifice. Thus, small changes of the transducer position on the chest wall and of its tilting and rotation result in significant changes of calculated orifice area. This is also the main reason that considerable experience and operator skill are necessary for the correct application of this method and why significant interobserver variability has been noted for these measurements². One of the most important advances in echocardiography during the last decade has been the development of 3D techniques.

This method allows instant acquisition of a complete 3D data set without complex post-processing. 3DTTE reduces the potential sources of error (direct anatomic area calculation)

and relies only on the quality of the apical acoustic window.

Pearson's correlation coefficient demonstrated in our study a good agreement between area determined by 3DTTE and the area of stenosis determined invasive by Gorlin formula or intraoperative by the surgeon, superior to the 2DTTE method. Also, areas determined by 3D echo were on average slightly smaller than those by 2DTTE; possibly, this fact simply reflects the greater potential of 3D echo to detect the true anatomic orifice area and the tendency of 2D echo to overestimate this area because of difficulties in defining the optimal imaging plane. In contrast to 2D echo, in 3D method the interobserver variability for measurements appears to be significantly less than with 2D echo^{1,2}. Therefore, this study confirms recent data showing that 3DTTE may be integrated in the standard examination facilitating the exact spatial localization of pathological structures and avoiding the need for mental reconstruction of 3D valve anatomy by the examiner.

LIMITATIONS

Rheumatic mitral valve stenosis still remains an important public health concern, and the assessment of the severity of mitral valve stenosis requires accurate measurements of the mitral valve orifice area. Direct measurement of the mitral valve area (MVA) can be performed by planimetry using two-dimensional (2D) echocardiography¹. However, planimetry by 2-D echo requires significant experience and operator skill to define the correct image plane that displays the true mitral valve orifice¹⁻³. Some studies suggest that adding three-dimensional (3D) imaging

to standard 2D echocardiography could be helpful in the quantification of valvular diseases^{4,5}.

The aim of this prospective study was to evaluate three aspects of 3D transthoracic echocardiography (3DTTE): (i) the accuracy of the method (vs. surgical inspection) in patients undergoing surgery for mitral stenosis; (ii) to compare the accuracy of 3DTTE with 2DTTE; (iii) to compare the valvular area measured 3DTTE and 2DTTE with the area determined by Gorlin method and intraoperative area in patients with mitral stenosis.

CONCLUSIONS

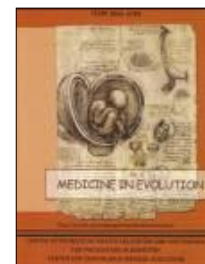
Three-dimensional TTE provides accurate analysis of patients with mitral stenosis, and could be used not only for complete recognition of the valvular morphology but also for the accurate identification of the severity.

3DTTE appears to be superior to conventional echocardiographic techniques, particularly to planimetry using 2DTTE. Measurements are simple and can be performed within a few minutes.

REFERENCES

1. Chu JW, Levine RA, Chua S, Poh KK, Morris E, Hua L, et al. Assessing mitral valve area and orifice geometry in calcific mitral stenosis: a new solution by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr* 2008; 21(9):1006-9.
2. Binder TM, Rosenhek R, Porenta G, Maurer G, Baumgartner H. Improved assessment of mitral valve stenosis by volumetric real-time three-dimensional echocardiography. *J Am Coll Cardiol* 2000;36(4):1355-61.
3. Uno K, Takenaka K, Ebihara A, Nawata K, Hayashi N, Nagasaki M, et al. Value of live 3D transoesophageal echocardiography in the diagnosis of mitral valve lesions. *Eur J Echocardiogr* 2009; 10:350-1.
4. Wei J, Hsiung MC, Tsai SK, Ou CH, Chang CY, Chang YC, et al. The routine use of live three-dimensional transesophageal echocardiography in mitral valve surgery: clinical experience. *Eur J Echocardiogr* 2010; 11:14-8.
5. Solis J, Sitges M, Levine RA, Hung J. Three-dimensional echocardiography. New possibilities in mitral valve assessment. *Rev Esp Cardiol* 2009; 62(2):188-98.
6. Carabello BA. Advances in the hemodynamic assessment of stenotic cardiac valves. *J Am Coll Cardiol* 1987; 10:912-9.

THE COMPLEX APPROACH OF PATIENTS WITH NEUROLOGIC DISORDERS AND OSTEOARTHRITIS



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ABSTRACT

Aim and objectives: To point the importance of a long-term rehabilitation therapy in patients with residual hemiparesis and osteoarthritis.

Material and methods: 59 patients suffering from residual hemiparesis and ipsilateral or/and contralateral osteoarthritis (knee, hip, ankle, hands osteoarthritis, spinal stenosis or spondylosis) followed a physical therapy program made of two annual cures at Săcelu Rehabilitation Centre in Gorj County. The patients were assessed by Visual Analogue Scale and Hemiplegic Evaluation Score at the beginning of the study, after 6 months and after 1 year.

Results: We noticed statistically significant decreases in pain levels and statistically significant improvements in overall functioning both at the intermediate and final assessments in all of the study patients.

Conclusions: Because of its various methods (electrotherapy, massage, kinesitherapy, aquatic therapy and mud-bath therapy), the rehabilitation provides an important therapeutic tool in the management of neurologic and osteoarthritic patients.

Key words: hemiplegia, osteoarthritis, rehabilitation, assessment

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INTRODUCTION

Cerebrovascular accident (stroke) often results in impaired motor control and persistent weakness that may lead to chronic disability, including deficits in gait and balance function¹. Stroke is the leading cause of chronic disability in the United States, with increased prevalence expected from the aging baby boomer generation². Persistent lower limb weakness from hemiparesis often results in functional motor deficits for many with stroke^{3, 4}. Hemiparetic gait, compounded with balance deficits, limits mobility and increases fall risk, with nearly 70% suffering fall-related injuries in the first year post stroke. These deficits also lead to significant limitations in performing basic activities of daily living, which negatively affect these individuals' ability to participate in community life⁵⁻⁷.

Osteoarthritis is the major cause of dependence and home isolation for the

old population. The impact of this disease can be devastating, especially because of the fact that elder age is often a period of great losses such as that of general health status, friends, family members and financial independence^{8, 9}. Quality of life in patients with osteoarthritis has become a very important matter. Osteoarthritis is by far the most frequent joint disease and the second cause of disability for persons 50 years older. This fact implies a huge economic impact and makes of osteoarthritis a real public health problem. Because of the important evolutions in technology and medicine in the last century, the individuals live longer. It is no longer proper to quantify medical success in the number of years somebody lives after an injury. Functional ability and independence have become important assessment criteria in rehabilitation medicine¹⁰.

AIM AND OBJECTIVES

1. To point the importance of the complex approach in patients suffering from neurologic disorders (residual hemiparesis after stroke) and osteoarthritis with different sites (knee, hip, ankle, hand or spinal column);
2. To assess from the functional point of view the way in which a long-term physical therapy program (performed in a

- rehabilitation centre) can influence quality of life and functioning in patients with residual hemiparesis and osteoarthritis;
3. To appreciate the impact of the pre-existing ipsilateral or contralateral osteoarthritis disease upon the evolution of patients with residual hemiparesis.

MATERIAL AND METHODS

During an 18-month period (between June 2009 and December 2010) we studied a number of 59 patients suffering from residual hemiparesis and ipsilateral or/and

contralateral osteoarthritis (knee osteoarthritis, hip osteoarthritis, ankle osteoarthritis, hands osteoarthritis, degenerative spinal stenosis or spondylosis). The patients were

between 40 and 60 years old. 31 of the patients (52.5%) were men and 28 of the patients (47.5%) were women. The patients' distribution according to their age group, gender and environment is presented in detail in figure 1. All of

the 59 patients had given their informed consent for participation in the study and for using the results of the study, as well as photo and video materials exclusively for scientific purposes.

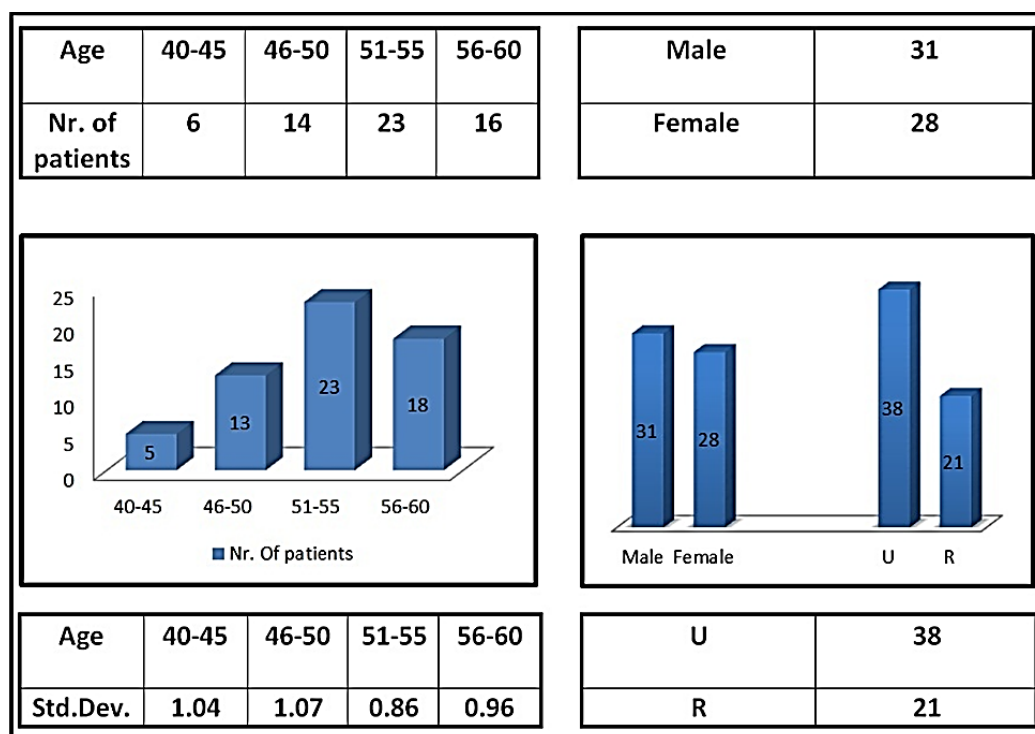


Fig.1 Study patients' distribution according to their age groups, gender and environment.

The 59 patients followed a sustained physical therapy program made of two annual cures (18 daily sessions every 6 months) at Săcelu Rehabilitation Centre in Gorj County. The rehabilitation had the following aims: pain release, prevention or correction of the posture disorders, functioning improvements (increase in range of motion, muscle strengthening, improvement in stability, control, coordination and equilibrium in order to prevent the falls, gait training and optimal performing of activities of daily living) (see figures 2-7).

Each of the patients followed three assessments (initially, after 6 months and finally after one year). Every assessment consisted in completing the

Visual Analogue Scale (VAS) for pain and a functional assessment questionnaire for hemiplegic patients (HES: Hemiplegic Evaluation Score). The last one evaluates functioning in all body parts (upper limbs, lower limbs and spinal column) when performing the activities of daily living. The hemiplegic score ranges from 0 (total disability) to 5 (normal functioning). VAS is an instrument used to measure the amount of pain a patient feels. It is a 100 mm-long horizontal line, which may contain word descriptors at each end. The patient represents their perception of the amount of pain he feels by marking a horizontal line between the two points (0-no pain; 10-very severe pain, worst pain ever)¹¹.

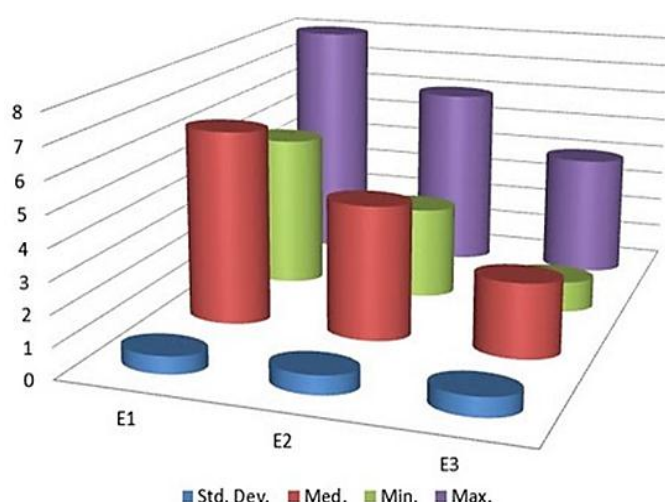


Fig. 2-7. Images during the rehabilitation program of a patient with hemiparesis and knee osteoarthritis (electrotherapy, massage, kinesitherapy and gait training) (authors' personal collection, having the patient's informed consent).

RESULTS

Regarding the progression of VAS values in the study patients we noticed statistically significant decreases in pain levels both at the intermediate and final assessments ($p < 0.05$) (see figure 8). We also noticed statistically

significant improvements in overall functioning (represented by HES values) both at the intermediate and final assessments ($p < 0.05$) (see figure 9).



VAS	E1	E2	E3
Min	5	3	1
Max	8	6	4
Med	6.31	4.35	2.41
Std. Dev	0.57	0.61	0.62

Fig.8 The progression of VAS in patients with hemiparesis and osteoarthritis.

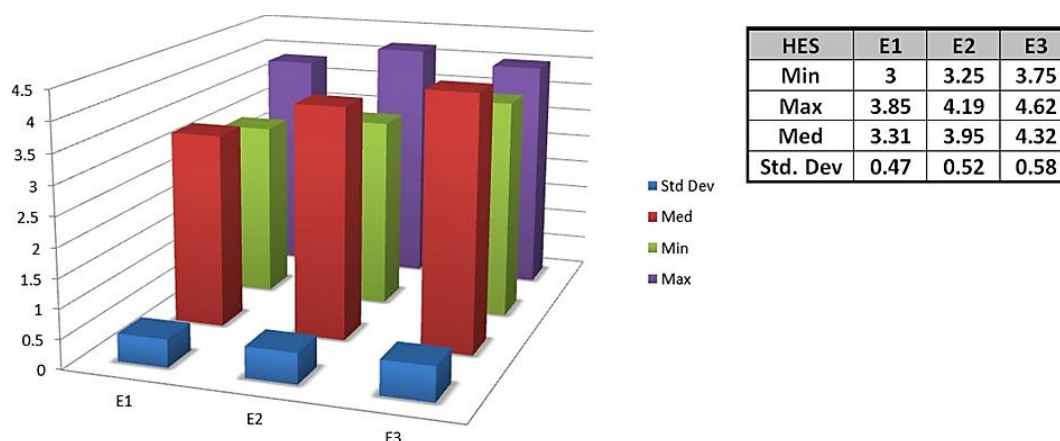


Fig.9 The progression of HES in patients with hemiparesis and osteoarthritis

DISCUSSION AND CONCLUSIONS

The treatment of patients suffering from associated hemiparesis and osteoarthritis is a real challenge of nowadays rehabilitation medicine. Disabilities of a chronic neurologic patient such as the patients with a residual hemiparesis are increased by the functional disorders caused by the multiple sites of the osteoarthritic disease. Pain and reduced everyday functioning are the most common complaints in these patients. Because

of its various methods (electrotherapy, massage, kinesitherapy, aquatic therapy and mud-bath therapy), the rehabilitation provides an important therapeutic tool in the management of neurologic and rheumatic patients. A long-term physical therapy followed consequently every 6 months in a specialised rehabilitation centre proved its benefits regarding pain relief and general health status in patients with residual hemiparesis and osteoarthritis.

REFERENCES

- Roy A, Forrester LW, Macko RF. Short-term ankle motor performance with ankle robotics training in chronic hemiparetic stroke. *J Rehabil Res Dev* 2011; 48(4): 417-30.
- Heart disease and stroke statistics [Internet]. Dallas (TX): American Heart Association; 2009. Available from: <http://www.americanheart.org/statistics> [2009].
- Katz RT, Rymer WZ. Spastic hypertonia: Mechanisms and measurement. *Arch Phys Med Rehabil* 1989; 70(2): 144-55.
- Young RR. Spasticity: A review. *Neurology* 1994; 44(11 Suppl 9): S12-20.
- Macko RF, Smith GV, Dobrovolsky CL, Sorkin JD, Goldberg AP, Silver KH. Treadmill training improves fitness reserve in chronic stroke patients. *Arch Phys Med Rehabil* 2001; 82(7): 879-84.
- Silver KH, Macko RF, Forrester LW, Goldberg AP, Smith GV. Effects of aerobic treadmill training on gait velocity, cadence, and gait symmetry in chronic hemiparetic stroke: A preliminary report. *Neurorehabil Neural Rep* 2000; 14(1): 65-71.
- Forster A, Young J. Incidence and consequences of falls due to stroke: A systematic inquiry. *BMJ* 1995; 311(6997): 83-6.
- World Health Organization. WHO technical Report Series. The burden of musculoskeletal conditions at the start of the new millennium. Geneva: WHO 2003.
- Lozada CJ. Management of osteoarthritis. In: Firestein GS, editor. *Kelley's textbook of rheumatology*, eighth edition. Philadelphia: Saunders Elsevier; 2009. p. 1563-77.
- Fayers PM, Machin D. Quality of life: The assessment, analysis and interpretation of patient-reported outcomes, second edition. West Sussex: Wiley; 2007. p.3-30.
- Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990; 13: 227-36.

THE MANAGEMENT OF INCISIONAL HERNIA IN AN EASTERN EUROPEAN EMERGENCY CENTER



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ABSTRACT

Incisional hernia is a constant presence in an emergency department of surgery, due to the important failure rate for closure of abdominal surgical wounds. There are several risk factors well recognize for this failure, of a great importance being wound infection, suture tension, associated pathology and surgeon experience. On the other hand, long terms outcomes are related with surgical technique, postoperative complications rate and the use of prosthetic mesh.

Key words: incisional hernia, abdominal closure, outcomes.

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INTRODUCTION

Open surgery it was for a long time period the "golden standard" for this pathology, using primary closure of the abdominal wall or prosthetic mesh. In this moment, in open surgery primary suture is reserved for small abdominal defects, less 5 cm², but even in these cases it is well demonstrated the suture tension and there are necessary additional procedures (relaxing incisions) ¹. Prosthetic mesh procedures are for this moment the most efficient method ², with superior outcomes, of a great importance being to avoid the suture tension and a correct dimension of the prosthetic material.

In this way, Finan et al ³, presents the 3 years outcomes with no

recurrence for 73,8% patients with mesh comparing with 56,3% patients with primary abdominal closure. Similar results are published by Burger and Luijndik ⁴, with the superiority of longterms outcomes in mesh procedures.

There are several complications of both methods, but intestinal obstruction due to the intimate adhesion of the bowels to the sintethic texture is the most severe, and in this way several authors describe a second Vicryl mesh between bowels and the polypropylene mesh or the prefascial mesh repair, with well longterms outcomes. (Mates, leber).

MATERIAL AND METHODS

425 incisional hernia cases were included in this study, all cases admitted and treated in Emergency Surgical Department of City Hospital Timisoara during 12 years period (1998-2010), with an average of 35 cases each year.

Sex repartition it was preponderant for feminine gender:

- Men: 97 cases (23%)
- Women: 328 cases (77%)

Age repartition reveal a preponderance for the IV, V, VI and VII decades of both genders (89, 69%) :

- Decade IV : 76 cases
- Decade V : 118 cases
- Decade VI : 114 cases
- Decade VII : 68 cases

From the total of 425 incisional hernias, 161 cases were admitted in emergency, the rest of cases were admitted after a medical examination.

In our study, according to size, there were:

- Small incisional hernias: 179 cases (less 5 cm)
- Medium or large incisional hernias : 227 cases (5-20 cm)
- Giant incisional hernias :19 cases (more 20 cm)

89 cases (21%) were represented by incisional recurrence hernias.

According to the surgical method, in our study we found:

- 106 procedures using prosthetic materials
- 319 procedures using the suture of anatomical tissues of the abdominal wall

Postoperative complications were represented by:

- Wound infection: 31 cases
- Wound haematoma: 10 cases
- Eviscerations: 4 cases

There were 77 cases with recurrence in our study (18, 2%):

- 49 cases: first recurrence;
- 17 cases: second recurrence;
- 9 cases: third recurrence;

- 2 cases: forth recurrence.

Hospitalization days was in average: 10 days



Fig.1 Large incisional hernia.

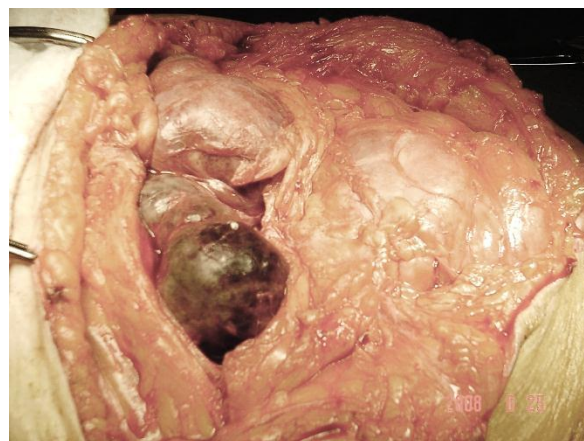


Fig.2 Bowell ischemic necrosis.

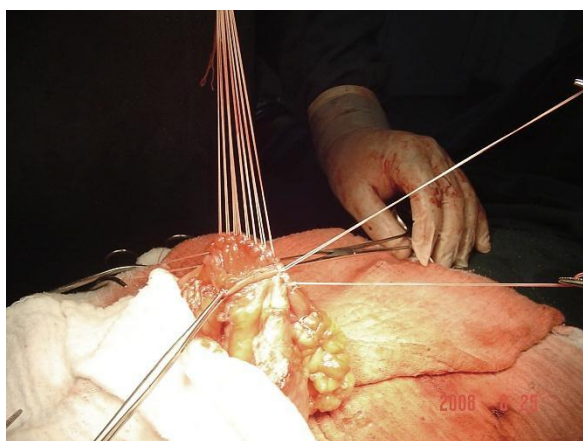


Fig.3 Bowell resection.

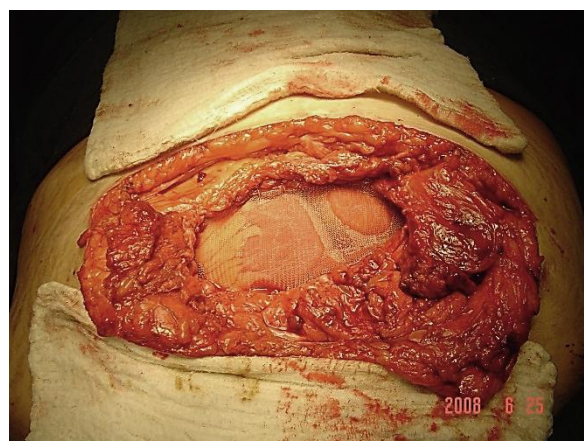


Fig.4 Prosthetic mesh, sandwich procedure.

DISCUSSION

1. 425 cases of incisional hernias were treated in our department, 101 cases in emergency,
2. Age it was not a significant factor, with an important distribution after the forth decade.
3. Small and medium incisional hernias were preponderant in our study, and anatomical suture was the main surgical procedure.
4. Prosthetic mesh procedures were performed in large incisional hernias and it was a preference for "sandwich" method.
5. There was no laparoscopic procedure in our serie.
6. Reccurence was a significant part of our series, and is necessary to evaluate each case for the optimal therapeutic procedure.

CONCLUSIONS

Incisional hernia is an important field in general surgery, with no ideal

outcomes, but with a significant preference for synthetic materials.

REFERENCES

1. Vrijland W, Jeekel J. Prosthetic mesh repair should be used for any defect in abdominal wall. *Curr Med Opin* 2003, 19
2. Flum DR, Horvath K, Koepsell T. Have outcomes of incisional hernia repair improved time ? A population based analysis. *Ann Surg* 2003, 237:129-135.
3. Finan KR, Kilgore ML, Hawan MT. Open suture versus mesh repair of primary incisional hernias. *Hernia* 2009, 13: 173-182.
4. Burger J, Luijendijk R, Hop W et al. Long-term follow-up of randomized controlled trial of suture versus mesh repair of incisional hernia. *Ann Surg* 2004, 240: 558-585.

FREQUENCY OF PULMONARY HYPERTENSION IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION



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ABSTRACT

The objective of the study was to determine the frequency of pulmonary hypertension in a group of patients with heart failure with preserved ejection fraction.

Material and methods: We examined 62 patients (39 women and 23 men) referred for echocardiographic evaluation, diagnosed with isolated HFpEF. In all these patients we performed physical examination, ECG and 2-D transthoracic echocardiography, with measurements of left atrium and left ventricle dimensions, indices of diastolic function, pulmonary artery systolic pressure.

Results: From the 62 patients, 15 patients (24,2%) had also pulmonary hypertension. The mean PASP in the whole group was 41.3 mm Hg. The prevalence of PH was 30.76% (12 pts) in women and 7.69% (3 pts) in men.

Conclusions: Pulmonary hypertension has a quite high frequency in patients with HFpEF. Female gender can be a predictor of the presence of pulmonary artery hypertension. The frequency of systemic hypertension was higher in pts with PH compared to those without PH.

Key words: heart failure, pulmonary hypertension.

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INTRODUCTION

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing, around 50% of all patients with heart failure having a normal ejection fraction ¹. Patients with heart failure with preserved ejection fraction have an increased mortality and morbidity similar to patients with systolic heart failure and reduced ejection fraction. For unknown reasons, a group of patients with HFpEF will develop pulmonary hypertension (PH) ^{2, 3, 4}. The prognosis of patients with

heart failure and preserved ejection fraction worsens with pulmonary hypertension and development of right ventricular failure. Left-sided heart failure is known to cause pulmonary hypertension, but the development and severity of PH in heart failure is variable, and contributing factors are not fully understood ⁵. Recent studies have demonstrated that PH can occur in heart failure with preserved ejection fraction.

THE OBJECTIVE OF THE STUDY

Was to determine the frequency of pulmonary hypertension in a group of

patients with heart failure with preserved ejection fraction (HFpEF).

MATERIAL AND METHODS

We examined 62 patients (39 women and 23 men) referred for echocardiographic evaluation, diagnosed with isolated HFpEF. In all these patients we performed physical examination, ECG and 2-D transthoracic echocardiography, with measurements of left atrium and left ventricle dimensions, indices of diastolic function (Fig. 1, 2), pulmonary artery systolic pressure (PASP). Pulmonary hypertension was defined as pulmonary artery systolic pressure \geq

37 mm Hg, estimated by the tricuspid regurgitation velocity signal and the maximum gradient (Fig. 3, 4). Assessment of left ventricular diastolic function was limited to the mitral deceleration time in all patients and to the ratio of early to late mitral diastolic flow (E/A ratio) in patients with normal sinus rhythm. We divided patients in 2 groups: one with HFpEF and pulmonary hypertension and one with HFpEF without pulmonary hypertension.

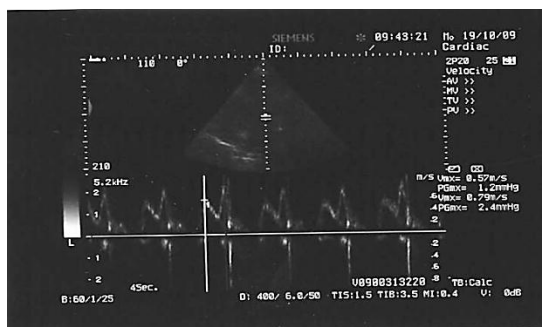


Fig.1 Transmitral flux with LV diastolic dysfunction, E/A<1

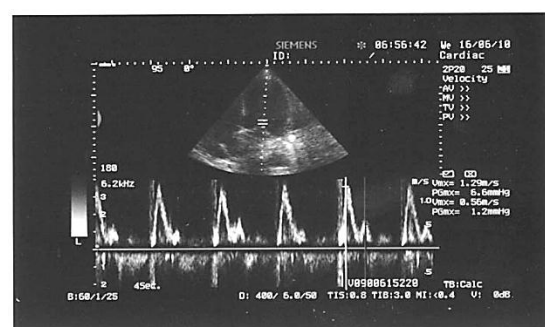


Fig.2 Transmitral flux with severe diastolic dysfunction, restrictive pattern, E/A>2

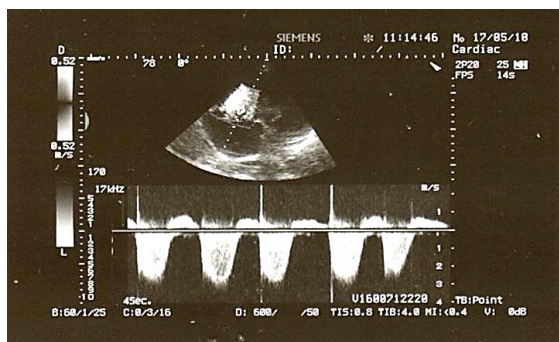


Fig.2 Severe tricuspid insufficiency with Gmax 54 mm Hg in a patient with severe PH (PASP 74 mm Hg).

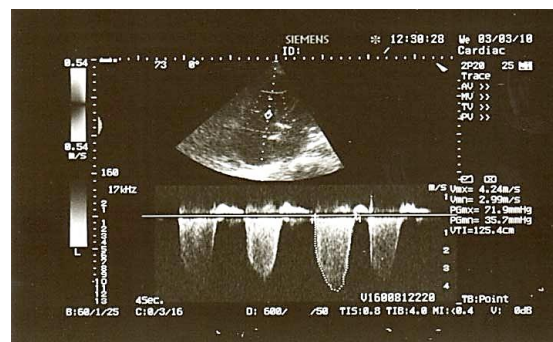


Fig.3 Severe tricuspid insufficiency with v max 4.24 m/s in a patient with severe PH (PASP 87 mm Hg).

RESULTS AND DISCUSSIONS

From the 62 patients, 15 patients (24,2%) had also pulmonary hypertension. The mean PASP in the whole group was 41.3 mm Hg. The prevalence of PH was 30.76% (12 pts) in women and 7.69% (3 pts) in men. The mean age of the whole group was 67.3 years. All the patients were in sinus rhythm. We compared the clinical characteristics of the 2 groups (with and without PH). The patients with PH were more often females and had a higher incidence of arterial hypertension (53.33% vs 40.42%). The analysis of echocardiographic data revealed that pts with PH had a higher left atrial diameter (44.9 vs 37.2 mm) and incidence of mitral regurgitation (60% vs 31.91%) and a lower EF (57.3% vs 61.2%).

The fact that left-sided heart failure is the most common cause of pulmonary hypertension has long been recognized ⁶. Although common in patients with left heart failure, the development of pulmonary hypertension is very variable. The factors that predispose to development of pulmonary hypertension in the presence of chronic pulmonary venous hypertension are not fully understood. Although a number of case reports described severe pulmonary hypertension in patients with heart

failure with preserved ejection fraction, the frequency with which these patients develop pulmonary hypertension and its severity remain poorly defined. It is expected that elderly patients would be more susceptible to the development of pulmonary hypertension, because of age related vascular stiffening, including age-related pulmonary artery stiffening ^{7, 8, 9, 10}. Studies show that this age-related increased arterial stiffening is worse in women than in men ^{7, 10}. This can be an explanation why elderly women who develop heart failure with preserved ejection fraction are more prone to developing pulmonary hypertension as a result of chronic pulmonary venous hypertension associated with heart failure with preserved ejection fraction.

It is likely that heart failure with preserved ejection fraction is an unrecognized cause of pulmonary hypertension and that unexplained dyspnea and pulmonary hypertension in elderly patients with a normal ejection fraction should lead to the consideration of heart failure with preserved ejection fraction or of idiopathic pulmonary arterial hypertension. Idiopathic pulmonary arterial hypertension is a disease of children and young adults, yet

increasingly the diagnosis is made in elderly patients ^{11,12}. The challenge is to differentiate between heart failure with preserved ejection fraction with secondary pulmonary hypertension

and idiopathic pulmonary arterial hypertension with secondary diastolic dysfunction. Echocardiography can be a useful diagnostic tool.

CONCLUSIONS

Pulmonary hypertension has a quite high frequency in patients with HFpEF. Female gender can be a predictor of the presence of pulmonary

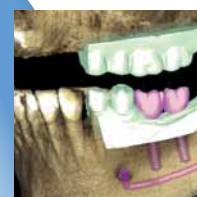
artery hypertension. The frequency of systemic hypertension was higher in pts with PH compared to those without PH.

REFERENCES

1. Owan T, Redfield M. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis.* 2005; 47:320-32.
2. Kessler KM, Willens HJ, Mallon SM. Diastolic left ventricular dysfunction leading to severe reversible pulmonary hypertension. *Am Heart J.* 1993; 126:234-5.
3. Willens HJ, Kessler KM. Severe pulmonary hypertension associated with diastolic left ventricular dysfunction. *Chest.* 1993; 103:1877-83.
4. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol.* 2004; 43:1432-8.
5. Abramson SV, Burke JF, Kelly JJ, Jr, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. *Ann Intern Med.* 1992; 116:888-95.
6. Thompson W, White PD. Commonest cause of hypertrophy of the right ventricle-left ventricular strain and failure. *Am Heart J.* 1936; 12:641-9.
7. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension.* 2004; 43:1239-45.
8. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FCP, Lakatta EG. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation.* 1993; 88:1456-62.
9. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation.* 1989; 80:1652-9.
10. Redfield MM, Jacobsen SJ, Bourlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community based study. *Circulation.* 2005; 112(15):2254-62.
11. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* 1987; 107:216-23.
12. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005; 111:3105-11.



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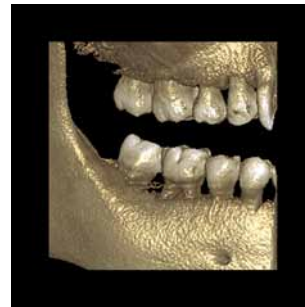
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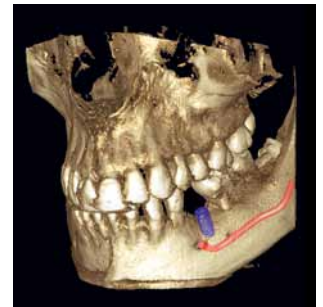
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HYGIENE CONDITIONS IN DENTAL OFFICES DURING TREATMENT PROCEDURES AND RELATION WITH PATIENTS' DENTAL HEALTH



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ABSTRACT

In dental medical offices, the patients treated are exposed to the environmental risk factors, through infectious diseases transmitted by the doctor's hands or by airways from nose and throat as sources. In the study performed, we investigated the breaking of the hygienic conditions as risk factor of the treatment procedures in some dental medical offices in Timisoara. The method consisted of a longitudinal retrospective epidemiological inquiry, using a specific questionnaire applied on a sample of 55 patients, which presented a specific dental pathology and were treated in 23 dental medical offices in Timisoara, in 2008. We identified a predominance of dental decay as main pathology (45% patients) and the pain as most frequent symptom. As breaking the hygienic conditions in dental medical offices resulted in crowding and insufficient air refresh. At the beginning of the treatment, dental physicians insufficiently applied important prophylactic measures: suction machine, glass of water, drill and gauntlets change, hand pieces' disinfection. At the end of the treatment, we identified a low level of the cleaning measures applied.

Keywords: risk factors, treatment procedures, dental medical offices.

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INTRODUCTION

In the dental medical office the patient is exposed to the environmental infections, intra (autogenic) and interpersonal, transmitted through the dentist's hands or through the air, with the source of germs in the nose and throat.

The aim of this study was to investigate the level of breaking the hygienic rules in the dental office (especially for treatment procedures) as risk factor for patients' and doctors' health, in the dental medical offices in Timisoara, Romania.

MATERIAL AND METHODS

The method consisted of a longitudinal retrospective epidemiological inquiry, using a specific questionnaire, applied on a sample of 55 patients, with a specific dental pathology and treated in 23 dental medical offices in Timisoara, in 2008. The specific questionnaire consisted of 14 items, referring to dental pathology, patients' perception about the hygiene conditions applied by the dental doctor before and during the dental treatment, the satisfaction level of the patient after the dental

treatment and the evolution of the dental health after the treatment. The questionnaire was applied individually, confidence being observed. The 14 items that make up the questionnaire were obtained on the basis of a review of the literature, focus group discussions, the professional experience of the researchers, and previous studies. The test - retest reliability and its sensitivity were assessed (Martinez & Sossa, 2005). Data were analyzed using the statistical Program SPSS 13.

RESULTS AND DISCUSSIONS

Sample structure (patients' distribution by sex and age groups)

The sample was homogeneous, consisting of 51% women and 49% men. The age group 20-24 years was best represented, with a frequency of 74%. One explanation is the specificity of these dental offices for students' treatment.

Dental pathology met into the sample

Dental pathology was represented especially by old dental decays (45% of the patients) and the aesthetic aspect distortion (21%) (figure 1). The main symptom accused by patients was the pain in cold and sweet medium (35%), followed by mild pain (15%) and pain that ceases under medication (6%). In a

recent study, pain intensity associated with the most recent toothache was high with 45.1% of the subjects reporting the highest pain possible. In our study 51% of the patients performed in the past a treatment of the affected tooth.

A high prevalence of toothaches, with 44.3% having experienced more than five toothaches during the preceding 10 years was found in Maryland, United State. The majority of subjects ultimately sought pain relief from a dentist (Cohen, 2009).

Hygiene conditions perceived by patients in the dental office

Infections present a significant hazard in the dental office because they

can be transmitted by blood or saliva through direct or indirect contact, droplets, aerosols, or contaminated instruments and equipment.

Because the incidence of certain microbial cross-infections in the dental environment has not been well documented, dental medicine personnel may not take the problem of cross-infection as seriously as they should, and they may transmit or contract more infections than they realize (Mastai, 1994).

In our study, the majority of the patients (70%) considered the dental office as having a good hygiene. 9% of the patients considered the ventilation insufficient and 8% mentioned the crowded space (figure 2). Hygiene and asepsis of the dental offices depend on medical ethics and legal obligation. From other studies resulted the necessity for cleaning of the floor and door mats daily (100%); disinfection done daily in 83% of the dental offices (Mastai, 1994).

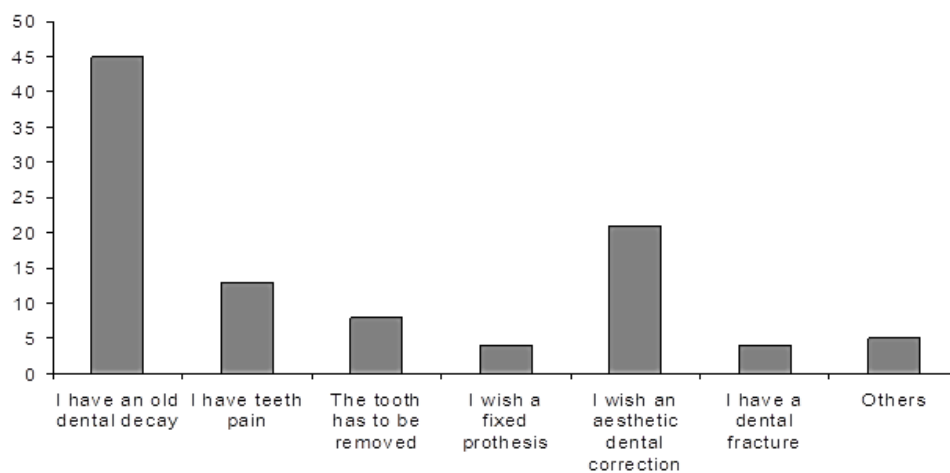


Fig.1 Distribution of patients depending on the perceived dental problem

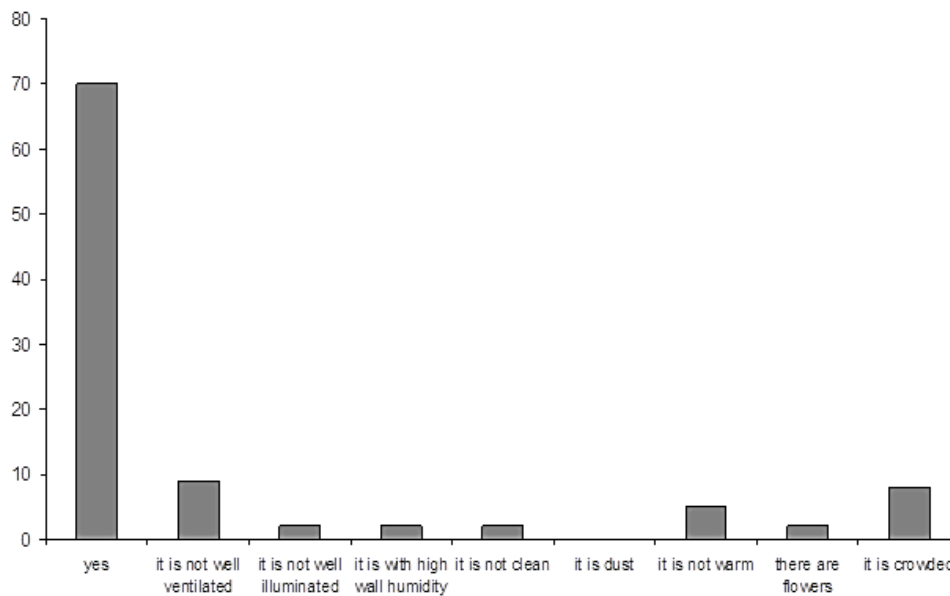


Fig.2 Distribution of patients depending on perceiving the hygiene conditions in the dental office.

Hygiene conditions perceived by patients during the dental treatment procedures

Therapeutic acts often surgically practised in the dental office can lead to the transmission of infectious diseases such as A.I.D.S (Acquired Immunodeficiency Syndrome). To prevent this, researchers proposed guideline base acts for antisepsis and asepsis (Onana Nqongang, 2002). In the investigated sample, 72% of the patients observed that the dental doctor washed his/her hands, 27% did not pay attention and 3% observed that dental doctor did not washed his/her hands before the treatment.

Also, 16% of the investigated patients saw that the doctor changed

the water glass at the beginning of treatment, and 13% observed that the doctor put on the gloves. It is important to mention that, during the treatment, only 8% to 10% of the patients observed the doctor performing the following procedures: put on the mask, tied the cloth for protection, changed the instruments on the table, changed the suction machine, changed the drill, disinfected the hand pieces, cleaned the work table, used the instruments covered (wrapped) by sterile champ.

These results suggest the rare usage of these procedures or a decreased perception of the patients when they are under the dental treatment (figure 3).

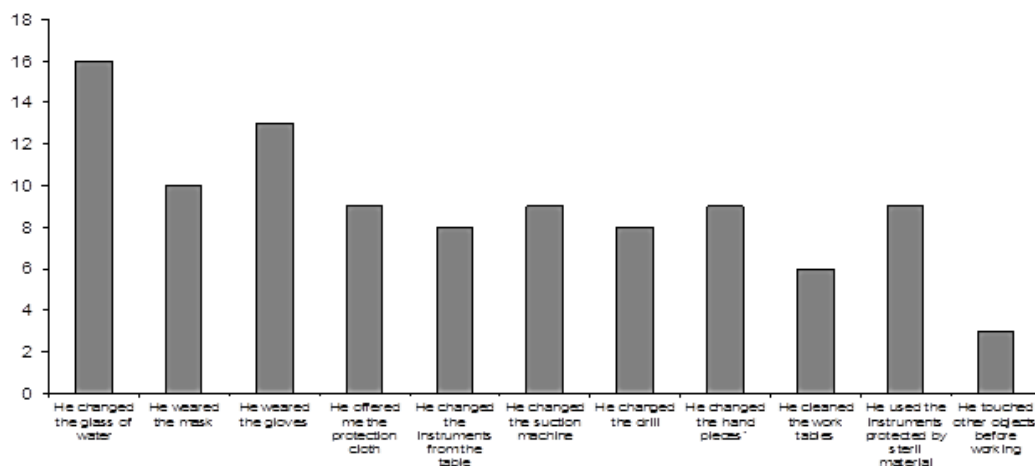


Fig. 3. Patients` distribution (%) depending on the perception of the doctor`s behavior at the beginning of the dental treatment.

In other studies were investigated: cleaning or disinfection of the suction machine which was done with soap (24%) or with bleaching-water (47%), the hand-pieces and the turbines, which are cleaned and/or disinfected after each usage in (94%) with alcohol (17%) or with bleaching-water (32%) and sterilized with a heat sterilizer (45%), an autoclave (40%) or cold disinfected (15%). It was observed that the frequency of the treatment of the

instruments was well-respected (83%). Nevertheless the products used were very varied and were not always used in the prescribed order. Hand-washing was systematic after each patient; 50% of the practitioners used soap bars or powered soap and 50% used an antiseptic or a disinfectant solution (Onana Nqongang, 2002).

With regard to the protection of the practitioners, from other studies resulted that 72% do not wear caps,

56% do not wear eyeglasses, 40% do not wear masks, 95% do not use rubber dams, 56% do not disinfect the radiographic films and 37% do not disinfect the impressions; the habitual attire consists of a smock worn over street clothes (78%) and street shoes (90%) (Yam, Diallo & Sembene, 1989).

In the performed study 16% of the patients observed that the doctor used

the suction machine during the treatment, 15% that doctor isolated the tooth with compresses/swab rolls and she/he washed her/his hands after the treatment, and 14% patients saw that doctor used sterile needles. Only 10% of the patients observed that the doctor gathered the instruments after the end of the work and 11% that she/he disposed of the gloves (figure 4).

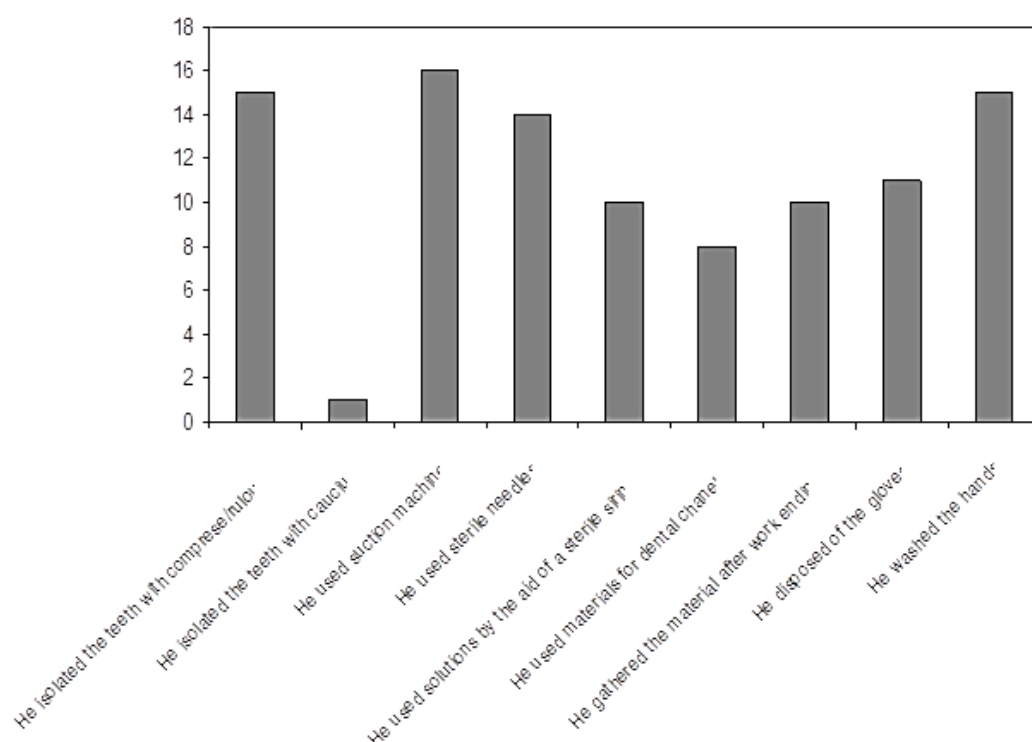


Fig 4. Patients` distribution (%) depending on the doctor`s behavior perceived during the treatment.

The patients` perception about the length of the dental treatment`s

The length of the treatment performed by the dental doctor on the patients investigated was 1-3 sessions (reported by 68% patients) and over 6 sessions (20% patients).

The contentment level of patients treated in dental offices

The majority (91%) of patients were content as regards the way they were treated by the dental doctor. This increased level of contentment suggests

the dental treatment efficiency. Referring to hygienic conditions observed in the dental offices, 86% patients said they were observed and only 9% patients said they were deficient.

85% of the patients were content about the way in which the hygiene requirements were applied during the treatment. There is a difference of 6% between the level of contentment of patients referring to the treatment`s efficiency and the level of contentment

of patients referring to the presence of hygiene conditions in the dental offices.

The tooth health evolution after the dental treatment

70% of the patients declared the evolution of the tooth health was good and very good, 25% considered the evolution satisfactory and 5% nesatisfactory.

The investigated patients were predominantly young people (74% with age group 20 - 24 years) and preoccupied to keep their dental health and aesthetic aspect. This result is sustained by other studies in which students were highly motivated about maintaining their dental health (Cortez, 2002).

CONCLUSIONS

The specific dental pathology of the investigated patients was dental decay (45% patients) and aesthetical dental problems (21% patients). The main symptom reported by patients was the pain (71% patients).

The majority of patients (70%) considered that in the dental offices where they were treated the hygiene requirements were applied. The patients who declared the contrary indicated the existence of vitiated air in dental offices due to poor ventilation and crowding.

In conformity with the patients' perception, the dental doctor respected the hygiene requirements before the treatment began (72% of patients), respected a little (8 - 16% patients) the important prophylaxis measures at the beginning and during the treatment procedures, such as: aspirator, glass of water, drill, gloves change, the hand pieces' disinfection, cloth for protection tying, tooth isolation, sterile needle, suction machine use, and applied restrictive cleaning measures at the end of the treatment (the gathering of used instruments, the disposal of gloves). The treatment length was 1-3 sessions

(68% patients) and more than 6 sessions (20% patients). There are two possible explanations referring to the patients' reporting of prophylaxis measures applied in dental offices: the dental doctors did not efficiently apply the prophylactic measures or the patients' perception level was diminished during the treatment.

The contentment level of patients as to hygiene conditions in dental offices, the way in which the dental doctor applied prophylaxis measures during the treatment procedure and the way in which the dental doctor behaved to the patients was high, which suggests the efficiency of dental treatment but, at the same time, a tendency of patients to minimize their perceptions about unsatisfactory conditions. A possible explanation could be the very good and good tooth health after the treatment (70%) or satisfactory (25% patients).

In conclusion, the tooth health in the patients treated for dental decay and tooth restoration was good and very good, although the patients' perception showed a partial application of hygiene requirements during the dental treatment.

REFERENCES

1. Cohen La., et al., Tooth pain: behavioral impact and self-care strategies, Spec. Care Dentist, 2009;29(2):85-95
2. Cortez Fj., et al., The evolution of dental health in dental students at the University of

- Barcelona, Journal of Dental Education, 2002;66(10):1203-1208
3. Martinez C.R., Sossa M.P., Validation of an Asthma Knowledge Questionnaire for use with Parents or Guardians of Children with Asthma, Archives of Bronchi-pneumology, 2005;41(8):419-424
 4. Mastaj La., et al., Infection control in the dental practice with emphasis of the orthodontic practice, Compendium, 1994;15(1):74, 76, 78-80, 86
 5. Onana J., Ngongang A., Hygiene and methods of decontamination, disinfection and sterilization in dental offices in Yaounde, Odontostomatol Trop. 2002;25(97):45-51
 6. Yam Aa., Diallo B., Sembene M., Asepsis and vigorous antisepsis against infectious disease transmission in the dental office, Odontostomatol Trop. 1989;12(4):147-8, 150

ASPECTS REGARDING MODIFICATIONS AT MACROSCOPIC, HISTOPATHOLOGICAL AND RADIOGRAPHIC LEVEL IN INFLAMMATORY ROOT APICAL RESORPTIONS



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ABSTRACT

Introduction: Literature data shows a high frequency of teeth with periapical lesions presenting incipient resorptions visible on optic or SEM microscopy.

Objectives: Our study aimed to determine the correlations between radiographic, macroscopic and histopathological aspects of apical dental surfaces in teeth with periapical lesions.

Materials and methods: The study group included 30 patients with 105 teeth destined to extraction because of severe periapical lesions and coronal destructions. The teeth were assessed using radiographic examination and, after extraction, with visual and histopathological examination. The digital scanning and processing of radiographic images allowed detection of apical resorptions from incipient to severe. The extracted teeth were processed for histopathological exam. The root apical third of each tooth was assessed using optical microscopy. The results were expressed using descriptive statistic and Microsoft Excel graphs.

Results and discussions: The association between radiographic and histopathological exam allowed diagnosis of 5,71% incipient resorptions, 7,61% medium resorptions and 4,76% severe root apical resorptions. Regarding the possibilities of radiographic evaluation to detect root apical resorptions, 100% severe resorptions, 89% medium resorptions and 66% incipient resorptions were detected on radiographic images. The incipient root resorptions are associated with the absence of cement on reduced depth areas interrupted by areas of repair cement or hypercementosis.

Conclusion: Histopathological exam allowed the correlation between morphopathological, macroscopic and radiographic features for each category of root apical resorption.

Key words: root apical resorption, histopathological exam, SEM microscopy, radiographic exam.

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INTRODUCTION

The knowledges regarding macroscopic, radiographic aspects and morphology of external root apical resorptions are important for dental practitioner because of high frequency of periapical lesions in endodontic pathology. Literature data show a high

frequency of teeth with periapical lesions presenting root apical incipient resorptions undetected by radiographic exam ^{1, 2}. The dentists must be aware that root apical resorptions represent bacterial colonisation areas that can't be eliminated after endodontic therapy ³.

OBJECTIVES

The aim of our study was to determine the correlations between radiographic, macroscopic and

histopathological aspects of apical dental surfaces on teeth with periapical lesions.

MATERIAL AND METHODS

The study group included 30 patients with 105 teeth prepared for extraction because of severe periapical lesions and coronal destructions. The teeth were assessed using radiographic exam and, after extraction, teeth were assessed using visual exam and histopathological exam. The classification of root apical resorptions was performed accordingly to Laux&col. (2000) criteria ¹. Panoramic radiographs were performed in the same conditions with ortopantomograph Ortophos (Siemens). The periapical radiographs were performed with a radiographic device (Siemens) (50kV, 7 mA). The macroscopic assessment was performed on images recorded with Canon Power Shot A560 (4 X, 7,1 MP). The digital scanning and processing of radiographic images allowed detection of incipient apical resorptions. The extracted teeth were processed for

histopathological exam (optic microscopy). The teeth fixed in phormol 10% were cleaned in tap water for 4-5 hours. The decalcification stage was performed in trichloroacetic acid 5-10%. This stage is requested to allow a treatment for hard tissues similar with soft tissues. Teeth were immersed in baths of ethylic alcohol 80-90°, followed by immersion in amilic alcohol. Teeth were engrained in paraffin blocks in three successive baths for 4-6 hours. The paraffin blocks were cut in slices of 4 µm. Finally teeth were stained with hematoxilin-eosine. The aim of histopathological processing was to highlight individual features of each type of root apical resorption (incipient, moderate, severe). The root apical third of each tooth was examined using optical microscopy. The results were expressed using descriptive statistic and Microsoft Excel graphs.

RESULTS AND DISCUSSIONS

In figures 1-3 are presented ortopantomographs showing teeth

with different types of inflammatory root apical resorptions.



Fig.1 Incipient root apical resorption (3.7.)

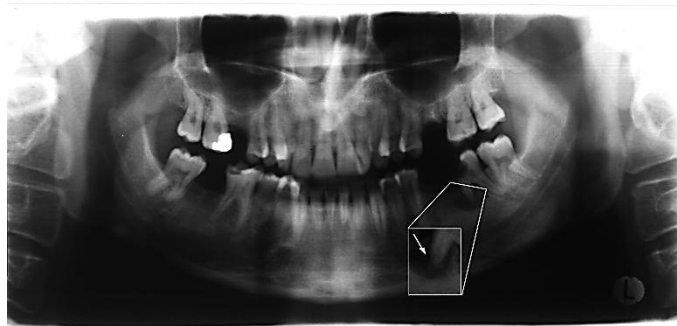


Fig.2 Moderate root apical resorption (3.7.)

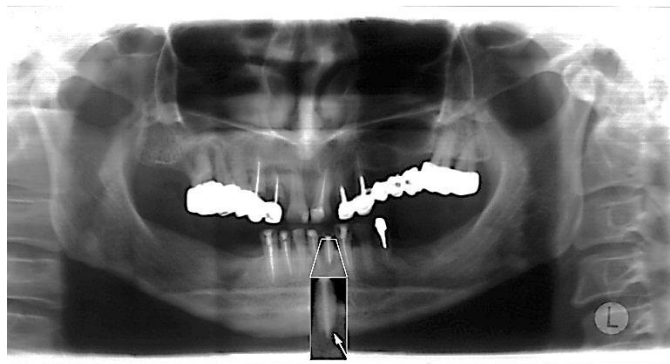


Fig.3 Severe root apical resorption (3.2.)

In figures 4-5 are presented macroscopic aspects of apical

resorptions associated with their radiographic images.



a



b



c

Fig.4 a - Radiographic aspects (2.1., 2.2.); b - Macroscopic aspect of incipient apical resorption (2.1.); c - Macroscopic aspect of moderate apical resorption (2.2.).

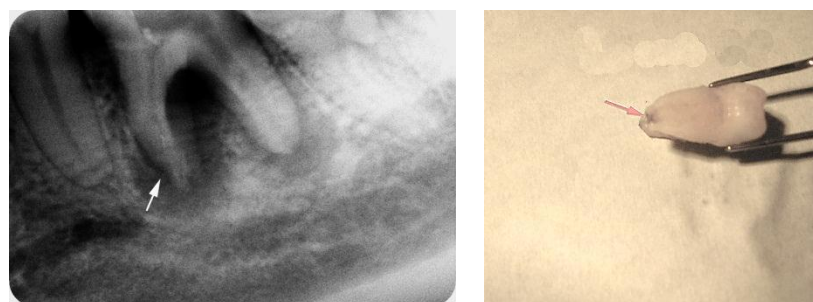


Fig.5 a – Radiographic aspect (3.6.); b. Macroscopic aspect (3.6.)

In figure 6 are presented results related to the prevalence of diverse categories of root apical resorptions in the group of extracted teeth. The association between radiographic exam

and histopathological exam allowed diagnosis of 5,71% incipient resorptions, 7,61% medium resorptions and 4,76% severe root apical resorptions.

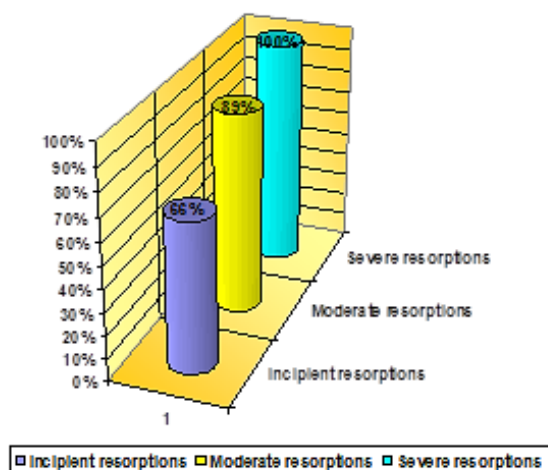


Fig.6. Prevalence of root apical resorptions for teeth with periapical lesions.

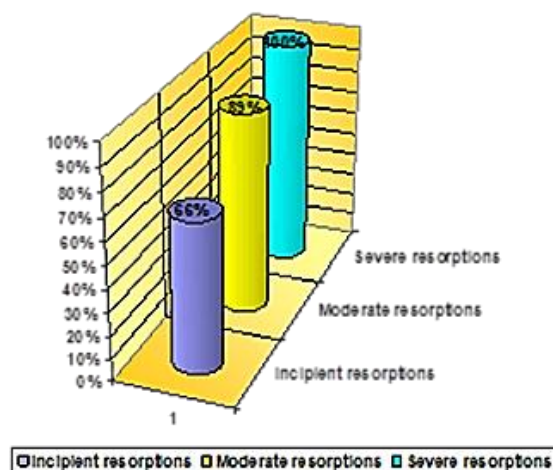


Fig.7. Sensitivity of radiographic exam in the diagnosis of root apical resorptions.

In figure 7 are presented results related to the sensitivity of radiographic exam in the detection of root apical resorptions. Regarding possibilities of radiographic exam to detect root apical resorptions, 100% severe resorptions, 89% moderate resorptions and 66% incipient resorptions were detected on radiographic images.

In figures 8-10 are presented histopathological aspects of root apical resorptions (incipient, moderate, severe). Incipient root apical resorptions appear as smooth areas

alternating with reduced depth resorptive geodes, or the absence of cement on reduced depth areas interrupted by areas of repair cement or hypercementosis. Moderate root apical resorptions are associated with irregular cement surface interrupted by areas of cellular degenerescence. Severe root apical resorptions can be correlated with deep resorptive geodes on the cement surface.

Our results sustain literature data regarding correlations between radiographic and morphopatological aspects o root apical resorptions ^{4,5}. The

presence of root apical resorptions can be detected using radiographic exam but the accuracy of radiographic

diagnosis depends on numerous factors and can be validated only with histopathological exam ^{6,7}.

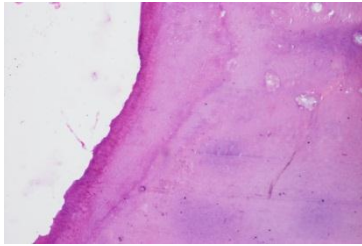


Fig.8. Incipient root apical resorption (HE x 4).

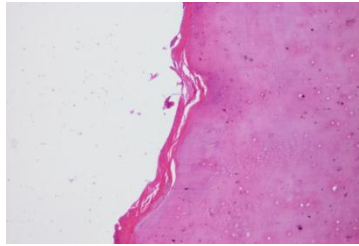


Fig.9. Moderate root apical resorption (HE x 4).

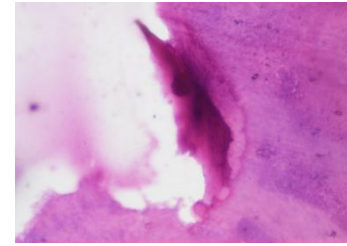


Fig.10. Severe root apical resorption (HE x 10).

CONCLUSIONS

Teeth with severe chronic periapical lesions present a high percent of external root apical resorptions (18,1%). The correlation between macroscopic aspects and radiographic images shows for radiographic exam a moderate sensitivity (66%) in the diagnosis of

incipient root apical resorptions and a high sensitivity (89%-100%) for moderate and severe root apical resorptions. Each category of root apical resorption presents specific macroscopic, radiographic and histopathological features.

REFERENCES

1. Andreasen FM, Sewerin I, Mandel U, Andreasen JO. Radiographic assessment of simulated root resorption cavities. *Endodontics and Dental Traumatology* 1987; 3, 21-7.
2. Goldberg F, De Silvio A, Dreyer C. Radiographic assessment of simulated external root resorption cavities in maxillary incisors. *Endodontics and Dental Traumatology* 1998; 14, 133- 6.
3. Jimenez-Pellegrin C., Victor E. Arana-Chavez. Root resorption repair in mandibular first premolars after rotation. transmission electron microscopy analysis combined with immunolabeling of osteopontin. *Am Orthod Dentofacial Orthop* 2007;132:230-6
4. Laux M., Abbott P., Pajarola G., Nair P. Apical inflammatory root resorption: a correlative radiographic and histological assessment. *International Endodontic Journal* 33,483-93; 2000
5. Lomc, Ali G., Sen B, Cancaya H. Scanning electron microscopic observations of apical root surfaces of teeth with apical periodontitis. *Endodontics and Dental Traumatology* 12,70-6; 1996
6. Tronstad L. Root resorption - etiology, terminology and clinical manifestations. *Endodontics and Dental Traumatology* 4, 241-52. 1988
7. Vier FV. & J.A.P.Figueiredo .Prevalence of different periapical lesions associated with human teeth and their correlation with the presence and extension of apical external root resorption. *International Endodontic Journal*, 35, 710-719, 2002.

MORPHOLOGICAL INDICATORS IN THE APPRECIATIONS OF THE RISK OF MAXILLARY CYSTS RECURRENCE



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ABSTRACT

Aim and objectives. The present study aims at identifying the main morphological markers so that we can appreciate the risk of postoperative recurrence of the maxillary cysts.

Material and methods. 188 maxillary cystic lesions were clinically, radiologically and histopathologically examined within 3 years.

Results. The presence of the active odontogenic epithelial rests in the cystic wall, the separation of the epithelium away from the connective tissue of support, the areas of myxoid dystrophy, the incidental appearance of metaplastic mucous cells indicate a high risk of postoperative lesion recurrence.

Conclusions. The identification of some structural marks of the walls and the cystic content lies at the basis of the appreciation of the risk of postoperative recurrence of the maxillary cysts.

Key words: cyst, morphological indicators, recurrence.

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INTRODUCTION

The high frequency of the cystic lesions at the maxillary bones level is explained by the coexistence of the ecto-mesenchymal derivatives with those ectodermal from the odontogenesis inside the connective

bone tissular mass. The presence of the epithelial remanences represents the source of formation of the maxillary cysts, both odontogenic and nonodontogenic.

AIM AND OBJECTIVES

Although easy to identify clinically and radiologically, the symptomatic maxillary cysts present a complex tissular differentiation, in which the inductive ecto-mesenchymal aspect determines the histological subtype

and the preoperative and postoperative evolution of the lesions as well. The present study aims at identifying the main morphological markers so that we can appreciate the risk of postoperative recurrence of the maxillary cysts.

MATERIALS AND METHODS

We studied 178 patients who presented 188 maxillary and mandibular cysts, examined clinically, radiologically and hystopathologically within 3 years. Nine patients presented two cysts, each of them. The parameters which were examined- age, gender, initial symptomatology, anatomic localization, the degree of affection of the neighbouring anatomic structures, radiologic dimension, postoperative evolution- were referred to the hystopahtologic type of the cyst. The cytological smears obtained after a fine needle aspiration

punction (PAF) and citomarking (n=40) were worked out through cytological exams using colours PAP, APT-Drăgan, Giemsa. The biopsy pieces were worked out according to the routine method by inclusion to paraffin, sectioning at 5 microns. Serial sections were performed. They were worked out through cytological exams using hystological and hystochemical usual staining and immunohistochemical in the system DAKO En Vision and LSAB 2 for messenchymal and epithelial markers.

RESULTS

According to the modified WHO classification ⁶ in our study, most of the cysts were inflammatory cysts, 77,1% of the cases; most of these inflammatory cysts were radicular cysts 62,7%, followed by the residual cysts - 12%. The dentigerous cysts as well as the keratocysts were each identified in the same percentage of 9%. The paradental, periodontal lateral, nasal palatine,

eruption and solitary cysts were identified in a percentage bellow 3%. We noticed a postoperative recurrence case of a radicular cyst, with clinical manifestation of infection, and also three cases of the keratocyst recurrence, two asymptomatic, identified after radiologic exam and one with clinical symptomatology.

In most histological sections, the covering epithelium is either incomplete or alternates in the cell stratification and differentiation, having reactive-hyperplasia or degenerative aspects. The epithelium separation from the connective tissue of support is frequently noticed at the odontogenous keratocysts, but not in other types of maxillary cysts.

Ultrastructural studies showed that in the depth of the lamina densa, the collagen presents signs of dissolution and, often, disappears completely. The three cases of odontogenic recurrent keratocysts presented invariably this lining epithelium separation from the subjacent connective tissue, fact that may determine the recurrence of these lesions (fig.1, 2).

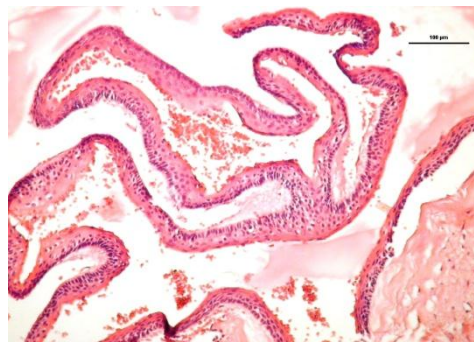


Fig.1 The wall of an odontogenic keratocyst, with detachment on extended areas of the odontogenic epithelium from the connective tissue, hematoxylin-eosin, X200

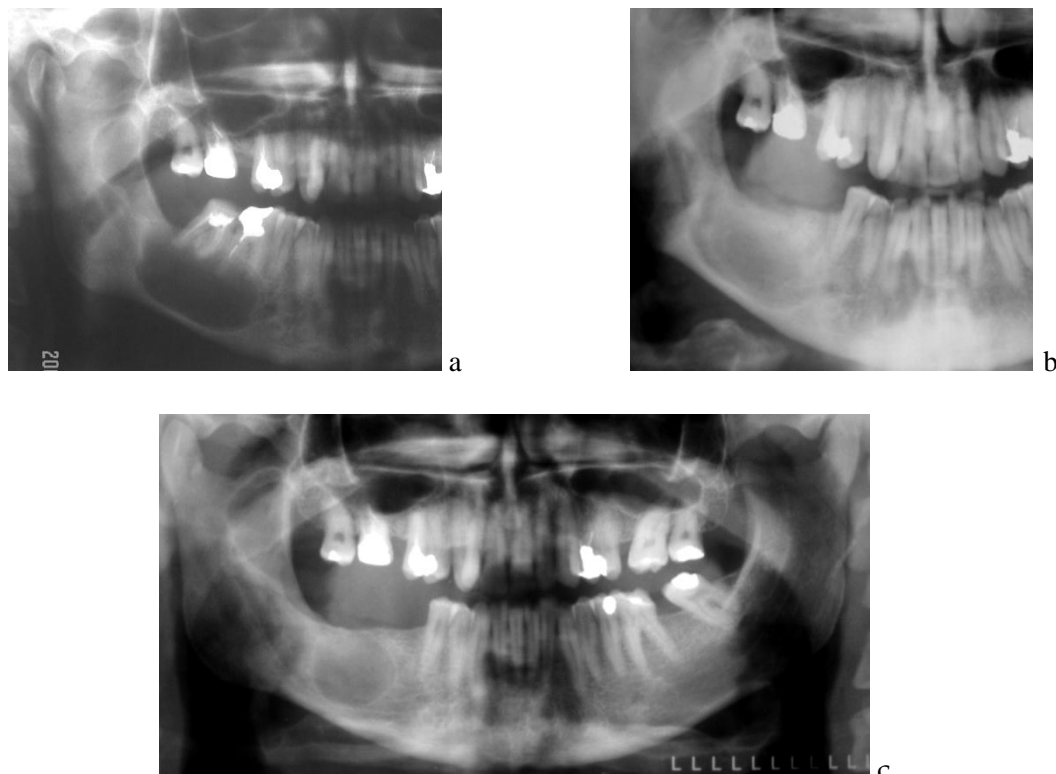
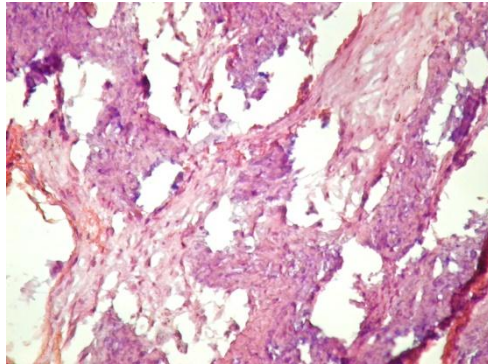


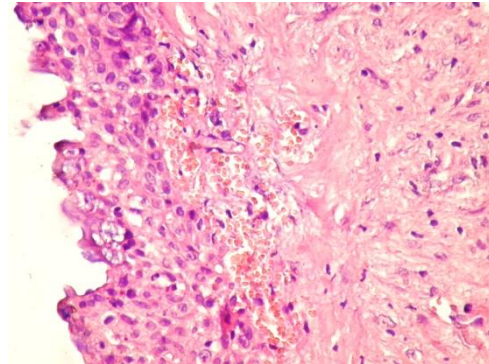
Fig. 2 Odontogenic mandibular recurrent keratocyst: a) preoperative aspect, b) 6 months postoperative, c) 14 months postoperative.

The areas of myxoid dystrophy from the cyst wall suggests unstable

local tissue which can be a sign of the recurrence risk (fig.3).



3



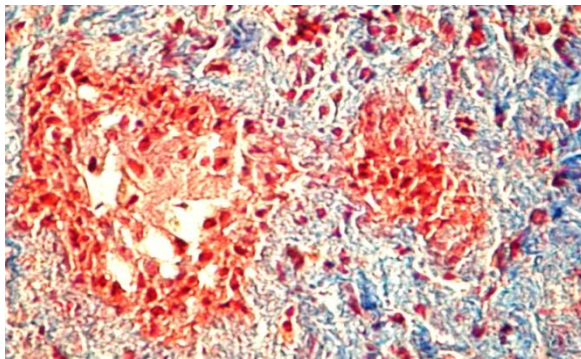
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Fig. 3 Cementoid-like material, here and there with osteoid aspect with pseudotrabeacular architecture without formation of the spongy bone areolas, formed at the periphery of a giant cyst of mandibular bone, hematoxylin-eosin, X 400

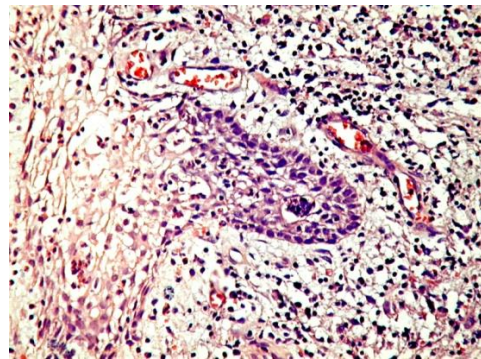
Fig. 4 Stratified odontogenic lining epithelium of the lumen of a dentiger cyst, presenting cellular differentiation with mucous secretions and cills, hematoxylin-eosin, X 400

The incidental appearance of the metaplasia mucous cells in the ameloblastoma and their quite frequent existence in the odontogenic cysts illustrates the potential of differentiation of the odontogenic

epithelium (fig.4). The active odontogenic epithelial rests in the cyst wall represent the most important indicator of the postoperative recurrence risk (fig.5).



5



6

Fig.5 Active odontogenic epithelium in the wall of a dentiger cyst, trichromic col., X 400

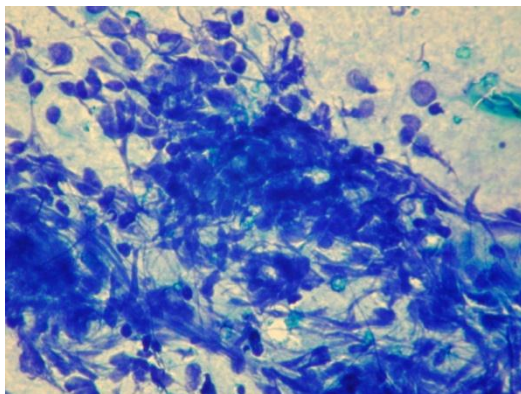
Fig.6 Epithelial Odontogenic Island with ameloblastomatous transformation, reversal of the cellular polarity, supranuclear vacuolization, perilesional angiogenesis, polymorphic inflammatory infiltrate, hematoxylin-eosin, X200

At two cases, we identified the lining epithelium of the cyst lumen characterized by ameloblastoma aspect, of basaloid type, which involves the risk of recurrence or neoplastic transformation (ameloblastoma, the carcinoma with squamous cells, the central mucoepidermoid carcinoma) (fig. 6). The cytological aspects aimed

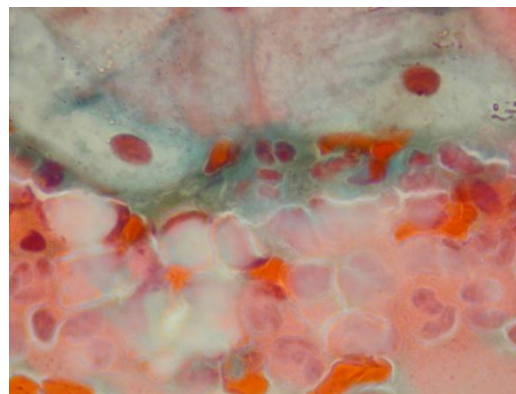
to identify the cellularity of the cystic lesions in order to establish the subtype of the lesion and the activity score of the odontogenic epithelium, suggesting the evolutive prognostical possibilities of the lesion. The big cells crowdings, the ulceration of the cyst wall, the intracystic hemoraggy, the suppuration, the inflammatory necrose, the

microcalcifications, the presence of the foamy macrophages of resorption indicate an intense cellular activity, which suggests a lesion instability

(fig.7, 8). The presence of the cholesterol crystals in the dentigerous cysts shows an aggressive potential of evolution.



7



8

Fig.7 Radicular inflammatory cyst in phase formation with high cellularity, mixed cellular arrangement, slight nuclear alteration, inflammatory diathesis Cytological smear obtained after a fine needle aspiration punction, col. APT-Drăgan, ob. im.

Fig. 8 Suppurative dentigerous cyst with intracystic hemorrhage, high cellularity and important inflammatory diathesis. Citomarking smear, col. Papanicolaou, ob. im.

DISCUSSIONS

The presence of the odontogenic epithelial rests in the cyst wall, the epithelium separation from the connective tissue of support, the areas of myxoid dystrophy, the incidental appearance of the metaplastic mucous cells, indicate a high risk of postoperative lesion recurrence.

On the other hand, the presence of the dental mataplastic tissues, the fibrous connective support with local hyalinisations and also at the epithelio-connective interface, indicate a chronic evolutive potential, locally aggressive, being dependent also on the evolution of the intracystic inflammatory process.

Epithelial nests and islets with clear cells, rich in extensive glycogen in the connective tissue; multilocular cysts; the compartmentation of the cystic cavity; the multicentric origin of the cystic lesion; the mucinous metaplastic epithelium, apocrin, ciliated (for the mucoepidermoid, ameloblastoma); the parakeratinisation of the ephitelium

(the odonotogenic keratocyst); the basal buddings; the solid epithelial proliferations, all these are considered risks of the recurrence.

Some etiological factors seem to continue their action of forming of cysts even after the removal of the initial lesion ^{1, 4, 5}.

The proliferative activity of the inductive ephitelium, due to the frequency of the mitosis in the lesion area represent a risk factor of the recurrence. The increased mitotic activity leads to the rapid proliferation of the lining epithelium in the keratocysts case, so that this very mecanism is considered to cause the increase of the keratocysts, rather than the osmotic pressure inside the cyst. In the same time, this active epithelial proliferation with the formation of microcysts in the adjacent osseous wall is a main factor of the increased frequency of the keratocysts recurrence ³. As for the other types of maxillary

cysts, the recurrence is due to the incomplete extirpation of the cystic wall. The professional studies show that the postoperative lesion

recurrence usually appears within the first 5 years after the surgery, although there is a recurrence case after 30 years in our casuistics ².

CONCLUSIONS

Although both the clinical exam and the radiological one can detect the maxillary cysts, they can not specify their lesion nature and the recurrence risk, so that the histopathological interpretation of the biopsies of extirpation of the cysts lesions walls has to be done.

We consider that the identification of some structural marks of the cystic wall and content is of huge importance for the postoperative predictive-prognostic-evolutive evaluation. In the same time, it is a major factor in the appreciation of the postoperative recurrence risk of the maxillary cysts. The physiopathological dynamic of the

maxillary cysts needs a detailed analysis of the different aspects of each case so that the most accurate operatory technique could be chosen. It is important that we choose the type of treatment which will keep the neighbouring anatomic structures, assure an optimal osseous healing and prevent the recurrence.

It is advisable that the patients should be watched after the surgery within a period of 1-2 years, in the case of the cysts without recurrence risk, and within 5 years if there are at least 2 morphological indicators which show the risk of the lesion recurrence.

REFERENCES

1. Berkowitz B.K.B., Moxham B.J., Newman H.N. The periodontal ligament in health and disease, 2nd ed, Mosby-Wolfe, Barcelona, 1995.
2. Brondum N., Jensen V.J. Recurrence of keratocysts and decompression treatment, Oral surgery, Oral Med, Oral Path, 1991;7: 265-9.
3. Cawson R.A., Odell E. W. Cawson's essentials of oral pathology and oral medicine, 7th edition, Churchill Livingstone, London, 2002.
4. Kierzenbaum A.L. Histology and Cell Biology, Mosby, 2002.
5. Parums Dinah V. Essential Clinical Pathology, Blackwell Science, Oxford, 1996.
6. Sciubba JJ et al. Atlas of Tumour Pathology, Tumors and Cysts of the Jaw, AFIP Whashington DC, 2001.

FIVE YEAR CLINICAL EVALUATION OF PRESSED CERAMIC VENEERS



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ABSTRACT

Objectives. The purpose of this study was to evaluate the clinical performance of pressed ceramic veneers (IPS Empress, Ivoclar Vivadent) in Romanian patients after a five-year observation period.

Methods. 27 patients (5 males, 22 females), presented in the Department of Prosthetic dentistry, Faculty of Dentistry Timisoara, Romania, were included in our study. They were treated with 76 pressed ceramic veneers, during the period March- July 2005. Evaluation of the restorations was performed at baseline, after six months and every year during the 5-year follow-up period. Modified U.S. Public Health Service (USPHS) criteria were used to examine the marginal adaptation, marginal discoloration, secondary caries, pulp vitality, gingival health, and color match. Each restoration was examined for cracks, fractures and debonding. Success rate describing relative failures of the restorations was determined using Kaplan-Meier statistical analysis.

Results. After 60 months of clinical service, the success rate of pressed ceramic veneers was 94.73 %, absolute failure consisted in fracture (one veneer), and relative failure consisted in chipping (2 veneers) and debonding (one veneer). The results of the clinical investigation regarding marginal adaptation revealed 93.42% Alpha scores among the 76 initially placed veneers. Considering pulp vitality, anatomic form and color match were rated with Alpha scores in the majority of cases.

Conclusion. IPS Empress pressed ceramic veneers exhibited a good clinical outcome after 5 years of clinical service and can be considered an esthetic, conservative and durable alternative for the restoration of frontal teeth.

Keywords: porcelain veneers, clinical evaluation, chipping, debonding.

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INTRODUCTION

Ceramic veneers are a well-established treatment method for conservative esthetic restoration of malformed, discolored, misaligned, traumatized, fractured, and worn anterior teeth ^{1, 2}. After over 30 years of service, ceramic veneers can be considered a predictable restorative procedure for the treatment of anterior teeth ². Long-term success of ceramic veneers is determined by material properties and fatigue resistance of ceramic and adhesive/luting cement system used ³. The periodontal response varied in literature from

clinically acceptable to excellent ⁴. Regarding the aesthetic properties of porcelain veneers, these restorations maintain their characteristics in time and patients' satisfaction was generally high. The success rate of porcelain veneers was clinically evaluated and showed a range from 18 months up to 12 years ^{4, 5}. The most common types of failure seen in ceramic veneers are fracture, microleakage and debonding ^{3, 4}. The purpose of our clinical study was to evaluate the clinical performance of ceramic veneers after five years of clinical service.

MATERIAL AND METHODS

We selected 27 patients from the outpatient's clinics of the Department of Prosthodontics, Faculty of Dentistry Timisoara, Romania, who needed prosthetic restoration of anterior maxillary teeth with ceramic veneers. Patients with extensive loss of tooth structure, periodontal problems and poor oral hygiene were excluded.

Written informed consent was obtained from all participants and the study was approved by the Bioethics Committee of the "Victor Babes" University of Medicine and Pharmacy Timisoara.

All recruited patients presented aesthetic deficiencies (contour, size, position, color) of anterior maxillary teeth and were treated during the period March- July 2005 by one dentist with over 15 years experience in prosthetic dentistry.

Tooth preparation was performed taking into account the technique described by Magne et al ², according to which preparation depth has to be guided by the final volume of the restoration. All the finish-line margins were placed supragingival and the

shade was taken before and after preparation with Vitapan 3D Master shade guide.

After preparation, impressions were taken using a polyvinyl siloxane impression material (Flexitime, Kerr). Temporary restorations were made chair-side (Protemp 3 Garant, 3MESPE) and were cemented with an eugenol-free temporary cement (Temp-Bond Clear).

After the pressed ceramic veneers (IPS Empress, Ivoclar Vivadent) were fabricated according to standard laboratory procedures, patients were recalled for an appointment to try and bond the veneers. Before cementation, veneers were cleaned in an ultrasonic bath, tried on, pretreated with 9.5% hydrofluoric acid for 90 s (Porcelain Prep kit, Ultradent), rinsed with air-water spray for 60 s, air dried and silanized in accordance with the manufacturer's instructions.

Tooth surfaces were etched for 15 s with phosphoric acid gel and then thoroughly washed by using a water spray for at least 15 s. The adhesive (Optibond Solo Plus, Kerr) was applied

and the veneers were bonded with a dual-cured cement (Maxcem Elite, Kerr). Residual excess cement was removed, the cervical area was rechecked for any remaining excess cement. The patients were treated with

one to maximum six pressed ceramic veneers (IPS Empress, Ivoclar Vivadent). Patients with parafunctional habits were provided with night guards following treatment.

Table 1 USPHS criteria used for clinical evaluation of the restoration ^{6,7}

Characteristics	Rating	Criteria
Secondary caries	Alpha	No evidence of caries contiguous with the margin of the restoration
	Bravo	Caries evident contiguous with the margin of the restoration
Marginal adaptation	Alpha	No visible evidence of crevice along margins; no catch or penetration of explorer
	Bravo	Visible evidence of crevice and/or catch of explorer; no penetration of explorer
	Charlie	Visible evidence of crevice and/or catch of explorer; penetration of explorer
Marginal discoloration	Alpha	No discoloration on the margin between the restoration and the tooth structure
	Bravo	Superficial discoloration on the margin between the restoration and the tooth structure
	Charlie	Discoloration has penetrated along the margin of the restorative material in pulpal direction
Anatomic form	Alpha	The restoration is continuous with tooth anatomy.
	Bravo	The restoration is slightly under- or over-contoured
	Charlie	The restoration is not continuous with the tooth anatomy- restoration material is missing
Color match	Alpha	No mismatch in color, shade or translucency
	Bravo	Mismatch between restoration and tooth structure within the normal range of color, shade and/or translucency
	Charlie	Mismatch between restoration and tooth structure outside the normal range of color

All 76 patients were initially recalled after one week post cementation for to re-check occlusion, interproximal contacts, marginal integrity and gingival health. Both pre-operative and postoperative photographs were taken for each patient in order to evaluate the change in appearance (Fig.1, Fig.2). All records resulted were updated at least yearly as patients are normally scheduled for annual check-ups after they receive treatment and are asked to contact the clinic whenever they have problems with the veneers or the abutment teeth.

Registration of the records of all patients (n=27), 5 men, 22 women, mean age 33 years, range 21-48 years, who received porcelain laminate veneers (n=76), was performed at the end of the study, during the period May- July 2011, by the authors.

At baseline recall and at every next annual check-up, the veneers were classified according to the modified United State Public Health Service (USPHS) criteria ^{6, 7} (Table 1). The restorations were visually inspected with dental mirror and probe and clinically examined with wax-free dental floss. Deviation in color match

and anatomic form were recorded. Each restoration was examined for cracks, fractures and debonding. The patients were questioned about possible postoperative complaints and pulp vitality was tested. For statistical evaluation, the survival rate evaluating absolute failures and the success rate describing relative and absolute failures were determined. Absolute failure was defined as clinically

unacceptable fractures and cracks, which required replacement of the entire restoration, and secondary caries. A relative failure was defined as minimal cohesive ceramic fractures and cracks with limited extension, which were clinically acceptable, as well as adhesion loss which could be successfully re-bonded. For the Kaplan Meyer statistical analysis, restoration related analysis was used.



Fig. 1- Preoperative case of four maxillary incisors requiring ceramic veneers.



Fig. 2- Final result after cementation of four pressed ceramic veneers

RESULTS

The study population consisted in 27 patients: 22 (81%) women (mean age 33 years, range 20-41 years) and 7 (19%) men (mean age 38, range 29-50 years).

The number of patients and restorations examined at each of the following annual check-ups are summarized in Table 2.

Two veneers showed minimal ceramic cohesive fractures (chippings) and one presented absolute failure because of an extensive fracture (Fig.3). Result statistical evaluation of all parameters for clinical evaluation are presented in Tabel 3.

For statistical evaluation, a survival rate evaluating absolute failures and success rate describing relative and absolute failures were determined. Absolute failure was defined as clinically unacceptable fractures and cracks which required replacement of the entire restoration and secondary

caries. A relative failure was defined as minimal cohesive ceramic fractures and cracks with limited extension, which were clinically acceptable, as well as adhesion loss which could be successfully re-bonded.

At the end of the 5-year observation period, the lowest survivability estimator was obtained when considering the cracks as failure determinants. In this case, the Kaplan-Meier estimator was 0.9089. When considering pulp vitality, color match and anatomic form, no degradations were registered, the Kaplan-Meier values remaining at the maximum value of 1 throughout the observation period. The image below (Fig. 4) shows the relevant part of the Kaplan Meier plot for all the considered conditions. Because all the values are contained between 0.9 and 1, only that part of the grid is displayed.



Fig. 3 - Fracture of the one ceramic veneer after 2 years

	Time(months)	6	12	24	36	48	60
Patients under observation	At baseline	27	27	27	27	27	27
Veneers under observation		76	76	76	74	74	73
Marginal adaptation	Alfa	76	76	76	73	71	71
	Bravo	-	-	-	1	3	3
	Charlie	-	-	-	-	-	-
Secondary caries	Alfa	76	76	76	74	73	73
	Bravo	-	-	-	-	1	1
	Charlie	-	-	-	-	-	-
Pulp vitality	positive	76	76	74	74	74	73
	negative	-	-	-	-	-	-
Color match	Alfa	75	75	75	73	73	72
	Bravo	1	1	1	1	1	1
	Charlie	-	-	-	-	-	-
Anatomic form	Alfa	76	76	76	74	74	73
	Bravo	-	-	-	-	-	-
	Charlie	-	-	-	-	-	-
Crack	none	76	75	74	72	70	69
	small/acceptable	-	1	2	2	4	3
	large	-	-	-	-	-	1
Fracture	none	76	76	75	73	72	70
	minimal/acceptable	-	-	1	1	2	2
	extensive	-	-	-	-	-	1
Retention of the veneer	bonded	76	76	76	73	72	71
	rebonded	-	-	-	1	2	2
	lost	-	-	-	-	-	-

Table. 2 - The number of patients and restorations examined at each of the following annual check- ups

Table. 3 - Statistical analysis of USPH criteria for ceramic veneers evaluation after five years

	6	12	24	36	48	60
Marginal adaptation	1	1	1	0.9864865	0.9464938	0.9464938
Secondary caries	1	1	1	1	0.9864865	0.9864865
Pulp vitality	1	1	1	1	1	1
Color match	1	1	1	1	1	1
Anatomic form	1	1	1	1	1	1
Crack	1	0.9868421	0.9608726	0.9608726	0.9089335	0.9089335
Fracture	1	1	0.9868421	0.9868421	0.9601707	0.9207116
Retention of the veneer	1	1	1	0.9864865	0.9598247	0.9598247

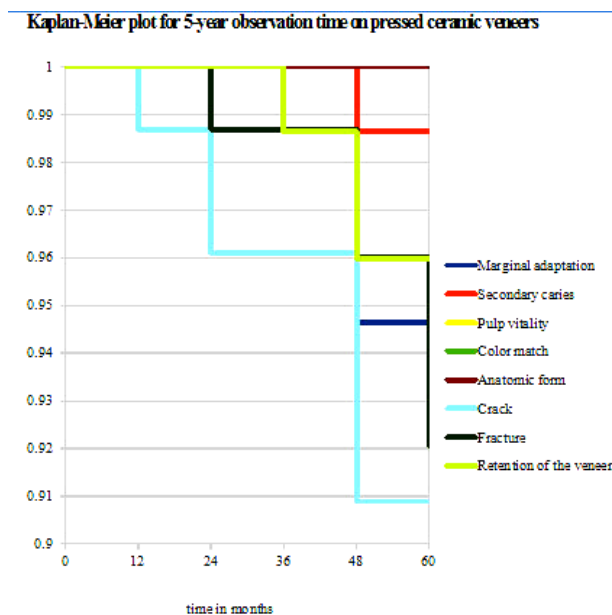


Fig. 4 - Kaplan Meyer plot for five- year observation time of pressed ceramic veneers.

DISCUSSION

In this clinical study, pressed ceramic veneers (IPS Empress) were evaluated after five years of clinical service. Porcelain veneers have been considered, by Magne et al., to biomimetically restore the mechanical behavior of the tooth crowns on which they are placed ². After over 30 years of service, ceramic veneers can be considered a predictable restorative procedure for the treatment of teeth in the anterior zone ^{3, 4, 7}. Factors affecting the longevity of veneers are multiple. Some of them are dependent of the material properties and fatigue resistance of the ceramic and adhesive luting cement system used. Factors concerning tooth preparation design are important.

A literature review by Peumans et al ⁸ concluded that the adhesive porcelain veneer complex was very strong, with optimal bonding being achieved when the preparation was contained in enamel, correct adhesive treatment procedures carried out and a suitable luting composite used. It was also concluded that the maintenance of aesthetics by porcelain veneers was excellent in the medium to long term, the periodontal response good, and that patient satisfaction was high.

Dumfahrt and Schaffer ³ have reported a 10-year evaluation of 191 porcelain veneers, calculating an estimated survival probability of 91% at 10 years, with six of the total of seven failures occurring when the veneers were partially bonded to dentine. They reported marginal discoloration in 17% of cases, and concluded that porcelain veneers were a predictable treatment modality. Another long-term (10 years), prospective evaluation of 87 porcelain veneers in 25 patients has been reported by Peumans et al ⁷. No veneers had been lost and the

proportion of veneers that remained "clinically acceptable" decreased from 92% at 5 years to 64% at 10 years, with porcelain fractures and large marginal defects being the principal reasons for failure. Marginal defects were especially noted at locations where the veneer ended on an existing composite restoration and, at such locations, severe marginal discoloration and recurrent caries were frequently observed. Of the restorations deemed to have failed, most were reparable and only 4% required replacement at the 10-year recall.

In the present study, the longevity of pressed ceramic veneers bonded with light-cured composite was evaluated over a period of five years. No endodontic complication and one secondary cavity (0.8%) were detected after observation periods of 6, 12, 24, 36, 48, and 60 months.

Regarding marginal adaptation, 95.945% Alpha rating was particularly satisfying. Significantly lower Alfa ratings were reported in previous studies after 5 and 10 years ^{3, 4}, as compared to this study. Peumans et al.⁷ found 36% of the veneer restoration margins to be clinically detectable by probing and described a clear increase in Bravo ratings over an observation period of up to 10.5 years. Guess and Stappert ⁹ reported that a decrease in marginal adaptation (20/25% Bravo rating) was accompanied by an increase in marginal discolorations in the form of higher Bravo ratings after 62 months. Only Fradeani et al. ⁴ reported results analogous to the present study in terms of marginal adaptation (92% Alfa rating after 12 years) and discoloration (86.4% Alfa rating after 12 years). The authors believe that the favorable quality of restoration margins obtained in this

study can be correlated to the preparation, cementation and finishing procedures adopted.

The satisfactory clinical results for porcelain veneers were achieved using a supragingival preparation and a light-cured composite adhesive as luting agent ^{10, 11, 12}. In the present study, two veneers demonstrated small cohesive fractures (chipping), though remaining clinically serviceable; cracks occurred in one restoration.

At the end of the 5-year observation period, the lowest survival rate was obtained when considering the cracks as failure determinants. In this case, the Kaplan-Meier estimator was 0.9089. When considering pulp vitality, color match and anatomic form, no degradations were registered, the Kaplan-Meier values remaining at the maximum value of 1 throughout the observation period.

Our study showed very good results for color match and anatomic form. Similarly to the results of Fradeani et al. ⁴ and D'Arcangelo et.al ¹⁵, a decrease in color quality and anatomic appearance during follow-up period was not found. Fradeani ⁴ reported chippings in 1.2% of the IPS Empress veneers after 6 years. Similar results for feldspathic ceramics were obtained by Dumfahrt and Schaffer ³ (2% after 10 years), Peumans et al. ⁸ (9% after 10 years) and Guess and Stappert ⁹ (8.3% of the full veneer restorations after 5 years). Regarding cracks, similar percentages were reported in previous investigations ^{13, 14}. Concerning loss of retention, Guess and Stappert⁹ reported a percentage of 2.3% of veneers after 5 years, and Fradeani et al. ⁴ reported 3.3% after 12 years. In our study, only one veneer detached after an observation period of 60 months.

CONCLUSION

Within the limitation of the present study, the 76 IPS Empress pressed ceramic veneers exhibited a good clinical outcome after 5 years of clinical

service and can be considered a conservative, aesthetic and durable alternative for the restoration of anterior teeth.

REFERENCES

1. Calamia JR, Calamia CS. Porcelain laminate veneers: reasons for 25 years of success. *Dent Clin North Am.* 2007 Apr;51(2):399-417
2. Beser U, Magne P, Magne M. Ceramic laminate veneers: continuous evolution of indications. *J Esthet Dent* 1997; 9:209-19
3. Dumfahrt H, Schaffer H. Porcelain laminate veneers. A retrospective evaluation after 1 to 10 years of service: part II—clinical results. *Int J Prosthodont*, 2000, 13:9-18
4. Fradeani M, Redemagni M, Corrado M. Porcelain laminate veneers: 6- to 12-year clinical evaluation—a retrospective study. *Int J Periodontics Restorative Dent*, 2005, 25:9-17
5. Cvar JF, Ryge G. Reprint of criteria for the clinical evaluation of dental restorative materials, 1971. *Clin Oral Investig*, 2005, 9:215-232
6. Bayne SC, Schmalz G. Reprinting the classic article on USPHS evaluation methods for measuring the clinical research performance of restorative materials. *Clin Oral Investig*, 2005;9:209
7. Peumans M, De Munck J, Fieuws S, Lambrechts P, Vanherle G, Van Meerbeek B. A prospective ten-year clinical trial of porcelain veneers. *J Adhes Dent*, 2004, 6:65-76
8. Peumans M, Van Meerbeek B, Lambrechts P, Vanherle G (2000) Porcelain veneers: a review of the literature. *J Dent* 28:163-177
9. Guess PC, Stappert CF. Midterm results of a 5-year prospective clinical investigation of extended ceramic veneers. *Dent Mater*, 2008, 24:804-813
10. Gurel G. Porcelain laminate veneers: minimal tooth preparation by design. *Dent Clin North Am.* 2007 Apr;51(2):419-31

11. Magne P, Belser UC. Novel porcelain laminate preparation approach driven by a diagnostic mock-up. *J Esthet Restor Dent*, 2004, 16:7-16, discussion 17-18
Stappert CF, Ozden U, Gerds T, Strub JR. Longevity and failure load of ceramic veneers with different preparation designs after exposure to masticatory simulation. *J Prosthet Dent*, 2005, 94:132-139
12. Barghi N, Berry TG. Post-bonding crack formation in porcelain veneers. *J Esthet dent* 1997; 9:51-4.
13. Aykor A, Ozel E. Five-year clinical evaluation of 300 teeth restored with porcelain laminate veneers using total-etch and a modified self-etch adhesive system. *Oper Dent*, 2009 34:516-523
14. D'Arcangelo, Fr. De Angelis, M. Vadini, M. D'Amario. Clinical evaluation on porcelain laminate veneers bonded with light-cured composite: results up to 7 years. *Clin Oral Investigation*, 2011DOI 10.1007/s00784-011-0593-0

AESTHETICS: PERFECTION, NECESSITY OR COMPROMISE



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ABSTRACT

In some clinical cases, the perfection of prosthetic restorations must be combined with higher attention to the line of the smile and the zenith of the gingival tissue in order to obtain the best aesthetic effect.

The complexity of the clinical case derives from the fact that the only problem that brought the patient for a consult was the aesthetic one. Had it been only a problem of dental aesthetics, the solution would have been relatively simple. The complexity of the case and the difficulty in solving it derive from the gingival aesthetics problems.

Key words: full ceramic, smile, zenith, aesthetics

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INTRODUCTION

In some clinical cases, the perfection of prosthetic restorations must be combined with higher attention to the line of the smile and the zenith of the gingival tissue in order to obtain the best aesthetic effect. It isn't always easy. It requires perfect cooperation between the patient, the physician and the technician. These requirements can be met with a certain

amount of attention. Key words: full ceramic, smile, zenith, aesthetics

Reported case: Patient Z.R., office worker, presents herself to have the aesthetics problem in her frontal area solved. Upon the consult, the physician asserts the presence of 10 year old fixed metallic – ceramic prosthetic restorations, inadequate from an aesthetic point of view.



Unaesthetic gingival retraction appeared in time, unacceptable for the patient, and this was the reason she presented herself for the consult. The X-ray examination showed the presence of incomplete endodontic

treatments. After the ablation procedure, teeth 2.1, 1.1, 1.3, 1.4, 1.5 were enforced with fiber glass pivots and reconstructed LuxacoreZ (DMG) A3.



The gingival retraction was surgically resolved and during the healing process the patient benefited

from provisional acrylic crowns with the purpose of maintaining the gum but they also played an aesthetic and

functional part. Taking into consideration that the patient's option was a complete ceramic restoration, the preparation was changed from tangential to rounded lines. The impression was made with Ultrapack retraction cord and Honigum (DMG) addition silicone, in a spoon. After the model was molded in the dental laboratory, and once the mobile abutments have been sectioned, the full ceramic restorations have been

produced. As mutually agreed upon with the patient, individual crowns were produced for improved aesthetics.

After the occlusal equilibration and after verifying the accommodation, the color and the shape, it has been found that the restorations, despite being impeccable from a technical point of view, did not meet the patient's aesthetic expectations.



A compromise was made between the length of the crowns, the gingival zenith and the line of the smile. After having adapting the length of the crowns to the aesthetic requirements, the restoration were

individualized and glazed. Cementation was achieved by using RelyX Unicem A2 Universal Self-Adhesive Universal Resin Cement (3M).



The evolution was spectacular, the aesthetic impact being greater at 6 months than upon cementation.

DISCUSSIONS

The complexity of the clinical case derives from the fact that the only problem that brought the patient for a consult was the aesthetic one. Had it been only a problem of dental aesthetics, the solution would have been relatively simple. The complexity

of the case and the difficulty in solving it derive from the gingival aesthetics problems. Gingival surgery was of great help, allowing us to put the gum back in the desired position. The balance between surgery and prosthetics lead to spectacular results.

REFERENCES

1. M. Fradeani, G. Barducci, Prosthetic Treatment a systematic approach to esthetic, biological and functional integration, 2008, Quintessence Publishing
2. J. Tinschert, G. Natt, Oxidkeramiken und CAD/CAM- Technologien, Deutscher Zahnaerzte Verlag Koln.
3. Bratu D., Nussbaum R. - Bazele clinice și tehnice ale protezării fixe, Editura Signata 2001
4. Chu SJ. Precision shade technology: Contemporary strategies in shade selection. *Pract Proced Aesthet Dent* 2002; 14:79-83.
5. Dancy WK, Yaman P, Dennison JB, O'Brien WJ, Razzoog ME. Color measurements as quality criteria for clinical shade matching of porcelain crowns. *J Esthet Restor Dent* 2003; 15:114-121.
6. Dietschi D, Ardu S, Krejci I. Exploring the layering concepts for anterior teeth. In: Roulet JF, Degrange M (eds). *Adhesion: The Silent Revolution in Dentistry*. Chicago: Quintessence, 2000:235-251.
7. Ikeda T, Nakanishi A, Yamamoto T, Sano H-Color differences and color changes in Vita Shade tooth -colored restorative materials. *Am J Dent*.2003; 16(6): 381-4.
8. Lichter JA, Solomowitz BH, Sher M. Shade selection. *Communicating with the laboratory technician*. *NY State Dent J* 2000; 66(5):42-46.
9. Reich S, Hornberger H. The effect of multicolored machinable ceramics on the esthetics of all-ceramic crowns. *J Prosthet Dent* 2002; 88:44-49.
10. Rolf Ankil. Zwischen allen Stühlen. *Quintessenz Zahntech* 2006; 32(3)

EVALUATION FOR OPTIMIZATIONS AND REOPTIMIZATIONS OF REMOVABLE PARTIAL DENTURES MADE TO PATIENTS IN DOLH COUNTY



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ABSTRACT

Aim: The evaluation of frequency and quality in optimization/reoptimization of removable partial dentures depends on various parameters and was performed in order to maintain functional comfort. It increases some functional prosthesis performance and maintains homeostasis of the remaining structures of the oral cavity in contact with these.

Methods: The study was conducted over a period of three years (2009-2012) on a group of 52 patients with periodical appointments, from which 36 have requested optimization/ reoptimizations of removable partial dentures with clasps. These percentages were quantified dependent on causes that determine improvement in efficiency, on affected materials and on repairing alternatives.

Results and discussion: According to this study, acrylic base of prosthesis represents the component with majority of optimizations and reoptimizations, while major connector reoptimization is situated on the opposite side. 76% of patients need immediate optimization in adaptation of RPD, 42% of these being corrections of occlusal disharmony. Only 37% of reoptimizations are caused by accidents, the rest being related to poor technology. The most common ways in reoptimization of removable partial denture were repairing and lining (28%), then classic replacement of damaged clasps in 34% of cases and welding only in 17% of cases.

Conclusions: Statistical evaluation of this study is important for directing the functional rehabilitation maneuvers and efficiency of dentures, the use of new materials and technologies. Therefore, it can show trends in prosthetic rehabilitation, the guidelines to approach in this branch.

Keywords: optimization, reoptimization, removable partial dentures.

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INTRODUCTION

Proper functioning of removable partial denture – RPD is revealed by their stability, expressed by their ability to resist horizontal and rotational stresses they are subjected to during stomatognathic system functions. Patients with such prosthetic pieces must adapt their dynamics and be periodical checked to use them on long term. In our country, treatment options for partial denture clasps rework cost is determined by repairing costs of implants, the prosthetic solution is on long- time for patients with low incomes or problems that contraindicate implants ^{1, 2, 3, 4, 5}.

The importance of study for optimization and reoptimization of RPD derives from necessity to improve quality, efficiency and performance of these prostheses, both immediately after their insertion in oral cavity, as well as in time. The team dentist - dental technician is one who can solve problems, can intervene both on metal component as well as on acrylic one.

RPD optimizations refers to overall improvement of quality/ performance for new dentures and **reoptimizations** are related to restoring integrity of removable partial dentures after various accidents or changes of prosthetic field, when prosthesis have stayed longer in oral cavity, and their condition must be improved ³.

Rudd & col. ⁶ have found that there are 243 possible errors related to the manufacturing process from impression to final processing into an analysis of possible causes that lead to damage RPD after. Many of these are caused by: inadequate design ^{7, 8} made without a thorough knowledge of the biomechanics of these prostheses, the aesthetic compromises made on strength of prosthetic components, neglect of some aspects of prosthetic

technology, rush in completing the prosthetic device.

The continuing evolution through last generation digital simulation software allowed prostheses design optimization and offered objective connections on fracture strength of the prosthesis in conditions where they are perfectly cast or have defects. This opens the door to increase the long life RPD ^{1, 3}. Durham et al. ⁹, shows that one of the main causes of instability for RPD is connected to incorrect contact, and often ineffective with abutments clasps. Other authors consider that the lack of final impression made with metal framework in the oral cavity would be the cause for inadequate limitations of the prosthesis, which determines its instability ^{9, 10}.

The issues of structural changes of materials during the technological process are causes that lead to many failures in prosthetic resolutions ¹⁰. For example the 6% polymerization shrinkage and distortion of heat curing resins, that can be reduced down to 3%.

Hidden defects, arising from CoCrMo casting alloys, lead to rapid deterioration of the metal component of the prosthesis. Often, these remain undiagnosed. Analysis of occlusal disharmonies and their removal is essential for the proper adaptation of the denture clasps both immediately after insertion in the mouth, and after a while. The modern system of T-Scan® system is used to restore the functionality of RPD in 100% cases. This replaces the old measurements of occlusion premature contact and interference in occlusion wax or articulation paper, and quantifies objective and computerized action of occlusal forces, establishing with precision the anterior guide way ^{12, 13}.

Fayyaz M, Ghani F ¹⁴ conducted a study regarding the RPD based on a questionnaire completed by dentists. The authors found that more than half of the dentists were experiencing clasp fit and clasp seating problems or their RPD, generating pain complaint in abutments. Many did not know methods for adjustment or replacement of RPD clasps. Relatively high costs of this work justify the need for dentures' integrity restoration after various

injuries or visible changes in the structures of the oral cavity. This is for they can still be used under optimum conditions for restoration of functional stomatognathic system and preserving the remaining oral structures ¹¹.

The emergence of new work tools, the performance of devices such as laser welding of metal components made it possible the reoptimization of fractured metallic components or even their replacement ¹⁵.

OBJECTIVES

This paper aim is to achieve a statistical study on RPD optimization

and reoptimization, to highlight their importance and necessity.

MATERIAL AND METHOD

Between 2009 and 2011, a total of 52 patients with RPD were evaluated regularly every 6 months, 44 women and 8 men, treated in two dental practices: CMI Dr. Gaman Simina and Faculty of Dentistry Craiova. Patients in rural areas were in number of 14, and those in urban areas in number of 38. 36 of these had requested enhancements or reoptimizations of the

used dentures. Following aspects were studied: frequency of cases with optimizations and reoptimizations and the reason of their request, the component on which it occurred: acrylic or metal, acrylic component level fault location, fault location in the metal component, the cause of fracture and how to optimize and reoptimize removable partial dentures.

RESULTS

Collected data were made based on clinical examination and questionnaires to determine the cause of reoptimization request. We took into consideration: the appearance of functional adaptation of the prosthesis, data on technical characteristics of the prosthesis, aesthetic comfort, masticatory, hygiene and number of interventions – aftercare (adjustments) that has been done. Costs of repair were acceptable and led patients to agree with them. Follow-up the questionnaires completed by patients, resulted that the success rate

immediately upon insertion of prostheses in the mouth amounted to 22% of RPD and increased to 56% after optimization. More than 35% of patients were satisfied with the denture's appearance, restoring of masticatory function and its stability during the immediate adaptation to prosthetic piece. This high percentage was due to dentures' immediate retouching measures beginning with the day of their insertion into oral cavity and monitoring in the following days. The conducted study revealed that 89.11% of prostheses required

optimizing and reoptimizing maneuvers. The evaluation of retention and comfort in mastication, phonation, appearance of the prosthesis after a period of 6 months, 1 year, 1 year and 6 months, 2 years, 2 years and 6 months, and 3 years revealed that the degree of adaptation increased to 82 %, even if local conditions have changed to the period after the dentures insertion in oral cavity. Professional assessment revealed that in 73% of cases there is poor hygiene of the denture and

abutment teeth, leading to repeated cleaning action, which is why some patients have abandoned the treatment.

Following assessments were separated into several parts, which are presented in the charts below. A first assessment was made on the number of patients and optimizations and reoptimization made - 76% of patients addressed to dentist because they require immediate optimization during adaptation RPD, while reoptimizations amount are only to 12%.

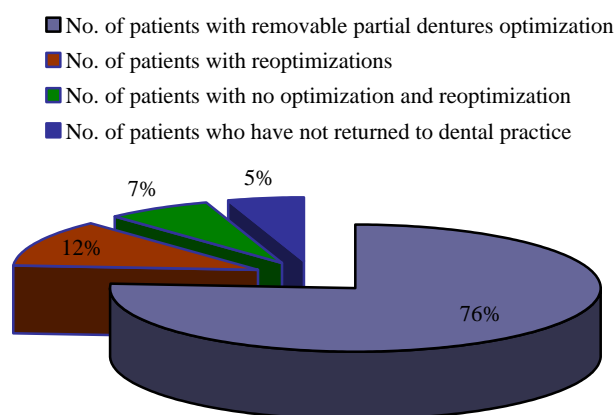


Chart no. 1. Number of patients evaluated with optimizations / reoptimizations of RPD

Causes that determine the need of RPD reoptimization are primarily related to errors in the RPD technology, followed by accidental disability of patients in handling these parts. Not to

be neglected are the aspects of faulty design, which in the absence of a thorough knowledge of biomechanics can lead to rapid failure of prostheses.

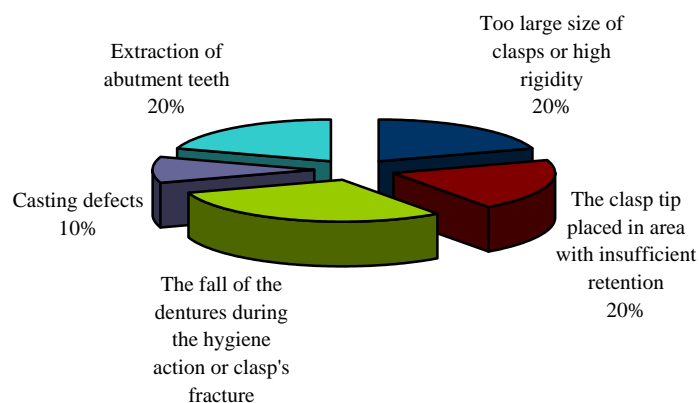


Chart no. 2. Percentage distribution of causes that determine the need of removable partial dentures reoptimization

Analyzing the cases from this point of view, we found the involvement of acrylic component to have double frequency compared to the metal component, in the different rehabilitation procedures of the dentures. The primary action upon the acrylic component materialized itself in increased rate of occlusal adjustment - 42%, made especially as dentures optimization. In case of acrylic

component reoptimization, the base lining is the most common labor, which is seen in the correlation between it and the frequency of terminal edentation in lower jaw. Our study shows that the optimization of the metal component took place especially upon the cast clasps, whether in optimization phase or in the reoptimization one, the option of damaged classic clasp replacement being applied in 34% of cases.

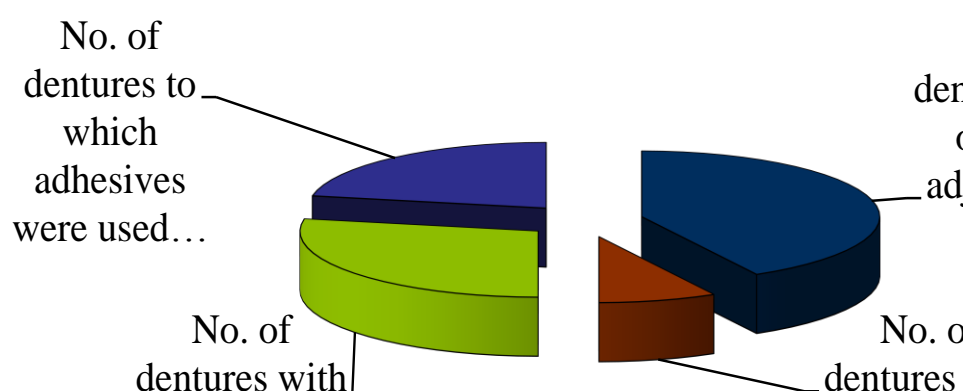


Chart no. 3. Distribution of cases after the intervention location in the acrylic component

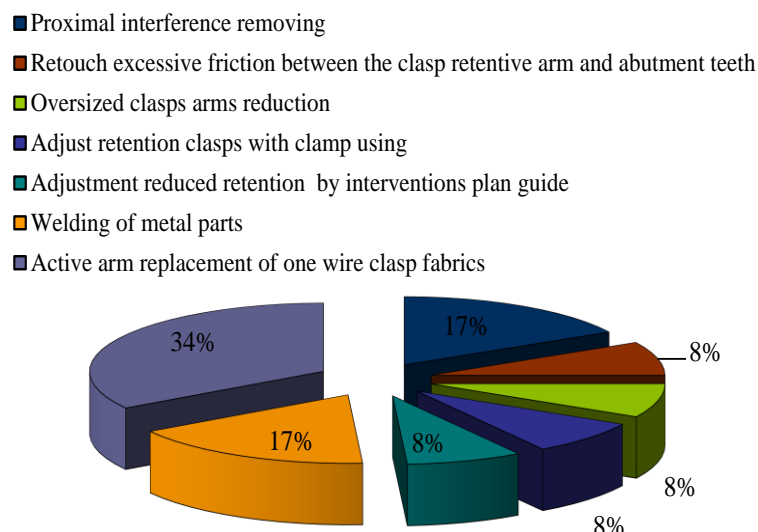


Chart no. 4. How to optimize the metal component by adjusting the excessive retention / reduced retention
At 80% of all patients, the removable partial dentures regained the efficiency after reoptimization.

Most optimizations involved the acrylic component, following the ulceration or inflammatory changes occurred in the soft tissue, located

adjacent to the denture base, generated by its over extended edges or occlusal dysfunctions.

DISCUSSION

The optimization of removable partial dentures is necessary for their optimal functioning. Most authors agree that occlusal adjustment is required after insertion of the prosthesis in the mouth and are beneficial to long-term use of removable partial dentures ^{1, 3, 12, 13, 16, 17, 18}. We believe that the percentage obtained by us in this study can be improved, especially in the active dispensarization of patients.

Polyzois G and collaborators ¹⁹ conducted a comparative study on five commercial types of adhesives concluding that denture adhesives increase the denture dislodgement forces, but with differences among them. Using adhesives can mask the deficiencies existing in prosthesis. Our study shows that only 22% of patients are using the adhesives especially from their own initiative, to increase the performance of the prosthesis ¹⁰.

The defects in the processed material or acrylate are commonly recognized as existing in all types of prostheses. The problem of their existence diagnosis and the knowledge of the areas that can affect the denture's lifetime are essential. The aim is to offer a guarantee on each prosthetic piece ¹⁸.

Co-Cr alloys popularity is due to their mechanical strength, hardness, low weight, increased Young's modulus, low cost, resistance to corrosion in the oral cavity ^{20, 21, 22, 23}. Following tests that simulated 5 years of clinical use, H. Cheng ²¹ shows that most Co-Cr alloy clasps exhibited a residual retentive force to satisfy the requirements for clinical use. The

problem of dental clasps reoptimization is strongly debated in the literature by several authors ²⁴. It seems that repair of dental clasps is the easiest, if compared to that of special attachments. In this respect, E. Hofmann ¹¹ shows that the most difficult to resolve are reoptimizations of telescopic systems and of different attachments; the easiest to fix are the clasps cast. Wagner concludes that the elements of maintenance, support and stabilization have a damage rate of 66.7%, the telescopic crowns- 33.3%, while the cast clasps- 44.8%. The number of dental clasps reoptimization is greater than in other metal components of removable partial dentures, the explanation being that they are vulnerable parts of the metal component of removable partial dentures, which is mentioned by other authors ²⁴. Repeated tractions of the dentures for their removal from the prosthetic field lead to their fracture or sometimes to permanent deformation ^{1, 18, 24}.

Ahmad Mahmoud Abdel Aziz, and other authors in the literature ^{25, 26, 27} state that the finite element method can predict the permanent deformation of the clasps, which shall enhance the optimization of clasps design for denture ²². What we observed in practice, is that excessive retention of clasps can irreversibly affect the abutments, while those with insufficient retention act worse on all components of the oral structure. Even if the clasps are the main components in RPD maintenance, the aids are not to be neglected.

Acrylic component reoptimization are correlated especially to accidents and need of bone resorption and atrophy compensation ^{1, 2, 3, 4, 5}. The intimate contact of the soft tissue with the residual ridges, the margin expansion in functional limitations is essential for the denture's stability, and prevents accumulation of food debris

under it ²³. The percentage of saddle relining made in our study is optimal if we consider that all tissue bearing areas of our patients were well healed.

The laser welding made possible the achieving of dentures from the components casted separately, which were joined afterwards, increasing their accuracy ¹⁵.

CONCLUSIONS

Clinical results show interdependence between the use of RPD and need of optimization and reoptimizations as follows:

1. In the oral rehabilitations with removable partial dentures, in order to obtain conservation of remaining oral structures, we need to dispensary the patients.

2. The more frequent optimizations were represented by occlusal adjustments, followed by reoptimizations of acrylic component - repairs and relinings.
3. Regarding the metallic component, we found fractures of retentive arms, cracks in major connector, reoptimizations that are manageable and solved by welding.

REFERENCES

1. Forna Norina Consuela. Protetica dentară, vol. II, Editura Enciclopedică, București 2011.
2. Bratu Dorin, Emanuel Bratu, Sergiu Antonie. Restaurarea Edentațiilor Parțiale Prin Proteze Mobilizabile, Editura Medicala, București, 2008.
3. Borșun Cristina, Leretter M., Liliana Sandu: Tehnologia Protezelor Parțiale Mobilizabile, vol. I și II, Editura Eurobit, Timișoara, 2002.
4. Lascu Liana Maria: Proteza Parțială Mobilizabilă Scheletată, Editura Medicală Universitară "Iuliu Hațieganu" Cluj-Napoca, 2006.
5. Păuna Mihaela, Gabriela Hagieac, Eugen Popa: Aspecte practice în protezarea edentației parțiale vol.1, Editura Cernaprint, București, 2003.
6. Rudd RW, Rudd KD. A review of 243 errors possible during the fabrication of a removable partial denture: part III. J. Prosthet Dent. 2001; 86(3): 277-88.
7. Carr A.B., McGivney G.P., Brown D.T. McCracken's removable partial prosthodontics 11th ed., St. Louis: Mosby; 2005.
8. Principles, concepts, and practices in prosthodontics - 1994. Academy of Prosthodontics. J. Prosthet Dent. 1995; 73(1): 73-94.
9. Dunham D., Brudvik J.S., Morris W.J., Plummer K.D., Cameron S.M. A clinical investigation of the fit of removable partial denture prosthesis clasp assemblies. J. Prosthet Dent. 2006; 95(4): 323-6.
10. O'Brien W.J. Dental materials and their selection. 3rd ed., Chicago: Quintessence Publishing, Inc.; 2002, p. 74-89.
11. Hofmann E., Behr M., Handel G. Frequency and costs of technical failures of clasp - and double crown-retained removable partial dentures. Clin Oral Investig. 2002 Jun; 6(2):104-8.
12. Tekscan: T-Scan III System: Computerized Analysis of Dental Occlusion, www.tekscan.com/occlusal-analysis-system.
13. Freilich M.A., Altieri J.V., Wahle J.J., 1992. Principles for selecting interocclusal records for articulation of dentate and partially dentate casts. Journal of Prosthetic Dentistry 68: 361-367.
14. Fayyaz M., Ghani F. Appropriateness of knowledge and practices of dentists relating to using clasps in removable partial dentures. J. Oral Rehabil. 2008 Nov; 35(11): 810-5.
15. Brudvik James S., Seungbum Lee, Steve N. Croshaw, Dave L. Reimers. Laser Welding of Removable Partial Denture Frameworks Int J Prosthodont 2008; 21: 285-291.
16. Vanzerveren C. D'hoore W. Bercy P., Leloup G. - (2003). "Treatment with removable partial dentures:a longitudinal study. Part II, J. Oral Rehabil. 30: 459-469.

17. Mercuț V., M. Scriciu, M. Suci, M. Popescu, V. Sfredel, D. Iorgulescu, P. Mărășescu, R. Mercuț. Modifications of the morphology of the dental - maxillary apparatus consecutive to bruxism, *Medicine in Evolution* Volume XVI, No. 4, 2010, pp.: 39-46.
18. Ionescu A. Tratatamentul edentației parțiale cu proteze mobile. *Clinica și tehnica de laborator*, Ed. Național, 1999.
19. Polyzois G., Lagouvardos P., Frangou M., Stefaniotis T. Efficacy of denture adhesives in maxillary dentures using gnathodynamometry: a comparative study, *Odontology*. 2011 Jul; 99(2): 155-61.
20. Sato Y., Abe Y., Yuasa Y., Akagawa Y. Effect of friction coefficient on Akers clasp retention. *J. Prosthet Dent*. 1997 Jul; 78(1): 22-7.
21. Cheng H., Xu M., Zhang H., Wu W., Zheng M., Li X. Cyclic fatigue properties of cobalt-chromium alloy clasps for partial removable dental prostheses. *J. Prosthet Dent*. 2010 Dec.; 104(6): 389-96.
22. Românu M., Bratu D. *Materiale dentare - noțiuni teoretice și aplicații practice*, Ed. Brumar, 2003.
23. Manolea Horia, Virgil Deva, Evantia Coles, Florin Bobia, Oana Diaconu, Celesta Nemțaru, Marina Amărăscu, Simina Găman, Petre Mărășescu, Mirela Opri, Radu Raca: *Materiale Dentare*, Craiova, 2011.
24. Borțun Cristina, Sandu Liliana, Leretter M., Samoilă C. Modalități practice de optimizare a retenției croșetelor turnate, *Revista Națională de Stomatologie, Chirurgie Maxilo-Facială și Chirurgie Orală*, 2003, vol. I, nr. 4: 50-56.
25. Mahmoud Ahmad Abdel Aziz, Noriyuki Wakabayashi, Hidekazu Takahashi. Prediction of permanent deformation in cast clasps for denture prostheses using a validated nonlinear finite element model *Dental Materials* Volume 23, Issue 3, Pages 317-324, 2007.
26. Wang H.Y., Zhang Y.M., Yao D., Chen J.H. Effects of rigid and nonrigid extracoronary attachments on supporting tissues in extension base partial removable dental prostheses: a nonlinear finite element study. *J. Prosthet Dent*. 2011, 105(5): 338-46.
27. Ge Q.M., Zhang F.Q. Circulating test and analysis of clasp retention. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2003 Nov; 38(6): 420-2.

DENTIST – STUDENT INTERNATIONAL COMMUNICATION STRATEGY



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ABSTRACT

In medicine the language is the support of dialogue and the main means for intellectual psychotherapy.

By joining verbal, nonverbal and extra-sensory communication, this successfully contributes to disease prophylaxis and treatment.

The dentist shall communicate in a professional manner both with adult patients as well as with children and teenagers. As this paper relates to children, one should be very familiar with the child's personality, both as a biological approach, as well as psychologically, s/he being integrated in the child's familiar, school environment, and the socio-economic environment of the community s/he belongs to.

Further to a statistical and clinical study performed on a group of students of both genders, with ages between 11-12 years, indicating the importance of communication between the dentist and the student, in terms of dental cavity occurrence one can notice a significant difference of a 26% lower risk in dental cavity occurrence in the group where the dentist communicated with the students, by using all the educational, professional and scientific communication means.

Key words: oral health, education, communication means.

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INTRODUCTION

We can consider inter-human doctor-patient communication at any age a beneficial psychotherapy to obtain positive results and the prophylaxis of many diseases.

Doctor-patient communication determines empathy relations having catharsis effect, personality restructuring starting with early childhood until old age. Proper communication is therapeutic especially in psychological suffering but also in psycho-somatic disorders so frequent and wide spread in the current stage of human society's development. The connection by direct communication with the patient as well as the healthy person represents an entire verbal and meta-verbal therapy.

In medicine the language is the support of dialogue and the main means for intellectual psychotherapy.

There is semantic value to verbal communication which is extremely important, by its result over the patient's psychic, over his/her psycho-education condition often having a decisive influence over neurovisceral functions and even over the prevention of pathological disorders. By verbal communication the information is rendered benefiting from special techniques rooted into medical practice by direct doctor-patient contact. Nonverbal communication. Not entirely communication by verbal lexical transfer can be a complex communication, but there is communication by expression, view, gestures that influence the patient's confidence level very much. Extra-sensory communication displayed by suggestion or sometimes hypnosis complements the communication complexity with psychotherapeutic effect. Calmness and suggestion can be induced and generated together with

the sound model expressing the lexical content that influences the patient's state in a certain manner. We may claim that linking of verbal, nonverbal and extra-sensory communication successfully contributes to disease prophylaxis and treatment. Inter-human communication, to be completed for a positive psychotherapeutic purpose or the simple dialogue with the patient may have antagonist results which are mutually excluded as follows:

- the psychotherapeutic effect in line with all the therapeutic methods used by the doctor
- the negative, iatrogenic effect, when the patient's condition or suffering becomes aggravated

Within his/her practice the dentist has a professional relationship with the adult patients but with children as well. In comparison with the doctor's relationship with the adult patients, his/her relation with children is a relationship of professional communication with the "binomial" respectively child – parents, and nowadays the grandparents are added as well, so in some instances we may state that this is a "trinomial".

One should not consider the child as a miniature adult but to acknowledge his/her anatomic, physiologic, immunologic, genetic, and psychological and reactivity features, particular and specific to different periods of childhood. Therefore the child should be considered under all aspects regarding his/her biological and psychological personality being integrated in his/her familial, school, and socio – economic environment of the community s/he belongs to.

The way s/he can be influenced in this period is extremely important and

therefore the doctor-child communication shall make its mark in a significant positive or negative manner, depending on the doctor's insight and inventiveness to win their attention and influence them.

In this paper we are proposing a study of the communication effect for dental cavity prophylaxis in a group of 60 students aged between 11-12 years

from a Secondary School in Arad, for a period of two years. At the beginning of the study the entire group underwent a clinical examination of the entire oral cavity and the following were found: a group of 7 students indicated superficial and deep dental cavities of upper incisors and temporary molars which have been completely filled and restored.

MATERIAL AND METHODS

The group of students consisted of a number of 60 students of both genders, divided in two subgroups I and II, of 30 students each, aged

between 11-12 years, students in the VIth grade A and B. The subgroups were separated into two parallel classes A and B.

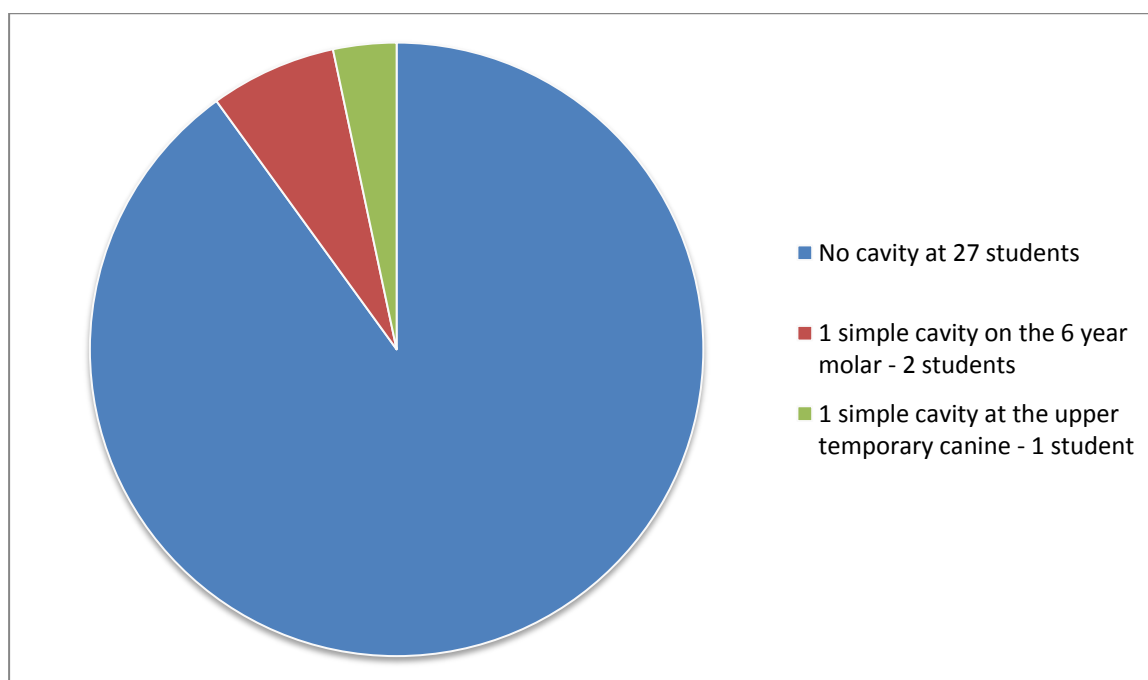


Fig.1. 10% of the subgroup I - to incipient cavities

In subgroup I which includes students of VI A grade, the dentist permanently attended to educating in keeping a correct dental hygiene, by micro-classes that students could find enjoyable. Thus the dentist used attractive educational material for

dental cavity prevention, with short films, featuring students with improper dentition for their age that negatively modified their face's physiology. In addition, slides were presented with students indicating obvious cavities, trainings about the negative effect of

cavities and their consequences, the way pain occurs in deep cavities and its intensity, correct and periodic teeth brushing, as well as notions about a proper food intake.

Subgroup II consisted of a number of 30 students with the same age of B class, with whom general discussions were had related to teeth anatomy, behavior and discipline, tangential and superficial discussions about the importance of oral hygiene, without presenting the educational material presented to subgroup I.

In subgroup I of the 30 students, during the two years of study, were

reported 3 incipient simple cavities distributed as follows:

- At a student, an incipient cavity on the upper temporary canine
- At two students one simple incipient cavity each on the 6 year upper and lower molar.

At subgroup II of the 30 investigated students incipient cavities occurred after 2 years distributed as follows:

- At five students incipient cavities on the 6 year molars
- At two students incipient cavities on the upper central incisors
- At 4 students cavities on the temporary molars

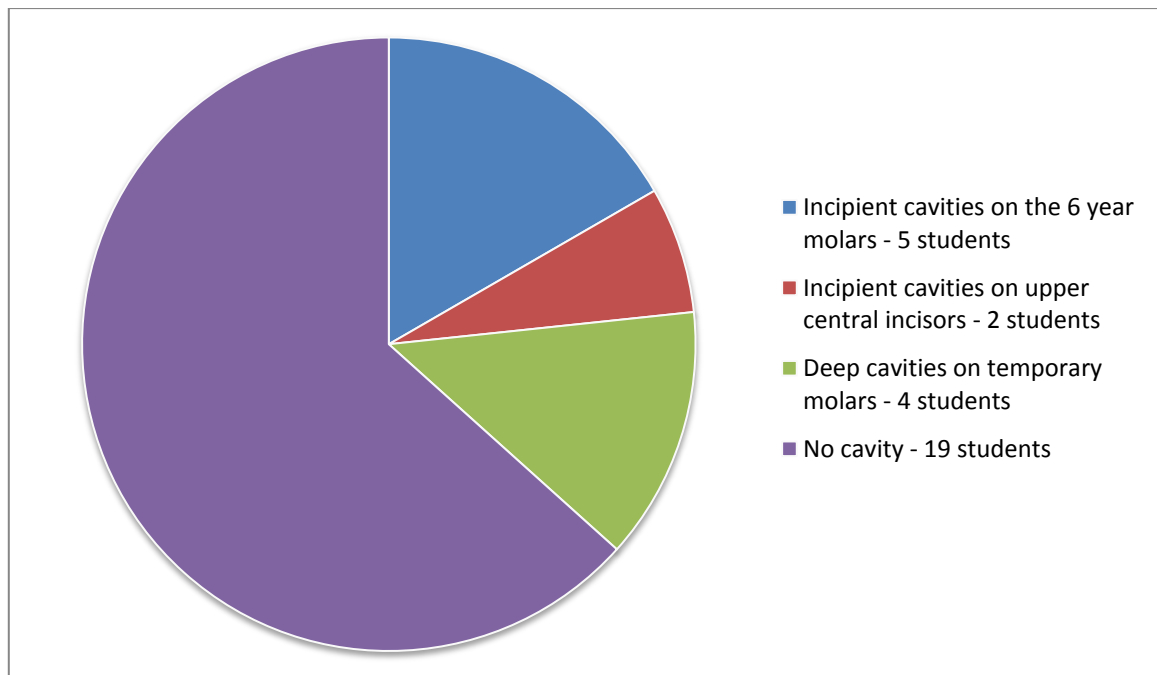


Fig.2. 36% of the subgroup II - to incipient and deep cavities

Further to the clinical study carried out on the two subgroups one can notice a significant difference, 26% higher for subgroup II in occurrence of superficial and deep cavities where

there was a lapse of communication and dental sanitation or in case they were performed in a superficial or tangential manner.

CONCLUSIONS

Direct communicational connection with the patient as well as with the healthy person represents verbal

therapy with positive effect over the state of health.

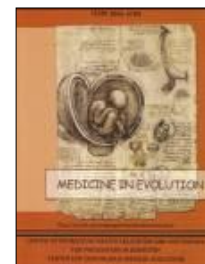
A significant difference can be noted from 10% to 36% in dental cavity occurrence, due to lack of proper communication and medical education.

The psychotherapeutic and communicational mode has a positive effect, in line with all the other therapeutic methods used by the dentist.

REFERENCES

1. Enatescu, V., Strugaru, Sorina, Abordarea informational a aspectelor iatrogene din comunicarea medic-bolnav, Simpozionul "Psihoterapia", Sibiu, 20-21 apr 1973 - (Informational Approach of Iatrogenic Aspects in the Doctor-Patient Communication, "Psychotherapy" Symposium, Sibiu, April 20-21, 1973)
2. Enatescu, V., V.R., A Model of the Psychic's Levels, in Trends in Romanian e-Health, Eurobit Publishing House, Timisoara 2003, 4-13
3. Goldis Gh. - Etica medicala in practia pediatrica; al 6-lea congres National de Pediatrie, Mamaia, 2003- (Medical Ethics in Pediatrics Practice; The 6th National Pediatrics Congress, Mamaia, 2003)
4. Holdevici Irina, Ameliorarea performantelor individuale prin tehnici de psihoterapie, Editura Orizonturi 2004 - (Improvement of Individual Performance by Psychotherapy Techniques, Orizonturi Publishing 2004)

MESUREMENT OF DENTAL FEAR AND ASSESING THE NEED OF PHARMACOLOGICAL MANAGEMENT OF PAIN IN DENTISTRY, A SURVEY OF THE POPULATION IN TIMISOARA



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ABSTRACT

Aim: The objectives were to determine the existence of dental fear among children and adults to assess the need and demand for sedation or general anesthesia (GA) for dentistry among adults; to determine the nature of the relationship between dental anxiety and age and to report the need of using the MDAS in the dental office.

Materials and methods: 1052 children, aged 14 – 18, and 1991 adults from all different social classes, aged 18 and above have completed the MDAS questionnaire. Additional questions were added for adult people in the purpose to determine if fear is a cause for not going/ missing dental appointments, the cause of dental fear and to asses the need for dental treatment under sedation/GA.

Results: The survey completion was excellent with no missing values for the MDAS questionnaire. All of the participants supplied their age and social class and answered all additional questions from the questionnaire. The survey sampling was successful in retrieving participants from all age groups and genders.

Conclusions: The results were consistent with the contention that there is need and demand for sedation and GA services for dentistry. Therefore, it can be concluded that the evidence shows that there is both significant need and significant demand for sedation and anesthesia services for dentistry.

Keywords: MDAS, dental fear, sedation, GA.

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AIM

Dental anxiety remains a barrier to dental care for a consistent proportion of the population¹. Fear and anxiety of dentistry are common findings²⁻¹⁸.

Although related, they differ in that fear may be considered the physiological process that occurs in the body when threatened by danger, whereas anxiety is the anticipation of the possibility of danger and is perceived to be less immediate in nature^{19, 20}. Their presence in dental patients may lead to avoidance of appropriate care and therefore an impairment of their oral health^{2, 10, 13, 21, 22, 23}. Many patients are unable to benefit from appropriate dental care due to their fear and anxiety^{2, 21, 22}. Treatment options to help these patients including behavioral modification, systematic desensitization, hypnosis, and guided relaxation²⁵ need to be considered.

Nevertheless, for many individuals these techniques are insufficient and they may require sedation or general anesthesia (GA) in order to undergo dental procedures. A survey conducted in the United Kingdom published in 1987 showed that 31% of those

interviewed preferred sedation or GA during dental treatment²⁶.

A number of scales have been used to determine the level of fear and anxiety²⁵. The most widely used is Corah's Dental Anxiety Scale (DAS).²⁷ Others include Gatchel's 10-point scale,² Milgrom's single-item scale³, Kleinknecht's Dental Fear Survey (DFS).²⁸, Spielberger's State-Trait Anxiety Inventory (STAI)²⁹, The Dental Belief Scale (DBS)³⁰. Another dental anxiety measure with more psychometric details is the Modified Dental Anxiety Scale (MDAS)³¹.

A survey was considered appropriate to provide a picture about the dental fear in children and adults among Timisoara.

The aims of this paper were:

1. to determine the existence of dental fear among children and adults
2. to report the need of using the MDAS in the dental office
3. to assess the need and demand for sedation or general anesthesia (GA) for dentistry among adults to determine the nature of the relationship between dental anxiety and different dental maneuvers.

MATHERIALS AND METHODS

The Modified Dental Anxiety Scale is a brief, 5 item questionnaire with a consistent answering scheme for each item ranging from 'not anxious' to 'extremely anxious'³¹.

It asks participants to rate their emotional reaction to the prospect of a dental visit the day previous, then when in the waiting room, receipt of drilling, scaling and a local anaesthetic injection. Precoded responses range from 'not anxious' (scoring 1) to

'extremely anxious' (scoring 5). It is summed together to construct a Likert scale with a minimum score of 5 and a maximum of 25. It is the most frequently used dental anxiety questionnaire in the UK³³ and does not increase patient fears when completed^{34, 35}. Existing data suggest that completion of the questionnaire can significantly reduce state anxiety in the practice setting³⁶. It has good psychometric properties, is relatively

quick to complete and scoring is easy³⁷,³⁸. A cut-off value of 19 and above has been determined empirically³¹ to indicate high dental anxiety that may require special attention by dental personnel.

In addition, other questions were asked on the use of dental therapists to determine,

- If fear is a cause for not going/missing dental appointments
- The cause of dental fear
- The need for dental treatment under sedation/GA, the findings of which will be reported in this study.

There were two main groups in this study: children, aged 14 - 18, and adults, aged 18 and above.

Children from 4 different schools, attending the gymnasium, the classes VIII, IX, X, XI and XII, were asked to complete the MDAS, with no additional question, in school during the home room. Parents meeting have been organized to receive the approbation from each parent for their children to complete the questionnaire.

28 parents didn't accept their children to complete the MDAS questionnaire, and a total of 67 children missed the home room during which the questionnaire was completed. A total of 1052 children, aged 14 - 18 answered the MDAS.

The second group viewed persons aged 18 and above from all social category:

1. Students
2. Working person with university degree

3. Working person with high school degree
4. Unemployed persons
5. Pensioners

Everybody answered the questionnaire during work, the acceptance being very high, people finding it interesting to discover their level of fear. A total of 1991 people from all possible social classes answered the MDAS questionnaire and the additional questions.

All the data were entered into the computer and analyzed using the Statistical Program for Social Sciences (SPSS, Version 12). Frequency tables and cross tabulations were generate. All cross-tabulations were confirmed using the statistical software Stata (Stata Corp LP, College Station, Tex). The use of a sampling error of 3% in the sample size calculation was based on the assumption that a simple random sample was to be used. As this survey was not a simple random sample but rather a 2-stage stratified random sample, the calculated sampling error for this survey was 3.31%, based on the estimate variances of the Jack-knife method⁽⁴³⁾. Calculation of the design effect for this study was 1.26. Chi square analysis was used to test for differences in proportions and the binomial test was used to compare an observed proportion (ie, the proportion preferring sedation for various techniques) with an expected proportion (ie, the proportion having had sedation for those techniques). All tests used the value $P < 0.05$ as being significant.

RESULTS

All subsequent data reports are based on weighted data of those

dentate respondents who completed the survey.

The survey completion was excellent with no missing values for the MDAS questionnaire. All of the participants supplied their age and social class and answered all additional questions from the questionnaire. The survey sampling was successful in retrieving participants from all age groups and genders. The gender distributions were 47% male and 53% female.

The distribution of the respondents fear by age is shown below. 80% declared previous painful dental treatments as cause of their fear, 10% had general fear of any sort of medical

interventions. It can be seen that there was no difference among the age groups and fear (chi-square, $P > 0.05$). There was also no relation with education level, the distributions by education of the respondents being similar (chi-square, $P > 0.05$).

The results regarding time since last dental visit are shown that 61,6% had not been to the dentist in over one year, with the main reasons summarized in the table below. Fear of dentistry was the reason why 38% of the respondents had not been to the dentist in the past year, which equated to 5,3% of all respondents.

Age in years	No fear	Low fear	High fear	Anxiety
15- 18 years	18%	68%	10%	4%
18 and above	32%	36%	24%	8%

Education Demographics at adults	Weighted percentage
Student	18%
High school with graduation	17%
University degree	35%
Not working	10%
Pensioners	20%

Reasons for avoiding dental visits	Percentage of all respondents	Percentage distribution for those who have avoided the dentist in the past years
Cost	7,9%	21,1%
Lack of time	3,1%	6,7%
Teeth haven't been bothering	11,3%	26,5%
Fear or anxiety	5,3%	38%
Previous painful dental experience	8,7%	7%
Something else	1,6%	0,7%
Total	37,9%	100%

Prevalence of dental fear or anxiety was assessed by the responses to the question "How would you rate your feelings toward having dental treatment done?". The results were dichotomized according to their self-reported level of anxiety. Those that answered that they were either not at As shown in below, when asked, "Have you ever missed, cancelled, or avoided a dental appointment because of fear of anxiety?," 21,9% of the respondents indicated yes. Overall,

5.5% reported high levels of fear. Females were more than 2.5 times as likely to report having high fear towards dental treatment (7.9% vs 3.1%), which was statistically significant (chi-square, $P < 0.001$).

all afraid, a little afraid, or somewhat afraid would be grouped together as having no fear or a

low level of fear, while those that reported that they were either very afraid or terrified were grouped together as having a high level of fear.

Avoidance of dental visits	Frequency	Percentage	Dichotomized grouping of dental fear	Frequency	Percentage	Time since last dental visit	Percentage
Avoided/cancelled dental treatment	438	21,9%	No fear	499	25,06%	Less than 1 year ago	38,9%
Never avoided/cancelled dental treatment	1553	78%	Low fear	789	39,62%	Between 1 - 3 years ago	52,4%
Total	1991	100%	High fear	506	25,41%	Between 3 - 6 years ago	3,2%
			Anxiety	197	9,89%	Between 6 - 10 years ago	3,8%
			Total	1991	100%	More than 10 years ago	1,7%
						Total	100%

Of those with a high level of fear, 49.2% had indicated that they had at some point missed, cancelled or avoided a dental appointment because of fear or anxiety, which was significantly different from the 5.2% in

the no or low fear group ($P < 0.001$). This table also shows that 44,6% of those who avoided the dentist because of fear or anxiety self-reported themselves as having no or a low level of dental fear.

Level of dental fear and anxiety related to avoidance of dental treatment		
	Avoided/cancelled dental treatment	Never avoided/ cancelled dental treatment
No fear	(43) 9.8%	(817) 52,6%
Low fear	(143) 32,6%	(509) 32,8%
High fear	(215) 49,2%	(227) 14,6%
Anxiety	(37) 8,4%	0%
Total	(438) 100%	(1553) 100%

Respondents were asked about their interest in having either sedation or GA for their dental treatment. Sedation or GA was defined as "having an intravenous needle in the arm and medications administered in order to be anywhere from lightly asleep to totally asleep." When cross-tabulated with their level of fear regarding dental treatment, 26% of those with high fear

are definitely interested in sedation or GA with another 10,9% possibly interested depending on the cost. Only 2,1% of those with high fear were not interested. For those with no or low fear many were not interested, yet 87,8% were interested depending on the cost and 4,5% were definitely interested.

Interest in sedation or G.A. during dental visits	Percentage
Not interested	42,1%
Possibly interested	43,7%
Definitely interested	14,2%
Total	100%

Level of dental fear related to interest in sedation or G.A.	Not interested	Interested depending on the cost	Definitely interested
No fear	86,3%	63,7%	1,7%
Low fear	11,4%	24,1%	2,8%
High fear	2,1%	10,9%	26%
Anxiety	0,2%	1.3%	69,5%

Concluding on the questions of the MDAS questionnaire the most feared dental maneuver was the thought of receiving a local aneastetic injection

and also the thought of drilling. A large percent felt the fear already from the waiting room, as the results in Table below show:

Level of dental fear related to different dental maneuver	Sitting in the waiting room	drilling	Injection with local anaesthetics	Extraction	Bont preparation	Implant insertion	Endodontics	Periodontal surgery	Dental cleaning
No fear	64,9%	18,8%	8%	5,1%	5,2%	2,7%	16,9%	3,2%	61,6%
Low fear	31,1%	47,9%	21,7%	27,4%	77%	37,7	34,6%	29,7%	24,4%
High fear	3,9%	31,2%	63%	58,1%	12,2%	44,4%	42%	56%	13,1%
Anxiety	0,1%	2,1%	6,3%	9,4%	5,6%	15,2%	6,5%	11,1%	0,9%

DISCUSSION

It is necessary to pay attention in the dental office to the issue: fear. Every patient should complete the MDAS questionnaire so the level of fear can be measured. Non - pharmacological management until pharmacological management of patient's fear should be available in dental offices.

Painful dental treatment done in very young aged patients affects the patient for life and creates a fearful child, and adult which is avoiding dental treatment.

There was a high level of fear among children which also tend to avoid dental meetings.

The results of the study are consistent with those found internationally. The 5.5% in the high

fear group is within the range of other reported studies from Europe, although somewhat lower compared to the studies done in Asia and the United States.

This is also the first published study of the people in Timisoara demand for sedation or GA for dentistry. The question assessing demand for sedation or GA for dentistry made it clear that the procedure was to take place in a dental office prepared for such interventions. The 12.4% that were definitely interested in sedation or GA is consistent with the results of previously reported surveys.^{13,23,44,45} When combined with those who may be interested in this service depending on the cost, it turned out that over half

of the adult population is interested. It is noteworthy that 1,7% of those in the no or low fear group were definitely interested in sedation or GA and 63,7% interested depending on cost. One may speculate that this could be for such things as overall comfort, anticipation of prolonged dental procedures, or for those with severe gagging reflex. Many of the questioned who would want dental treatment under sedation or GA, would think the option twice due to it's cost or due to previous negative experiences with sedation or GA or fear of anesthesia itself. If an individual has had previous negative experiences such as nausea or vomiting, this may make a choice for sedation or GA less likely.

For all of the procedures assessed, high preference rate suggest that there

is a large demand for these services, people being definitely interested in sedation or GA when in severe pain, in need for dental treatment that they think it might be painful or had previous painful experiences with.

Its presence leads to patients avoiding dental treatment, thereby jeopardizing their ability to optimize their oral health.

These results are also consistent with the contention that there is need and demand for sedation and GA services for dentistry.

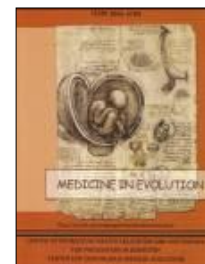
Therefore, it can be concluded that the evidence shows that there is both significant need and significant demand for sedation and anesthesia services for dentistry.

REFERENCES

1. Smith T, Heaton L. Fear of dental care: are we making any progress. *Journal of the American Dental Association*. 2003;134:1101-1108
2. Gatchel RJ, Ingersoll BD, Bowman L, Robertson MC, Walker C. The prevalence of dental fear and avoidance: a recent survey study. *J Am Dent Assoc*. 1983;107(4):609-610.
3. Milgrom P, Fiset L, Melnick S, Weinstein P. The prevalence and practice management consequences of dental fear in a major US city. *J Am Dent Assoc*. 1988;116(6):641-647.
4. Gatchel RJ. The prevalence of dental fear and avoidance: expanded adult and recent adolescent surveys. *J Am Dent Assoc*. 1989;118(5):591-593.
5. Stouthard ME, Hoogstraten J. Prevalence of dental anxiety in The Netherlands. *Comm Dent Oral Epidemiol*. 1990;18(3):139-142.
6. Teo CS, Foong W, Lui HH, Vignehsa H, Elliott J, Milgrom P. Prevalence of dental fear in young adult Singaporeans. *Int Dent J*. 1990;40(1):37-42.
7. Domoto PK, Weinstein P, Melnick S, et al. Results of a dental fear survey in Japan: implications for dental public health in Asia. *Comm Dent Oral Epidemiol*. 1988;16(4):199-201.
8. Hakeberg M, Berggren U, Carlsson SG. Prevalence of dental anxiety in an adult population in a major urban area in Sweden. *Comm Dent Oral Epidemiol*. 1992;20(2):97-101.
9. Moore R, Birn H, Kirkegaard E, Brodsgaard I, Scheutz F. Prevalence and characteristics of dental anxiety in Danish adults. *Comm Dent Oral Epidemiol*. 1993;21(5):292-296.
10. Weinstein P, Shimono T, Domoto P, et al. Dental fear in Japan: Okayama Prefecture school study of adolescents and adults. *Anesth Prog*. 1993;39(6):215-220. Ronis DL. Updating a measure of dental anxiety: reliability, validity, and norms. *J Dent Hygiene*. 1994;68(5):228-233.
11. Hagglin C, Berggren U, Hakeberg M, Ahlqvist M. Dental anxiety among middle-aged and elderly women in Sweden. A study of oral state, utilisation of dental services and concomitant factors. *Gerodontology*. 1996;13(1):25-34.
12. Dionne RA, Gordon SM, McCullagh LM, Phero JC. Assessing the need for anesthesia and sedation in the general population. *J Am Dent Assoc*. 1998;129(2):167-173.
13. Doerr PA, Lang WP, Nyquist LV, Ronis DL. Factors associated with dental anxiety. *J Am Dent Assoc*. 1998;129(8):1111-1119.
14. Kaakko T, Milgrom P, Coldwell SE, Getz T, Weinstein P, Ramsay DS. Dental fear among university students: implications for pharmacological research. *Anesth Prog*. 1998;45(2):62-67.
15. Ragnarsson E. Dental fear and anxiety in an adult Icelandic population. *Acta Odontologica Scandinavica*. 1998;56(2):100-104.
16. Thomson WM, Locker D, Poulton R. Incidence of dental anxiety in young adults in relation to

- dental treatment experience. *Comm Dent Oral Epidemiol.* 2000;28(4):289-294.
17. Smith TA, Heaton LJ. Fear of dental care. Are we making any progress. *J Am Dent Assoc.* 2003;134:1101-1108.
18. Tasman A, Kay J, Lieberman JA. *Psychiatry.* Philadelphia, PA: WB Saunders Co; 1997.
19. Task Force on DSM-IV APA. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR.* 4th ed. Washington, DC: American Psychiatric Association; 2000.
20. Domoto P, Weinstein P, Kamo Y, Wohlers K, Fiset L, Tanaka A. Dental fear of Japanese residents in the United States. *Anesth Prog.* 1991;38(3):90-95.
21. Locker D, Liddell A, Burman D. Dental fear and anxiety in an older adult population. *Comm Dent Oral Epidemiol.* 1991;19(2):120-124.
22. Taani DSMQ. Dental fear among a young adult Saudian population. *Int Dent J.* 2001;51:62-66.
23. Locker D, Shapiro D, Liddell A. Who is dentally anxious? Concordance between measures of dental anxiety. *Comm Dent Oral Epidemiol.* 1996;24(5):346-350.
24. Milgrom P, et al. *Treating Fearful Patients: A Patient Management Handbook.* Reston, Va: 1985.
25. Lindsay SJE, Humphris G, Barnby GJ. Expectations and preferences for routine dentistry in anxious adult patients. *Br Dent J.* 1987;163:120-124.
26. Corah NL. Development of a dental anxiety scale. *J Dent Res.* 1969;48(4):596.
27. Kleinknecht RA, Thorndike RM, McGlynn FD, Harkavy J. Factor analysis of the dental fear survey with cross-validation. *J Am Dent Assoc.* 1984;108(1):59-61.
28. Spielberger C, Gorsuch R, Lushene R. *STAI manual for the State-Trait Anxiety Inventory.* Palo Alto, Calif: Consulting Psychologists Press; 1983.
29. Milgrom P. Behavioral methods and research issues in the management of the adult dental patient. *Anesth Prog.* 1986;33(1):5-9.
30. Humphris G, Morrison T, Lindsay SJE. The Modified Dental Anxiety Scale: UK norms and evidence for validity. *Community Dental Health.* 1995;12:143-150.
31. Thomson W, Locker D, Poulton R. Incidence of dental anxiety in young adults in relation to dental treatment experience. *Community Dentistry and Oral Epidemiology.* 2000;28:289-294. doi: 10.1034/j.1600-0528.2000.280407.x.
32. Dailey Y, Humphris G, Lennon M. The use of dental anxiety questionnaires: a survey of a group of UK dental practitioners. *British Dental Journal.* 2001;190:450-453.
33. Humphris G, Hull P. Do dental anxiety questionnaires raise anxiety in dentally anxious adult patients? A two wave panel study. *Primary Dental Care.* 2007;14:7-11. doi: 10.1308/135576107779398165.
34. Humphris G, Clarke H, Freeman R. Does completing a dental anxiety questionnaire increase anxiety? A randomised controlled trial with adults in general dental practice. *British Dental Journal.* 2006;201:33-35. doi: 10.1038/sj.bdj.4813772.
35. Dailey Y, Humphris G, Lennon M. Reducing patients' state anxiety in general dental practice: a randomized controlled trial. *Journal of Dental Research.* 2002;81:319-322. doi: 10.1177/154405910208100506.
36. Newton J, Edwards J. Psychometric properties of the modified dental anxiety scale: an independent replication. *Community Dental Health.* 2005;22:40-42.
37. Humphris G, Freeman R, Campbell J, Tuutti H, D'Souza V. Further evidence for the reliability and validity of the Modified Dental Anxiety Scale. *International Dental Journal.* 2000;50:376-370.
38. Coolidge T, Chambers M, Garcia L, Heaton L, Coldwell S. Psychometric properties of Spanish-language adult dental fear measures. *BMC Oral Health.* 2008;8:15. doi: 10.1186/1472-6831-8-15.
39. Tunc E, Firat D, Onur O, Sar V. Reliability and validity of the Modified Dental Anxiety Scale (MDAS) in a Turkish population. *Community Dentistry and Oral Epidemiology.* 2005;33:357-362. doi: 10.1111/j.1600-0528.2005.00229.x.
40. Coolidge T, Arapostathis K, Emmanouil D, Dabarakis N, Patrikiou A, Economides N, Kotsanos N. Psychometric properties of Greek versions of the Modified Corah Dental Anxiety Scale (MDAS) and the Dental Fear Survey (DFS) *BMC Oral Health.* 2008;8:29. doi: 10.1186/1472-6831-8-29.
41. Yuan S, Freeman R, Lahti S, Lloyd-Williams F, Humphris G. Some psychometric properties of the Chinese version of the Modified Dental Anxiety Scale with cross validation. *Health and Quality of Life Outcomes.* 2008;6:22. doi: 10.1186/1477-7525-6-22.
42. Groves RM, Kahn RL. *Surveys by Telephone: A National Comparison with Personal Interviews.* Boston, Mass: Academic Press, Inc; 1979.
43. The modified dental anxiety scale: UK general public population norms in 2008 with further psychometrics and effects of age, Gerry M Humphris, ¹ Tom A Dyer,² and Peter G Robinson² August 2009
44. Need and Demand for Sedation or General Anesthesia in Dentistry: A National Survey of the Canadian Population, B Chanpong, DDS, MSc, D. A Haas, DDS, PhD, and D Locker, DDS, PhD, August 2004

THE MIOFUNCTIONAL THERAPY USING MYOBRACE IN THE TREATMENT OF CLASS II/2 DENTAL ANOMALY CASE PRESENTATION



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ABSTRACT

Myobrace is an orthodontic functional appliance, available in seven sizes. It includes a rigid inner core (DynamiCore) that is applied in the transversal development of the dental arches. The outer surface presents dental insertions (4 to 4) designed for the upper and lower jaw. Myobrace aligns the dental units in the anterior segment and also positions the mandible in class I relationship. It can be used during the mixed dentition as well as during the permanent dentition, at any age. Though, the optimal age for its use is considered to be the eruption period during the late mixed dentition.

Myobrace is available in seven different sizes, numbered from 1 to 7. It also contains a ruler used for direct selection of the correct functional appliance. The measurements are realized over the four incisors (distally from the lateral incisors), on the vestibular areas.

The article presents a female patient, aged 10, V.T., presented in our service with class II/2 dental anomaly. We used Myobrace orthodontic therapy for the treatment of this particular case. The final photographs show the results after 10 months of orthodontic therapy with this miofunctional appliance.

Key words: miofunctional appliance; class II/2 dental anomaly; Myobrace; deep bite.

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INTRODUCTION

Class II/2 dental malocclusion is defined by distalised references at the first molar level and repositioning of all upper incisors; the lateral incisors are positioned vestibular¹. It is also characterized by deep bite, element considered to be a vertical anomaly. It has two forms; true and false anomaly².

Myobrace is a functional intraoral appliance that has interior slots available in different sizes and

DynamiCore, a rigid core that helps in the conformation of the dental arch and in the alignment of the dental units. This appliance is available for patients with mixed or permanent dentition, with slight or moderate malocclusions. Though, the optimal age for the appliance of this mean of treatment is the eruption and growth period of the mixed late dentition.

MATERIAL AND METHOD

The dento-maxillary complex integrates dental units, periodontal membranes, alveolar bone, temporo-mandibular joint and the coating muscular components. This system is considered to be alive and it is easy adaptable to external stimulations, especially during the growth period of the dento-facial complex. The bone is

the hardest tissue of the body, but it is as well most receptive to the environmental stimulations³. An orthodontist may as consider not enough the use of own functional forces in order to obtain orthodontic correction. Here is the point where Myobrace can be used.

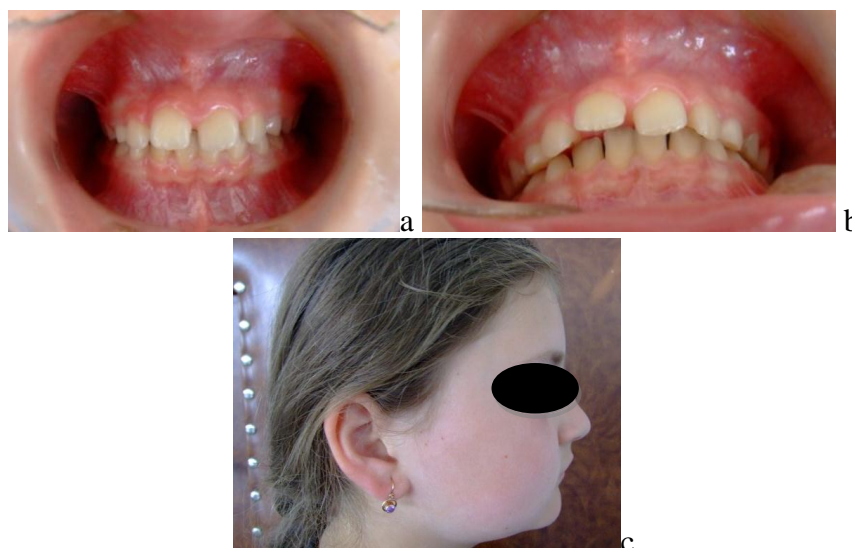


Fig. 1 Patient, V.T., aged 9 and 1/2 is presented in our service in May 2010.
a. intraoral frontal view b. intraoral profile view c. facial lateral analysis.

Facial examination: Shortened lower face; right profile

Intra-oral examination: deep bite; distalised references at the first

permanent molars; lateral incisors placed vestibular; Mixed dentition

The measurement of the mesio-distal dimensions of the upper incisors

was made using the ruler from endowment, in order to choose the suited dimension for the functional appliance. For the presented case we used Myobrace with DynamiCore

number 5. Our recommendation, to use this appliance during sleep period (minimum 8 hours), and at least 2 hours during daily activities was followed rigorously by the patient.

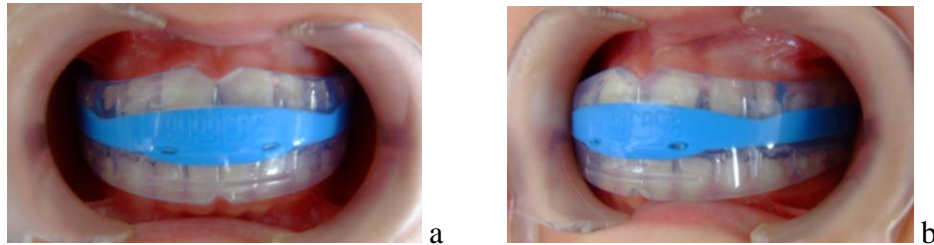


Fig.2 Intraoral image of Myobrace number 5. a. frontal view, b. lateral view.

RESULTS

The presented patient has been checked every month during the therapy period. Meanwhile all temporary dental units have been physiologically replaced with permanent teeth. Myobrace has been

used according to our recommendations. We observe: class I molar and canine relationships; 1/3 frontal overbite; alignment of the superior incisors; normal overjet.

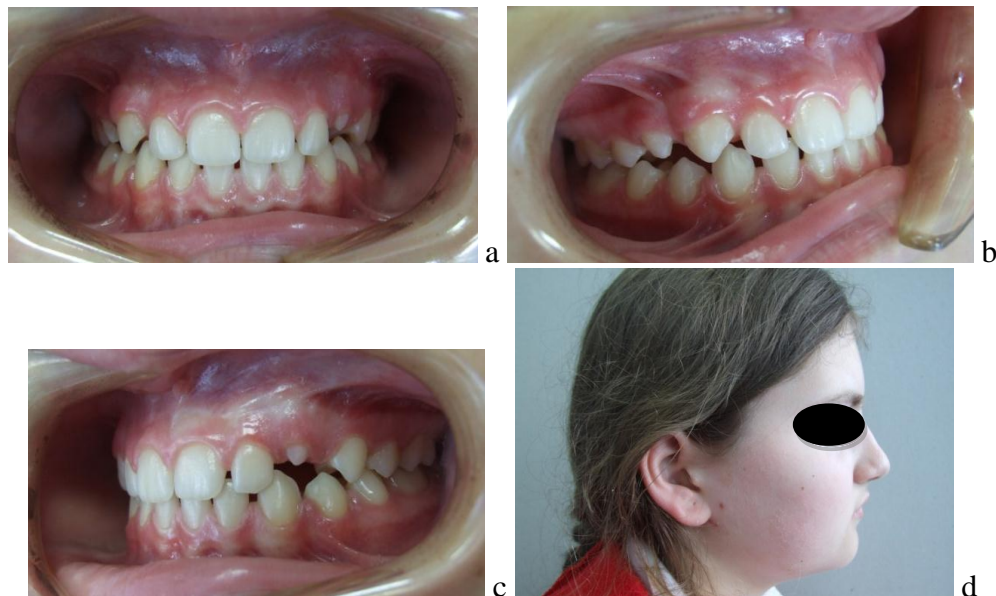


Fig.3 Aspects after 10 months of Myobrace therapy. a. Intraoral frontal view. b. intraoral lateral right view. c. intraoral lateral left view. d. profile facial view.

DISCUSSIONS

Myobrace is an innovative concept in orthodontic therapy. Presenting high

design techniques, it accomplishes the alignment of the anterior dental units,

and places the mandible in class I relationship. These flexible devices have dental slots that are individually sized and DynamiCore, an active internal core which controls the

development of the dental arch. Myobrace is available for use in children with mixed or early permanent dentition, who require orthodontic therapy ⁴.

CONCLUSIONS

The treatment of class II/2 malocclusion during puberty usually leads to success, but perfection cannot be achieved. If the face develops without proper dental and alveolar compensation or therapy, the facial appearance will be flat, and with an insufficient development of length of the inferior dental arch, therefore presenting dental and alveolar deep bite, as well as basal deep bite⁵.

The awareness of the functional pattern of Myobrace is very important. This device shares some characteristics with conventional therapy appliances. The combination between the internal rigid core and the flexible external part helps the alignment of the dental units during the late mixed dentition, but also during the early permanent

dentition. It presents a clear advantage towards other positioners ⁶.

The annulment of vicious habits leads to visible improvement of the malocclusion. In some clinical situations, Myobrace system may eliminate the treatment stage with fixed orthodontic therapy. Therefore, it is considered to be a viable alternative in dental alignment for children and adults ^{7,8}. It can be removed by patients, modulates the perioral muscular system and adjusts different dental anomalies. Because it is a mobile orthodontic appliance, the success of the therapy depends highly on the regularity of its use ^{9,10}. We strongly recommend wearing Myobrace during the sleeping period and also minimum 2-3 hours a day.

REFERENCES

1. Laura Mitchell - An Introduction to Orthodontics
2. Contemporary Class II orthodontic and orthopaedic treatment: a review , Australian Dental Journal, Volume 52, Issue 3, September 2007, Pages 168-174.
3. Thomas M. Graber, Robert I. Vanarsdall, Jr.- Orthodontics- Current principles and Techniques, third edition.
4. www.myobrace.com, Myobrace manual.
5. Tancan Uysal, Ahmet Yagci, Sadik Kara, Sakru Okkesim - Influence of Pre-Orthodontic Trainer treatment on the perioral and masticatory muscles in patients with Class II division 1 malocclusion.
6. Richard A.Litt, Leth Nielsen - Interceptive treatment of Class II, Division 2
7. E. McKie, A Crowe, W. McCombes, R Freeman - Dental nurses as trainers and assessors: vocational dental trainer attitudes.
8. Niko Bock, Sabine Ruf - Post-treatment occlusal changes in Class II division 2 subjects treated with the Herbst appliance
9. Declan Millett, Richard Welbury - Orthodontics and Paediatric Dentistry.
10. H. Devreese, G. De Pauw, G. Van Maele, A. M. Kuijpers-Jagtman and L. Dermaut - Stability of upper incisor inclination changes in Class II division 2 patients.

THE TOPOGRAPHY AND SHAPE OF THE MANDIBULAR CANAL IN EDENTULOUS PATIENTS



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ABSTRACT

The knowledge of the topography of the mandibular canal (MC) inside the mandible becomes important when surgical decisions are to be taken, especially in edentulous patients.

Aims. To examine the topography of the MC in vertical and horizontal dimensions, as well as its shape variations.

Material and Methods. Twenty edentulous patients were analyzed using computer tomography. The distances from the MC to the buccal and lingual compact plates, as well as to the alveolar crest and inferior border of the mandible, were assessed in the molar and premolar regions.

Results. The mean distance from the MC to the lingual compact plate was similar in the two regions (3.1 ± 1.3 mm and 3 ± 1.3 mm, respectively), whilst the same distance measured to the buccal compact plate varied from 4.6 ± 1.3 mm in the molar area to 2.8 ± 1.2 mm in the premolar area. When comparing the distances to the alveolar crest, MC was closer to this in the molar area (6.7 ± 2.6 mm) than in the premolar area (9.2 ± 3.7 mm). The mean distance between the MC and the inferior border of the mandible was slightly higher in the premolar region (7.5 ± 1.4 mm), when compared to that measured in the molar region (7.3 ± 1.8 mm). A strong positive correlation between the vertical and horizontal diameters of the MC was found in the molar area ($r=0.72$, $p=0.0003$, $n=20$).

Conclusion. In edentulous patients, the distances from the MC to the lingual compact plate and mandibular inferior border were comparable in the two regions, while the other evaluations were different.

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INTRODUCTION

The knowledge of the topography of the mandibular canal (MC) becomes important when surgical decisions are to be taken, especially in edentulous patients. High-resolution thin section CT with cross-sectional oblique and panoramic CT reconstructions has been shown to be an excellent tool for the preoperative evaluation of the mandible for dental implant surgery. Oblique cross-sections throughout the entire surgical field allow visualization of osseous topography as well as related internal anatomic structures such as the inferior alveolar canal, the mental foramina, and the incisive canal. The surgeon-restorative dentist team can plan so fixture positioning more effectively, thereby minimizing surprises in the operating room. The ultimate prosthesis is optimized because the surgeon can take full advantage of the available bone to achieve proper fixture alignment. However, although CT scans are more precise, panoramic radiography is sufficiently accurate for routine clinical

purposes; CT scans have an additional advantage in presurgical planning, since they reveal the horizontal dimension and shape of the mandible, and the topography of the MC.

In atrophic mandible the distance of the MC to the lingual and buccal surface was shown to remain constant, whereas the distance to the cranial and caudal surface is markedly reduced according to the degree of atrophy. The mass of compact and spongy bone tissue is reduced to a level of 50% or less of the original volume. In general, the cortical lamina around the mandibular canal is more often found on the caudal side than on the cranial side. At extreme rates of reduction of residual ridges the mandibular canal is enclosed by compact bone tissue.

We aimed to examine the topography of the MC in vertical and horizontal dimensions, as well as its shape variations on cone beam computed tomography (CBCT) images of edentulous patients, and to statistically evaluate the results.

MATERIAL AND METHODS

Twenty edentulous patients were analyzed using cone beam computed tomography (CBCT) images. Assessment of the distances from the MC to the buccal and lingual compact plates, and to the alveolar crest and inferior border of the mandible was performed in the premolar and molar regions (**fig.1**). All subjects were scanned using a CBCT machine – iCat (Imaging Sciences International). The CT data were analyzed using dedicated software – iCatVision. The scanning protocol comprised: sensor dimension – 20 X 25 cm; grayscale resolution – 14 bit; voxel dimension – 0.25 mm;

acquisition time – 13.9 seconds; 120 KV, 5 mA.

The Student's *t*-test was used to compare the difference between the sample mean distances, measured to the same landmarks in molar and premolar regions. The Pearson correlation coefficient was used to test the covariation of vertical and horizontal diameters in the two regions. Data analysis was done using StataIC 11 (StataCorp.2009. Stata: Release 11. Statistical Software.

College Station, TX, USA). A *p*-value < 0.05 was considered statistically significant.

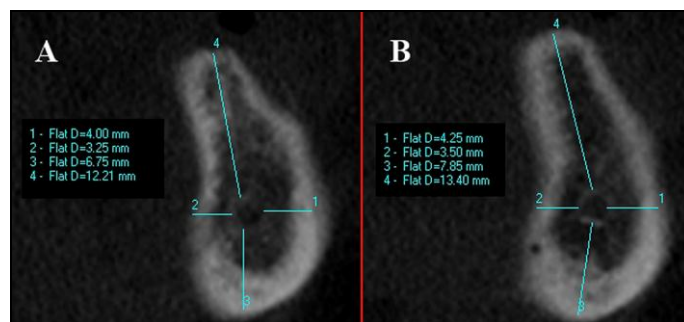


Fig.1. Measurements performed in the molar (A) and premolar (B) regions of an edentulous mandible. CBCT, coronal MPR.

RESULTS

The mean distances measured from the MC to the external four landmarks are listed in Table 1. The difference between the sample mean distance from the *MC* to the *buccal compact plate* in molar and premolar regions was 1.8, with a 95% CI from 1.16 to 2.4, $p < 0.001$ (Fig.2). The difference between the sample mean distance

from the *MC* to the *alveolar crest* in premolar and molar regions was 2.45, with a 95% CI from 0.4 to 4.5, $p = 0.02$ (Fig.3).

A strong positive correlation was found between the *vertical and horizontal diameters* of the MC in the molar area ($r = 0.72$, $p = 0.0003$, $n = 20$).

Table 1 The distances measured from the MC to the external four landmarks (mm)

Landmark	Mean (SD)	
	Molar region	Premolar region
Lingual compact plate	3.1 (1.3)	3 (1.3)
Buccal compact plate	4.6 (1.3)	2.8 (1.2)
Alveolar crest	6.7 (2.6)	9.2 (3.7)
Inferior border	7.3 (1.8)	7.5 (1.4)

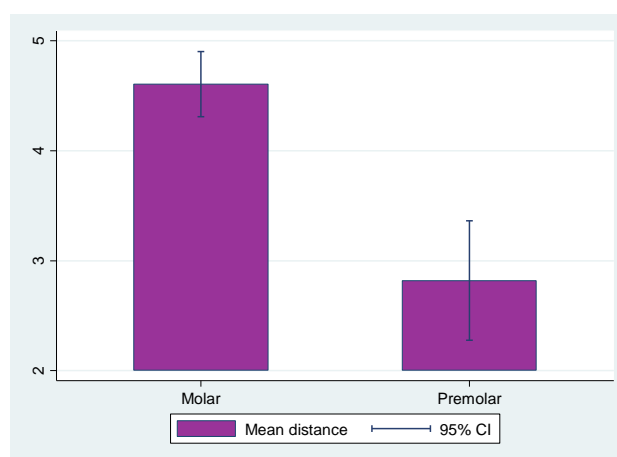


Fig.2. The mean distances (mm) measured from the mandibular canal to the buccal compact plate in the two regions.

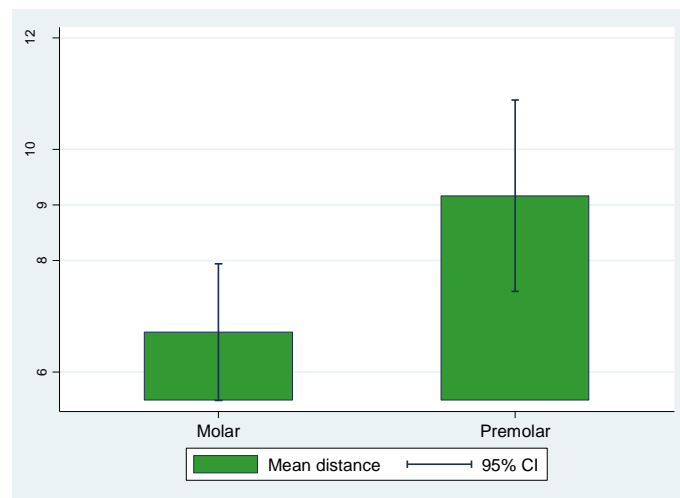


Fig.3. The mean distances (mm) measured from the mandibular canal to the alveolar crest in the two regions.

DISCUSSION

The inferior alveolar nerve (IAN) courses in the mandibular canal (MC) and it is vulnerable in various instances, such as dental implant surgery, orthodontic treatment, endodontic treatment, and mandibular anterior segmental osteotomy.

In order to assess a safe thickness for harvesting a mandibular block graft an anatomical study was performed on dentulous and edentulous mandibles, and it was found that the safe thickness to harvest ramus grafts was, on the buccal side in the molar region, 2.5 to 3.0 mm. Our study confirms that in edentulous mandibles this thickness for bone harvesting allows sparing the IAN.

The evaluation of the buccolingual dimension showed that the MC was located either in contact with or close to the lingual cortical plate (≤ 2 mm) in the molar region of the majority of the cases, which is a value smaller than we obtained in the present study; the differences should be racial, and also the fact that the respective study was performed on dry skulls should be taken into account. As it proceeds anteriorly the MC moves

toward the buccal aspect of the mandible.

In edentulous mandibles the position of the MC was found closer to the lingual compact plate in the region of the third molar, equidistant to the lingual and buccal compact plates in the region of the first and second molars, and closer to the buccal compact plate in the region of the first premolar. In our study, the MC was almost equidistant to the lingual and buccal compact plates in the molar region, and closer to the buccal one in the premolar region.

The MC was found located variably above the inferior border of the mandible, at distances ranging from 7.60 mm to 11.80 mm, the highest location being found in edentulous mandibles. Our results however correlate with the minimal value of this range, being of 7.30-7.50 mm. The differences should be related to the different methods used for measurements, and the racial differences between the lots of samples. It was previously concluded that CT gave the most accurate position of the mandibular canal as compared to other

methods of determination, and is therefore probably the best method for preoperative planning involving the area close to the mandibular canal. Moreover, CBCT reformatted panoramic images outperform the digital panoramic images in the identification of the mandibular canal;

due to the fact that the CBCT images are reformatted slices of the mandible, they are free of magnification, superimposition of neighboring structures, and other problems inherent to panoramic radiology and this results in very clear images that better depict the mandibular canal.

CONCLUSIONS

In edentulous patients, the distances from the MC to the lingual compact plate and mandibular inferior border were comparable in the two regions, while the other evaluations

were different. The MC was rather tall and narrow in the molar region, and it became almost circular in the premolar area.

REFERENCES

1. Angelopoulos C, Thomas SL, Hechler S, Parissis N, Hlavacek M. Comparison between digital panoramic radiography and cone-beam computed tomography for the identification of the mandibular canal as part of presurgical dental implant assessment. *J Oral Maxillofac Surg.* 2008; 66(10):2130-2135.
2. Gowgiel JM. The position and course of the mandibular canal. *J Oral Implantol.* 1992; 18(4):383-385.
3. Hwang K, Lee WJ, Song YB, Chung IH. Vulnerability of the inferior alveolar nerve and mental nerve during genioplasty: an anatomic study. *J Craniofac Surg.* 2005; 16(1):10-14; discussion 14.
4. Kilic C, Kamburoglu K, Ozen T, Balcioglu HA, Kurt B, Kutoglu T, Ozan H. The position of the mandibular canal and histologic feature of the inferior alveolar nerve. *Clin Anat.* 2010; 23(1):34-42.
5. Klinge B, Petersson A, Maly P. Location of the mandibular canal: comparison of macroscopic findings, conventional radiography, and computed tomography. *Int J Oral Maxillofac Implants.* 1989; 4(4):327-332.
6. Leong DJ, Li J, Moreno I, Wang HL. Distance between external cortical bone and mandibular canal for harvesting ramus graft: a human cadaver study. *J Periodontol.* 2010; 81(2):239-243.
7. Ozturk A, Potluri A, Vieira AR. Position and course of the mandibular canal in skulls. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011.
8. Schwarz MS, Rothman SL, Chafetz N, Rhodes M. Computed tomography in dental implantation surgery. *Dent Clin North Am.* 1989; 33(4):555-597.
9. Tal H, Moses O. A comparison of panoramic radiography with computed tomography in the planning of implant surgery. *Dentomaxillofac Radiol.* 1991; 20(1):40-42.
10. Tantanapornkul W, Okouchi K, Fujiwara Y, Yamashiro M, Maruoka Y, Ohbayashi N, Kurabayashi T. A comparative study of cone-beam computed tomography and conventional panoramic radiography in assessing the topographic relationship between the mandibular canal and impacted third molars. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007; 103(2):253-259.
11. Ulm C. [Anatomic-roentgenologic study of the mandibular canal in atrophic mandible]. *Wien Klin Wochenschr.* 1989; 101(11):390-393.
12. Yu IH, Wong YK. Evaluation of mandibular anatomy related to sagittal split ramus osteotomy using 3-dimensional computed tomography scan images. *Int J Oral Maxillofac Surg.* 2008; 37(6):521-528.

ODONTO-PERIODONTAL MANIFESTATIONS IN CALCIUM AND VITAMIN D PROLONGED DEFICIENCY



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ABSTRACT

Introduction: The bone is the recipient of wide informational and operational exchange provided by the balance or imbalance of the hormonal bone-building combination and also by numerous non-hormonal factors: genetic, nutritional, mechanical, etc. In adults, the significant and prolonged reduction of tissue calcium and magnesium, form the clinical picture of spasmophilia.

Material and method: 23 patients (19 females and 4 males) of various ages, who came for examination presenting obvious symptoms of spasmophilia decompensation, were evaluated. The entire group has been subjected to a detailed examination of the oral cavity. We have functionally explored calcium and phosphorus metabolism through the determination of concentration levels of calcemia, phosphoremia, calciuria and phosphoremia from 24-h urine collection; we have determined the concentration level of alkaline and acid phosphatase and we have used the provoked hypercalciuria test and the 30 mg vitamin D2 test. Parathyroid function has been evaluated through the determination of phosphorus clearance (Cl P) in 24-h urine and by calculating the urine phosphorus (mg/24 hours) / blood phosphorus (mg/1000) ratio (Pu/Ps).

Results. Following the exploration of the parathyroid function using phosphorus clearance (Cl P) and the urine phosphorus / blood phosphorus ratio (Pu/Ps) in the studied group, 12 patients out of 23 presented individual values above the top value of the normal value, demonstrating the existence of an increased parathyroid tone. For the urine phosphorus / blood phosphorus ratio (Pu/Ps), individual values are very dispersed, most being above the normal value. The provoked hypercalciuria test demonstrated the absence of elimination, the calciuria level being lower than in the control sample. In addition, the presence of increased amounts of osteoid tissue is supported by a slightly elevated alkaline phosphatase value. In the studied group, the 30 mg vitamin D2 test showed a significant retention of urinary calcium.

Conclusions: The exploration of calcium and phosphorus metabolism and of the hormonal factors coordinating it confirms the observations which sustain that odonto-periodontal lesions, of various degrees, emerge in young ages. Calcium and vitamin D long deficiency in the population of our country triggers early demineralization of the cancellous bone tissue, which predominates in the maxilla and mandible.

Keywords: calcemia, phosphaturia, calciuria, phosphoremia, spasmophilia, osteoporosis, periodontal disease, common calcium pool, clearance, cortical bone, trabecular bone.

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INTRODUCTION

The bone is the recipient of wide informational and operational exchange provided by the balance or imbalance of the hormonal bone-building combination and also by numerous non-hormonal factors: genetic, nutritional, mechanical, etc. (fig. no. 1).

In adults, the significant and prolonged reduction of tissue calcium and magnesium levels form the clinical picture of spasmophilia, which as demonstrated through explorations using ^{45}Ca is normocalcemic, but hypocalcic (1).

An early clinical sign of bone demineralization process accompanying spasmophilia is represented by odonto-periodontal lesions, and later, after the installation of estrogen deficiency in women, a menopausal characteristic, osteoporosis appears.

In females, the depletion due to pregnancy and lactation periods is added to the deficiency process. RIGGS estimates that during lifetime, women lose about 35% of the cortical bone and 50% of the trabecular bone, while men have a positive balance by 25-30% higher compared to women (2, 3).

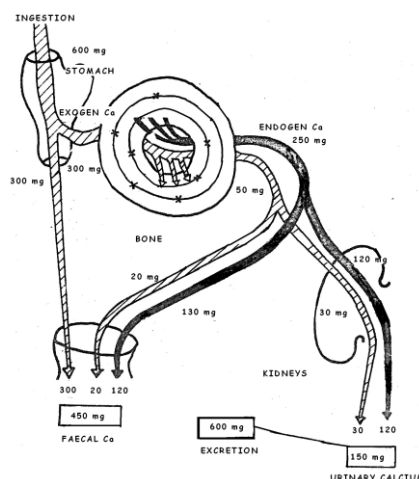


Fig.1- The path of calcium in the body (according to Lichwitz).

AIM

This study is aimed to present using concrete evidence, the odonto-periodontal result of calcium and vitamin D deficiency, especially among young people (from the age of 20 years) and especially in women considering

that osteoporosis developed due to postmenopausal estrogen deficiency represents nothing but the aggravation of a preexisting demineralization process.

MATERIAL AND METHOD

23 patients (19 females and 4 males) of various ages who came for examination presenting obvious

symptoms of spasmophilia decompensation, have been evaluated. Clinically, spasmophilia has been

confirmed by the Chvostek sign and by the Trousseau sign (elicited following arm compression and hyperpnoea for 3 minutes). The examination of the oral cavity for the entire group of patients revealed carious processes, multiple dental restorations and periodontal pain characterized by the presence of plaque and tartar, gingival inflammation to various degrees, the presence of periodontal pockets with different depths in periodontal probing, enlargement of periodontal space, decrease of alveolar bone density, generalized horizontal alveolysis and vertical localized alveolysis (detected radiographically).

The whole group underwent functional exploration of calcium and phosphorus metabolism through the determination of concentration levels of calcemia, phosphoremia, calciuria and phosphaturia from 24-h urine.

Especially helpful was the determination of alkaline and acid phosphatase values, which offer information both on the presence of the osteoid tissue, and on the osteoblastic reactivity (4).

To explore the skeleton and the common calcium pool the provoked hypercalciuria test and the 30 mg vitamin D₂ test, proposed by Lichwitz and collaborators, were used.

Since phosphaturia shows diurnal variations, the parathyroid function has been assessed through the determination of phosphorus clearance (Cl P) from 24-h urine and calculation of the urine phosphorus (mg/24 hours) / blood phosphorus (mg/1000) ratio (Pu/Ps). Clearance value has been determined using the calculation formula for the endogenous creatinine clearance: $Cl = U \times V / P$, where U = urine concentration of P in mg/dl, V = urine volume per minute and P = plasma phosphorus content in mg/dl. The normal value of Cl P = 8-15 ml/minute. Radiological evidence of odonto-periodontal changes of the maxillar and mandibular bone was obtained for each patient through the panoramic radiograph, which has been interpreted based on the age group to which the patient belonged to (20-30 years, 30-40 years, 40-50 years, 50-60 years and over 60 years).

RESULTS

A representative case of this study was the one of a 23-year-old young woman, who showed increased dental sensitivity and especially gingival sensitivity. Clinical examination revealed the presence of a low number of dental restorations and even a lower number of carious processes. However, the patient presented an advanced generalized gingivitis, the decapitation of interdental papillae, loss of the "orange peel" aspect and bleeding during touching and brushing, without the presence of tooth mobility. The radiograph showed generalized horizontal alveolysis, enlargement of

periodontal spaces and a slight alveolar bone demineralization. Clinically, the Chvostek sign was intensely positive, and the provoked hyperpnoea showed the presence of the Trousseau sign.

The whole group underwent functional exploration of calcium and phosphorus metabolism through the determination of concentration levels of calcemia, phosphoremia, calciuria and phosphaturia from 24-h urine and the parathyroid function has been assessed through the determination of phosphorus clearance and the calculation of urine phosphorus (mg/24 hours) / blood phosphorus (mg/ 1000) ratio.

Table I shows the laboratory results obtained following the examination of the 23 patients. Evaluation of the parathyroid function using phosphorus clearance (Cl P) and the urine phosphorus / blood

phosphorus ratio (Pu/Ps). In the study group, 12 patients out of 23 showed individual values above the upper limit of the normal value, demonstrating the existence of an increased parathyroid tone (*fig. no. 2*).

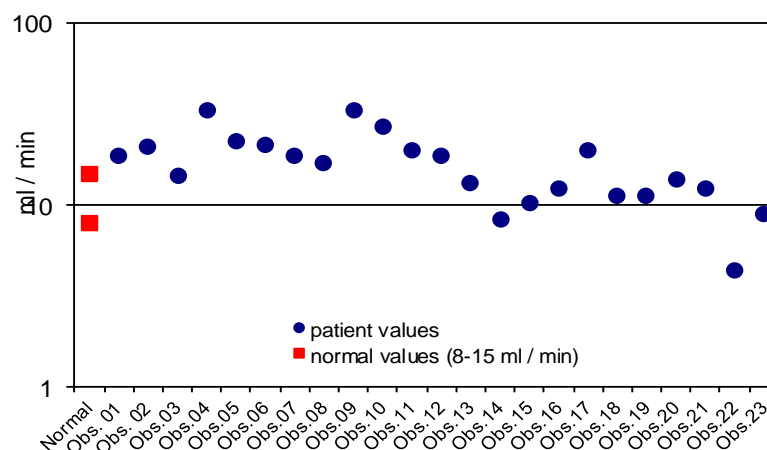


Fig. 2 - Phosphorus clearance

As to the urine phosphorus / blood phosphorus ratio (Pu/Ps), individual

values are highly dispersed, most being above the normal value.

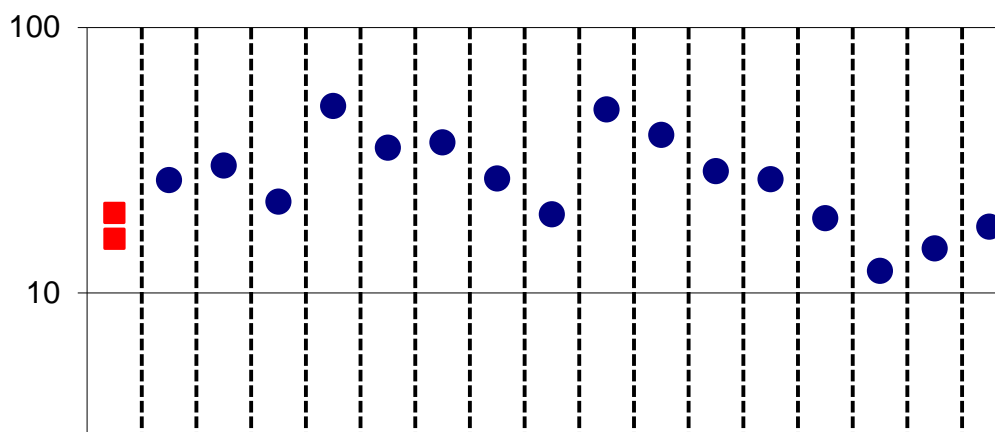


Fig. 3 - Urinary phosphorus / blood phosphorus ratio (Pu/Ps)

Functional exploration of calcium metabolism using the provoked hypercalciuria test and the 30 mg vitamin D test.

In our group of patients (table I), we have used the functional exploration method of the skeleton proposed by Lichwitz and

collaborators (5), based on studies related to the path of calcium in the body, the dynamic exploration of bone mineralization, using hypercalciuria induced with 176 mg Ca and the one with 30 mg vitamin D, to which we added a 3 g calcium lactate supplement per day (*fig. no. 4*).

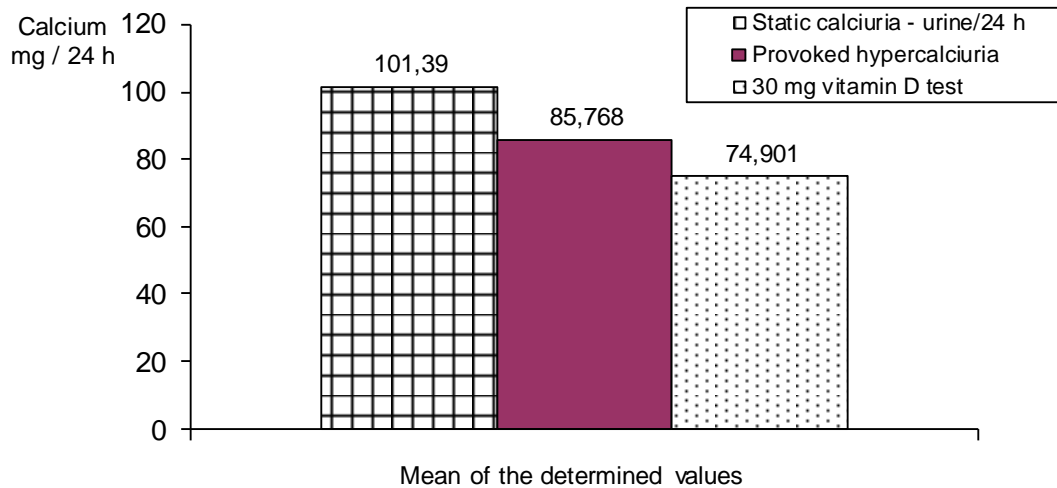


Fig. 4 - Static calciuria, provoked hypercalciuria test and 30 mg vitamin D test.

Provoked hypercalciuria test

If subjects are given intravenous injections of calcium, we exclude the intestinal factor and we may assess to some extent the size of the osteoid range, measuring the renal excretion of calcium, compared with the static test. In normal mineralization, 25-40% of the injected calcium is excreted. In the presence of increased amounts of

osteoid tissue, which characterizes osteomalacia, excretions are below 25 %. In our group excretions were absent, and calciuria level was lower than the one in the control sample (Table I and fig. no. 4). The presence of increased amounts of osteoid tissue is supported also by a slightly elevated alkaline phosphatase value (Table I).



Fig. 5a - Panoramic radiograph for the 20-30 years age group – male

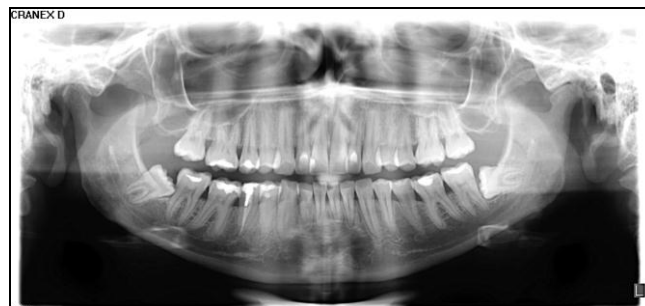


Fig. 5b - Panoramic radiograph for the 20 - 30 years age group – female

30 mg vitamin D2 test

The vitamin D test provides information not only on the possibility and capacity of intestinal calcium absorption, but also on the presence of the osteoid tissue. In the studied group, urinary calcium retention is significant (Table I and *fig. no. 4*). For the 7 patients older than 50 years, the behavior in these two tests is similar, i. e. the retention of calcium in the osteoid tissue.

Radiographic exploration of the odonto-periodontal changes and of the maxillary and mandible bone in**case of calcium and vitamin D deficiency, by age.**

For the 20-30 years age group (*fig. 5a, fig. 5b*) for both genders, there are noticed dental fillings, carious processes, and also the presence of periodontal disease in the early stage, with generalized enlargement of the periodontal spaces in females, and localized enlargement in males, vertical localized alveolysis in the side groups of teeth. As to bone density and mineralization, it is noticed in females a stronger demineralization of the bone structure, especially in the mandible, where bone trabeculae are tenuous.

THE 30 - 40 YEARS AGE GROUP

The panoramic radiograph reveals the presence of edentia, prosthetic restorations, root remnants and an advanced chronic periodontitis, involving the enlargement of periodontal spaces in teeth 1.7, 2.2, 2.3, 3.7, 4.6; the presence of generalized

horizontal alveolysis (especially in the front region), of the vertical one in teeth 3.3 and 3.5 and furcation defects in molars. Significant changes of bone density (cancellous bone) may be observed in the maxilla.



Fig. 6 – Panoramic radiograph for the 30 - 40 years age group

THE 40 - 50 YEARS AGE GROUP

Fig. no. 7 shows the radiograph of a female patient. Being known the implications of hormonal changes around this age, together with calcium and vitamin D deficiency, it is noticed a generalized demineralization of bone structure, fairly uniform in the maxilla and mandible, and the presence of an

advanced chronic periodontitis with generalized horizontal alveolysis, vertical alveolysis mainly in the lateral teeth, unevenness of the bone form, enlargement of the periodontal spaces, presence of fillings and of endodontic treatment, following caries progression, edentia and prosthetic restorations.

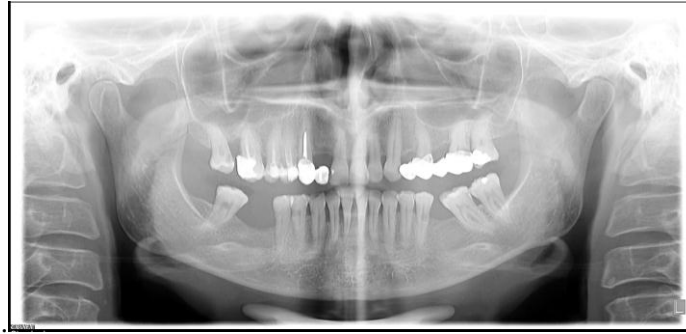


Fig. 7 - Panoramic radiograph for the 40 - 50 years age group.

THE 50 - 60 YEARS AGE GROUP

As with aging (*fig. nos. 8a and 8b*), changes in the oral cavity become more advanced, with the preservation of differences between genders, women being usually more affected. Numerous carious processes, restorations, endodontic treatments, apical processes, root remnants, edentia (many of them of periodontal nature), old and poor prosthetic restorations are noted. In both genders, the diagnosis is of advanced chronic periodontitis,

accompanied by pronounced unevenness and demineralization of the bone form, especially in women, and in the maxilla accompanied by generalized horizontal alveolysis proving the chronic evolution of periodontal disease, and also vertical alveolysis, with the presence of periodontal pockets that may be active, case in which the chronic periodontitis becomes exacerbated.



Fig. 8a - Panoramic radiograph for the 50-60 years age group - male



Fig. 8b - Panoramic radiograph for the 50-60 years age group - female

AGE GROUP >60 YEARS

Panoramic radiographs for this age group reveal the presence of generalized horizontal alveolysis, vertical alveolysis extended to full teeth groups, presence of large areas of apical and marginal radio-transparency, damaged furcations of molars, presence of root remnants,

multiple edentulous sites, and prosthetic restorations not adapted due to the progression of the periodontal disease and the loss of the bone support. In addition, bone demineralization is very advanced, especially in the maxilla (6).



Fig. 9 - Panoramic radiograph for age group over 60 years.

DISCUSSIONS

Studies with radioactive calcium (^{45}Ca) proved that beside the stable calcium from the bone, there is a mobile form as well, amounting to 6-7 g, which represents the "common calcium pool" or the calcium entering the exchanges. The common calcium pool consists of: 1g calcium from blood and extravascular fluids; 2g mobile calcium from tissues and 3-4 g mobile calcium from the bone. Main constants: calcemia, phosphoremia, calciuria and phosphaturia values in the studied group (table I) are within normal parameters, demonstrating that calcium homeostasis is maintained at optimum values thanks to the intervention of parathyroid hormone (PTH), calcitonin and vitamin D₃, although the common calcium pool in spasmophilia is low (*Milhud*). Between the circulating calcium and the

interstitial calcium take place highly active exchanges, the entire plasma calcium amount being changed at this level every 20 minutes. In this process, the parathyroid plays an active role, which is able to regulate the release of PTH in every minute, according to the physiological requirements. By its osteolytic effect, it acts primarily on the osteocyte, managing to maintain constant the calcemia value, within normal limits (7, 8).

Assessment of the parathyroid function using the phosphorus clearance (Cl P) and the urine phosphorus / blood phosphorus ratio (Pu/Ps).

Starting from the idea that PTH controls also phosphorus metabolism, reducing phosphoremia and increasing phosphaturia values, Cl P and the Pu/Ps ratio may represent an indirect way of assessing the parathyroid

function, given that PTH determination is impossible.

The clinical interest for phosphaturia determination, according to some authors, is reduced because its value is closely related to the dietary phosphorus content. Meat and meat products provide large amounts of phosphorus and phosphaturia value corresponds to the 2/3 of the ingested phosphorus. Phosphaturia would therefore have diagnostic significance only if the quantities of phosphorus from the diet would be mentioned during the exploration period which in normal conditions is not possible. However, phosphorus clearance and the Pu/Ps ratio are useful parameters for assessing parathyroid function. Cl P value and Pu/Ps ratio vary with both diet and the schedule, being stable in the morning and high during the afternoon. Given the diurnal variations of the phosphaturia values, we have calculated Cl P in 24-hours urine, and the Pu/Ps ratio taking into account the amount of variations during 24 hours.

The obtained data show that in chronic food deficit of calcium and vitamin D, the parathyroid tone remains high, to achieve calcium homeostasis (vital for the normal activity of the body). Calcium requirement is taken from the main source (the bone) and partly from the common calcium pool. PTH acts rapidly on the osteocyte, causing osteolytic osteolysis which does not hinder the bone collagen; collagen damage occurs later, when emerges the action of osteoclasts and estrogen deficiency, which quickly lead to osteoporosis. In other words, physiological osteopenia prepares the ground for osteoporosis (9).

Some observations support the idea of an early demineralization of the odonto-periodontal system.

A significant factor in the demineralization process is the geographic latitude. According to observations of American researchers, it has been demonstrated that the number of carious teeth, extracted and restored in children aged 12-14, grows from the Gulf of Mexico to the Canadian border by 15% per degree of latitude, which means an increase of 200% in northern USA (*Cârligeriu and collab.*) (10). Thus, the influence of geographical latitude is explained by the fact that in the south, the number of sunny hours to which is exposed the individual is greater, leading to a better vitamin D synthesis, which provides better bone mineralization of the hard bone tissue.

Given that in the temperate region of our country, at least 6-7 months a year sun exposure is reduced or absent, the synthesis of vitamin D in the skin is low. To this it is added a low calcium diet, so the phenomenon appears to be identical to the one from northern USA.

A group of researchers from the Center for Hygiene and Public Health, Radiation Hygiene of Timisoara have studied from 1988 to 1989 the content of bone-seeking radionuclides in the teeth after the Chernobyl nuclear accident. From the ashes of incinerated teeth, researchers have determined the concentration level of strontium, radium and calcium (11).

This study found that in all age groups, including in children, regardless of gender, the calcium content of the tooth is very low, compared to the normal values published by Derhes (children = 276 mg/g of tissue; adults = 213 mg/g of tissue). And these authors relate tooth calcium deficiency to the dietary deficiency of milk and dairy food, and in females, the higher deficiency was caused by the body depletion during pregnancy and lactation periods.

Using Ca45 it was established that the fetus during the intrauterine life receives from mother about 30 g calcium, mostly deposited in the skeleton. In pregnant women, calcium losses are increased in relation to the requirements of the fetus during the third trimester of pregnancy and the lactation period. During pregnancy and a 6-month nursing period, a woman loses about 80 g of Ca, which can hardly be compensated for.

Functional exploration of the metabolism of calcium using the provoked hypercalciuria test and the 30 mg vitamin D test

Cross- and longitudinal studies that have measured the bone mineral density acknowledge two distinct phases of bone mass loss with age: a slow phase, which exists in both genders and occurs after peak bone mass achievement and a second phase, rapid, which characterizes only the postmenopausal women (12).

The *slow* phase of bone loss begins around the age of 30-40 years, and it continues throughout life, affecting in a similar way the trabecular and the cortical bone.

The *accelerated* phase that occurs in menopause affects mainly the trabecular bone. Estrogen deficiency in this period, associated with low intake of calcium and the deficiency of vitamin D contribute to the acceleration of the demineralization process.

The mandible and maxilla contain large amounts of trabecular bone, as well as the vertebral bodies, distal forearm, ankle, which explains tooth loss at this age. If for the menopausal

period we have these explanations, for the *odonto-periodontal demineralization syndrome* in childhood, the deficiencies of calcium and vitamin D, which characterize the temperate region in which we live, still remain in discussion.

Regardless of the presence of osteoid tissue, a large amount of calcium injected or absorbed in the two samples is retained also in the common calcium pool, which in these conditions was found to be low, in addition to the prolonged deficiency of calcium and vitamin D, to which is subjected the population of our region (13).

Radiograph exploration of the odonto-periodontal changes and of the maxillary and mandible bone in case of calcium and vitamin D deficiency, on age groups

Radiological exploration of the bone mineral mass does not acknowledge the early-stage diagnosis, as demineralization signs occur only when 30% of the bone mineral is lost. There is a long period when bone manifestations are asymptomatic, but very important for the clinician.

Currently, the most popular method for investigating bone mineral density is the dual-energy X-ray absorptiometry (DEXA), but not for the mandible and maxilla (14, 15). By this method, bone density is measured in grams/square centimeter, both in the central and peripheral bones. This study is accurate, fast to execute (2-4 minutes) and the patient receives a low dose of radiation (1-5 μ Sv). DEXA is the most popular method used after the changes were determined using ultrasound densitometry (16).

CONCLUSIONS

1. The exploration of calcium and phosphorus metabolism and of the hormonal factors coordinating it (PTH, vitamin D and calcitonin) in

a group of patients predominantly under the age of 50 years confirm the observations which argue that odonto-periodontal lesions, of

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| <p>various degrees, emerge in young ages.</p> <p>2. Calcium and vitamin D long deficiency in the population of our country, characterizing the temperate region, triggers early demineralization of the cancellous bone tissue, which predominates in the maxilla and mandible, fact that explains the emergence of lesions of various degrees and in various age groups.</p> <p>3. The data found in our study confirm the need to establish an early and sustained prophylaxis with increased intake of calcium and vitamin D.</p> <p>4. The period until the age of 50 years is, for both genders, the one of "physiological osteopenia", which</p> | <p>prepares the ground for osteoporosis as disease.</p> <p>5. The increased parathyroid tone in response to the prolonged deficiency of calcium and vitamin D accelerates bone calcium turnover, without affecting the osteoid tissue, and it has the clear role to maintain calcium homeostasis and to complete partially the "common calcium pool".</p> <p>6. The dynamic exploration of the path of calcium in the body using the provoked hypercalciuria test and the 30 mg vitamin D test, strongly positive, demonstrate that the body shows a "hunger" for calcium, for bones, as well as for the common calcium pool.</p> |
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REFERENCES

- Velea R., Lungu G., Velea I.- „Manifestări odonto-parodontale în spasmofilie”, Revista Română de Osteoporoză, 1998, vol II, nr 1, pag. 35-40
- Yusuke A., Kazuo K., Makoto M.- „Vitamin D and periodontal disease”, Journal of Oral Science, 2009, Vol. 51, No. 1, 11-20
- Grant W.B.- „A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries”, Dermato-Endocrinology 3:3, July/August/September 2011, 193-198, Landes Bioscienc
- Jagelaviciene E., Kubilius R.- „The relationship between osteoporosis of the organism and periodontal disease”, Medicina (Kaunas) 2006; 42(8)
- Herghelegiu A., Gălușcă B., Zbranca E.- „Aspecte fiziopatologice ale osteoporozei postmenopauzale”, Revista Română de Endocrinologie și Metabolism, ed. „Gr. T. Popa”, Iași, vol. 3, nr. 4, 2004
- Onisei D., Onisei D.- „Parodontologie clinică”, Editura Mirton, Timișoara, 2011
- Lungu G., Velea I., Velea Rodica- „Spasmofilia clinica, diagnostic, tratament”, Ed. Mirton, Timișoara, 1995.
- Milcu S., Niculescu G., Scarlat M.- „Osteoporoza”, Ed. Militară, București, 1992
- Sahota O., Munday M.K., San P., Godber I.M., Lawson N., Hosking D.J.- „Relatiile între vitamina D și parathormon: homeostazia calciului, turn-overul osos și densitatea minerală osoasă la femeile în postmenopauză cu osteoporoză stabilită”, Bone, 2004, 35, 312-319
- Heumier D.- „Mecanisme cellulaires du vieillissement osseux”, Ed. Med et Hyg, Geneve, 1985, pag 43
- Cărligeriu V., Bold A.- „Tratat de odontoterapie conservatoare și restauratoare, vol I”, Ed. LITO UMFT, Timișoara, 2006
- Popescu D., Margocsy N., Pomoje R., Toro L., Crețu I., Toro T., Căpălnășan I., Nodiți M.- „Cercetarea conținutului de radionucleoizi osteotropi la populația din zona de sud-vest a țării, în vederea grupelor de risc pentru sănătate. Investigarea valorii de indicator a dinților în estimarea încărcăturii corporale cu Sr-90 și Ra-226.”- Centrul de igienă și sănătate publică, Timișoara. Com, la a XXII a ed. a sesiunii Științifice, iulie 1989
- Lichwitz A., De Seze S., Hioco D., Bardier PH., Parlier R.- „Les explorations fonctionnelles du squelette.” Sem. Hop Paris 33, 1957, 59, 3455-3459.
- Sultan N., Rao J.- „Association between periodontal disease and bone mineral density in post-menopausal women: A cross sectional study”, Med. Oral. Patol. Oral. Cir Bucal., 2011 May 1; 16 (3): e 440-7
- Koduganti R., Gorthi C., Reddy P.V., Sandeep N.- „Osteoporosis: A risk factor for periodontitis”, Journal of Indian Society of Periodontology, May-Aug 2009, vol 13, issue 2, pag. 90-96
- Alekna V., Tamulaitiene M., Krasauskiene A.- „Diagnostics and treatment of osteoporosis.”, Endocrinology in Lithuania 2003, 11:94-108.

ADDITION PLASTY-MODERN COMPONENT OF THE COMPLEX MARGINAL PERIODONTAL DISEASE TREATMENT



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ABSTRACT

Marginal periodontitis represents nowadays one of the main causes of oral disfunction. Treatment can only begin after a thorough research of the patient based on what the treatment plan can be established. In our study, guided tissue regeneration was applied in pouches with vertical bone loss and only minimal interdental papillae loss. Bio-oss granules are mixed with either serum or blood or plasma. After applying the addition material into the bone defects, the membrane is put over the treated area. The position of the membrane proved to have an indirect relationship with the amount of regenerated bone. We have noticed that the weakest results were obtained when the membrane was collapsed inside the bone defect. If the membrane is placed higher coronary, more space is going to be obtained for regeneration. What the classification of the periodontal lesions according to the remaining bone walls is concerned, we can conclude that the number of lesions with only 2 spare walls (919 cases) is comparable to the number of lesions with 3 walls (16 cases).

Periodontal lesions with only 1 wall were present in only 5 cases. We concluded that the level of gingival insertion and the quantity of obtained bone as well as the level of gingival insertion over a period of 3-4 years is superior as compared to GTR combined with bone addition. The success of GTR is due to the fact that bone addition facilitates the maintaining of the space needed for regeneration, because of the position, stability and characteristics of the barrier membrane.

Key words: periodontal lesion, tissue regeneration.

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INTRODUCTION

Marginal periodontitis represents nowadays one of the main causes of oral disfunction. Treatment can only begin after a thorough research of the patient based on what the treatment plan can be established. In our study, guided tissue regeneration was applied in pouches with vertical bone loss and only minimal interdental papillae loss. Bio-oss granules are mixed with either serum or blood or plasma. After applying the addition material into the bone defects, the membrane is put over the treated area. The position of the membrane proved to have an indirect relationship with the amount of regenerated bone. We have noticed that the weakest results were obtained when the membrane was collapsed inside the bone defect. If the membrane is placed higher coronary, more space is going to be obtained for regeneration. What the classification of the periodontal lesions according to the remaining bone walls is concerned, we can conclude that the number of lesions with only 2 spare walls (919 cases) is comparable to the number of lesions with 3 walls (16 cases). Periodontal lesions with only 1 wall were present in only 5 cases. We concluded that the level of gingival insertion and the quantity of obtained bone as well as the level of gingival insertion over a period of 3-4 years is superior as compared to GTR combined with bone addition. The success of GTR is due to the fact that bone addition facilitates the maintaining of the space needed for regeneration, because of the position, stability and characteristics of the barrier membrane.

Marginal periodontitis represents nowadays one of the main causes of

oral disfunction. Various forms of periodontal disease have high incidence without being influenced by age or sex, appearing in all population groups.

Chronic marginal periodontitis are microbial diseases which in most of the cases have destructive, irreversible consequences on the whole periodontal complex, causing alveolar bone resorption. The variety of lesional periodontal processes which cause inflammation, dystrophic-degenerative tissue alteration and proliferative phenomena, need a complex local and general treatment, which is diversified in order to act on all ethiological factors.

Treatment can only begin after a thorough research of the patient based on what the treatment plan can be established, with steps following tissue equilibration between the different components of the marginal periodontium.[2]

Addition therapy represents, in the field of surgical treatment, an efficient mean for the reconstruction of bone defects. Periodontal surgery aims to remove pathologic tissue from periodontal pouches in order to obtain healing and to remodel soft and hard tissues in order to have good control of bacterial plaque.[5]

The rationale of guided tissue engineering is to stop apical migration of the epithelium, placing a membrane on the root surface, which doesn't allow the contact between the gingival tissue and the root surface. In this manner, cells derived from the periodontal tissue, are selectively induced on the root surface and the periodontal tissue is regenerated.[9]

INTRODUCTION

In our study, guided tissue regeneration was applied in pouches with vertical bone loss and only minimal interdental papillae loss. Favorable results are conditioned by the following local characteristics:

- Minimal gingival retraction,
- High consistence of the gingival mucosa,
- Reduced dental mobility.[1]

Applying bone addition materials results in the stimulation of bone regeneration as well as the stabilization of teeth.[4] All these implants are introduced in the defect after rigorous treatment of periodontal structures, without over filling the defect.

Obtaining good results within the surgical treatment with addition materials associated or not with guided tissue regeneration is conditioned by creating a 1,5 – 2 mm thick pouch having sufficient vascular resources and a high amount of keratinized mucosa to assure full covering of the membrane, preventing premature postoperative exposure.[8]

The presence of a high quantity of keratinized mucosa has as effect the apparition of less tumefaction and postoperative discomfort.

After decolating the muco-periostium, the alveolar bone is decolated on a sufficient extend to acces the alveolar puches, the cement and the pathologic tissue. After exposing the bone defects resulted through the evidation of the periodontal pouches, the addition material is placed.[6] Marginal periodontitis represents nowadays one of the main causes of oral disfunction. Treatment can only begin after a thorough research of the patient based on what the treatment plan can be established. In our study, guided tissue

regeneration was applied in pouches with vertical bone loss and only minimal interdental papillae loss.

Bio-oss granules are mixed with either serum or blood or plasma. After applying the addition material into the bone defects, the membrane is put over the treated area. The position of the membrane proved to have an indirect relationship with the amount of regenerated bone.

We have noticed that the weakest results were obtained when the membrane was collapsed inside the bone defect. If the membrane is placed higher coronary, more space is going to be obtained for regeneration.

What the classification of the periodontal lesions according to the remaining bone walls is concerned, we can conclude that the number of lesions with only 2 spare walls (919 cases) is comparable to the number of lesions with 3 walls (16 cases). Periodontal lesions with only 1 wall were present in only 5 cases. We concluded that the level of gingival insertion and the quantity of obtained bone as well as the level of gingival insertion over a period of 3-4 years is superior as compared to GTR combined with bone addition.

The succes of GTR is due to the fact that bone addition facilitates the maintaining of the space needed for regeneration, because of the position, stability and characteristics of the barrier membrane. Marginal periodontitis represents nowadays one of the main causes of oral disfunction. Various forms of periodontal disease have high incidence without being influenced by age or sex, appearing in all population groups.

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complex, and causing alveolar bone resorption. The variety of lesional periodontal processes which cause inflammation, dystrophic-degenerative tissue alteration and proliferative phenomena, need a complex local and general treatment, which is diversified in order to act on all etiological factors. Treatment can only begin after a thorough research of the patient based on what the treatment plan can be established, with steps following tissue equilibration between the different components of the marginal periodontium.[2] Addition therapy represents, in the field of surgical treatment, an efficient mean

for the reconstruction of bone defects. Periodontal surgery aims to remove pathologic tissue from periodontal pouches in order to obtain healing and to remodel soft and hard tissues in order to have good control of bacterial plaque.[5]

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MATERIAL AND METHOD

In our study, guided tissue regeneration was applied in pouches with vertical bone loss and only minimal interdental papillae loss. Favorable results are conditioned by the following local characteristics:

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having sufficient vascular resources and a high amount of keratinized mucosa to assure full covering of the membrane, preventing premature postoperative exposure.[8] The presence of a high quantity of keratinized mucosa has as effect the apparition of less tumefaction and postoperative discomfort. After decolating the muco-periosteum, the alveolar bone is decolated on a sufficient extend to access the alveolar

puches, the cement and the pathologic tissue. After exposing the bone defects resulted through the evication of the periodontal pouches, the addition material is placed.[6]

Bio-oss granules are mixed with either serum or blood or plasma:

- blood is taken from the lesion or by venous punction during the surgical procedure.

- plasma is obtained from the blood after being placed on anticoagulant medium - Tri-sodium citrate 3,8 % 1/5 proportion, tri-sodium EDTA or heparine -centrifuged at 2000 - 3000 rpm for 10 - 12 min. Plasma is obtained through decantation. The approximative preparation time is 15 - 20 min.

- serum is obtained from coagulated blood, centrifuged at 2000 - 2500 rpm for 10 - 15 min and separated by decantation. The approximative preparation time, if blood is not placed on coagulation activation pads, is 45 - 60 min.

It can be noticed that the serum or plasma preparation can not be done during the surgical procedure, because it takes too long, it must be done in a laboratory. Se poate constata că prepararea serului sau plasmei nu se poate face în cadrul actului operator, deoarece necesită timpi prea lungi de obținere, nu se pot obține decât într-un laborator dotat cu centrifugă și ridică reale probleme de menținere a sterilității produsului în procesul de decantare și transport laborator - cabinet / sală de operații.

The utilization of blood seems to be a much better option, the only objection being the stress of the patient during the venous punction during the surgical procedure. The solution that proved to be the most practical and safe remains physiological serum, packed in sterile recipients.

After applying the addition material into the bone defects, the membrane is put over the treated area.



In this study, resorbable collagen membranes have been used because they only need one surgical procedure and mechanical deterioration of newly formed tissues is avoided.

RESULTS

The membranes act like a barrier against cell migration as well as microbial migration from the oral biofilm, because the pores have a dimension of less than 0.2 microns, assuring only the passage of the proteic protein.[3]

To be able to act like a barrier, the membrane doesn't have to resorb for a

sufficient time in order to allow the regeneration of bone structures (minimum 6-8 weeks). Resorption is made by enzymes and starts by the action of collagenase which determines a fragmentation of the collagen molecule. Under the action of temperature (37°), the fragments are denaturated to gelatine under the influence of

gelatinase and further, based on gelatinase and peptidase, it transforms to oligopeptides and aminoacids, which are then completely resorbed by the surrounding tissues.[7]

The membrane has to fully cover the bone defect and have a 2-3 mm extension to the lateral and the apical, so that it fully adapts to the defect. In the same time, it doesn't have to over cover the bone because it would interfere with the vascularization of the defect. The position of the membrane proved to have an indirect relationship with the amount of regenerated bone. We have noticed that the weakest results were obtained when the membrane was collapsed inside the bone defect. If the membrane is placed higher coronary, more space is going to

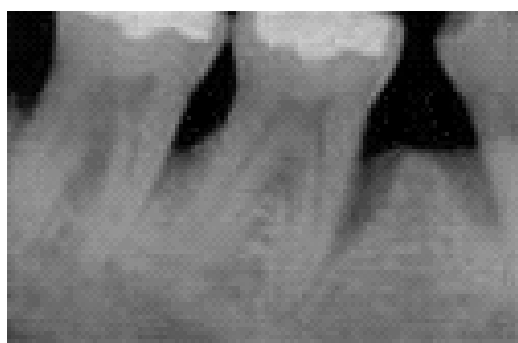
be obtained for regeneration.[10] After positioning the membrane over the bone defect and fixing it, the muco-periosteum is repositioned and sutured. Statistical evaluation of the 29 cases showed more interdental periodontal lesions (28 cases) as compared to inter-root lesions (1 case).

What the classification of the periodontal lesions according to the remaining bone walls is concerned, we can conclude that the number of lesions with only 2 spare walls (919 cases) is comparable to the number of lesions with 3 walls (16 cases). Periodontal lesions with only 1 wall were present in only 5 cases.

In case of 3 wall defects, bone regeneration of 80-90% has been determined.



In cases with only 2 walls bone regeneration was achieved at 70-75% of the initial volume.



For the cases with only 1 wall bone regeneration was achieved at approximately 30% of the initial volume.

CONCLUSIONS

Following the clinical study we concluded that the level of gingival

insertion and the quantity of obtained bone as well as the level of gingival

insertion over a period of 3-4 years is superior as compared to GTR combined with bone addition. The succes of GTR is due to the fact that bone addition facilitates the maintaining of the space needed for regeneration, because of the position, stability and characteristics of the barrier membrane.

Bio-oss gave very good results in creating and maintaining space because of it's biocompatibility and due to the fact that it is easy resorbable. We concluded that bone regeneration

under the membrane has a direct relationship with the aspect of the defect, the number of left walls, the depth of the defect and it's width.

The obtained results certify the superiority if the GTR method. Utilization of the method showed a great progress in tissue regeneration and attachment gain. The succes is eloquent especially for vertical defects sorrounded by 2 or 3 walls where the regeneration rate was very good. Results regarding bone gain are in concordance with previous studies.

REFERENCES

1. Becker W, Becker BE, Berg L, Camsam C. Clinical and volumetric analysis of three-wall intrabony defects follow in open flap debridement, J Periodontol 1996;57; 277-285.
2. BUCUR A . Compendiu de chirurgie oro-maxilo-faciala vol I si II Editura Q Med Publishing 2009.
3. Caffesse RG, Nasjleti CE, Morrison EC, Sanchez R. Guided tissue regeneration: comparison of bioabsorbable and nonbioabsorbable membranes. Histologic and histometric study. J Periodontol 1994;65:583-591.
4. Cortellini P, Pini Prato GP, Tonetti MS, Guided tissue regeneration of human intrabony defects. I. Clinical measures. J Periodontol 1993;64:254-260.
5. DUMITRIU H. - Parodontologie, Editura Viața Medicală Românească, București, 1997,
6. Ganuta N, Bucur A, Canavea I, Cioaca R, Garfunkel A, Malita C: Chirurgie Oro-Maxilo-Faciala, Volumul I. Editura National, Bucuresti, pag. 184-209; 1999
7. Gottlow J, Laurell L, Teiwik A, Genon P. Guided tissue regeneration using bioresorbable matrix barrier. Pract Periodont Aesthet Dent 1994;6:71-80.
8. Lindhe J.: Clinical Periodontology and implant Dentistry. 1997.
9. Sato N. Control of the periodontal pocket from the long-term maintenance. Decisive treatment for the periodontal pocket. The Quintessence 1990;9:123-144.
10. Tonetti M., Cortellini P.: GTR în deep intrabony defects: case selection and treatment considerations. 1997.

A SINGLE SITE, OPEN NON-CONTROLLED STUDY OF EFFICACY AND TOLERABILITY OF TWO FORMULATIONS OF THE MEDICAL DEVICE GENGIGEL® BABY GEL (0.2% HYALURONIC ACID) IN THE TOPICAL TREATMENT OF TEETHING IN INFANTS



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ABSTRACT

The objective of this study was to collect preliminary data on tolerability and efficacy on infants teething of two gel formulations of a high molecular weight Hyaluronic Acid (Gengigel® Baby), actually marketed as medical device. Main outcome parameters for efficacy were: pain, swelling, gingival rush, hyper-salivation, redness, abnormal teeth depth and mucosal laceration subcutaneous. In addition a comparison with previous Lidocaine administration and an Investigator assessment of overall therapeutic efficacy were performed.

Conclusion: These positive data will be the statistical bases to plan future clinical trial on Gengigel® Baby Gel.

Key words: teething, hyaluronic Acid, clinical evaluation, topical treatment.

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INTRODUCTION

The localized symptoms of teething vary between individuals ⁸. Common symptoms as soreness and swelling of the gums before a tooth eruption are the cause for the pain and fussiness a baby experiences during this change. Teething can begin as early as 3 months and continue until a child's third birthday. Even if occasionally a slight rise of temperature may occur when the teeth come through the gum, generally teething has not been shown to cause fever or diarrhea ¹⁵. A recent review on parents habits of relieving the symptoms associated with teething ¹², evidenced the following: more than 50% of the 1500 participants allowed

their infants to bite on chilled objects, 65.6% rubbed the gums with topical analgesics and 76.1% used systemic analgesics. Regarding the use of topical anesthetics present in a variety of prescription and non-prescription preparations for teething, it must be recorded that in 2003, there were 8576 exposures to local/topical anesthetics reported to the American Association of Poison Control Centers, with 67% of cases in the age group younger than 6 years old. According to the available literature involving topical anesthetic exposures in infants, from 1983 to 2003 there were 7 deaths in younger than 6 years old ⁴.

MATERIAL AND METHODS

Study design: The study was a single-centre, pilot, open label, non-controlled trial planned as follows:

1st phase: 12 subjects treated with the 1st formulation of the tested drug;

2nd phase: 6 subjects treated with the 2nd formulation of the tested medical device; the trial was implemented in accordance with the Helsinki Declaration (and subsequent amendments) and performed following the Good Clinical Practice. All the patients enrolled gave their informed consent to taking part in the study.

Tested Medical Device: The Medical Device on study was a gel (0.2% HA) in 15 ml tube, already authorized as Medical Device(CE mark) of Class IIa as per Annex IX of the Council Directive 93/42/EEC. The two formulations of the Medical Device (named in the present article as 1st Gengigel® Baby gel and 2nd Gengigel® Baby gel, respectively) have the same Hyaluronic Acid (HA) concentration, but the 2nd Gengigel®

Baby gel is more dense compared to the first formulation. The gel was administered three to five times a day by the parents applying it directly on the gingival tissue of the infant, massaging it on, with clean fingers.

Methods: Eighteen infants (aged between 6 and 36 months) suffering of teething were recruited. The infants were eligible if teething was diagnosed by the presence of at least 3 of the following clinical symptoms: pain, swelling, gingival rush, hyper-salivation, redness, abnormal teeth depth, subcutaneous mucosal laceration.

The exclusion criteria were: hospitalization and/or immobilization and/or confinement to bed; history of severe renal insufficiency, severe cardiac dysfunction or allergic reactions to HA and to any ingredient of the tested medical device. In addition were excluded the infants whose parents suffered from any form of psychiatric disorder or other condition

which, in the opinion of the Investigator, might invalidate the required prescription or complicate the communication with the subject. Within one day before the study and during the period of study was not permitted the concomitant use of Lidocaine or topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Concomitant treatment with Systemic NSAIDs was not allowed during the course of the study and within 3 day before.

The efficacy of the treatment was evaluated by Investigator at baseline, at day 3 visit and at final examination (after 7 days) on the basis of the following parameters: pain, swelling, gingival rush, hyper-salivation, redness. The parameters were arbitrarily scored according to intensity with the following VRS (Verbal Rating Scale): absent= 0, moderate= 1, intense= 2.

The following additional secondary efficacy parameters were assessed by Investigator at day 0, 3 and 7 of treatment: abnormal teeth depth (scored according to intensity with the following VRS minimal= 0, moderate= 1; extreme= 2) and mucosal laceration subcutaneous (scored as: minimal= 0, perceptible= 1; intense= 2). During the study period the parents were instructed by Investigator to collect on diary cards and daily assessed the day pain, night pain, swelling, gingival rush, hyper-salivation. These parameters were scored for intensity according to the following VRS: absent=0, moderate=1, intense= 2. For a global rating of the comparison with previous Lidocaine administration was used the following VRS: 1 = no

difference; 2 = minimal difference; 3 = moderate difference; 4 = intense difference; 5 = very intense difference. At the end of the study, the Investigator expressed an assessment of the overall therapeutic efficacy: very good: symptom-free (complete symptom remission); good: considerably improved; satisfactory: moderately improved; poor: unchanged (persistence of symptom score); very poor: worsening (progression of symptoms).

As far as tolerability of the study treatment was concerned, the occurrence of adverse events during the trial was monitored. The overall assessment of tolerability by the Investigator was expressed at the final examination by means of the following score: very good (no adverse events, nor organic toxic diseases and good acceptability of the treatment by infant); good (no adverse events and organic toxic diseases); moderate (slight and transient adverse events); poor (persistent adverse events); very poor (severe adverse events and organic toxic diseases).

Statistical analysis: Statistical analysis were performed using the SAS statistical package version 9.2 (SAS Institute Inc, US). The data concerning all the variables were presented by means of usual descriptive statistics: mean standard deviation (SD), standard error of the mean (SE), median, minimum and maximum, absolute and relative frequencies.

Two-tailed tests were used for the parameters analysed and a 5% level of statistical significance was chosen. The non-parametric data were analysed by means of the Wilcoxon tests.

RESULTS

Pain: Pain reduction between the two time-points (baseline and day 7)

was statistically significant ($p < 0.01$) within the whole population of 18

treated subjects (fig. 1); also considering separately the group of infants treated with the 1st formulation of Gengigel® Baby gel and the group treated with the 2nd formulation of Gengigel® Baby gel, a statistically significant difference ($p < 0.01$) was evidenced in the mean pain reduction.

Swelling: In the 18 infants, the values of the swelling intensity, evaluated by a 3 points VRS, were absent = 0, moderate = 7 and intense = 11 at baseline, while after 7 days of treatment (final visit) were changed as follows: absent = 6, moderate = 12 and intense = 0. The difference between the values at the time of the final examination and at baseline ($p < 0.01$) was statistically significant (fig. 2). In addition, the reduction from baseline to the final examination was statistically significant ($p < 0.01$) also in the group of 12 infants treated with the 1st formulation of Gengigel® Baby gel.

Gingival rush: The decrease of this parameter between the two -points

(baseline and day 7) was statistically significant within all population treated (18 subjects, $p < 0.01$) (fig. 3); on the other hand the same statistical significance ($p < 0.01$) was evidenced within subjects treated with the 1st formulation of Gengigel® Baby gel group.

Redness: At the final examination, the total population and both the study groups treated (12 and 6 infants, respectively) showed a statistically significant decrease of the symptom redness (fig. 4).

Hyper-salivation: Good improvement of this symptom ($p < 0.01$) occurred in the global population treated (at baseline: absent = 0, moderate = 4 and intense = 14; at the final visit: absent = 0, moderate = 17 and intense = 1; (fig. 5) and it had decreased significantly ($p < 0.01$) also within the group of 12 infants treated with the 1st formulation of Gengigel® Baby gel.

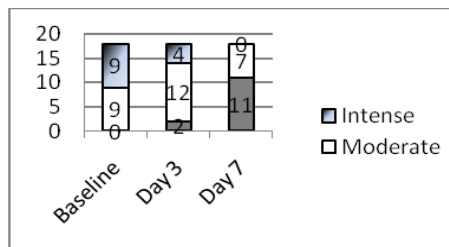


Fig.1 Pain reduction between the time-points within the whole population of 18 treated infants ($p < 0.01$ between baseline and day 7).

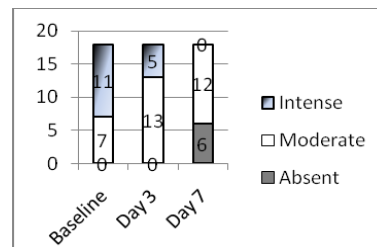


Fig.2 Swelling between the time-points within the whole population of 18 treated infants ($p < 0.01$ between baseline and day 7).

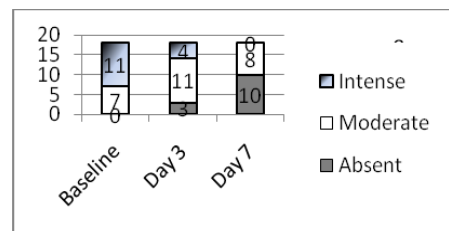


Fig.3 Gingival rush between the time-points within the whole population of 18 treated infants ($p < 0.01$ between baseline and day 7).

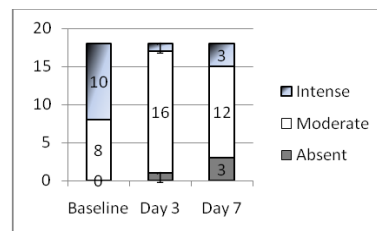


Fig.4 Redness between the time-points within the whole population of 18 treated infants ($p < 0.01$ between baseline and day 7).

Teeth depth, mucosal laceration: No statistically significant difference was evidenced for the parameters abnormal teeth depth and subcutaneous mucosal laceration, nor in the total population (18 infants), nor in the two groups treated with the 1stGengigel® Baby gel or the 2ndGengigel® Baby gel formulation.

Investigator's global assessment: The overall assessment was very satisfactory with reference to the total

infants treated (Table 1) In fact the assessment confirmed the above mentioned results: good or very good efficacy (67.67%), satisfactory or good duration of effect (83.33%) and rapidity of effect (72.22%). The results performed by the two different Gengigel® Baby gel formulations can be considered superimposable. Anyway, these positive results should be considered carefully as the number of subjects analyzed is quite low.

Table 1 Investigator's Global Overall Assessment at the end of treatment period (18 subj).

	Very poor	Poor	Satisfactory	Good	Very good
Efficacy	0 (0%)	2 (11,2%)	4 (22,2%)	11 (61,1%)	1 (5,5%)
ration of effect	0 (0%)	3 (16,6%)	7 (38,8%)	7 (38,8%)	1 (5,5%)
apidity of effect	0 (0%)	5 (27,7%)	9 (50%)	3 (16,6%)	1 (5,5%)

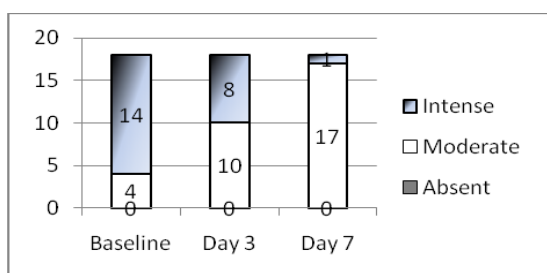


Fig.5 Hyper -salivation between the time-points within the whole population of 18 treated infants (p<0.01 between baseline and day 7).

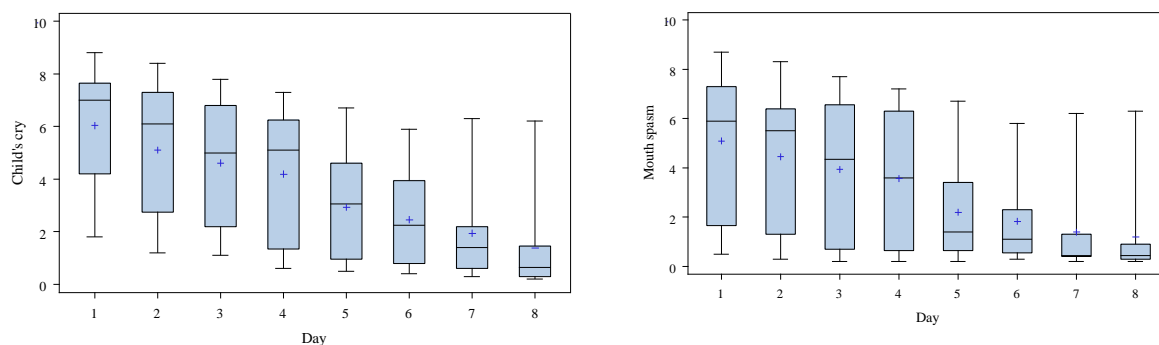


Fig.6 Boxplots of the evaluation of infant cry (a) and mouth spasm (b), using VAS scores, by day as reported on diary cards; infants treated with 1st formulation of Gengigel® Baby gel (12 subjects).

+ = mean values

Investigator's comparison with previous Lidocaine use: For this 5-point-VRS scores observed at the final visit for treated infants the Investigator

appreciated a minimal or moderate difference in 50% and an intense difference in 50% of subjects treated with the 1stGengigel® Baby gel, while

the comparison between the 2ndGengigel® Baby gel formulation and the previous Lidocaine use evidenced a minimal or moderate difference in 83.34% and an intense difference in 16.67% of treated cases.

Other symptoms: Additional considerations can be made on the twelve subjects treated with the 1stGengigel® Baby gel formulation, as diary cards were collected by parents. In these the infants cry (fig. 6) and mouth spasm analysis reduction (VAS mm) confirmed the positive results for Gengigel® Baby gel formulation, as previously evidenced. In addition a general trend to improvement was evidenced with score 0 since day 3 and

4 for daily pain, night pain and gingival rush.

Tolerability and Adverse Events: Tolerability was good in all the treated infants. The only adverse events were reported with the 1stGengigel® Baby gel formulation administration: fever and diarrhea. Both were considered moderate and not related with the study medication. No serious adverse event or reaction was reported during the study. In addition the Investigators' global safety assessment confirmed the safety and tolerability of the study medications. All these observations are supportive of an excellent tolerability profile.

CONCLUSION

The rapid change in the oral cavity during paediatric age requires fast renewal of periodontal tissues. HA, a polysaccharide naturally occurring in the oral mucosa, plays an essential role in maintaining the functional balance required for intercellular exchange. In fact, depletion of HA results in a consequent reduction of the protection mediated by the oral mucosa. Several pre-clinical and clinical studies ^{1, 2, 4, 6, 16, 11} highlighted the anti-inflammatory, regenerating, healing action and anti-edematous function of HA in the treatment of pathological conditions of oral cavity. Recently, several products containing high molecular weight HA have been developed; In particular, since 2000, Gengigel® Baby, the gel formulation tested in this trial, has been marketed in various European countries for gingival inflammatory conditions or gums trauma, as well as for any condition where the gingival mucosa requires increased concentrations of HA. This medical devices characterized by the absence of preservatives, alcohol

and dyes; therefore its administration in children, and particularly in infants is safe and can help creating a natural protective layer on the gingival tissue. In previous clinical trials ^{5, 7, 9, 10, 13, 14} Gengigel® Baby gel was able protect the mucosa, by preventing the deficiency of natural gingival HA. The result is a periodontal tissue/fluid balance with accelerated healing and repair properties. These properties could be of interest either for accelerating the wound healing process, or for treating the complex physical symptoms (i.e. soreness and swelling of gums, crying, sleeplessness, restless sleep at night and mild fever) related to teething in infants. Gengigel® Baby was considered particularly suitable for this clinical trial based on the direct knowledge derived from the clinical practice, and on the absence of any contraindications (other than hypersensitivity to HA and excipients), precautions or warning. In addition it must be noted that no Adverse Drug Reaction (ADR) were reported during the 10 years marketing time in Europe. In this open, non-

controlled study the two tested gel formulations had the same HA concentration and different density and were administered three to five times a day by the parents. The aim of the study was not to identify a difference in the efficacy of the two formulations, but to collect preliminary data on the outcome tested in order to plan future clinical trials. In this respect all infants enrolled in this trial, irrespective of the formulation used, showed an improvement of the symptoms: in fact the 18 treated subjects there was a statistically significant ($p \leq 0.01$) difference between day 0 and day 7 for the primary variables of interest (i.e. pain, swelling, gingival rush, hyper-salivation, redness). The study showed

that this positive evaluation of Gengigel® Baby is reported not only by the Investigator (through the assessment of symptoms at different visits and by the global assessment reported at the final visit), but also by the parents in the diary cards.

The tolerability of both formulations is supportive of an excellent tolerability profile: only two moderate adverse events, unrelated to the study gel were reported (fever and diarrhoea). This study confirms the previous clinical experiences, showing that Gengigel® Baby can be considered a useful therapeutic tool for the treatment of teething in infants: these positive data will be the statistical bases to plan future clinical trials.

REFERENCES

1. Bartold, P.M. Platelet-driven growth factor stimulates hyaluronate but not proteoglycan synthesis by human gingival fibroblasts in vitro. *J Dent Res* 1993, 72: 1473-1480.
2. Bartold, P.M. The effect of interleukin-1-beta on Hyaluronic acid synthesized by adult human gingival fibroblasts in vitro. *J Periodontal Res* 1988, 23: 139-147.
3. Curtis LA, et al., Are one or two dangerous? Lidocaine and topical anesthetic exposures in infants. *J Emerg Med*. 2009 Jul; 37(1):32-9. Epub 2008 Feb 14. Review
4. Irwin, C.R., et al., Effects of cytokines on gingival fibroblasts in vitro is modulated by the extracellular matrix. *J Periodontal Res* 1994, 29: 309-317
5. Jervoe-Storm, X. et al., Employ of locally applied hyaluronic acid during a three mont initial treatment. *Paradontologie*. 2003; 14/1:41-49
6. Kim SK et al., The effect of hyaluronic acid on anti-inflammatory action in mouse. *J Korean Assoc Oral Maxillofac Surg*. 2010 Feb;36(1):16-22
7. Mantovani S et al., Preliminary clinical evaluation of a hyaluronic acid based product in oral disorders: double blind trial *AttualitàTerapeuticaInternazionale*. 1998; 7: 1-3.
8. McIntyre GT, McIntyre GM. Teething troubles? *Br Dent J*. 2002 Mar 9;192(5):251-5
9. Mesa FL et al., Antiproliferative effect of topic hyaluronic acid gel. Study in gingival biopsies of patients with periodontal disease. *Histol Histopathol*.2002; 17(3):747-53. PubMed PMID: 12168783.
10. Nobre de Araújo M et al., Peri-implant maintenance of immediate function implants: a r randomized controlled clinical trial comparing hyaluronic acid and chlorhexidine. *Int J Dent Hyg* 2007; 5:87-94.
11. Oksala, O. et al., R. Expression of Proteoglycans and hyaluronan during wound healing. *J HistochemCytochem* 1995, 43: 125-135.
12. Owais AI et al., O. Challenging parents' myths regarding their infants's teething. *Int J Dent Hyg*. 2010 Feb; 8(1):28-34.
13. Pagnacco A., et al., Double blind clinical trial vs. placebo of a new sodium hyaluronate-based gingival gel. *Attualità Terapeutica Internazionale*. 1997; 4: 1-7.
14. Pistorius A et al., The clinical application of hyaluronic acid in gingivitis therapy. *Quintessence Int*. 2005 Jul-Aug; 36 (7-8):531-8.
15. Tintinalli, Judith (2004). *Emergency Medicine: A Comprehensive Study Guide*, Sixth edition. McGraw-Hill Professional. p. 1483
16. Weigel, P.H. et al., A model for the role of Hyaluronic acid and fibrin in the early events during inflammatory response and wound healing. *J. TheorBiol* 1986, 119: 219-234.

COMPARATIVE STUDY OF EDUCATIONAL ORAL HEALTH PROGRAMMES ON THE WORLD



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ABSTRACT

Health promotion is the process of enabling people to increase control over, and to improve, their health. Children with caries have a slower growth rate compared with children without it, which can be attributed to the pain during eating. Oral health promotion focuses largely on disease, and health is defined as the absence of caries and periodontitis. Oral health education aims to impart knowledge to people and influence their choice of lifestyle. Oral health education for children should be considered a priority. School instructors play an important role in achieving the best oral health outcomes for school children because in some areas children have limited access to dental care and the school instructors are the first health professionals to come in contact with children. The prevalence of childhood caries is a public health problem. According to statistics, 61% of 6-12-year-old children have at least one tooth cavity, and/or filling in their deciduous teeth, and 40% of 6-14-year old individuals have at least one cavity and/or filling in their permanent teeth. Traumatized baby teeth may lead to tooth loss and, among other factors such as childhood illnesses, may affect the developing permanent teeth. It is therefore important to prevent dental trauma in children. A safe environment at home, in schools and in the community, including safer playgrounds and roads with well-organized traffic, can help minimize the risks.

Key words: Oral Health, Educational Programmes, Impact, children, school education

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INTRODUCTION

Health promotion is the process of enabling people to increase control over, and to improve, their health. To reach a state of complete physical, mental and social well-being an individual or group must be able to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is, therefore, seen as a resource for everyday life, not the aim of living ¹. Health is a positive concept emphasizing social and personal resources, as well as physical capacities. Therefore, health promotion is not just the responsibility of the health sector, but goes beyond healthy lifestyles to well-being.

Tooth decay is a problem in young children and is aggravated due to existing barriers that prevent them from obtaining dental care. The availability of effective preventive methods improves dental treatment so that children no longer suffer from dental problems ².

Recent progresses in preventive dentistry and their correct application in many developed countries have resulted in marked decrease in the rate of oro-dental diseases in children and teenagers, while the rate of oro-dental diseases is on the rise among children in developing countries ^{1,2}.

Dental caries in primary dentition not only shows children's oral health ³, but also predicts the probability of caries in permanent dentition and general health status.

Many investigations have shown the association between periodontal diseases and systemic diseases, including coronary heart disease and diabetes.

Children with caries have a slower growth rate compared with children without it, which can be attributed to the pain during eating.

Oral health promotion focuses largely on disease, and health is defined as the absence of caries and periodontitis ³. Oral health education aims to impart knowledge to people and influence their choice of lifestyle.

Oral Health is an integral component of general health. It has also become clear that causative and risk factors in oral diseases are often the same as those implicated in the major general diseases (WHO, 2003):

- ¹. The overall health, well being, education and development of children, families and communities can be affected by oral health. Though there has been considerable improvement in the oral health of children in the last few decades, dental caries (tooth decay) still remains one of the most commonly occurring oral health problems in the children all over the globe. A considerable population of children in the developing nations is being affected by tooth decay and most of the time their proper treatment is given the last priority owing to limited access to oral health services;
- ². The lack of availability and affordability of oral health services not only results in aggravation of the disease but also enhances the cost of treatment and care. There is no single country that claims to have caries free children;
- ³. Adverse experience during childhood may lead dental phobia, impacting on attitudes to oral health and self care as well as availing oral health care services for life. Poor oral health in childhood often continues into adulthood, effecting economic productivity and quality of life;
- ⁴. In many countries, a large number of children and parents have

limited knowledge of the causes and prevention of the most common oral diseases. Similarly, the schoolteacher's oral health knowledge has also not been satisfactory;

5. It is evident that cultural beliefs and social taboos play an important role in the perception of the causes of dental decay and gum diseases. In India, a very less percentage of mothers have received proper advice on oral care of the children from dentists or health care workers. In many countries, the number of children brushing;

Oral health education for children should be considered a priority. School

instructors play an important role in achieving the best oral health outcomes for school children because in some areas children have limited access to dental care and the school instructors are the first health professionals to come in contact with children ⁸. Considering the "important role" of school instructors, it is essential to explore their knowledge.

This study was conducted to evaluate the impact of educating school health care instructors with the aim of taking a step toward enhancing preventive policy in oro-dental hygiene by measuring their level of oral health knowledge and their opinions about the impact of oral health and preventive dentistry.

METHODOLOGY

Oral health promotion through schools is the best modality to improve the oral health comportament.

The following guidelines could be included in the formulation of an oral health policy:

- Teachers, parents, students and all other relevant school personnel are involved in the planning, development and review process;
- The School Health Team and Community Advisory Committee meet periodically to review development and maintain coordination between the school and community;
- The school curriculum includes oral health in the school health education programme and as an integral part of other relevant subject areas, such as personal development, math's, biology, chemistry and social science;
- Teachers and other school staff receive systematic and ongoing training in oral health and prevention of oral diseases;

- The school canteen, cafeterias, snack bars, tuck shops and vending machines serve nutritious foods and drinks that are conducive to good oral health. School canteen staff and food providers are educated about diet and oral health;
- If feasible and appropriate, the school considers school-based public health preventive interventions such as water and milk fluoridation;
- The school ensures that sufficient facilities are available for oral health activities in school and the premises are adequately safe to prevent craniofacial trauma;
- The school ensures that there is appropriate accident prevention policy and practice in school;
- In case of emergency, clear protocol is provided to ensure vital actions are taken without delay;
- The school monitors oral health related injuries, sickness and absenteeism;

- Working with the school health services, the school assesses the oral health status of students regularly and ensures that students have access to oral health care services.

Teachers are trained to undertake certain screening and assessment procedures:

- The school plays a key role in advocating and lobbying for water fluoridation in areas of poor dental health and for the availability of affordable fluoride toothpaste;

- School health services offer screening and treatment for oral disease and work collaboratively with the school staff, parents and the community to promote oral health;

Parents are educated about the value of good oral health and essential oral health practices at home. They are encouraged to take an active role in school committees and participate in oral health activities and programmes in school and the community.

RESULTS

In a research study in Yazd City, Iran, knowledge of 72 school health care instructors was evaluated through a questionnaire which included 7 questions about their basic knowledge about oral health and 20 questions about their awareness. The following results were achieved: The rate of general knowledge in younger instructors with fewer years of experience was more than the instructors with more experience, which might be attributed to recent graduation of younger instructors from the university.

A longitudinal study related to dental caries and gum diseases is essential to find out the impact of school oral health education programmes involving school teachers. This can be possible by motivating the children to adopt positive attitude and correct practices towards better oral health which is an integral part of general health and healthy food behavior ⁴.

The oral health care treatment that is funded by the public health insurance system. The Romanian dental workforce, setting out the numbers of dentists and other dental workers. It highlights that there has been a rapid expansion in the number

of dental students and young dentists and a shortage of dental nurses (chair-side assistants). A section on dental education at undergraduate, specialist and continuing levels follows. Finally the paper gives brief details of oral epidemiological studies that have been performed in Romania and the costs of oral health care in the country ⁵.

At present, common oro-dental diseases such as dental caries and gingival-periodontal diseases are considered health-threatening diseases. The prevalence of childhood caries is a public health problem ⁷. According to statistics, 61% of 6-12-year-old children have at least one tooth cavity, and/or filling in their deciduous teeth, and 40% of 6-14-year old individuals have at least one cavity and/or filling in their permanent teeth. These diseases have a great effect on the economy of a society due to high prevalence in all social classes.

In a study made in our country we can see that the primary services in oral health is not very accessible, because is expensive. Then the importance of oral health education is even more important because of that. The district health insurance houses make contracts for the dental services with private dental offices (clinics). Approximately

60% of Romanian dentists own their dental offices (clinics) ³. The remaining dentists work as employees in schools and in universities, often part-time. The number of contracts that each district health insurance house can place is limited. Less than half of all Romanian dentists, both those who own their own practices and those who work in Government-owned buildings, have contracts with the health insurance houses. They also see patients privately ⁵. In Bucharest, only about 10% of dentists have health insurance house contracts but in some rural areas 60-70% has such contracts. Only about 30% of dentists who qualified recently have contracts with health insurance houses. Just fewer than 40% of Romanian dentists only treat patients under private arrangements ⁶.

There have been no comprehensive national epidemiological surveys of oral health. A number of local studies have been organized by the staff of dental medicine faculties but without any overall plan. Two "national pathfinder" studies of caries in 12-year-olds have been published [11]. The first suggested that in 1992 the national mean DMFT for 12-year-olds was 4.1 [8]. The second suggested that in 2000 it was 2.8 [11]. In 2007, expenditure from public funds on all health care was 4.8% of which 4.2% was from the National Health Insurance House and 0.6% for preventive programmes administered by the Ministry of Public Health [1]. In addition, an unknown amount of private funds were paid directly to dentists by patients themselves. Public funds allocated oral healths in 2007 were 0.87% of total funds allocated for all health by the NSHIH. In addition, in the Constanta and Iasi districts, just under €100,000 was allocated by the Ministry of Public Health from the preventive programmes budget for weekly rinsing

with a fluoride solution by children ¹⁰. An unknown amount of private fees were also paid for oral health care. In present in Romania we don't have a national program in the Oral Health field.

I propose to do a pilot study with a **health-Promoting School**:

- Fosters health and learning with all measures at its disposal.
- Engages health and education officials, teachers, students, parents and community leaders in efforts to promote health.
- Strives to provide a healthy environment, school health education, and school health services along with school/community projects and outreach, health promotion programmes for staff, nutrition and food safety programmes, opportunities for physical education, and recreation and programmes for counseling, social support and mental health promotion.
- Implements policies, practices and other measures that respect an individual's self-esteem, provide multiple opportunities for success, and acknowledge good efforts and intentions as well as personal achievements.
- Strives to improve the health of school personnel, families and community members as well as students; and works with community leaders to help them understand how the community contributes to health and education.

This is very important because Dental trauma, which usually affects the upper front teeth, may result from accidents, sport related injuries, violence, and epilepsy. Traumatized baby teeth may lead to tooth loss and, among other factors such as childhood

illnesses, may affect the developing permanent teeth. It is therefore important to prevent dental trauma in children. A safe environment at home, in schools and in the community, including safer playgrounds and roads with well-organized traffic, can help minimize the risks.

The prevalence of oral cancer varies greatly between countries, with a particularly high incidence observed in the Indian subcontinent, Australia, France, South America and Sub-Saharan Africa. While 95% of the disease cases are diagnosed among adults aged over 40 years, risk behaviors (eg excessive alcohol and tobacco use) during childhood and adolescence could have a significant impact on the risk of cancer, as well as other leading cause of death and disability. Cigarette smoking and "spit or chewing" tobacco use among adolescents in the US has been increasing each year, with 35% of those who use tobacco having tobacco-related oral lesions.

A study in China was a National Program: Milk, an essential component of children's diet, can be added with fluoride and used in school-based preventive programmers. Fluoridated milk is distributed by teachers daily in schools or day care centers. Outcomes aim to define in tangible and measurable terms what is to be achieved through the interventions. They help evaluate the impact and achievements of a Health-Promoting School. Children's health status, learning achievements, health-related behaviors, quality of the school environment and school health programme implementation are useful indicators, as are beliefs, attitudes and the impact on quality of life and on society. Hence, the outcomes of an oral health orientated Health-Promoting School can include improvement in oral health status, knowledge, beliefs, attitudes, behaviors and conditions that are related to health and oral health.

DISCUSSIONS

Tooth decay and periodontal diseases are gradually increasing in children, emphasizing the necessity of educating school health care instructors as the first step in preventing oro-dental diseases. Oral diseases are both individual and community health problems.

Preventive education of dental care must enhance the opportunity for a life free of oral diseases. This research study evaluated the effectiveness of an educational oral health program school, health care instructors on the basis of pre-test and post-test answer sheets. The results showed that educating school health care instructors has a great influence on improving their knowledge about oro-dental health.

Therefore, it is recommended that governmental insurance should cover dental treatments. Remarkable improvements were seen in adults after performing educational services in oral hygiene in one survey.

The target group in the teacher's community of any particular school should be identified. An ideal target group would comprise of the class teachers, teachers appointed for physical education, life sciences teachers and the Principal as they directly come in contact with the school children.

An effort should be made to interact with each teacher of the target group to know more details regarding their daily routine, prior engagements, their interest in the programme & their

opinion regarding methodology of its execution. They should be made well aware of the fact that the success of this programme would depend upon their whole hearted participation and not merely the interest. A pre training evaluation of the target group is must to assess their pre-conceived ideas and knowledge regarding oral health so as to orient the training process likewise. This assessment can be carried out by framing a set of relevant questions and answers regarding their knowledge, attitude and practice. The teachers should be advised to prepare and conduct a list of activities like essay writing on healthy smile, skits related

to oral diseases, drawing competitions on beautiful smile and quiz competitions comprising of few questions on oral structures etc in which the students can participate and gain knowledge regarding oral health in the process. The concerned teachers can be suggested to keep a log book which can reflect the various activities conducted by them and methods employed to bring awareness regarding oral health. A constant and regular interaction with the concerned teachers is mandatory to assess and evaluate the progress regarding awareness of oral health, change in food behavior and treatment needs.

CONCLUSIONS

1. Because one of the most important determinants of dental caries is low socioeconomic status, preventive dentistry programs could result in a higher level of oral health.
2. Public insurance provides limited coverage for oral health; therefore, for better oral health care it is necessary to design and introduce a new insurance system, covering all types of dental treatments.
3. Training of general dental practitioners for the treatment of young children is another way to promote dental health in children.
4. The government should also provide screening services for early detection of dental diseases. As a result, coordination of services between schools and dental profession is highly recommended.
5. The oral health education of the children by the school teachers could bring down the plaque scores in children and improve the knowledge, attitude and practice of the children regarding oral health.
6. There was a significant increase in proportion of filled teeth in the senior age group after one year of implementation of the programme.
7. Once trained, teachers can continue to impart oral health education to the children for many more coming years provided they are motivated regularly.
8. School based oral health education programme can be an effective method for prevention and control of dental problems in developing countries.

REFERENCES

1. McDonald RE, Avery DR, Dean JA. Dentistry for the Child and Adolescent , 8th ed. St. Louis: Mosby; 2004: 50-59, 739- Soussan Irani, Marjane Meschi, Azizollah Goodarzi , Influence of Education on Oro-dental Knowledge among School, Dental Research, Journal of Dental Clinics, Dental Prospects 2009;
2. Romanian College of Dental Physicians. Website [accessed 2011 Nov 2] at: www.cmdr.ro
3. National Social Health Insurance House. Website [accessed 2011 Nov 2] at: www.cnas.ro
4. Order of Romanian Dental Technicians. Website [accessed 2011 Nov 2] at: www.otdr.ro

5. Romanian Association of Public Oro dental Health. Website [accessed 2011 Nov 5] at: www.oralhealth.ro
6. Kravitz A. & Treasure E, editors. Manual of Dental Practice. Brussels: Council of European Dentists; 2008.
7. Amariei C, Nucă C, Ilia. AJ, Arendt C. Organization of the orodental health care system in Romania during transition period [poster]. 12th congress of the European Association of
8. Dental Public Health; 2007 Sept 21-22; Leuven, Belgium. Abstract No 3.
9. Amariei C, Totolici D, Ungureanu L, Balaban D. Aspects regarding the dental caries prevention program in Constanta County, Romania [poster]. FDI Annual World Dental Congress; 2003 Sept 18-21; Sydney, Australia. Abstract No PP72
10. WHO, Oral health promotion through schools WHO/NMH/NPH/ ORH/ School/03.3 series on school health document eleven Oral Health Promotion: An Essential Element of a Health-Promoting School World Health Organization Geneva, 2003, Education Development Center, Inc.
11. Biesbrock AR, Walters PA, Bartizek RD, Initial impact of a national dental education program on the oral health and dental knowledge of children, Procter & Gamble Company Health Care Research Center, Cincinnati, Ohio, USA.
12. Cardenas LM, Ross DD, Effects of an oral health education program for pregnant women, Department of Pediatric Dentistry and Community Oral Health, University of Tennessee Health Science Center, Memphis, USA.

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BLOOD ANTIOXIDANT STATUS BETA-BLOCKERS TREATMENT



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ABSTRACT

Beta-blockers have been used to treat ischemic heart disease, due to negative chronotropic and inotropic properties, thus inducing a decrease in myocardial consumption of oxygen and nutrients, allowing a better balance between nutritional needs and the supply provided by the coronary blood flow. Recent developments in cell biology allowed us to understand that not all beta-blockers are equal, as their intracellular mechanisms of action can be very different. Selection of the most appropriate drug for an individual patient should be based on pharmacokinetic and pharmacodynamic differences among the drugs, cost, and whether there are concurrent medical problems. For some diseases (e.g., myocardial infarction, migraine, cirrhosis with varices, and congestive heart failure), it should not be assumed that all members of this class of drugs are interchangeable; the appropriate drug should be selected from those that have documented efficacy for the disease. β_1 -Selective antagonists are preferable in patients with bronchospasm, diabetes, peripheral vascular disease, or Raynaud's phenomenon. Although no clinical advantage of β receptor antagonists with intrinsic sympathomimetic activity has been clearly established, such drugs may be preferable in patients with bradycardia.

In addition, third generation β antagonists that block α_1 receptors, stimulate β_2 receptors, enhance NO production, block Ca^{2+} entry, open K^+ channels, or possess antioxidant properties may offer therapeutic advantages. Our work sought to put in the evidence the change of the blood antioxidant status in patients with ischemic cardiopathy, patients treated with beta blockers.

Keywords: Stable angina, Beta blockers, Plasma antioxidative activity.

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INTRODUCTION

The various β receptor antagonists that are used for the treatment of hypertension and angina appear to have similar efficacies. Selection of the most appropriate drug for an individual patient should be based on pharmacokinetic and pharmacodynamic differences among the drugs, cost, and whether there are concurrent medical problems.

For some diseases (*e.g.*, myocardial infarction, migraine, cirrhosis with varices, and congestive heart failure), it should not be assumed that all members of this class of drugs are interchangeable; the appropriate drug should be selected from those that have documented efficacy for the disease. β_1 -Selective antagonists are preferable in patients with bronchospasm, diabetes, peripheral vascular disease, or Raynaud's phenomenon. Although no clinical advantage of β receptor antagonists with intrinsic sympathomimetic activity has been clearly established, such drugs may be preferable in patients with bradycardia.[2]. In addition, third generation β antagonists that block β_1 receptors, stimulate β_2 receptors, enhance NO production, block Ca^{2+} entry, open K^+ channels, or possess antioxidant properties may offer therapeutic advantages [6].

It's known that carvedilol has significant antioxidant properties compared with other β -blockers. The objective of this study was to determine if these antioxidant effects are detectable in patients with stable angine and to compare carvedilol with the selective β -blocker metoprolol [6,7]. Metoprolol is a β_1 -selective receptor antagonist that is devoid of intrinsic sympathomimetic activity and membrane-stabilizing activity. Metoprolol is almost completely

absorbed after oral administration, but bioavailability is relatively low (about 40%) because of first-pass metabolism. Plasma concentrations of the drug vary widely (up to seventeenfold), perhaps because of genetically determined differences in the rate of metabolism. Metoprolol is extensively metabolized in the liver, with CYP2D6 the major enzyme involved, and only 10% of the administered drug is recovered unchanged in the urine. The half-life of metoprolol is 3 to 4 hours, but can increase to 7 to 8 hours in CYP2D6 poor metabolizers. It recently has been reported that CYP2D6 poor metabolizers have a fivefold higher risk for developing adverse effects during metoprolol treatment than patients who are not poor metabolizers [2]. Metoprolol generally is used in two divided doses for the treatment of stable angina. For the initial treatment of patients with acute myocardial infarction, an intravenous formulation of metoprolol tartrate is available. Oral dosing is initiated as soon as the clinical situation permits. Metoprolol generally is contraindicated for the treatment of acute myocardial infarction in patients with heart rates of less than 45 beats per minute, heart block greater than first-degree (PR interval ≥ 0.24 second), systolic blood pressure < 100 mm Hg, or moderate-to-severe heart failure. Metoprolol also has been proven to be effective in chronic heart failure. It has been shown in randomized trials to be associated with a striking reduction in all-cause mortality and hospitalization for worsening heart failure and a modest reduction in all-cause hospitalization [2, 3]

Carvedilol is a third-generation β receptor antagonist that has a unique pharmacological profile. It blocks β_1 , β_2 ,

and α_1 receptors similarly to labetalol, but also has antioxidant and antiproliferative effects. It has membrane-stabilizing activity but it lacks intrinsic sympathomimetic activity. Carvedilol produces vasodilation. It is thought that the additional properties (*e.g.*, antioxidant and antiproliferative effects) contribute to the beneficial effects seen in treating congestive heart failure. Carvedilol does not increase β receptor density and is not associated with high levels of inverse agonist activity [2].

Carvedilol has been tested in numerous double-blind, randomized studies including the following: U.S. Carvedilol Heart Failure Trials Program, Carvedilol or Metoprolol European Trial (COMET) [9]. Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) [8] trial, and the Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) trial. These trials showed that carvedilol improves ventricular function and reduces

mortality and morbidity in patients with mild-to-severe congestive heart failure. Several experts recommend it as the standard treatment option in this setting. In addition, carvedilol combined with conventional therapy reduces mortality and attenuates myocardial infarction. In patients with chronic heart failure, carvedilol reduces cardiac sympathetic drive, but it is not clear if α_1 receptor-mediated vasodilation is maintained over long periods of time.

Carvedilol is rapidly absorbed following oral administration, with peak plasma concentrations occurring in 1 to 2 hours. It is highly lipophilic and thus is extensively distributed into extravascular tissues. It is >95% protein bound and is extensively metabolized in the liver, predominantly by CYP2D6 and CYP2C9. The half life is 7 to 10 hours. Stereoselective first-pass metabolism results in more rapid clearance of S(-)-carvedilol than R(+)-carvedilol. [1, 11].

AIM

Our work sought to put in the evidence the change of the blood antioxidant status in patients with a form of ischemic cardiomyopathy-

stable angina , patients treated with two beta blockers-Metoprolol and Carvedilol.

MATERIAL AND METHODS

In the present study, 23 patients from County Clinical Hospital of Oradea, of different sex and age between 46-72 years old with stable angina, were monitored under treatment with beta blockers. They were randomly assigned to receive either carvedilol (25 mg bid) or metoprolol (50 mg bid). Patients with chronic renal failure, chronic obstructive lung disease, asthma, long-

term alcohol or drug abuse, smoking, hepatic, hematologic, neurologic, or collagen vascular diseases were excluded. It formed two groups of patients: the first group (I) including 12 patients age between 46-70 years which were monitored under Metoprolol treatment and the second group (II) including 11 patients age between 46-72 years which were monitored under Carvedilol treatment. We followed the

serum malonaldehyde (MDA), glutathione (GSH) and ceruloplasmin (CP) levels, before treatment and after

six months. Blood samples were collected from the cubital vein with the both drugs.

COLORIMETRIC DETERMINATION OF GSH

Collect blood without using an anticoagulant such as heparin, citrate, or EDTA. Allow blood to clot for 30 minutes at 25°C. Centrifuge the blood at 2,000 × g for 15 minutes at 4°C. Pipette off the top yellow serum layer without disturbing the white buffy layer. Store serum on ice. The serum will have to be deproteinated before assaying. If not assaying on the same day, the sample will still have to be deproteinated, and then stored at -20°C. The sample will be stable for at least six months.

The GSH Assay Kit utilizes a carefully optimized enzymatic recycling method, using glutathione reductase, for the quantification of GSH. The sulfhydryl group of GSH reacts with DTNB (5,5'-dithio-bis-2-(nitrobenzoic acid), Ellman's reagent) and produces a yellow colored 5-thio-2-nitrobenzoic acid (TNB). The mixed disulfide, GSTNB (between GSH and TNB) that is concomitantly produced, is reduced by glutathione reductase to recycle the GSH and produce more

TNB. The rate of TNB production is directly proportional to this recycling reaction which is in turn directly proportional to the concentration of GSH in the sample. Measurement of the absorbance of TNB at 405-414 nm provides an accurate estimation of GSH in the sample.

GSH is easily oxidized to the disulfide dimer GSSG. GSSG is produced during the reduction of hydroperoxides by glutathione peroxidase. GSSG is reduced to GSH by glutathione reductase and it is the reduced form that exists mainly in biological systems. Since glutathione reductase is used in the GSH assay, both GSH and GSSG are measured and the assay reflects total glutathione.

GSH measurement can be done in plasma, serum, erythrocyte lysates, tissue samples, and cultured cells using this kit. However, plasma and serum samples will have to be concentrated before assaying, and nearly all samples will require deproteination.

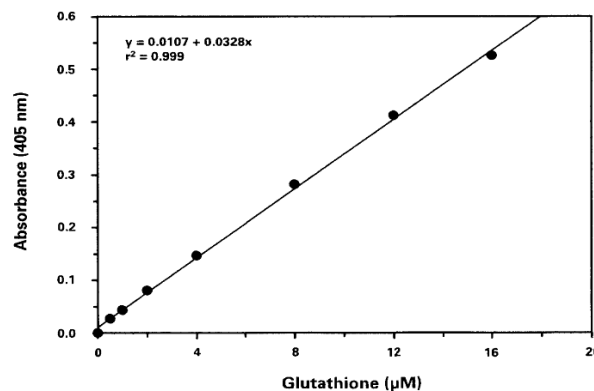


Fig. 1 Standard curve; Measure the absorbance in the wells at 405-414 nm using a plate reader at five minutes intervals for 30 minutes [7].

COLORIMETRIC DETERMINATION OF MALONDIALDEHYDE

Malondialdehyde is one of the products of lipid peroxidation; its determination represents a standard method of assessing the oxidative stress. The dosage method is based on the reaction with thiobarbituric acid (TBA). The biological sample is heated with TBA, in acidic medium. As a result of the reaction, one molecule of MDA reacts with two molecules of

TBA, with the production of a pink pigment, with a measured optical density at 530 nm, is using Pharmacia LKB Ultraspec. III spectrophotometer.

Normal values of the MDA serum levels are between 0.27 – 1.02 nmol/ml. Increased values of the MDA serum levels confirm the presence of the oxidative stress [4, 7].

COLORIMETRIC DETERMINATION OF CERULOPLASMIN

Ceruloplasmin (ferroxidase) is a 150 kD, blue α_2 - glycoprotein that is synthesized in the liver and it is accumulated in the matrix and the inner membrane of the mitochondria. Ceruloplasmin acts mainly as a ferroxidase, catalyzing the oxidation of Fe (II) to Fe (III), and as a Fe (II) carrier in the plasma in association with transferrin, the only protein which can carry iron in this state. Beside its detoxifying activity in the blood, ceruloplasmin also presents a dismutase-like activity (lower than that of the superoxide dismutase), it inhibits the peroxidation of polyunsaturated fatty acids (in vitro demonstration) and

it has immunologic activity. Ceruloplasmin limits the quantity of free radicals, acting as a plasmatic antioxidant [5, 10]. Normal ceruloplasmin serum levels are between 11-24 μ M. The principle of the method is based on the phenol oxidative property of ceruloplasmin, which catalyzes the oxidation of paraphenylenediamine, with the production of a violet compound. The optical density against a reference blank was measured at 530 nm, using Pharmacia LKB. Ultraspec. III spectrophotometer. Abnormal ceruloplasmin level impedes the mitochondrial respiratory process.

RESULTS AND DISCUSSIONS

Glutathione plays important roles in antioxidant defense of cells. The GSH Assay Kit utilizes a carefully optimized enzymatic recycling method. The method is simple, can rapidly be performed, and the results are presented in figure 2. In a cell, where free oxygen radicals accumulate, the fatty acids, which would normally be subjected to beta-oxidation within the mitochondria, will be subjected to lipid peroxidation, production of toxic and reactive species of oxygen which are

neutralized by antioxidants. Ceruloplasmin (CP) is an enzyme, which have antioxidant activity, inhibiting the lipid peroxidation and limiting the level of free radicals in cells. The oxidized ceruloplasmin level in blood serum is evidence the activity of antioxidant system in blood. Our results are presented in figure 3. In a cell, where free oxygen radicals accumulate, the fatty acids, which would normally be subjected to beta-oxidation within the mitochondria, will

be subjected to lipid peroxidation, production of toxic and reactive aldehyde metabolites such as malondialdehyde (MDA) which is

commonly used as an index of lipid peroxidation. Our results are presented in figure 4.

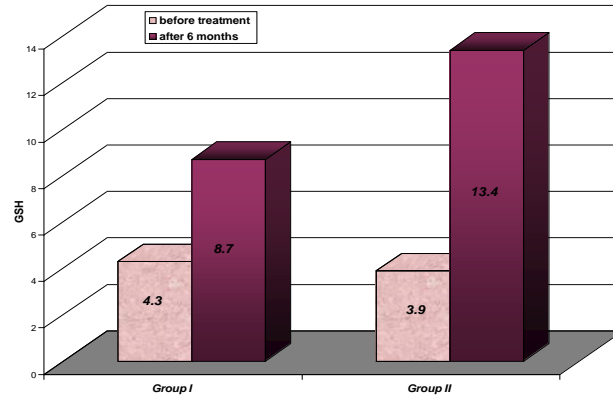


Fig. 2 The serum level of GSH (μM) before and after 6 months of treatment at Group I with metoprolol treatment and Group II with carvedilol treatment

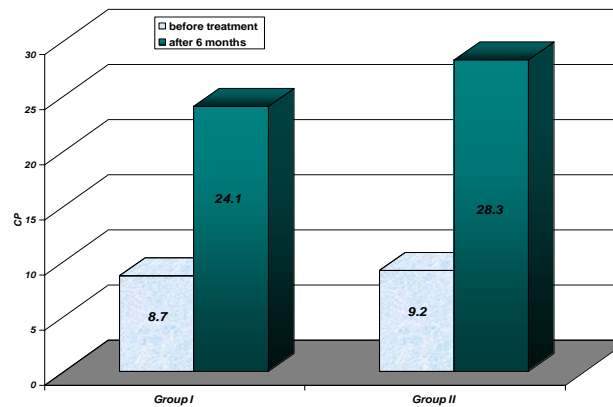


Fig. 3 The serum level of CP (μM) before and after 6 months of treatment at Group I with metoprolol treatment and Group II with carvedilol treatment

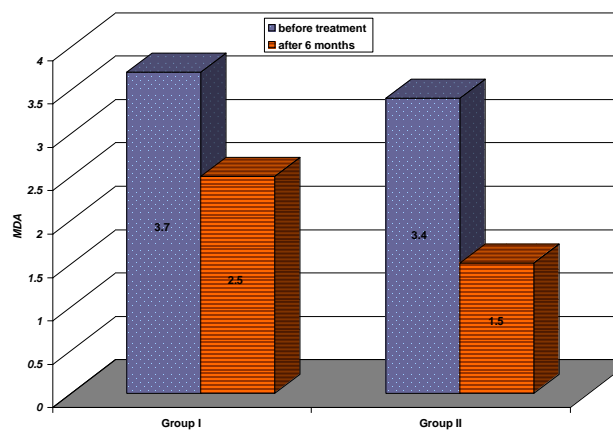


Fig. 4 The serum level of MDA (nmol/ml) before and after 6 months of treatment at Group I with metoprolol treatment and Group II with carvedilol treatment

CONCLUSIONS

We found that the level of MDA, as a measure of lipid peroxidation in clinical samples was decrease in all subjects, but the differences was higher in II group's than in I group's subjects. The level of CP and GSH was increase after six months from the beginning of treatment. The increase was higher in II

group's than in I group's subjects. Our results state important changes in blood antioxidant status in patients under beta-blockers treatment. Carvedilolul was more reactive than Metoprolol. This study represents only a starting point for future research.

REFERENCES

1. Abreu RMV, Santos DJSL, and Moreno AJM. Effects of carvedilol and its analog BM-910228 on mitochondrial function and oxidative stress. *Journal of Pharmacogy Experiments and Therapy*, 295: 1022-1030, 2000.
2. Bertram Katzung, Basic and Clinical Pharmacology, Editura Mc Graw Hill, 2008.
3. Brunton Laurence Lazo, John Parker Keith, Goodman & Gilman's, The Pharmacological Basis of Therapeutics , Editura Mc Graw Hill, 2009.
4. Dejica D., Stresul oxidativ în bolile interne, Casa Cărții de Știință, Cluj - Napoca, 2000., 67-84.
5. Macyntire G., Gutfreund K.S., Martin W.R., Camicioli R., Cox D.W., Value of an enzymatic assay for the determination of serum ceruloplasmin, *J. Lab. Clin. Med.*, 2004, 144, no 6: 294-301.
6. Mano A., Tong Chan S., Sanderson S., John E., Antioxidant Properties of Carvedilol and Metoprolol in Heart Failure: A Double-Blind Randomized Controlled Trial, *Journal of Cardiovascular Pharmacology*, 2001, Vol. 37, Issue 1, pp 48-54
7. Muresan M., Muresan, I., Burta L., Burta O., Micle, L., Micle, O. and Dorofteiu, M., 2003, Stresul oxidativ tn bolile medico-chirurgicale; Editura Universității din Oradea, 89-97.
8. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL, For the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group, Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study, *Circulation* 106: 2194-2199, 2002.
9. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, and Skene A for Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial, *Lancet* 362: 7-13, 2003.
10. Vasin A.V., Platonova, N.A., Povalikhin, R.G., Klotchenko, S.A., 2005, Mitochondrial ceruloplasmin of mammals, *Molecular Biology*; Vol 39(1), 48-60
11. Wei S, Chow LTC, Sanderson JE. Effect of cardeviol in comparison with metoprolol on myocardial collagen post infarction, *Journal of American Coll Cardiology* 2000; 36:276-81.

REMEDIES REGISTERED IN THE ANNUAL ACCOUNTS BOOK OF A PRIVATE RURAL PHARMACY IN 1928



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ABSTRACT

Introduction: information regarding the remedies used in different periods can be obtained directly by consulting the Pharmacopoeias and other organizational administrative documents such as inventories.

Materials and methods: in this paper we studied in parallel a annual accounts book from 1928 and the IVth Pharmacopoeia which was in force during that period. The aim of our study is to highlight the correlation between the medicines registered in the annual accounts book of the private rural pharmacy "Elena Deciu" and those of the IVth Pharmacopoeia edited in 1926. In our research we used the previous pharmacopoeias to mark the continuity or discontinuity of some of the remedies registered in the annual accounts book that was included into study.

Results: most of the medicines listed in the annual accounts book are found in the Pharmacopoeia that was in force at the time, but there are also registered remedies that were out of use according to the same Pharmacopoeias: ossa sepiae, sanguis draconis, etc.

Discussions and conclusions: we found that there is a difference between the remedies used in pharmaceutical practice, as the studied annual accounts book reflects directly in the study and the official rules settled by Pharmacopoeia.

Key words: Pharmacopoeia, pharmacy.

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INTRODUCTION

Information on remedies used in different periods of time can be obtained directly through consulting the pharmacopoeias. Also, the organizational administrative

documents such as inventories are important sources contributing to the reconstruction of „Medical Materia” in time and space.

MATERIAL AND METHOD

An inventory book elaborated in 1928 was used as documentary material highlighting the remedies used in that period of time in a rural private pharmacy „Elena Deciu”. In parallel with this document it was studied the existing Romanian Pharmacopoeia, fourth edition printed in 1926. It was followed to what extent there is synchronization between the

remedies used in therapeutic practice and those included in this Pharmacopoeia. Information about some aspects of continuity or discontinuity of some simple and compound remedies listed in the inventory book was obtained by parallel consulting the previous Pharmacopoeias.

RESULTS

The inventory book of the rural private pharmacy „Elena Deciu” was elaborated in 1928 and registered on

February 21, in Pătârlagele Court from Buzau County.

Monograph denomination					
	I	II	III	S	IV
Althaea radix, folia, flores	+	+	+	+	+
Arnica flores, radix	+	+	+	+	+
Balladonna radix, folia	+	+	+	+	+
China fusca cortex	+		+		+
China regia cortex	+		+	+	
China rubra	+	+	+		
Citrus aurantium folia, flores, fructus, cortex et oleum	+		+	+	+
Couso flores	+	+	+	+	+
Digitalis folia	+	+	+	+	+
Hyoscyamus, folia, semen	+	+	+	+	+
Jalapa radix, resina	+	+	+	+	+
Malva vulgaris, herba florens	+	+	+	+	+
Populus, gemmae	+	+	+		+
Sambucus flores, baccae, cortex interior	+	+	+		+
Scammonium (gumi-rezină)	+	+	+	+	+
Tilia, flores cum et sine bracteis	+	+	+	+	+

It is divide into eight parts, the first of them referring to „medicines and drugs” existing in the pharmacy on

April 15, 1928 and the third one to inventories remedies on December 31, 1928. The other six parts are balance

sheets. In the inventory book there are listed the three worlds: vegetal, animal și mineral plus the pharmaceutical forms. In the case of medicinal plants, many of these are included both in the inventory book and in the Pharmacopoeia 1926: Cortex Aurantii Fructus, Cortex Chinae, Cortex Cinnamomi, Flores Arnicae, Flores Kusso, Flores Malvae, Flores Sambuci, Flores Tiliae, Folia Althae, Folia Belladonae, Folia Digitalis, Folia Hyosciami, Gemmae Populi, Resina Jalapae, Resina Scamonee.

In the tradition of use of these herbal remedies, their mention in the previous pharmacopoeias may be followed in the table 1.

Among existing animal remedies in the inventory book it should be mentioned: Axungia, Cocconella, Cera Alba, Cera Flava, Cetaceum, Ossa Sepia. Their presence in the fourth edition of Pharmacopoeia and in the previous ones is presented in the following table:

Monograph denomination					
	I	II	III	S	IV
Axungia (adeps suillus)	+	+	+	+	+
Cera alba		+		+	+
Cera flava		+		+	+
Cetaceum (spermacetu)	+	+	+	+	+
Cocconella, carminum (Cocci Cacti, cârmâz)	+	+	+	+	+
Ossa seipiae	+	+			

Chemical remedies are both of mineral origin: alumen, silver nitrate, arsenic acid, Kaolin, mercury and those obtained by organic synthesis:

amidopyrin, methylenum coeruleum, naftolum. Continuity of their use can be followed in the table below:

Monograph denomination					
	I	II	III	S	IV
Acidum arsenicosum (șoricioaică)	+	+	+	+	+
Alumen venale (piatră acră)*	+	+	+	+	+
Amidopyrinum (piramidon; aminophenazonum)					+
Argentum nitricum		+			+
Hydrargyrum	+	+		+	+
Kaolinum (caolin, bolus alb)				+	+
Methylenum coeruleum (albastru de metilen)				+	+
Naphtolum				+	+

Of the pharmaceutical formulations included in the inventory book should be mentioned those obtained in the pharmacies: Emplastrum Diachilon, Emplastrum Cantharidatum,

Emplastrum Vigo, ampoules of Cacodylate, ampoules of Caffeine and Sodium Benzoate. Their presence in the pharmacopoeias printed till 1926 is showed in the following table:

Monograph denomination					
	I	II	III	S	IV
Emplastrum cantharidum	+		+	+	+
Emplastrum cantharidum perpetuum	+		+	+	+
Emplastrum diachylon compositum (Emplastrum lithargyri compositum, talion)	+		+	+	+
Emplastrum diachylon simplex (Emplastrum lithargyri simplex ; emplastrum plumbi)	+		+	+	+
Natrium cacodylicum solutum pro injectione					

In the tables above, the capital S refers to the Special Pharmacopoeia drafted under the guidance of the College of Pharmacists.

CONCLUSIONS AND DISCUSSIONS

Most of the remedies listed in the inventory book are found in the pharmacopoeia of 1926 or in the previous ones, the only exception of

our presentation being the injection solution of Sodium Cacodylate which appears in the fifth edition of Pharmacopoeia.

REFERENCES

1. Pharmacopea română, București, 1862
2. Pharmacopea Română, București, 1874
3. Farmacopea Română, București, 1893
4. Farmacopea Română, ediție specială, București, 1915
5. Farmacopeea Română, București, 1943

IDENTIFICATION AND ASSAY OF CEFACLOR BY SPECTRALE METHODS FROM CECLODYNE[®] CAPSULES OF 250 MG AND 500 MG



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ABSTRACT

We investigated three-dimensional (3D) transthoracic echocardiography (TTE) in the assessment of mitral stenosis. Bidimensional (2D) TTE and 3DTTE was performed in 42 patients with mitral stenosis concomitant with cardiac catheterisation, prior to valve surgery. Using a surgical scoring protocol for recognition of the valvular segments, 2D and 3D methods were compared. Adequate echocardiographic visualization of the mitral segments was more frequently obtained by 3DTTE than by 2DTTE. Total 3DTTE score were significantly better than 2DTTE score. Using surgical classification as gold standard, the sensibility and specificity were 93% and 87 % for 3DTTE, and 86% and 79% for 2DTTE. The opening area determined by 3DTTE showed better linear association with the area determined intraoperative or invasively by Gorlin formula compared with 2DTTE. In conclusions, 3DTTE was superior to 2DTTE for the analysis of mitral stenosis and could be used for the accurate identification of the severity.

Key words: mitral valve stenosis, mitral valve area, three-dimensional transthoracic echocardiography, bidimensional transthoracic echocardiography, Gorlin formula.

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ABSTRACT

Antibiotics are one of the most important class of drugs, that include chemical substances, obtained by extraction of different species of ascomycetes, synthetically or not. Cephalosporins contains a cyclic system of cromophor $O=C-N-C=C$ that it's responsible of UV absorption at wavelength of 260 nm. Based on what the BP specifies about cefaclor, that can be identified in water, at wavelength 264 nm, we identified the active substance from **Ceclodyne**[®] capsules of 250 mg and 500 mg, by UV-Vis spectroscopy. Although the literature provides the spectral methods only for

the identification of cefaclor and HPLC methods for it's dosage, given the fact that not all the laboratories are featured with the specific equipment, we report in the present paper an UV spectrophotometric method for cefaclor. The identified and dosed substance ($C_{15}H_{14}N_3ClO_4S$) is acid (6*R*,7*R*)-7-[[*(2R)*-2-amino-2-phenylacetyl]amino]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic. Aspect: it's a white or weak yellow powder, hardly water soluble, practically insoluble in methanol and methylene chloride.



Fig. 1 Powder appearance of cefaclor.

AIM

The aim of the present study is a method of identification and quantitative determination of cefaclor, a second generation, oral cephalosporin antibiotic. The cyclic condensed system

of cephalosporines presents a high absorption in ultra - violet at 260 nm wavelength because of the $O=C-N-C=C$ cromophor group.

MATERIALS AND METHODS

Reagents: distilled water, Cefaclorum S.R., Ceclodyne 250 mg, 500 mg, capsules. Equipment: analytical balance Sartorius, UV-Vis spectrophotometer Jasco V530, 1 cm quartz cuvettes, water distiller 2001/2 JFL. Preparation of solutions: Solution 1: cefaclor solution (r.s.) 30 mg/L.

Solution 2: cefaclor solution (r.s.) 18 mg/L. Solution 3: cefaclor solution (r.s.) 15 mg/L. Solution 4: cefaclor solution (r.s.) 7.5 mg/L. Solution 5: cefaclor solution (r.s.) 9 mg/L. Solution 6: cefaclor solution (r.s.) 4.5 mg/L. Solution 7: the powder of a capsule of Ceclodyne 250 mg dissolved in 1000

mL of distilled water, using a 1000 mL flask; by successively dilutions, we obtained a concentration of 12.5 mg/L. Solution 8: the powder of a capsule of Cecloidyne 500 mg dissolved in 1000 mL of distilled water, using a 1000 mL flask; by successively dilutions, we

obtained a concentration of 50 mg/L. Solution 9: the powder of a capsule of Cecloidyne 500 mg dissolved in 1000 mL of distilled water, using a 1000 mL flask; by successively dilutions, we obtained a concentration of 12.5 mg/L.

RESULTS AND DISCUSSION

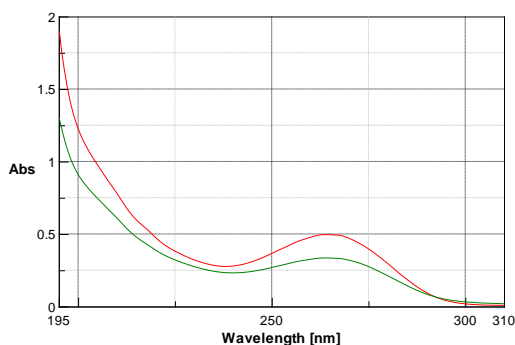


Fig. 2 The UV overlapping spectra of cefaclor and Cecloidyne 250 mg

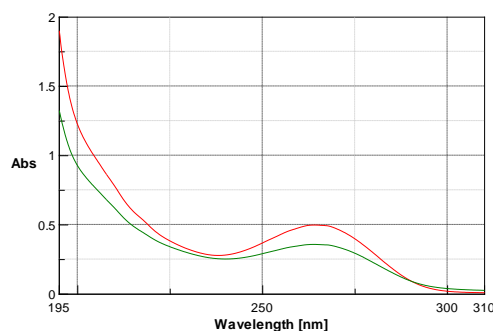


Fig. 3 The UV overlapping spectra of cefaclor and Cecloidyne 500 mg

We also tested the linearity, the repeatability and the stability of cefaclor solutions between the

concentration range of 4,5 mg/L and 30,0 mg/L.

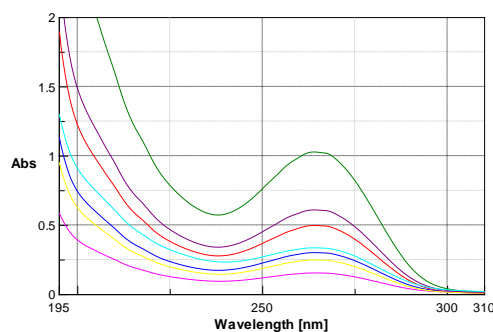


Fig. 4 The UV spectra of cefaclor solution (r.s.) and Cecloidyne (250 mg capsules)

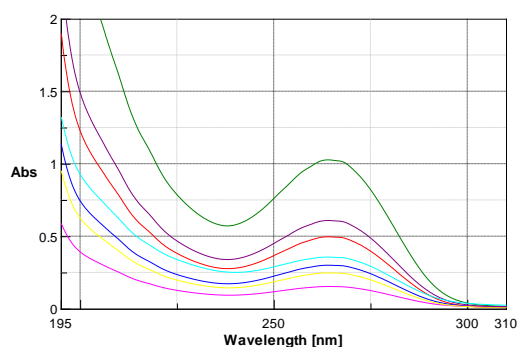


Fig. 5 The UV spectra of cefaclor solution (s.r.) and Ceclodyne (500 mg capsules)

Table 1 The absorbion of cefaclor and Ceclodyne (250 and 500 mg cps) solutions

Analyte	Absorbance at $\lambda = 264 \text{ nm}$
Cefaclor s.r. 30 mg	1,02992
Cefaclor s.r. 18 mg	0,61203
Cefaclor s.r. 15 mg	0,49947
Cefaclor s.r. 9 mg	0,30348
Cefaclor s.r. 7,5 mg	0,2507
Cefaclor s.r. 4,5 mg	0,15673
Ceclodyne 12,5 mg/cps 250 mg	0,3385
Ceclodyne 12,5 mg/cps 500 mg	0,35969

Repeatability: using the same solutions, in identical conditions, the results of successive determinations should not differ more than 1%. Still, we made measurements for the solution with 12.5 mg/L cefaclor from

250 mg Ceclodyne capsules and the result is that the spectra are almost confused, that way we can say that the repeatability is an observed parameter in this analysis.

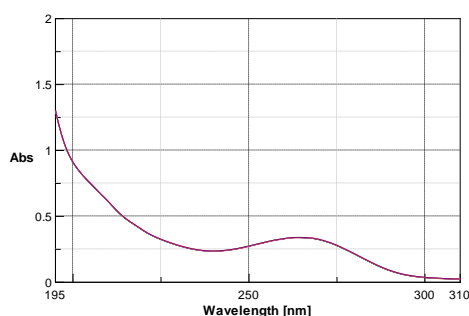


Fig. 6 Repeatability determined by 6 solutions (12.5 mg/L), from Ceclodyne 250 mg

Table 2 The absorbance of 12.5 mg/L solutions, from Ceclodyne 250 mg capsules

Test solution for capsule of 250 mg Cefaclor	Absorbance at $\lambda = 264 \text{ nm}$
Solution 1	0,33850
Solution 2	0,33956
Solution 3	0,33971
Solution 4	0,34016
Solution 5	0,34091
Solution 6	0,34095

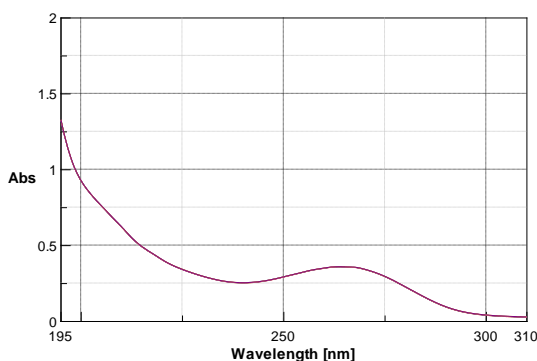


Fig. 7 Repeatability determined by 6 solutions (12.5 mg/L), from Ceclodyne 500 mg

Table 3 The absorbance of 12.5 mg/L solutions, from 500 mg capsules

Test solution for capsules of 500 mg Cefaclor	Absorbance at $\lambda = 264 \text{ nm}$
Solution 1	0,35969
Solution 2	0,36066
Solution 3	0,36077
Solution 4	0,36131
Solution 5	0,36142
Solution 6	0,36168

The linearity and linearity range: We search the linearity and linearity range by studying the correlation between concentration and response factor (the absorbance) for the reference solution and the sample solution. The evaluation of the results has been made by the analysis of the linear regression. The acceptability criteria used was the correlation coefficient value, that is necessary to be higher than 0.99. Testing the linearity of the method using the reference solution showed

linearity range (4.5 – 30.0 mg/L). The result of this study using the reference solution made us focus (dependent on the recorded absorbance) in choosing the linearity range for testing the linearity using the sample solution. The straight regression, for de range of concentrations elected, has a correlation coefficient R of 0.9998. We can say that the dosing method can be successfully used for the assay of cefaclor in the concentration field 4.5mg /L – 30 mg/l.

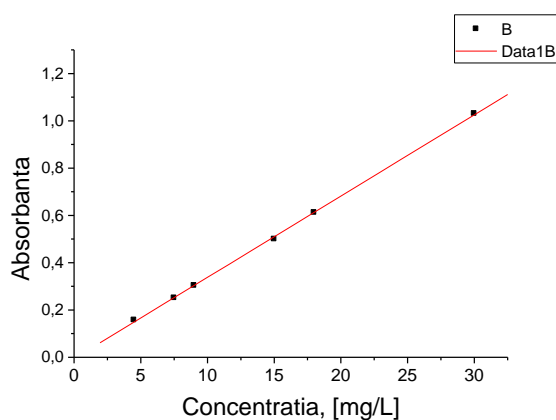


Fig. 8 Calibration curve for solution with reference cefaclor (s.r.)

Number of wavelength: Method with one wavelength		Standard blank: 0.0000
Maximum absorption: 264.0 nm		Nr. Conc.[mg/L] Abs
Response: Quickly		1 0.04500 0.2352
Bandwidth: 2.0 nm		2 0.07500 0.3579
Number of cycles: 3		3 0.09000 0.4263
Interval: 5 sec		4 0.15000 0.6233
Calibration curve: Linear		5 0.18000 0.7308
Expression: $Abs = A + B * Conc$		6 0.30000 1.1540
Factor: $A = 0.0897$ $B = 0.3558$		
Coefficient: 0.999547		
Date: 17.08.2009 13:12		

STABILITY

Stability: Stability is the ability of a solution to maintain its properties during a period. A medicine is stable if, maintained in appropriate conditions, is keeping his quality characteristics obtained when is prepared within the limits stipulated set by official rules, for a determined period. Still, we performed measurements for the

sample solution obtained within the Ceclodyne capsules. There were made at 24 h, 72 h, 120 h, 168 h (7 days from the prepared solution). These measurements occurred in identical conditions, using distilled water like standard blank. The samples were maintained refrigerated, between 0 and 5 °C, protected from light.

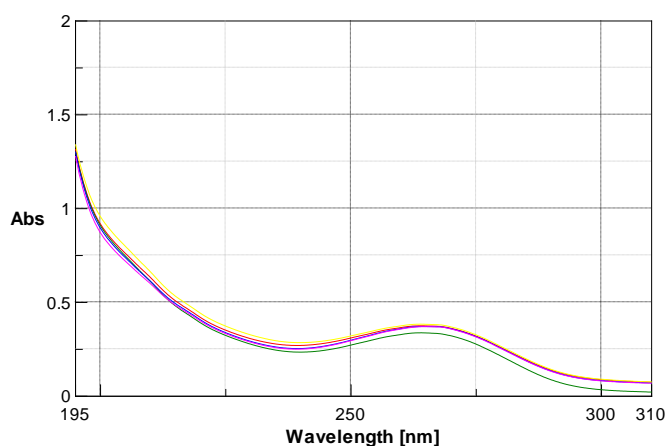


Fig. 8 Initially overlapping spectra at 24 h, 72 h, 120 h and 168 h

Table 4 Absorbance of Cefaclor solution capsules of 250 mg initially, at 24 hours, at 72 hours, at 120 hours and at 168 hours

Time now being considered for solution with Cefaclor 250 mg capsules	Absorbance at $\lambda = 264 \text{ nm}$
Initially	0,3385
At 24 hours	0,37213
At 72 hours	0,3710
At 168 hours	0,37579
At 120 hours	0,38445

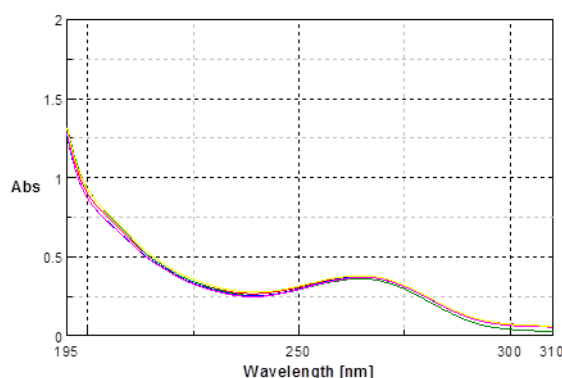


Fig. 9 Initially overlapping spectra at 24 h, 72 h, 120 h and 168 h

Table 5 Absorbance of Cefaclor solution capsules of 500 mg initially, at 24 hours, at 72 hour s, at 120 hours and at 168 hours

Time now being considered for solution with Cefaclor 500 mg capsules	Absorbance at $\lambda = 264 \text{ nm}$
Initially	0,35969
At 24 hours	0,37223
At 72 hours	0,36833
At 168 hours	0,37556
At 120 hours	0,37949

On these results, we will identify variations from declared quantity per dose.

$$\text{substanta activa} = \frac{A_p \times C_{et} \times M_{medie}}{A_{et} \times C_p}$$

(Expressed in g/dose)

$$\text{substanta activa} = \frac{s.a.\text{det} \times 100}{s.a.\text{decl}} \quad (\%)$$

from the declared mass of the substance) where:

A_p = the absorbance of the sample solution;

C_{et} = cefaclor mass weighed s.r. (g)

M_{medie} = average weight of a dose (g)

A_{et} = absorbance reference solution

C_p = sample taken in this table (g)

$$\text{cefaclor [mg/capsula]} = \frac{0,35969 \times 15 \times 574,46}{0,49947 \times 12,5}$$

Cefaclor [mg/capsula] = 496,43 mg/capsule

$$\text{cefaclor [mg/capsula]} = \frac{0,3385 \times 15 \times 292,2}{0,49947 \times 12,5}$$

Cefaclor [mg/capsula] = 237,63 mg/capsule

CONCLUSIONS

Discussion and Conclusions: We identified the cefaclor from Ceclodyne® capsules of 250 mg and 500 mg by UV spectrophotometry at 264 nm. We determined the quantity of cefaclor in Ceclodyne capsules using aqueous solutions. We observed the solutions in

UV light at 264 nm. The response was linear ($r^2 \geq 0.999547$) over the concentration range of 4,5 – 30,0 mg/L. The concentrations in cefaclor were 95,052% for Ceclodyne® capsules of 250 mg and 99,286% for Ceclodyne® capsules of 500 mg.

REFERENCES

1. Barber M.S., The Penicillins Business, Michael Barber&Associates, 1999
2. Bojiță M., Roman L., Săndulescu R., Oprean R.- Analiza și controlul medicamentelor, Editura Intelcredo, Deva, 2003, pag :290,291,353, 354.
3. Bârcă M. - Metode de analiză în controlul medicamentului, Ed. Tehnoplast, 2005
4. Farmacopeea Europeana, ed.V
5. Farmacopeea Britanică, ed.III

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Original studies must include a structured abstarct of maximum 150 words, containing the following titles and informations:

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- Conclusions;
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Themes may be selected from all medical fields. Manuscripts which offer a special gain for daily activity will have priority. The title must be clearly, precisely stated. It may be completed by a subtitle. It is advisable to include in the key words of the title the main message, the special element which may be observed from the case evolution. The content of a case report must be divided into three parts:

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