ISSN 1857-0666

Curierul medical

SCIENTIFIC MEDICAL JOURNAL

Ministry of Health of the Republic of Moldova
Nicolae Testemitsanu State University of Medicine and Pharmacy

Ministerul Sănătăţii
al Republicii Moldova.
Universitatea de Stat de Medicină şi
Farmacie „Nicolae Testemiţanu”

Issued bimonthly

Министерство здравоохранения
Республики Молдова.
Государственный университет медицины и
фармации им. Н. А. Тестемицану

Vol. 59, No 5
October 2016

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9 771857 066600

Printing House "Tipografia Sirius"
2, A. Lapusneanu str., Chisinau, MD-2004
the Republic of Moldova
www. sirius.md

ISSN 1857-0666

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Welcome to the scientific and medical journal Curierul Medical!

From its debut in 1958 the journal has striven to support the interests of Moldovan medicine concerning the new concepts of its development. The Editorial Board warmly welcomes both the readers of and the authors for the journal, all those who are enthusiastic in searching the new and more effective ways of solving numerous medicine problems. We hope that those who want to make their contribution into the science of medicine will find our journal helpful and encouraging.

The journal is accredited by the National Council for Accreditation and Attestation. The journal publishes official papers, scientific articles, editorials, clinical studies and cases, lectures, methodological guides, reviews, brief reports and correspondence. The journal welcomes articles in English, Romanian and Russian. The journal editorial policy provides the prompt publication of papers within 12 weeks after receiving them.

Bine ați venit la revista științifică medicală Curierul Medical!

De la prima apariție în 1958, revista susține și dezvoltă noile idei în domeniul medicinii, în Republica Moldova. Colegiul de redacție agrează cu multă considerație atât cititorii cât și autorii articolelor, pe toți acei care cu mult entuziasm caută noi și mult mai efective metode de soluționare a multiplelor probleme ale medicinii. Sperăm, că toți acei care doresc să-și aducă aportul la dezvoltarea științelor medicale, vor găsi revista noastră utilă și atractivă.

Revista este acreditată de către Consiliul Național de Acreditare și Atestare. Revista publică comunicări oficiale și, totodată, sunt editate diverse publicații, inclusiv independente: articole științifice, editoriale, cercetări și prezentări de cazuri clinice, prelegeri, îndrumări metodice, articole de sinteză, relatări scurte, corespondențe și recenzii. Revista publică articole în limba engleză, română și rusă. Politica de editare a revistei prevede examinarea operativă și publicarea articolelor timp de 12 săptămâni după înaintare.

Добро пожаловать в научно-медицинский журнал Curierul Medical!

С первого дня своего выпуска в 1958 году журнал стремится поддерживать и развивать новые идеи в области медицины в Молдове. Редакционная коллегия всегда рада как читателям, так и авторам статей, всем тем, кто с энтузиазмом ищет новые, более эффективные способы решения многочисленных задач медицины. Мы надеемся, что все те, кто хотят внести свой вклад в медицинскую науку, найдут наш журнал полезным и вдохновляющим.

Журнал аккредитован Высшей Аттестационной Комиссией Республики Молдова. В журнале печатаются официальные материалы, научные статьи, наблюдения из клинической практики, обобщающие статьи, краткие сообщения, методические указания, рецензии и корреспонденция. В журнале публикуются статьи на английском, румынском и русском языках. Издательская политика журнала предусматривает оперативное рассмотрение и публикацию статей в среднем в течение 12 недель после поступления.

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Index for subscription – 32130

RESEARCH STUDIES

Evaluation of Beta-lactam antibacterials and penicillins consumption

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Abstract

Background: The beta-lactam family of antibiotics includes the majority of the most heavily used antibacterials in clinical medicine. They are important, both historically and currently, because of their effectiveness and generally low toxicity. All around the world in hospitals consumption recorded in medium 30-50% of all antibiotics and that situation determined higher attention for dynamic use study of beta-lactam antibacterials and penicillins in hospitals.

Material and methods: For this study we used data of a six-year (2009-2014) period, in the Emergency Medicine Institute and their subdivisions with the highest consumption of antibiotics which shows the dynamics of the use of beta-lactam antibacterials and penicillins in grams and value indexes.

Results: In the evaluated period consumption of beta-lactam antibacterials and penicillins in EMI recorded a decline from 85.5 to 20.8 DDD/1000 or by 75.67%, in ICD departments from 367.92 to 133.91 DDD/1000 or by 63.60%, and respectively from 74.48 to 39.31 DDD/1000 in SSOTD or by 19.84%. Medium annual consumption in EMI recorded 65.42 DDD/1000 and respectively in ICD 178.29 and 73.68 DDD/1000 in SSOTD departments, while in international hospitals medium consumption constitutes 354.3 and in ICU 575 DDD/1000. In 2014 ICD departments recorded 6549.28 lei per DDD/1000 that was by 6.12 times more than the cost of 1069.62 lei registered in SSOTD departments and by 11.49 times than 569.84 lei recorded per DDD/1000 in all EMI.

Conclusions: In the evaluated period, EMI recorded the consumption of beta-lactam antibacterials and penicillins by 5.42 times less comparatively to 354.3 DDD/1000 registered in some international hospitals, which could be considered an important point for reviewing antimicrobial treatment of the hospitalized patients, as well as annual planning optimization and rational use of this group and all antibiotics necessities.

Key words: Beta-lactam antibacterials, penicillins, defined daily dose, consumption, hospitals.

Introduction

The beta-lactam antibactirials and penicillins remain the most heavily used antibacterials in clinical medicine. They are important, both historically and currently, because of their effectiveness and generally low toxicity. The international market of consumption of beta lactam antibiotics amounts annual sales of about US $15 billion and it makes up to 65% of the total antibiotics market. The annual consumption is estimated to be in the range of 10–30 million tons and this is increasing with time [1, 2]. All around the world in hospitals consumption of beta-lactam and penicillin antibiotics recorded on evarage 30-50% of all antibactirials. That situation determined a higher attention for this group of anti-infectives for systemic use in medicine [3, 4, 5, 6, 7, 8] and supposed to take priority in EMI, including surveillance, stringent use control and rational prescription, as well as supporting the importance of antimicrobial consumption [9, 10, 11].

The primary aim of the study was to evaluate institutional representative data on beta-lactam antibacterials and penicillins utilization in accordance with the World Health Organization (WHO) requirements, directed to determine the value of Defined Daily Doses per 1000 Occupied-Bed Days (DDD/1000) and value cost in dynamics per institution and most important departments [12].

Material and methods

For this study we used the data of a six-year (2010-2014) period, DDD/1000 consumption of beta-lactam and penicillin antibiotics in EMI (Emergency Medicine Institute) and their main subdivisions such as ICD (reanimation, intensive therapy and intensive neurological ”stroke” departments) and SSOTD (septic surgical and septic orhtotraumotology departments) [13], which shows the dynamics of consumption of anti-infectives for systemic use drugs, as classified by Anatomical Therapeutic Chemical (ATC), classification system of World Health Organization (WHO) indicated, in g (grams) and lei (value indexes). Statistical, analytical, mathematical, comparative, logical and descriptive were used as the methods of study.

Results and discussion

For determining the number of DDD/1000 we used data about total annual consumption of beta-lactam antibacterials and penicillins and the statistics data concerning the number of treated patients (only patients with health insurance and other free treated by the state categories of citizens). The total number of occupied bed/days in the institution was 188762 in 2009, 191556 in 2010, 186246 in 2011,199816 in 2012, 193019 in 2013and 187558 in 2014, and respectively for the coresponding departments of

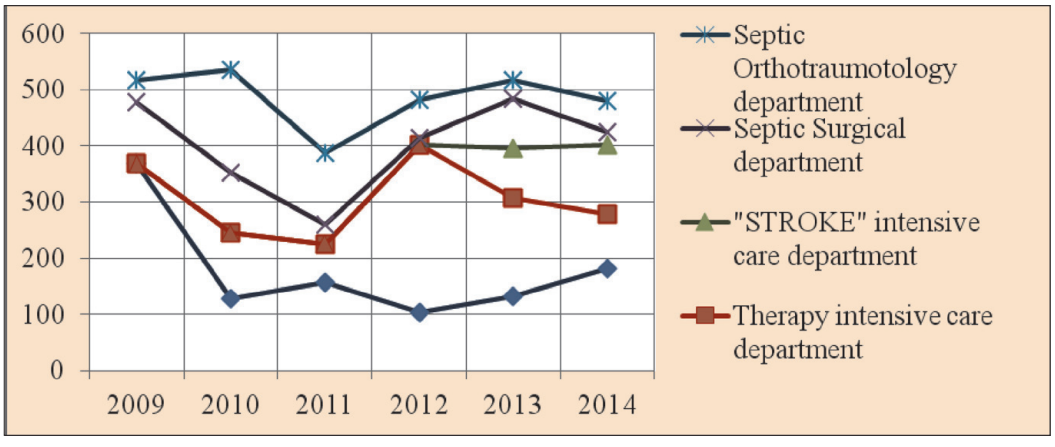

Fig. 1. Total beta-lactam antibacterials and penicillins consumption in DDD/1000 during 2009–2014.

EMI: reanimation (2009 = 3990; 2010 = 6551; 2011 = 6985; 2012 = 9051; 2013 = 7384; 2014 = 7361), intensive therapy (2010 = 2922; 2011 = 3327; 2012 = 3239; 2013 = 3407; 2014 = 3388), intensive neurological "stroke" (2013 = 2553; 2014 = 4193), septic surgical (2009 = 14030; 2010 = 14212; 2011 = 12875; 2012 = 12372; 2013 = 12464; 2014 = 12104), septic orthopedic-traumotology (2009 =10664; 2010 = 10017; 2011 = 9540; 2012 = 10178; 2013 = 9701; 2014 = 9535) [14, 15, 16, 17].

Consumption of beta-lactam antibacterials and penicillins is characterised by the use of beta-lactam antibacterials and penicillins parenteral (P) and enteral (E) forms with DDD 2.0(P) and 2.0(E) for ampicillinum, with DDD 1.0(P) and 1.0(E) for amoxicillinum, withDDD 3.0(P) and 1.0(E) for amoxicillinum+ acidum clavulan ICDm, with DDD 15.0(P) for ticarcillinum. Total beta-lactam antibacterials and penicillins consumption in DDD/1000during 2009-2014 is shown in figure 1.

From figure 1, it can be observed a total decrease of consumption in the group of beta-lactam antibacterials and penicillins from 516.88 in 2009 to 385.61 DDD/1000 in 2014 or by 25.40%. According to the annual medium consumption of 562.51 DDD/1000 could be placed as follows: first – reanimation department with 178.08 DDD/1000 or 31.66%, second – intensive therapy department with 131.82 DDD/1000 or 23.43%, third –intensive neurological «stroke» department with 105.25 DDD/1000 or 18.71%, fourth – septic orhtotraumotology department with 84.37 DDD/1000 or 15.00% and septic surgical department with 62.99 DDD/1000 or 11.20% on the fifth position. In figure 2 the total beta-lactam antibacterials and penicillins consumption of parenteral forms in DDD/1000 during 2010-2014 is shown.

In figure 2, parenteral forms of beta-lactam antibacterials and penicillins consumption is presented. The highest decrease of consumption in the evaluated period recorded the septic surgical department from 105.2 to 10.41 DDD/1000 or by 10.11 times, followed by the reanimation department from 356.14 to 181.09 DDD/1000 or by 49.15%, thirdly septic orthotraumotology department from 30.65 to 19.08 DDD/1000 or by 37.75% and on the last position – therapy intensive care department from 118.07 in 2010 to 97.11 DDD/1000 or by 17.75%. Only intensive neurological «stroke» department, from its establishment in the end of 2012, increased consumption from 86.96 in 2013 to 123.54 DDD/1000 in 2014 or by 42.07%.

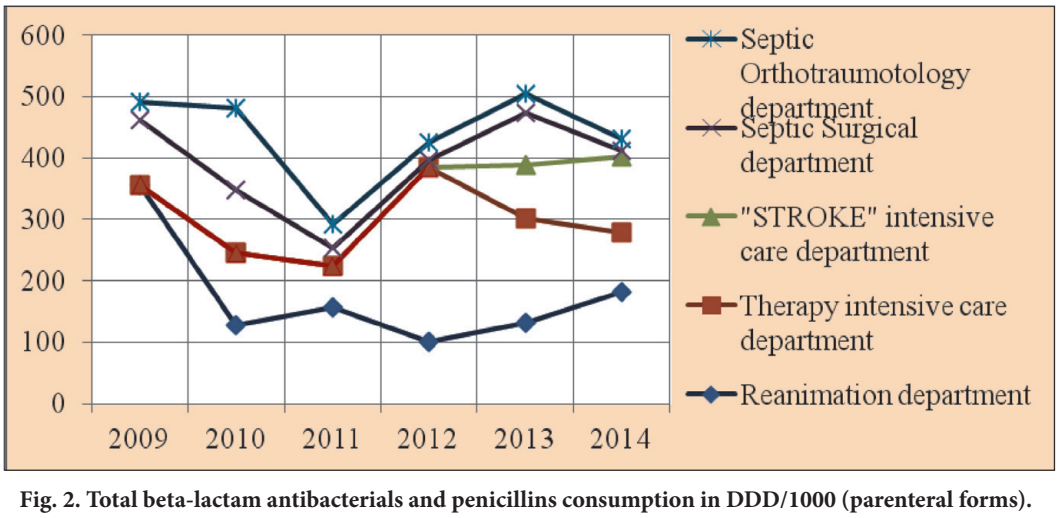

Fig. 2. Total beta-lactam antibacterials and penicillins consumption in DDD/1000 (parenteral forms).

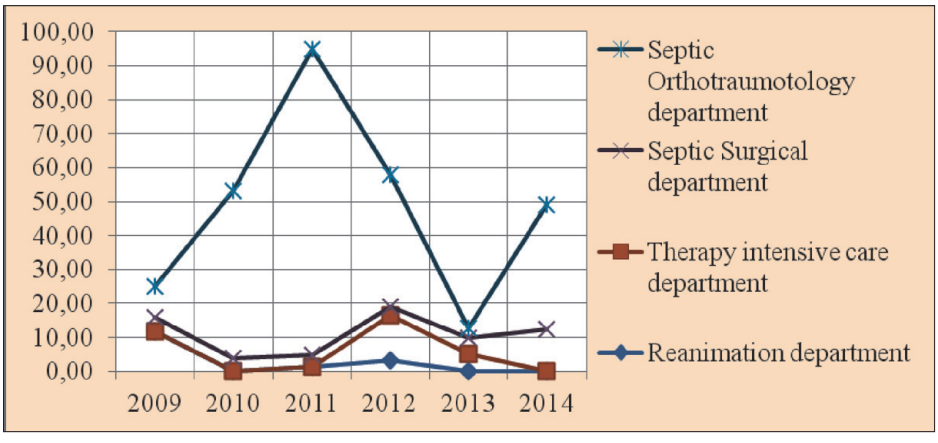

Fig. 3. Total beta-lactam antibacterials and penicillins consumption in DDD/1000 (enteral forms).

During 2009 to 2014 total departmental consumption of beta-lactam antibacterials and penicillins parenteral forms recorded a decrease from 491.99 to 431.23 DDD/1000 or by 12.35%. In figure 3 totals DDD/1000 of beta-lactam antibacterials and penicillins consumption during 2009-2014 are shown.

The data from figure 3, shows that in the evaluated period enteral forms of beta-lactam antibacterials and penicillins recorded an increament from 9.13 to 36.81 DDD/1000 or by 4.03 times in septic orthotraumotology department, from 3.99 to 12.31 DDD/1000 or by 3.08 times in septic surgical department. Other departments are characterized by an occasional consumption of this group of antibiotics. Totally during 2009 – 2014 years all departments recorded an increment from 24.90 to 49.12 DDD/1000 or by 97.27%.

Taking into consideration that in most scientific journals, published data about drugs consumption include the use of them in all intense care hospital unites; we determined the medium consumption of DDD/1000 separately for ICD and SSOTD of EMI. To determine this medium we summed the total of DDD/1000 separately for ICD and SSOTD and divided by the number of those departments (3 and respectively 2). The results are shown in table 1.

The data in table 1 shows that in the evaluated period total departamental consumption of parenteral forms was (356.14+67.93) =424.07 DDD/1000 in 2009 and respectively (133.91+14.75) =144.66 DDD/1000 in 2014, from which ICD represents respectively 83.98% and 90.08%, as well as SSOTD 16.08% and 9.92%. Total institutional use of parenteral forms recorded a significant decrease from 79.9 to 3.9 DDD/1000 or by 20.49 times and vice versa enteral forms an abrupt increase from 5.6 to 16.9 DDD/1000 or by 3.02 times.

The median registered consumption from the evaluation period of beta-lactam antibacterials and penicillins in ICD of EMI recorded 178.3 DDD/1000 or less by 2.52 to 3.93 times comparatively to 450 to 700 DDD/1000 registered in many ICD of international hospitals [5, 6, 19, 20].

In table 2 a comparison data on beta-lactam antibacterials and penicillins consumption in EMI and some international hospitals is shown.

From table 2, it could be observed that during the evaluated period consumption of beta-lactam antibacterials and penicillins in EMI recorded a spontaneus decrease from 85.5 to 20.8 DDD/1000 or by 4.11 times. Calculated beta-lactam antibacterials and penicillins medium annual

Table1

Beta-lactam antibacterials and penicillins consumption in (parenteral and enteral forms) in DDD/100

Department	Administration /Period of evaluation	2009	2010	2011	2012	2013	2014
ICD	Parenteral	356.14	122.54	111.76	192.17	129.79	133.91
	Enteral	11.78		0.644	8.337	2.64	
	Total	367.92	122.54	112.40	200.51	132.43	133.91
SSOTD	Parenteral	67.93	118.36	34.58	20.35	57.27	14.75
	Enteral	6.56	26.53	46.79	20.68	3.735	24.56
	Total	74.48	144.89	81.37	41.03	61	39.31
Total EMI	Parenteral	79.9	80	86.7	68.7	6.9	3.9
	Enteral	5.6	6.7	8.1	8.1	21.2	16.9
	Total	85.5	86.7	94.8	76.6	28.1	20.8

Table 2

Total DDD/1000 consumption of beta-lactam antibacterials and penicillins in EMI and same international hospitals

Institution/data/years	2009	2010	2011	2012	2013	2014
Emergency Medicine Institute	85.5	86.7	94.8	76.6	28.1	20.8
Total	662.4	558.2	622.1	542.4	546.9	464.1
Percentage	12.9%	15.54%	15.24%	14.12%	4.35%	4.48%
Large acute Australian public hospitals[5]	360.4	261.9	276.2	265.0	425.9	411.5
Total	931.8	933.7	946.5	931.6	943.4	922.6
Percentage	38.65%	28.05%	29.18%	28.45%	45.15%	44.6%
Programs/data/years	2012		2012 – 2013			
NAUSP; SAAUSP [6]			401.7; 425.8			
DANMAP; SWEDRES; NETHMAP	454; 302				313	
Total	931; 609		945; 943		712	
Percentage	48.77%; 49.59%		42.51%; 45.15%		43.96%	

expenditure of 65.42 DDD/1000 [(85.5+86.7+94.8+76.6+28.1+20.8):6] represents 11.56% from 562.51 DDD/1000 [(662.4+558.2+622.1+542.4+546.9+464.1):6] annual median of 6-year institutional antibiotics consumption. 6 years in large acute international public hospitals and data from other surveillance international programs show an increase of beta-lactam antibacterials and penicillins use from 360.4 to 411.5 DDD/1000 or by 14.18%, of which median share constituted 354.3 DDD/1000 [(360.4+261.9+276.2+265.0+425.9+411.5+401.7+425.8+454+302+313) :11] or 40% from the total consumption of 886.26 DDD/1000 [(931.8+933.7+946.5+931.6+943.4+922.6+931+609+945+943+ 712) :11], [5, 6]. From above mentioned analyses we can state that median annual consumption of beta-lactam antibacterials and penicillins in EMI recorded 5.42 (354.3: 65.42) times less than in majority of international hospitals. Nevertheless, consumption data can be found not corresponding to the median of all international hospitals, as an example is a Single University Hospital in Korea, where consumption of beta-lactam antibacterials and penicillins recorded 75 DDD/1000 in 2012 [18], which is more appropriate to the data registered in EMI.

The value cost of beta-lactam antibacterials and penicillins use per DDD/1000 in lei is presented in figure 4.

As could be stated from figure 4 during the evaluated period the main value cost per DDD/1000 from 6280,42 to 8041,7 lei or an increase by 28.04% recorded reanimation department, with the highest cost in 2011 of 23080.63 lei, consequently the second position by a decrease from 6227.42 lei in 2010 to 4985.7 lei per DDD/1000 or by 19.93% holds intensive therapy department, with the highest cost in 2011 of 19196 lei, the third position by an increase from 2598.50 lei in 2013 to 6620.4 lei per DDD/1000 or by 2.55 times holds intensive neurological «stroke» department followed by septic surgical department by the results from 1136.8 lei to 1428.04 lei per DDD/1000 or an increase by 25.62% with the highest cost in 2013 of 2494.45 lei per DDD/1000 and the fifth position – septic orthotraumotology department with the cost of from 622.38 to 711.19 lei and the highest cost in 2011 of 2369.68 lei per DDD/1000.

In figure 5 the total value cost of beta-lactam antibacterials and penicillins in DDD/1000 (parenteral forms) is presented.

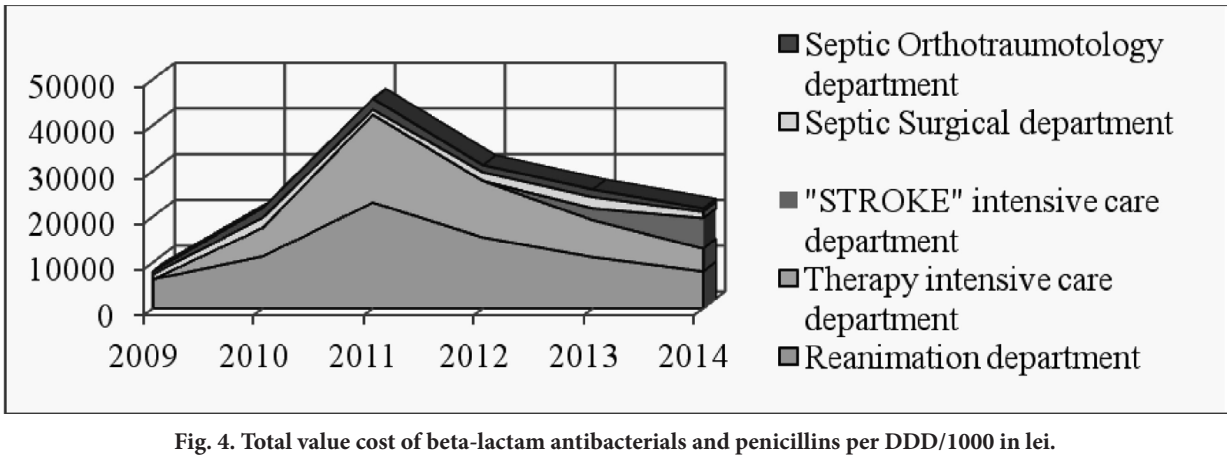

Fig. 4. Total value cost of beta-lactam antibacterials and penicillins per DDD/1000 in lei.

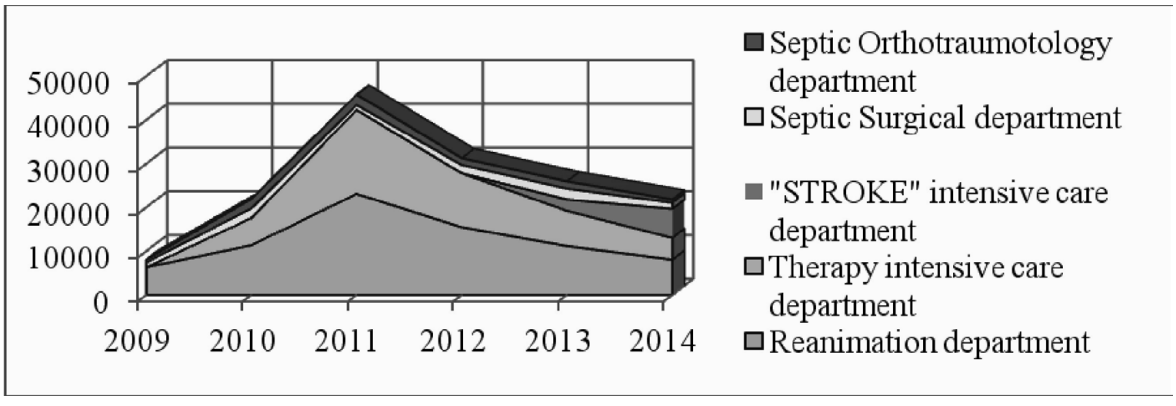

Fig. 5. Value cost of beta-lactam antibacterials and penicillins in DDD/1000 of parenteral forms in lei.

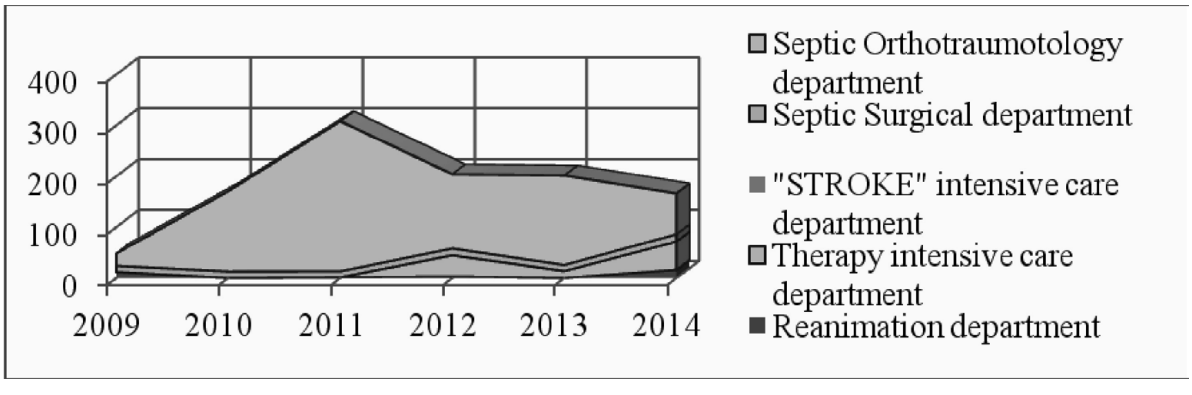

Fig. 6. Value cost of beta-lactam antibacterials and penicillins in DDD/1000 (enteral forms) in lei.

The cost of parenteral beta-lactam antibacterials and penicillins in DDD/1000 for all departments remains aproximately the same in comparison with the total consumption because of low cost of enteral forms for DDD/1000. In figure 6 the value cost in DDD/1000 in lei of beta-lactam antibacterials and penicillins enteral forms is shown.

Presented data in chart 6, demonstrates that from the total departments annual cost could be placed as follows: the first – septic orthotraumotology department with the value cost from 23.89 to 80.12 lei per DDD/1000, with the higher value of 294.48 lei in 2011, the second – therapy intensive care department with an increment from 41.64 to 55.38 lei, the third – septic surgical department with the value cost from 12.34 to 14.34 lei per DDD/1000.

To determine the medium cost of DDD/1000 was counted the total cost of DDD/1000 separately for ICD and SSOTD and divided by the number of those departments (3 and respectively 2) in the evaluated period.

Table 3

Medium cost of DDD/1000 in lei of beta-lactam antibacterials and penicillins (parenteral and enteral forms) in IC and SSOT departments of EMI

Department	Structure of consumption	2009	2010	2011	2012	2013	2014
ICD	Parenteral	6246.62	8778.86	21136.10	13866.25	7260.20	6549.27
	Enteral	33.80		11.78	22.37	6.87	41.02
	Total	6280.42	8778.86	21147.88	13888.62	7264.07	6549.28
SSOTD	Parenteral	861.46	2080.30	1599.00	1652.75	1970.80	1022.38
	Enteral	18.11	85.16	153.25	79.48	93.76	47.23
	Total	879.57	2165.46	1752.25	1732.23	2064.56	1069.62
Total EMI	Parenteral	687.84	2324.48	2316.66	2445.57	1504.38	544.14
	Enteral	14.76	18.73	23.82	22.79	38.39	25.70
	Total	702.6	2343.21	2340.48	2468.36	1542.77	569.84

As could be seen from table 3 in the evaluated period total medium cost of DDD/1000 for beta-lactam antibacterials and penicillins recorded an increase in ICD from 6280.42 to 6549.28 lei or by 4.78%, with the higher cost of 21147.88 lei in 2011. Consequently, in SSOTD from 879.57 to 1069.62 lei or by 21.61%, with the higher cost of 2165.46 lei in 2010, as well as for the entire institution a decrease from 702.6 to 569.84 lei or by 18.90% and the higher cost of 2468.36 lei in 2012. The share of value cost per DDD/1000 in 2014 constituted less by 6.12 times for SSOTD and by 11.49 times for EMI from value cost of 6549.28 lei for DDD/1000 recorded in ICD.

Conclusions

1. In EMI during the evaluated period the use of beta-lactam antibacterials and penicillins recorded a decrease from 85.5 to 20.8 DDD/1000 or by 75.67% and vice versa an increment from 360.4 to 411.5 DDD/1000 or by 14.18% in international hospitals was registered. Medium annual consumption within the evaluated period in EMI recorded 5.42 (354.3: 65.42) times less than in majority of international hospitals.

2. As to the annual medium consumption of 562.51 DDD/1000 all departments could be placed as follows: the first – reanimation department with 178.08 DDD/1000 or 31.66%, the second – intensive therapy care department with 131.82 DDD/1000 or 23.43%, the third – intensive neurological «stroke» department with 105.25 DDD/1000 or 18.71%, the fourth – septic orhtotraumotology department with 84.37 DDD/1000 or 15.00% and septic surgical department with 62.99 DDD/1000 or 11.20% on the fifth position.

3. Consumption in ICD departments of EMI in the considered period recorded a decrease from 367.92 to 133.91 DDD/1000 or by 63.60% and counted a medium of 178.79, while in ICU of international hospitals the medium consumption constitutes 575 DDD/1000 or by 3.22 times more.

4. Total institutional parenteral forms recorded a significant decrease from 79.9 to 3.9 DDD/1000 or by 20.49 times and vice versa enteral forms a spontanious increase from 5.6 to 16.9 DDD/1000 or by 3.02 times.

5. Total medium cost per DDD/1000 of beta-lactam antibacterials and penicillins recorded an increase in ICD from 6280.42 to 6549.28 lei or by 4.78% and consequently in SSOTD from 879.57 to 1069.62 or by 21.61%, as well as per entire institution a decrease from 702.6 to 569.84 lei or by 18.90%.

6. Obtained data about consumption dynamics of beta-lactam antibacterials and penicillins in EMI and their main departments in comparison with international hospitals represents important arguments and reserves for improving quality of treatment, planning and rational use of antibiotics in hospitals.

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The prevalence of perioperative complications in patients with obstructive sleep apnea versus without obstructive sleep apnea

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Abstract

Background: Patients with obstructive sleep apnea (OSA) have high risk of postoperative complications. The purpose of the study was to record the spectrum and frequency of postoperative complications in patients with OSA *versus (vs.)* without OSA depending on the type of surgery and type of anesthesia in a large cohort of patients.

Material and methods: We conducted a prospective, descriptive study (n=400). Ethics Committee approval was obtained and written informed consent was signed. STOP-BANG screening questionnaire was used for OSA screening (71.5% – OSA [+]). Adverse events and complications were recorded postoperatively (AOS [+] *vs.* AOS [-]). Statistics: Chi square test.

Results: The highest rate of complications was found in patients who have undergone surgery on the abdominal cavity under general anaesthesia, AOS [+] *vs.* AOS [-]: cardiovascular [59.2%] *vs.* [9,9%], respiratory [13.4%] *vs.* [3.4%], stroke [0.4%] *vs.* [0.0%], prolonged awakening from anesthesia [1.9%] *vs.* [0.4%], postoperative fever [2.4%] *vs.* [1.4%], difficult orotracheal intubation [2.2%] *vs.* [0.4%], unscheduled transfer to the intensive care unit [3.9%] *vs.* [0.2%].

Conclusions: OSA [+] patients who underwent abdominal surgery under general anaesthesia had a higher rate of complications compared to OSA [-] patients, and also compared to patients who had undergone peripheral limb surgery. Surgery on the musculoskeletal system is much better tolerated by patients with OSA, suffering a lower number and range of events and postoperative complications. Thus, loco-regional anesthesia is considered a priority in patients with OSA.

Key words: obstructive sleep apnea, preoperative screening, postoperative complications.

Introduction

Obstructive sleep apnea (OSA) is the most common sleep disorder in the adult population [1-5]. Current estimates suggest that moderately severe OSA is present in approximately 11.4% of men and 4.7% of women [1, 2]. According to I. Fitze et al. (2011) [6], the incidence of moderate OSA has increased by approximately 8% in the last 5 years. Intense and persistent snoring, accompanied by shortness of breath, prolonged respiratory pauses, observed by family members [7], excessive daytime somnolence [8] are symptoms that characterized obstructive sleep apnea.

The prevalence of OSA is higher in patients presenting for surgery than in the general population [9]. A significant proportion of OSA patients presenting for surgery remain undiagnosed. Patients with OSA have a higher propensity for perioperative complications following surgery under general anesthesia, whether or not surgery on treatment of obstructive sleep apnea.

Skilled surgeons and anesthetists in particular, should be aware that obstructive sleep apnea often remains undiagnosed and, therefore, should be aware of possible perioperative complications in these patients. The purpose of this study was to determine the prevalence of perianaesthetic complications in patients with obstructive sleep apnea versus without obstructive sleep apnea, depending on the type of surgery (on musculoskeletal or abdominal cavity) and the anesthetic technique (general, loco-regional or neuraxial).

Material and methods

A prospective cohort study was performed on a group of 400 patients enrolled for elective surgery on musculoskeletal system or abdominal cavity, with total intravenous anaesthesia or loco-regional anesthesia. The study was conducted at the Department of Anesthesiology and Reanimathology of Valeriu Ghereg (Clinical base of the Institute of Emergency Medicine) between March 2014 and June 2015. In the research we included adult patients, aged between 29 and 82 years (mean age – 56 years). All patients signed written informed consent for study enrollment. Ethical approval for the study was obtained from the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu".

STOP-BANG screening questionnaire was used for preoperative screening of patients. STOP-BANG questionnaire identifies patients with high risk of OSA [9]. Recently, the STOP-BANG questionnaire (snoring, daytime fatigue, observed episodes of apnea, high blood pressure, body mass index> 35 kg / m2, age> 50 years, neck circumference> 40cm, male) was validated as a way for screening of OSA in the preoperative period [9]. This questionnaire contains 8 questions with answers "yes" or "no." Patients are considered at high risk if they give OSA ≥3 answers "yes". Therefore, if the patient is placed in the low risk category of obstructive sleep apnea by STOP-BANG, the doctor can exclude the possibility that the patient has obstruc-

tive sleep apnea of moderate to severe degree, with a high degree of accuracy.

Postoperatively (until hospital discharge), all complications or adverse events that occurred, of any origin, were recorded. Additionally, we recorded all demographic parameters, the type of surgery and anesthetic technique used. The type of anesthesia was chosen depending on the patient's physiological state and surgery.

Depending on the score obtained in each questionnaire, the cohort of 400 patients was divided into "high-risk patients of OSA" (OSA [+]) and "patients without risk of OSA" (OSA [-]). For each group of patients, OSA [+] or OSA [-], postoperative complications were recorded: cardiovascular (hypertension, hypotension, cardiovascular instability, cardiac arrhythmia, myocardial infarction); respiratory (respiratory failure, need for postoperative artificial ventilation of the lungs over 60 minutes, pneumonia, laryngospasm); other adverse events and complications (unplanned transfer to ICU, difficult intubation, stroke, postoperative fever [higher than 38.5 °C). Hypertension was defined as an increase in systolic blood pressure ≥25% from baseline for a period of minimum 5 minutes. Hypotension was defined as a decrease in systolic blood pressure ≤ 90 mm Hg for a period of minimum 5 minutes. All adverse events and complications were recorded until hospital discharge.

Primary results of the questionnaires were recorded in Microsoft Excel table. The statistical analysis was performed with GraphPad Prism 4 software (Version 4.00) for statistical analysis (GraphPad Software, San Diego, California, USA). Statistics was performed by Chi square test and Fisher test. Results are presented as absolute and relative value (binary data) or as mean and confidence interval of 95% (continuous data).

Results

Patients' characteristics and factors of increased risk for obstructive sleep apnea in the OSA [+] and OSA [-] groups are presented in table 1.

Table 1

The general characteristics of patients according to increased or decreased risk of OSA

Parameters	OSA+ (n=286)	OSA- (n=114)	p
Age, years	57.8 (56.8-58.9)	51.7 (50.0-53.4)	0.0001
Men, *n* (%)	107 (37.4%)	25 (21.9%)	0.0001
Height, cm	167.5 (166,5-168,7)	166.0 (164.6-167.6)	0.13
Body mass, kg	90.2 (88.1-92.1)	75.3 (72.6-77.0)	0.0001
BMI†, kg/m^2	32.2 (31.5-32.9)	27.3 (26.6-29.1)	0,0001
Mallampati stage I-II III-IV	148 (37%) 138 (34.5%)	81 (20.2%) 33 (11.9%)	0,0001
Presence /Absence of comorbidities	236 (59%)/ 50 (12.5%)	57 (14.2%)/ 57 (14.2%)	0,0001

Note: for continuous data, results are presented as the mean and confidence interval 95%; for binary data, results are presented as absolute and relative terms. †– body mass index.

Comorbidities detected in patients enrolled in the research were: hypertension, heart failure, myocardial infarction, ischemic heart disease, atrial fibrillation, dysrhythmia, diabetes, asthma, stroke, hypothyroidism and others.

Using STOP-BANG screening questionnaire for OSA, we determined that from 400 patients, 286 patients are in the category of high risk for obstructive sleep apnea (OSA [+]) and only 114 patients are in the low risk category (OSA [-]). The total number of recorded complications was 401, of which, according to the questionnaire, patients with OSA [+] manifested a total number of 337 complications (83.83%), while OSA [-] patients showed a total of 65 (16.16%), confirming that patients with OSA [+] are at high risk of postoperative complications and adverse events (table 2).

Table 2

Distribution of postoperative complications and adverse events after Berlin questionnaire

Complications and adverse events	Number of complications OSA [+] group	Number of complications OSA [-]group	Total number of complications	p
Cardiovascular	238 (59.2%)	40 (9.9%)	278	0,0001
Respiratory	54 (13.4%)	14 (3.4%)	68	0,0001
UT ICU †	16 (3.9%)	1 (0.2%)	17	0,0002
Difficult OTI ‡	9 (2.2%)	2 (0.4%)	11	0,06
Prolonged awakening from anesthesia	8 (1.9%)	2 (0.4%)	10	0,1
Stroke	2 (0.4%)	0 (0%)	2	0,4
Postoperative fever	10 (2.4%)	6 (1.4%)	16	0,4
Total number of complications	337	65	402	

Note: †– unplanned transfer to Intensive Care Unit; ‡– difficult oro-tracheal intubation;

We made a comparative analysis between lots to determine postoperative complications and adverse events depending on the type of surgery and anaesthesia (tables 4 and 5). The highest number of complications was recorded in the OSA [+] undergoing abdominal surgery. The prevalence of complications was higher in OSA [+] patients who underwent abdominal surgery under general anaesthesia compared to OSA [-] who underwent abdominal surgery under general anaesthesia (147 versus 52, p<0.0001) (table 3). Similarly, the prevalence of complications was higher in OSA [+] undergoing peripheral limb surgery compared to OSA [-] patients (123 versus 53, p<0.0001) (table 4).

OSA [+] patients who underwent abdominal surgery under general anaesthesia had a higher rate of cardiovascular and respiratory complications compared to OSA [-] patients, and also higher cardiovascular complications compared to patients who had undergone peripheral limb surgery under regional anaesthesia (tables 3 and 4).

Discussion

The results of the present study showed that patients with OSA syndrome are at higher risk to present complications after abdominal surgery under general anesthesia compared to patients who do not present this syndrome. OSA [+] patients tolerate better the neuraxial musculoskeletal surgery under regional anesthesia.

This is because the obstructive sleep apnea syndrome is characterized by frequent episodes of interrupted breath-

Table 3

Postoperative complications and adverse events in patients with surgery on abdominal cavity

	OSA [+]	OSA [-]	Total	p
Surgery on abdominal cavity	163	61	224	0.0001
General anaesthesia	147	52	199	0.0001
Total cardiovascular complications	150 (54.1%)	27 (9.7%)	177	0.0001
Hypertension	104 (58.7%)	23 (12.9%)	127	
Hypotension	16 (9.03%)	0 (0%)	16	
Hemodynamic instability	4 (2.2%)	0 (0%)	4	
Cardiac dysrhythmia	25 (14.1%)	4 (2.2%)	29	
Myocardial infarction	1 (0.5%)	0 (0%)	1	
Total respiratory complications	49 (17.6%)	10 (3.5%)	59	0.0001
Respiratory depression	30 (50.8%)	8 (13.5%)	38	
Need for postoperative ventilation	14 (23.7%)	1 (1.6%)	15	
Pneumonia	3 (5.08%)	1 (1.6%)	4	
Laryngospasm	2 (3.3%)	0 (0%)	2	
Unplanned transfer to ICU	15 (5.4%)	1 (0.3%)	16	0.0005
Difficult intubation	9 (3.2%)	2 (0.7%)	11	0.06
Prolonged awakening from anesthesia	5 (1.8%)	2 (0.7%)	7	0.4
Stroke	2 (0.7%)	0 (0%)	2	0.4
Postoperative fever	4 (1.4%)	1 (0.3%)	5	0.3
Neuraxial anaesthesia	16	9	25	0.2
Total cardiovascular complications	9 (75%)	3 (25%)	12	0.1
Hypertension	6 (50%)	0 (0%)	6	
Hypotension	1 (8.3%)	1 (8.3%)	2	
Hemodynamic instability	1 (8.3%)	1 (8.3%)	2	
Cardiac arrhythmia	1 (8.3%)	1 (8.3%)	2	
Myocardial infarction	0 (0%)	0 (0%)	0	
Total respiratory complications	0 (0%)	0 (0%)	0	-
Respiratory depression	0 (0%)	0 (0%)	0	
Need for postoperative ventilation	0 (0%)	0 (0%)	0	
Pneumonia	0 (0%)	0 (0%)	0	
Laryngospasm	0 (0%)	0 (0%)	0	
Unplanned transfer to ICU	0 (0%)	0 (0%)	0	-
Difficult intubation	0 (0%)	0 (0%)	0	-
Prolonged awakening from anesthesia	0 (0%)	0 (0%)	0	-
Stroke	0 (0%)	0 (0%)	0	-
Postoperative fever	0 (0%)	0 (0%)	0	-

Table 4

Postoperative complications and adverse events in patients with surgery on musculoskeletal system

	OSA [+]	OSA [-]	Total	p
Surgery on musculoskeletal system	123	53	176	0.0001
General anaesthesia	9	9	18	1.0
Total cardiovascular complications	11 (45.8%)	2 (8.3%)	13	0.02
Hypertension	6 (46.1%)	1 (7.6%)	7	
Hypotension	3 (23.07%)	1 (7.6%)	4	
Hemodynamic instability	0 (0%)	0 (0%)	0	
Cardiac arrhythmia	2 (15.3%)	0 (0%)	2	
Myocardial infarction	0 (0%)	0 (0%)	0	
Total respiratory complications	2 (8.3%)	3 (12.5%)	5	1.0
Respiratory depression	0 (0%)	3 (60%)	3	
Need for postoperative ventilation	1 (20%)	0 (0%)	1	
Pneumonia	1 (20%)	0 (0%)	1	
Laryngospasm	0 (0%)	0 (0%)	0	
Unplanned transfer to ICU	1 (4.1%)	0 (0%)	1	1.0
Difficult intubation	0 (0%)	0 (0%)	0	-
Prolonged awakening from anesthesia	3 (12.5%)	0 (0%)	3	0.2
Stroke	0 (0%)	0 (0%)	0	-
Postoperative fever	0 (0%)	2 (8.3%)	2	0.1
Neuraxial anaesthesia	98	39	137	0.0001
Total cardiovascular complications	60 (81.08%)	7 (9.4%)	67	0.0001
Hypertension	11 (16.4%)	0 (0%)	11	
Hypotension	25 (37.3%)	4 (5.9%)	29	
Hemodynamic instability	11 (16.4%)	2 (2.9%)	13	
Cardiac arrhythmia	11 (16.4%)	1 (1.4%)	12	
Myocardial infarction	2 (12.9%)	0 (0%)	2	
Total respiratory complications	1 (1.3%)	0 (0%)	1	1,0
Respiratory depression	0 (0%)	0 (0%)	0	
Need for postoperative ventilation	0 (0%)	0 (0%)	0	
Pneumonia	1 (100%)	0 (0%)	1	
Laryngospasm	0 (0%)	0 (0%)	0	
Unplanned transfer to ICU	0 (0%)	0 (0%)	0	-
Difficult intubation	0 (0%)	0 (0%)	0	-
Prolonged awakening from anesthesia	0 (0%)	0 (0%)	0	-
Stroke	0 (0%)	0 (0%)	0	-
Postoperative fever	5 (6.7%)	1 (1.3%)	6	0.2
Peripheral nerve blocks	16	5	21	0.02
Total cardiovascular complications	9 (75%)	1 (8.3%)	10	0.02
Hypertension	6 (60%)	1 (10%)	7	
Hypotension	0 (0%)	0 (0%)	0	
Hemodynamic instability	0 (0%)	0 (0%)	0	
Cardiac arrhythmia	3 (30%)	0 (0%)	3	
Myocardial infarction	0 (0%)	0 (0%)	0	
Total respiratory complications	0 (0%)	1 (8.3)	1	1.0
Respiratory depression	0 (0%)	0 (0%)	0	
Need for postoperative ventilation	0 (0%)	0 (0%)	0	
Pneumonia	0 (0%)	1 (100%)	1	
Laryngospasm	0 (0%)	0 (0%)	0	
Unplanned transfer to ICU	0 (0%)	0 (0%)	0	-
Difficult intubation	0 (0%)	0 (0%)	0	-
Prolonged awakening from anesthesia	0 (0%)	0 (0%)	0	-
Stroke	0 (0%)	0 (0%)	0	-
Postoperative fever	0 (0%)	1 (8.3%)	1	1.0

ing during sleep, due to the recurrent obstruction of the upper airways. Despite these anomalies apnea doesn't occur during wakefulness, which indicates the existence of functional pathology on the control of breathing during sleep. A big tendency of upper airway collapse is characteristic to sleep apnea like during anesthesia. These episodes usually occur when the negative pressure of inspiratory muscles exceeds the upper airway dilator muscle activity (critical airway pressure) [10, 11]. General anesthetics have been shown to decrease the upper airway dilator muscle activity in a dose-dependent manner and thereby increase upper airway collapsibility [12]. Upper airway collapsibility may cause worsening of the sleep apnea and increase the risk of hypoxemia and cardiac arrhythmias, and postoperative complications.

The risk of perioperative complications depends on ASA (American Society of Anesthesiologists) class [13], age [14], emergency surgery, cardiac comorbidities [15], smoking [16], duration of surgery [17], type of anesthesia [18], as well as on the presence of comorbidities like chronic obstructive pulmonary disease, coronary artery disease, and renal failure [19]. The risk of postoperative complications depends also on the type of surgery, the rate of complications being higher in patients operated on abdomen [20].

Anesthetic medicines also impair the arousal response, a protective defense mechanism against sleep apnea that helps in overcoming the airway obstruction. Anesthetics, opioids, hypnotics, and benzodiazepines may also cause respiratory depression and thereby decrease the minute ventilation. Studies have shown that halothane reduces the ventilatory response to hypoxemia and hypercapnia [21]. This depression is most likely secondary to a selective effect of halothane on the peripheral chemoreflex loop. Similarly, a subanesthetic dose of isoflurane has been shown to reduce the hypoxemic ventilatory response via peripheral chemoreceptors [22].

Patients undergoing surgery frequently receive opioids for the pain control. Opioids have been shown to impair ventilatory function by affecting both peripheral and central carbon dioxide chemoreflex loops [23].

Similar to our research, R. Gupta et al. (2001) have shown an increased risk of postoperative complications (39% vs. 18%), a higher rate of transfer to Intensive Care Unit (24% vs. 9%) and increased length of hospital stay in patients with OSA, compared with control subjects matched for age, sex and body mass index (BMI) [24]. In another case-control study, P. Liao et al. (2009) found that patients with OSA had higher rate of postoperative complications (44% vs. 28%) [25]. R. Kaw et al. (2006) also demonstrated that patients with OSA had higher incidence of encephalopathy, postoperative infections (mediastinitis), and increased length of stay [26].

A recent retrospective cohort study on 18,000 adult patients, who suffered fracture of the femoral neck, showed that those anesthetized with neuro-axial block, compared with those with general anesthesia, have decreased rate of pulmonary and cardiovascular postoperative complications and decreased mortality by 25-29% [27].

Besides abolishing stimulatory effects of awakening, these include depression of hypoxic and hypercapnic response [28], request of compensation reflexes [29] and the response of excitement that normally protects against asphyxia. The same like in sleep, appears skeletal muscle tone depression with reduction of residual functional capacity, which predispose to atelectasis and upper airway muscle relaxation, which predisposes to obstruction. These effects are compounded by the reduction in phasic activity of the intercostal and accessory respiratory muscles, growing dependence of the diaphragm and the muscles of the upper airway during inspiration, further predisposing to airway obstruction [30].

The presence of a vigilant anesthesiologist, able to monitor and maintain vital functions during anesthesia, defends the patient to these effects. However, induced drug sedation and postanesthesic sleepiness, where the boundaries between wakefulness, sleep and anesthesia are less distinct, and a monitoring less rigorous, presents a potential danger for a patient with a disorder of breathing during sleep due to depression of these responses.

OSA is associated with a number of medical comorbidities including hypertension, heart failure, myocardial infarction, diabetes mellitus, gastroesophageal reflux disease, and stroke [31].

The limit of our study consists in the fact that STOP-BANG questionnaire is a screening tool aimed to identify the patients at risk for OSA [9]. This does not mean that the patients actually had OSA, as the diagnosis needs confirmation by polysmonography, which is the gold standard test to establish definitive diagnosis. However, STOP-BANG screening questionnaire is an instrument easy to use, which was validated for the preoperative assessment of patients [9].

Conclusions

1. Obstructive sleep apnea syndrome is a common type of sleep disordered breathing, with a high prevalence in the surgical population. In our study, the prevalence of OSA was 71.5%, as assessed by using the STOP-BANG screening questionnaire.
2. The majorities of patients with sleep apnea are undiagnosed and are therefore unaware of their OSA syndrome at the time of surgery. OSA [+] patients presented higher incidences of postoperative complications compared to OSA [-] patients.
3. Surgery and anaesthesia have been shown to cause worsening of sleep apnea in the perioperative period

that may lead to increase in the rate of perioperative complications. The type of surgery, as well as the type of anaesthesia, is independent risk factors for the occurrence of postoperative complications.

4. Loco-regional anesthesia represents a priority for patients at high risk for obstructive sleep apnea.

Declaration of conflicting interests

Authors declare no financial or non-financial conflicts of interest.

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Study of carotid artery changes in patients with ischemic stroke and metabolic syndrome

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Abstract

Background: The metabolic syndrome is a major and escalating public-health problem and a clinical challenge worldwide. The increasing prevalence of metabolic syndrome is associated with heart and cerebrovascular diseases.

Material and methods: A "case-control" study was performed on 125 subjects that were examined in the Cerebrovascular Diseases Neurology Department of the Emergency Medicine Institute, in the period of March 2015–July 2015. All subjects underwent a complete clinical examination and ultrasound examination of the extracranial carotids.

Results: The present study shows that the patients with metabolic syndrome (MS) have values of the intima-media thickness and the internal diameter of the common carotid artery significantly higher than the subjects without the metabolic syndrome ($p < 0.05$). Regarding the relationship between the number of risk factors and the markers of atherosclerotic carotid damage, a strong dependence between the two parameters was observed. Thus, it can be stated that 74% of the IMT variation and 77% of the luminal diameter variation is explained by the variation of the number of risk factors constituting MS.

Conclusions: The obtained results, suggest that the cluster of risk factors, the MS constituents are connected with the alteration of the carotid arteries, these changes explain the relationship between the MS and the high risk of heart and cerebrovascular pathologies. In MS the risk of cerebrovascular diseases is multifactorial and its early detection and its treatment can prevent vascular events.

Key words: metabolic syndrome, stroke, risk factor, atherosclerosis.

Introduction

The metabolic syndrome (MS) is a major and escalating public-health problem and a clinical challenge worldwide. The increasing prevalence of MS is associated with heart and cerebrovascular diseases. A recent meta-analysis of 37 longitudinal studies revealed a 78% risk increase for vascular events and death in people suffering from MS [1]. The literature data shows that 25-35% of the world population meets the MS criteria and it is estimated that the number will double by 2025 [2]. According to some data collected from specialty literature, over 50% of patients with acute vascular events meet the MS criteria [3, 4, 5], and the presence of MS constituent disorders influences the unfavorable development of vascular diseases and the cognitive status of the individuals with this syndrome [6].

The association of metabolic syndrome increases the thickness of the intima-media, proving that the summation of metabolic risk factors is due to the appearance of anatomic changes of the vessel wall [7, 8]. In MS the risk of cerebrovascular disease is multifactorial and its early detection and treatment can prevent vascular events.

The aim of the study. To evaluate the ultrasound markers of atherogenesis (intimia–media thikness (IMT) in the common carotid artery, luminal diameter of the common carotid artery and the presence of atheromatous plaques) in a group of subjects with ischemic stroke and MS compared to a control group of subjects with ischemic stroke, but without MS, and to identify the possible associations between these ultrasound parameters, anthropometric and clinical characteristics and other metabolic risk factors.

Material and methods

A "case-control" study was performed on 125 subjects that were examined in the Cerebrovascular Diseases Neurology Department of the Emergency Medicine Institute, in the period of March 2015–July 2015. The patients were selected according to the MS diagnostic criteria of the American Cardiology Association, the National Heart, Lung and Blood Institute and the International Diabetes Federation (2009). After the patients or their relatives signed an informed written consent, according to the declaration of Helsinki, the baseline data was collected by questionnaire. All subjects underwent a complete clinical examination and ultrasound examination of the extracranial carotids. Ischemic stroke diagnostic was made by a neurologist and confirmed by a brain CT scan.

Statistical analysis

Data were analysed by Microsoft Excel, GraphPad and SPSS 17 for Windows application, processing adapted medical statistics. We calculated average parameters, standard deviations; t-student was used for comparisons between two groups. A value of $p < 0.05$ was considered statistically significant. The graphs were done in Microsoft Excel and GraphPad. Patients were divided into two groups according to the presence / absence of the metabolic syndrome: Group I consisting of 68 patients with MS, respectively Group II consisting of 57 patients without MS, but who could also have one / two / no component of MS.

Results

Analysis variables in group 1 (68 subjects):

- There were 37 females (54.41%) and 31 (45.59%) males
- Mean age of patients was 67 ± 1.37 years (minimum 37 years, maximum 97 years), mean age of females was 71.3 ± 1.58 years and 61.8 ± 2.04 years for men, it was established a maximum incidence of stroke in the age group of 65-75 years: 9 (29.03%) men and 19 (51 35%) women.
- All subjects have suffered an ischemic stroke, 17 of them have suffered a repeated stroke (25%);
- The most common location was the basins of the middle cerebral artery – 50%, other locations were the carotid artery (carotid occlusion) – 3%, the vertebra-basilar territory – 29.4% and lacunar stroke – 17.6%.
- Most participants had 3 of the 5 criteria for defining SM (38 people, 56%, fig. 1).

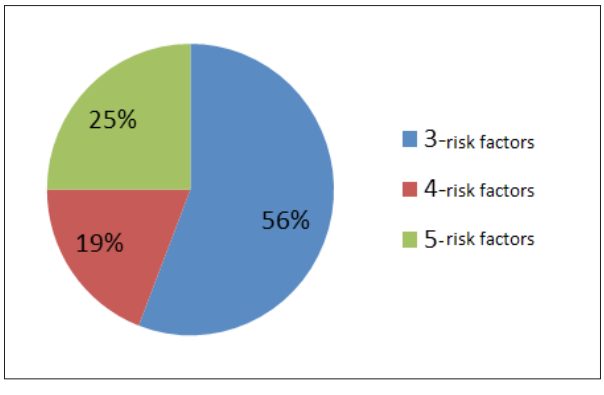

Fig. 1. The distribution of patients with ischemic stroke and MS according to the number of risk factors.

The prevalence of cardiovascular risk factors in the studied group (1st group) was (table 1):

- 36 patients (52.94%) were diagnosed with type 2 diabetes mellitus (DM), the majority were treated with oral antidiabetic 24 (66.7%), 13.89% were in dietary treatment and 19.44% in insulin treatment, the mean duration of diabetes until the stroke occured, was 7.36 ± 2.03 years,
- Hypertension was a preexisting risk factor to 98.53% of the subjects with stroke and MS, 22% had ischemic heart disease, 3 subjects had atrial fibrillation (AF),
- two smokers (2.9%) and 12 ex-smokers (17.65%) had been indentified, the average duration of the smoking cessation was 14 ± 3.36 years,
- 27 subjects from the main group were overweight (39.7%), 34 obese (50%) and 100% of all participants had high waist circumference (WC) according to IDF-2005 criteria (≥ 80 cm in women and ≥ 94 cm men),
- 56.94% suffered from dyslipidemia.

Table 1

The analysis variables in the group of study

Variables	Normal value	No / %	Mean ±DS
Basal plasma glucose (mmol/l)	<5,6 ≥5,6	9 (13.23%) 59 (86.77%)	8,57±4,05
Total Cholesterol (mmol/l)	<6,2 ≥6,2	48 (70.6%) 20 (29.4%)	5,7±1,12
Triglycerides (mmol/l)	<1,7 ≥1,7	36 (52.94%) 32 (47.06%)	1,74±0,85
Beta-lipoproteine (units)	<55 ≥55	49 (72.1%) 19 (27.9%)	46±13,6
Fibrinogen (g/l)	<4,0 ≥4,0	53 (78%) 15 (22%)	3,36±1,00
Systolic blood pressure (mm Hg)	<135 ≥135	2 (2.9%) 66 (87.1%)	144±10,2
Diastolic blood pressure (mm Hg)	<85 ≥85	26 (38.23%) 42 (61.77%)	87±7,3
BMI (kg/m^2)	<25 25-30 30-35 35-40 >40	7 (10.3%) 27 (39.7%) 17 (25%) 10 (14.7%) 7 (10.3%)	31,1 ±6,2
WC(cm)	Women <80 ≥80 Men <94 ≥94	 0 (0%) 37 (100%) 0 (0%) 31 (100%)	 102,05±12,98 107±10,38

Analysis variables in group 2 showed the following distribution (table 2):

- There were 20 women (35.08%) with the mean age 67.4 ± 2.03 years and 37 men (64.92%) with the mean age 65.38 ± 1.48 years, the average age being 66,09 ± 1.18 years,
- All subjects suffered an ischemic stroke, 13 of them had a repeated stroke (22.8%),
- 46 (80.7%) persons were suffering from hypertension, 15 (26.32%) had ischemic heart disease and 9 participants (15.79%) were diagnosed with AF,
- 14 smokers (24.56%) were identified, 13 of which were men (representing 35.13% of men), 16 were ex-smokers (mean duration of the non-smoking period was17.2 ± 3.7 years), 2 were females (10% of women) and the remaining males (37.84% of men),
- 2 people in the control group had type 2 diabetes (3.5%), both were on dietary treatment,
- 24 (42.11%) persons were overweight, and 16 (28.07%) obese,
- 34 (59.6%) individuals had a high waist circumference, according to IDF-2005 criteria,
- 15 (26.31%) subjects suffered from dyslipidemia.

Table 2

Analysis variables in the control group

Variables	Normal value	Nr./%	Mean ±DS
Basal plasma glucose (mmol/l)	<5,6 ≥5,6	45 (78.95%) 12 (21.05%)	5,07±1,13
Total Cholesterol (mmol/l)	<6,2 ≥6,2	45 (78.95%) 12 (21.05%)	5,13±1,34
Triglycerides (mmol/l)	<1,7 ≥1,7	54 (94.74%) 3 (5.26%)	1,11±0,78
Beta-lipoproteine (units)	<55 ≥55	55 (96.5%) 2 (3.5%)	38,9±9,77
Fibrinogen (g/l)	<4,0 ≥4,0	55 (96.5%) 2 (3.5%)	3,05±0,55
Systolic blood pressure (mm Hg)	<135 ≥135	11 (19.3%) 46 (80.7%)	146±11,4
Diastolic blood pressure (mm Hg)	<85 ≥85	14 (24.56%) 43 (75.44%)	82±5,6
BMI (kg/m²)	<25 25-30 30-35 35-40 >40	17 (29.82%) 24 (42.11%) 13 (22.8%) 3 (5.27%) 0 (0%)	27,4 ±4,54
WC (cm)	Women <80 ≥80 Men <94 ≥94	 5 (25%) 15 (75%) 18 (48.65%) 19 (51.35%)	 88,7±12,17 93,43±9,18

The descriptive analysis of the arterial parameters throughout the main group highlights their average values to limits that are considered pathological. Thus, the average value of CIM in subjects with MS was 0.99 ± 0.037 mm (95% CI 0.91÷1.07) and luminal CCA diameter was 6.94 ± 0.08 mm (95% CI ,6.78 ÷ 7.1 mm).

Atherosclerotic plaques were found in 59 (86.76%) participants. 9 participants were found without atherosclerotic plaques in extra-cranial carotid segment: 3 had AF, 2 had suffered from a lacunar stroke and 4 could not determine the cause of stroke. 36 patients (53%) with MS suffered from ischemic stroke and type 2 diabetes, the average values of IMT was 1.01 ± 0.05 mm and of internal diameter of the common carotid artery was 6.79 ± 0.09 mm (95% CI, 6.61 ÷ 6.97 mm).

Table 3

Anthropometric characteristics of the group of study, compared with the control group

Parameter	1st group	2nd group	p
Sex Male / Female	31/37	37/20	
Age (Years)	67 ± 1,37	66,09±1,18	0,63
BMI (kg/m²)	31,1±0,0,76	27,4 ±0,6	<0,001
WC (cm)	104±1,47	91,77±1,4	<0,001
Systolic blood pressure (mm Hg)	144±1,25	146±1,39	0,52
Diastolic blood pressure (mm Hg)	87±0,97	82±0,75	0,27

Comparing the two groups

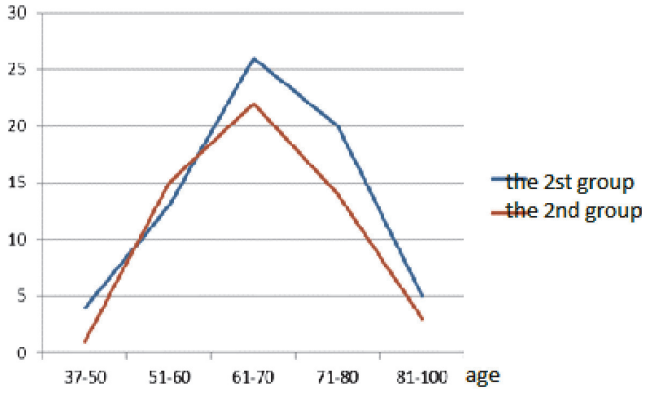

Fig. 2. Distribution on age.

The average values of IMT in patients hospitalized with ischemic stroke, but that did not meet the MS criteria (control group), was 0.84±0.037 mm (95% CI, 0.77÷0.91 mm), and the internal diameter of ACC was 6.5±0.09 mm (95% CI, 6.32÷6.68 mm). Atherosclerotic plaques were found in 24 (42.1%) participants from group 2.

There was no significant difference in age between the two study groups (p=0.63) (fig. 2).

It was found that the level of uric acid, beta-lipoprotein, triglycerides, fibrinogen in patients with ischemic stroke and MS is significantly higher than those without MS (p <0.05) (table 4).

It is necessary to point out that the number of constituent risk factors of the MS affects the IMT values, the internal diameter of carotid arteries and the development of carotid atheroma (fig. 3, 5, 7), so summing all the metabolic risk factors is reflected by the appearance of anatomical changes of the vessel wall [7, 8]. It has been noted that there is a significant difference between the IMT values and the diameter of common carotid artery (CCA) in these two groups (p <0.05, p <0.001) (table 5, fig. 4, fig. 6). The average luminal diameter of CCA in patients with five risk factors is lower than in those with 4 risk factors (fig. 7), the explanation of this phenomenon was found in specialty literature, all participants in this case study were suffering from type 2 diabetes mellitus (17 subjects, 25% of group 1), the mean duration of diabetes was 9 ± 2.1 years, and the research of this category of patients proved the internal carotid vessels remodeling, consequently an increase in IMT values and a decrease in the CCA internal diameter [10, 11, 14].

After searching the link between the values of intima-media and the metabolic profile, a weak relationship between IMT and total cholesterol (r = 0.13), IMT and glucose (r = 0.2) was detected. It did not reveal any correlation

Table 4

Biochemical characteristics of the various parameters in the study and control groups

Parameter	1st group	2nd group	p
Basal plasma Glucose (mmol/l)	8,56±0,49	5,07±0,15	<0,001
Total Cholesterol (mmol/l)	5,7±0,14	5,31±0,18	0,09
Triglycerides (mmol/l)	1,74±0,1	1,11±0,1	<0.001
Beta-lipoproteine (units)	45,8±1,67	34,9±1,3	<0.001
Fibrinogen (g/l)	3,36±1,12	3,05±0,07	0,045 (<0,05)
Uric Acid (mkmol/l)	405±19,31	331±10,63	0,007

Table 5

Ultrasound parameters

Parameter	Case group	Control group	p
IMT (mm)	0,99±0,037	0,84±0,037	0,0037
The CCA diameter (mm)	6,94±0,08	6,5±0,09	0,0005

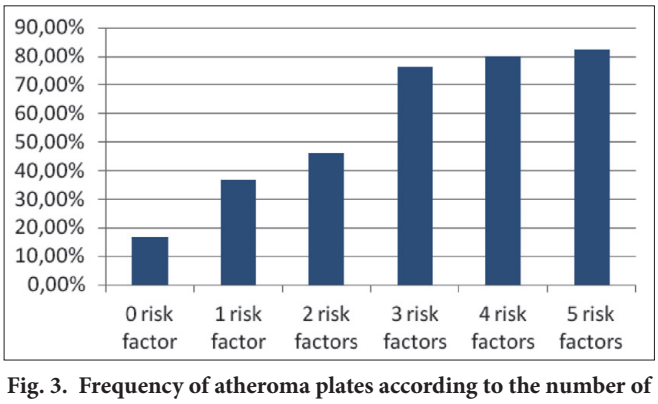

Fig. 3. Frequency of atheroma plates according to the number of the MS constituent risk factors in the general study group.

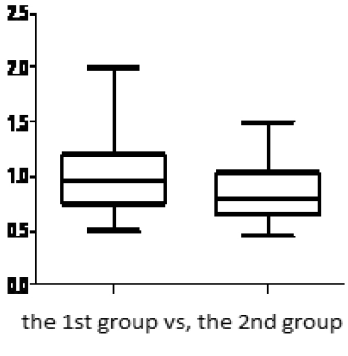

Fig. 4. The thickness of the intima – media at the level of the common carotid arteries, in the 2 groups.

between the beta-lipoprotein (r = 0.001) or triglycerides (r = 0.02) levels and the IMT values. There has been established the correlation between the anthropometric parameters and the values of intima-media complex: no connection detected between the systolic BP values (r = 0.04) and

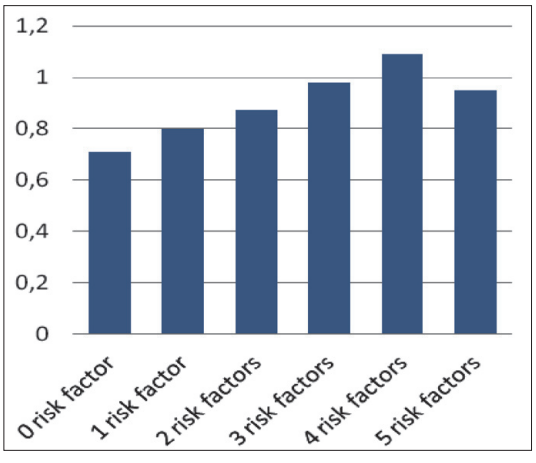

Fig. 5. The components of the metabolic syndrome in relation to IMT.

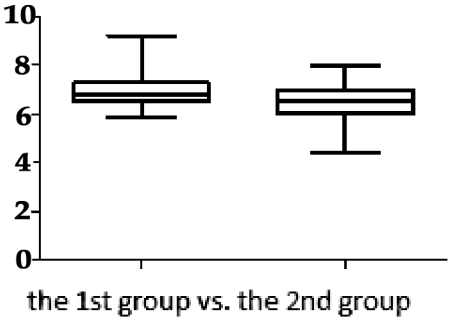

Fig. 6. The values of the luminal diameter at the level of the common carotid arteries, in the 2 groups.

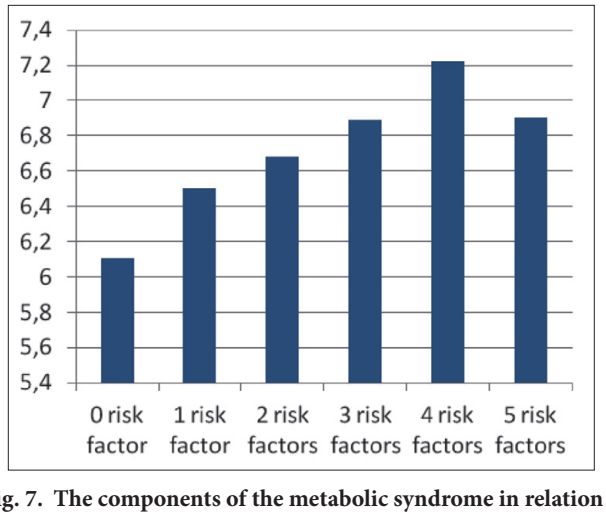

Fig. 7. The components of the metabolic syndrome in relation to internal diameter of the CCA.

diastolic (r = 0.09), a weak relationship with age was noted (r = 0.17), or BMI values (r = 0.35) (fig. 8), it can be stated that the most powerful relationship was with WC values (r = 0.54). It has been established a perfect correlation between the number of MS constituent risk factors and the markers of the atherosclerotic carotid damage, such as IMT (r = 0.86) and internal carotid diameter (r = 0.87).

The average values of IMT for the population with and

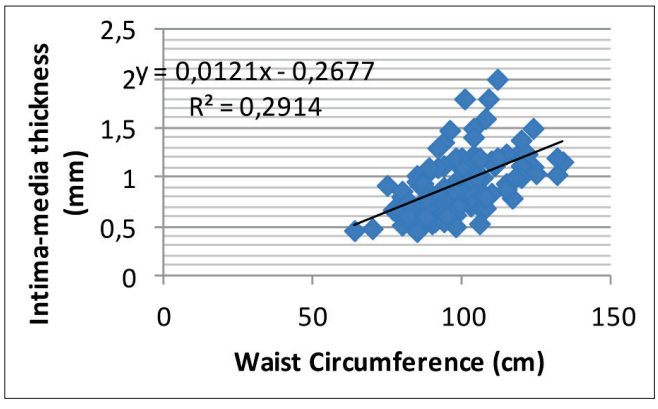

Fig. 8. The variation in the thickness of the intima-media common carotids according to the values of WC in the general group.

without atherosclerotic plaques have been compared (IMT = 1,01±0.035 mm, 95% CI, 0.94 ÷ 1.08 mm vs. IMT = 0.82 ± 0,037mm, 95% CI, 0.75÷0.89 mm), the IMT values were higher and statistically significant for the population with IMT carotid atheromatosis (p <0.001). A statistically significant difference was found between the values of the CCA diameter in patients with atherosclerotic plaques (average value 6.93 ± 1.0 mm) and in patients without plaques (0.13 mm ± 6.14) (p = 0.0028). Thus, the arterial diameter values and IMT can be each connected to the process of atherosclerosis. Their separate or combined expansion may indicate different arterial phenotypes with different atherosclerotic risk [12]. It has been proved that the IMT of ex-smokers and smokers (0.94 ± 0.034 mm, 95% CI, 0.87 ÷ 1.00 mm) is not statistically significant and it's higher than that of non-smokers (0.88 ± 0.04 mm, 95% CI, 0.8 ÷ 0.96 mm) (p = 0.18).

Discussion

In both groups, the arterial hypertension was present in most cases (> 80%) , being the most frequent risk factor of a stroke, a fact confirmed by other research studies [9].

Dyslipidemia, when the total cholesterol and triglycerides levels increase, represents a risk factor according to some studies, it had a different distribution in the two groups as follows: in group 1, the predominant hypertriglyceridemia (47.06% vs. 5.26%) and hypecholesterolemia (29.4% vs. 21.05%) compared to the control group. Type 2 diabetes was more prevalent in MS patients (52.94%) than in those without MS (3.5%). It was discovered that the levels of uric acid, beta-lipoproteins, triglycerides, fibrinogen and glucose of patients with ischemic stroke and MS are significantly higher than of those without MS (p <0.05).

The obesity of varying degrees was present in over 27% of subjects without MS and in 50% of patients with MS.

The present study shows that the patients with metabolic syndrome have values of the IMT and the internal diameter of the common carotid artery significantly higher than the subjects without the metabolic syndrome (p <0.05), which is consistent with the specialty literature [8, 13]. Regarding the relationship between the number of risk factors and the markers of atherosclerotic carotid damage, a strong dependence between the two parameters was observed. Thus, it can be stated that 74% of the IMT variation and 77% of the luminal diameter variation is explained by the variation of the number of risk factors constituting MS ($r^2 = 0.74$, $r^2 = 0.77$ respectively).

Atherosclerotic plaques at the level of the extracranial carotid section were found in 86.76% of the participants from the basic group compared to 42.1% from the control group.

Since most risk factors are part of the modifiable category, it is likely that stroke can be prevented by keeping them under control. Diagnosis and proper MS management can be an important part of stroke prevention.

Conclusions

The obtained results, suggest that the cluster of risk factors, the MS constituents are connected with the alteration of the carotid arteries, these changes explain the relationship between the MS and the high risk of heart and cerebrovascular pathologies. In MS the risk of cerebrovascular diseases is multifactorial and its early detection and its treatment can prevent vascular events.

The current study outlines four directions for further research: 1. An extension of the study group that would increase the statistical power, 2. An evaluation of other parameters and / or improvement of those already used, 3. To examine the participants of the study in certain periods of time, 4. To promote the research conclusions as an evaluation algorithm for primary care and as advice to the population.

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Impact of active tobacco smoking and other associated determinants on tuberculosis evolution and treatment outcome

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Abstract

Background: Tuberculosis and smoking represent a major global health problem that is well recognized in the Republic of Moldova and worldwide. There is strong relationship between social vulnerability and psychotropic substance abuse: tobacco smoking, alcohol abuse and illicit drug use. The aim of the study was the impact assessment of active tobacco smoking and associated determinants on evolution of pulmonary tuberculosis and treatment outcome.

Material and methods: pulmonary TB patients diagnosed in the period 1.1.2014-31.12.2014 in Chisinau city were distributed in two groups: study group constituted 209 patients with pulmonary TB and active smoking and control group (CG) – 79 patients with pulmonary TB never-smokers.

Results: Risk factors for development of active TB at smokers are poverty-related conditions, male sex, single matrimonial status, medico-biological conditions and alcohol addiction, low educational status, urban residence. Case-management of smokers with pulmonary TB was worsened by the lack of health insurance (two thirds), late detection and epidemiological danger due to positive bacillary smear status. Co-morbidities and TB-related radio-morphological features (bilateral localization, lung destructions, dissemination, and positive bacillary status) adjusted to risk factors contribute to low treatment outcome.

Conclusions: Targeted interventions for smoking quitting in the frame of risk subgroups will diminish the rate of severe and complicated forms of TB and will increase success rate, strengthening TB control at the community level.

Key words: tuberculosis, tobacco smoking, risk groups.

Introduction

Tuberculosis (TB) represents a major global health problem that is well recognized in the Republic of Moldova (MDA) [3]. Annually are registered almost 10 million new TB cases that in association with human immunodeficiency virus represent a leading cause of death. In 2014 were registered 5,4 million new cases among men, 3,2 million cases among women and 1.0 million sick children worldwide. In addition to this in 2014 were registered 1,5 million deaths due to tuberculosis, among them – 1,1 million were HIV negative and 0,4 million were HIV-positive [15]. The Republic of Moldova shows a slow decreasing of disease prevalence during the period 2013-2015 with 3904 TB patients in 2013, 3450 patients in 2014 and 3073 patients in 2015 [3]. The social determinants of TB are well recognised in MDA as well as worldwide . The continuous socio-economical, as well as, political crisis through which passes MDA determine the continuously increasing rate of socially vulnerable individuals [3]. It was defined a strong relationship between social vulnerability and psychotropic substance abuse: tobacco smoking, alcohol abuse and illicit drug use. Tobacco smoking is probably the most widespread with the major socio-economic impact. Smoking is defined as an addictive disease of persons who reported smoking at least 100 cigarettes during their lifetime and who, at the time when they participated in the survey, reported smoking every day or some days. About 1.1 billion people, that means one in every three adults, are smokers according to the World Health Organization [16]. Worldwide, tobacco smoking causes nearly 6 million deaths per year, and more than 8 million deaths annually are predicted by 2030 [6]. More than 160 million Americans are

living with tobacco addiction: 16.8% of all adults (40 million people): 18.8% of males and 14.8% of females in the US are smokers. Cigarette smoking is responsible for more than 480.000 deaths per year in the US and 42.000 deaths resulting from environmental (second-hand smoke) exposure [12]. According to the Demographic Study of Health in MDA in 2005 there were estimated 51,1% smoking men and 7,1% smoking women [10]. The prevalence of tobacco smoking is identified at 65% of general Moldovan adult population and Moldovan men are 4 times more predisposed to smoke than women. The current data established that the tobaccco smoke represents the second cause of chronic morbidities among Moldovan men and the seventh cause among women [10].

The chemical components of cigarette smoke depend on the structure of the cigarette and delivery way of the smoke. Most of the studies have reported the effects of the mainstream smoke and fewer identified effects of sidestream and passive smoking [3]. The International Organization for Standardization expressed that the puff volume is 35 milliliters, for a two-second puff duration and butt length is 26 mm for filter cigarettes. When alternative smoking regimens (e-cigarette, cigar or pipe) are used, level of potentially harmful substances in smoke emission usually differs from those measured in standard conditions. Cigarette smoke is a complex of chemical compounds that are transformed in aerosol or in gas phase due to burning process. Smoke from a burning cigarette is a concentration of liquid particles suspended in the atmosphere consisting mainly of nitrogen, oxygen, carbon monooxide and carbon dioxid. Chemical tobacco compounds can be distilled into smoke or can react with other constituents and then distilled to smoke. It was estimated that cigarette smoke contains 7.357 chemical components from different classes, including 20 carcinogenes (acrolein, formaldehyde, carbon monooxide, acealdehyde, phenol, potasium cianide, etc.) that cause cancer in laboratory animals and humans. The characterisitcs of the smoke vary due to cigarette design and chemical nature of the products: 1,3-butadiene exposes the greatest potential risk for cancer development; acrolein and acetaldehyde is the most potential irritant for respiratory tract; cyanide, arsenic, and cresols are the primary causes for cardiovascular risk. The concentration of chemical compounds differs according to: the smoke formation, the way through the cigarette is smoked and differences among cigarettes (tobacco type, tobacco preparation, the dimensions of the cigarettes, the weight of the tobacco rod, the porosity of the paper, the presence, type and the size of the filter) [5]. Mainstream smoke is released from the butt end of the burning cigarette during puffing. Sidestream smoke is emanated from the burning cigarette coal. The air surrounding an active smoker contains a mixture of sidestream smoke, smoker's exhaled mainstream smoke and smoke that passes the paper surounding the tobacco in burning. Toxic effects of the smoking are immediate, also called rapid toxic effects on the brain and are responsable for addictive power of nicotine. The initial increasing of dopamine activity due to nicotine inhalation determines the pleasant feelings for the smoker. The long anamnesis of smoking determines the reduction of dopamine receptor function and decreasing the number of dopamine receptors, that causes to consume more cigarettes [7]. It was demonstrated that earlier starting of smoking alters the development of the lung in adolescent period, limiting adult-future breathing capacity and physical potential. The most expressed are immediate toxic effects of tobacco smoke on the respiratory system. Cigarette smoking conduces primary mucociliary transport alterations, expressed through reduction of mucociliary clearance, due to diminishing of the ciliary beat frequency and changes of mucus properties [6]. The chronic stress inflamation causes mucus metaplasia of the respiratory epithelium (starting with hyperplasia, then metaplasia with keratinization of epithelium), diminishes the viability of cells, induces apoptosis, increases the size of goblet cells and consequently stimulates the upper airway mucous secretions [1, 7]. Smoking interferes in ciliogenesis process, determining the alteration in maturation and reduces the size of cilus, that predisposes bacterial colonization and infection of the respiratory tract. Airways of smokers are preferentially colonized by Gram negative bacteria, due to an increased resistance of Gram negative more than Gram positive microorganisms to the smoke, and due to an increased adhesion of microbs to epithelial cells. The exposure to high concentration of smoke stimulates the formation of bacteria biofilms. The bacteria-epithelium interaction causes the increased inflammatory reaction of epithelium, that is not linked to the toxins of the smoke. Due to stress inflammation an acute bronchospam, increased phlegm production, disturbances in air-blood distribution in lungs. All identified alterations decrease physical performance of the smokers due to reduced mecanical ventilation and decreased lung function.

Also the cigarette smoke determines cardiovascular toxic effects more relevant on the lipid profile, that may increase risk of thrombosis, vasoconstriction and increased blood pressure. Nicotine consumption increases heart rate 30 minutes after puffing. In association with a constantly increased blood pressure due to vasoconctriction the congestive heart failure is ten times more frequently than in non-smokers [3].

Second-hand smoke, called also environmental smoke is considered more carcinogenic than the smoke of the mainstream inhaled by the active smoker. Because the cigarette burns at a lower temperature and much more amount of tobacco is pyrolised during smouldering (80% of cigarette burns between puffs), the sidestream smoke contains a higher amount of carcinogenes (more than 40 of known), than the same volume of mainstream smoke: up to 50 times more formaldehyde, 3.5 times benzopyrene

and 7.2 times cadmium. Hundreds of studies performed after 1980 identified the relationship between exposing to environmental tobacco smoke and lung, nasal cavity, head and neck, stomach, cervix, bladder cancers and leukemia. The risk of cancer depends on the way of smoking (passive and active smoking), measures of the individual exposure, populational exposure to passive smoking, residential and occupational exposure. For every person who dies because of smoking, at least 30 people live with serious-smoking related disease. More frequently associated diseases are different types of cancers, diseases of cardio-vascular system and suddden death, diabetes, respiratory diseases (chronic obstructive pulmonary disease, emphysema, bronchiectasis) [9]. The tobacco smoking contributes to the development of lung cancer, followed by oral, pharingeal and esophageal cancers, as well as tuberculosis [4].

The risk is increased by the lack of ventilation, indoor pollution, and depends on the room size, the number of persons who smoke, the number of smoked cigarettes. Chronic respiratory diseases (CRD), such as: chronic bronchitis, chronic obstructive pulmonary disease, small airways disease, pulmonary emphysema, lung fibrosis, bronchiectasis, chronic rhinosinusitis and chronic pharingo-laringitis are results of an active or environmental smoking (passive smoking) [1]. Acute bronchitis, community aquired pneumonia, asthma exacerbation, acute middle ear infection, acute nasal irritation, acute conjunctivitis, and TB are more common in smokers than in non-smokers [2]. There is a little variety of studies on vulnerability of smokers to active TB. The pathways that increase the vulnerability of the smoker to mycobacterial infection are: chronic alterations of epithelium, decreasing local immune resistance, lower ability of smokers to maintain latent mycobacterial infection, that increase the risk of active TB up to three times.

Research review identified that chronic exposure to tobacco and to environmental pollutants, impairs the clearance of tracheo-bronchial secretions, as well as impairs the function of pulmonary alveolar macrophages. *In vitro* studies, determined that nicotine acts on acetiylcholine receptors of macrophages, that decreases the production of intracellular tumor necrosis factor (TNF-α) and impairs the killing of intracellular mycobacteria [7]. So, resulting deficiency in non-specific defense represents the main cause that contributes to the progression of active tuberculosis from latent TB infection [1].

It was identified a strong relationship between the duratation of smoking and the severity of TB. In addition, active as well as passive smoking reduces the effectiveness of chemopreventive treatment and the effectiveness of TB treatment (the risk of death among smokers is six times higher than in non-smokers, and the risk of relapse is three times higher than in non-smokers). Much more data we need to investigate for establishing the impact of: the age at which smoking was started, the duration and the intensity of smoking (the number of smoked cigarettes), type of tobacco and the quality of cigarettes on the risk of active TB development [1].

A special attention is actually paid to second-hand smoke that affects children and adults, sharing the same house/place with smokers with active TB. The sick smokers put their families at a greater risk for contracting mycobacterial infection and at a greater risk for active TB development [1]. Considering all related data, associated with unstable socioeconomical and epidemiological situation in MDA, as well as the large proportion of smokers in the general population it was identified the need for performing a research about the health consequences and the impact of the smoking on active TB evolution and treatment outcome. So, **the aim of the study** was the impact assessment of active tobacco smoking and associated determinants on evolution of pulmonary tuberculosis and treartment outcome. Established **objectives** were: 1. Assessment of general, socio-economical and epidemiological characteristics of active smokers with pulmonary TB; 2. Evaluation of case-management, clinical aspects, radiological aspects and treartment outcome of pulmonary TB at active smokers.

Material and methods

It was realised a retrospective and selective research of a study group (SG) consisting of 209 patients with pulmonary TB and active smoking and control group (CG) – 79 patients with pulmonary TB never-smokers, registered as a new case during the period 01.01.2014 to 31.12.2014. The patients' medical records were assessed after being hospitalized in the Municipal Hospital of Tuberculosis of Chisinau, where the patients were investigated and received TB treatment during the intensive phase. Including criteria in both groups were the diagnosis of new pulmonary TB cases, new case (patients never treated for TB, or have taken anti-TB drugs less than one month), signed informed consent. Individual research chart included the points with such data: anamnesis, data of clinical examination, results of radiological investigations (chest radiography, high resolution computer tomography), results of microbiological investigations (smear bacterioscopy at Ziehl-Neelson staining) and bacteriological examenations (culture on conventional solid medium Lowenstein-Jensen and liquide BACTEC MGIT) [4]. Investigations were performed according to National Policy – Tuberculosis in Adults. Smoking behaviour questionnaire included the questions about the number of cigarettes smoked per day, the period of time of "smoking pack years", type of smoked cigarettes (with or without filters). Statistical assessements were performed using soft Microsoft Excel XP and Statistica 10,0.

Results and discussions

Assessing current status of active smokers with pulmonary TB it was established that only 28 (13,6%) were light smokers with less than 10 pack years. The majority [163 (79,13%) patients] were moderate smokers, being assessed with 10-20 pack years and heavy smokers (more than 20 pack years) were 18 (8,7%) cases. The biggest part of SG [198 (96,1%) patients] smoked cigarettes with filter. Assessment of general, socioeconomical and medico-biological characteristics of active smoking patients with pulmonary TB in comparison with never-smokers is shown in the table 1. Distributing patients by sex it was estbalished the predominance of male sex in comparison with female in both groups: 158 (76,6%) males in comparison with 48 females (23,4%) in SG and 48 (60,7%) males *vs* 31 (39,3%) females in CG. Comparing the groups it was established that the males predominated in SG 158 (76,6%) vs 48 (60,7%) in CG. Females were more frequent in CG 48 (23,4%) than in SG 78 (98,7%) cases. Repartition of patients in age subgroups according to the WHO recommendations, identified that the largest subgroup in SG represented 25-34 year age group: 62 (30,1%) patients and in CG 35-44 year subgroup 78 (98,7%) patients. The younger group of patients aged 18-24 predominated in SG: 46 (22,3%) *vs* 7 (8,8%) cases in CG. Redistributing patients in two subgroups aged 18-44 and >45 it was established the predominance of younger subgroup (18-44 years) in both SG and CG: 156 (75,7%) patients 67 (84,8%) cases, respectively.

Assessing the place of stable residence it was identified that patients from urban area were more frequently in SG [162 (78,6%) cases] than in CG [45 (56,9%) cases] and patients from rural area were more prevalent in CG [34 (43,1%) cases] than in SG [44 (21,4%) cases]. Considering the educational level of selected patients it was determined that individuals with low level of school education (primary and incomplete secondary school) were identified in a similar proportion in both study and control groups: 123 (59,7%) and 51 (64,5%) cases, respectively. Socioeconomic (employment) status was higher in CG than in SG. One third of patients were employed in CG [23 (29,1%) patients] and 25 (12,2%) cases in SG. Two thirds of patients were unemployed in SG [156 (75,73%) cases] and 48 (60,6%) patients in CG. Other socio-economical categories were in a similar proportion, but the totality of economically disabled patients, that included all non-economically productive patients (unemployed, retired and students) statisticaly prevaled in SG: 181 (87,86%) *vs* 46 (58,23%) cases in CG. Considering the high rate of economically defavorised patients in both groups, the tobacco smoking worsens the financial state, predisposing the development of TB. Appreciating the civil status it was identified more frequently married persons in CG [51 (64,5%) cases] than in SG [84 (40,7%) cases] and single state individuals predominated

Tabel 1

Distribution of patients according to the demographic factors

Demographic factors	SG, n=206		CG, n=79	p value
	n (%)	n (%)		
Sex	Men	158 (76,6)	48 (60,7)	**<0,01**
	Women	48 (23,4)	31 (39,3)	**<0,01**
Young age (reproductive groups)	18-24 years	46 (22,3)	7 (8,8)	**<0,01**
	25 – 34 years	62 (30,1)	24 (30,4)	>0,05
	35-44 years	48 (23,3)	78 (98,7)	**<0,001**
>45 years old	45-54 years	38 (18,5)	10 (12,6)	>0,05
	>55years	15 (7,28)	2 (2,5)	>0,05
Residence	Urban	162 (78,6)	45 (56,9)	**<0,001**
	Rural	44 (21,4)	34 (43,1)	<0,001
Educational status	Low (primary/ Incomplete secondary)	123 (59,7)	51 (64,5)	>0,05
	Good (lyceum, high level)	83 (40,3)	28 (35,4)	>0,05
Socio economical status	Employed	25 (12,2)	23 (29,1)	**<0,001**
	Unemployed	156 (75,73)	48 (60,6)	**<0,01**
	Disabled	8 (3,8)	5 (6,3)	>0,05
	Students	2 (0,9)	1 (1,3)	>0,05
	Retired	15 (7,3)	2 (2,5)	>0,05
Civil status	Married	84 (40,7)	51 (64,5)	**<0,001**
	Single	117 (56,8)	25 (31,6)	**<0,001**
	Divorced&widow	5 (2,43)	3 (3,7)	>0,05
Life style	Under minimum standard life	123 (59,8)	32 (40,5)	**<0,01**
	Migration	28 (13,6)	10 (12,6)	>0,05
	Alcohol abuse	111 (53,8)	3 (3,8)	**<0,001**
	Drug use	4 (1,9)	0	>0,05
	History of emprisonment	8 (3,8)	0	>0,05
	Family cluster of TB	24 (11,6)	7 (8,8)	>0,05

in SG: 122 (59,3%) *vs* 28 (35,5%) cases in CG. Poor life conditions considered as under the minimum consumer basket predominated in SG: 123 (59,8%) *vs* 32 (40,5%) patients in CG. Although smoking is a leading cause of morbidity and mortality worldwide, it is not recognised as a disease by itself. Considering nicotine, the component of tobacco an addictive drug regulating the feelings of pleasure, in most cases the desire to smoke is combined with the consumption of other drugs such as alcohol or illicit drugs. Alcohol is the second most used addictive substance in the world, after tobacco smoking. Chronic alcoholism, as well as binge drinking and heavy drinking is 10 times more frequent at tobacco smokers than among nonsmok-

ers. Alcohol abuse and chronic alcoholism were identified at one half of smokers and only at a couple of non-smoking patients. Illicit drug use was identified only in SG. History of emprisonment was identified at a lower rate in SG. In this context it is important to note a very low rate of family TB clusters [24 (11,6%) cases] affiliated to each investigated patient. It is due to a low quality epidemiological cross-examination of the patient, rather than to the lack of close (family) contacts in the patient's environment.

Associated diseases were identified at one half of patients from both groups. No neoplastic diseases were identified at the selected patients. The effect of associated disorders or diseases is important because they endanger the TB treatment effectiveness. If the clinical state of the patient is not so worsened the TB treatment might be started primarily, subsequent treatment for underlined diseases will be performed when the clinical tolerance to the TB treatment is established (TB/HIV infection). One third of patients was identified with one comorbidity in both groups [59 (28,6%) cases in SG and 18 (22,78%) cases in CG]. There was not found a statistical difference between groups counting diagnosis clusters, except the group of chronic respiratory diseases, that predominated in the SG: 42 (20,4%) patients in comparision with 9 (11,4%) patients from CG. More patients from CG had gastrointestinal, diabetes mellitus, chronic renal diseases, but was not found a statistical difference between groups.

Studying case-management, diagnosis delay, medical staff involved in the patient's detection and clinical-radiological diagnosis it was established that three fourths of patients from SG exposed as a barrier for health care seeking the lack of health insurance comparing with only one half of CG. Delayed case detection, that means more than 60 days after the disease onset was registered more often in patients from the SG (two thirds) and only one third in CG. According to the actual recommendations the main way for new case detection is the microscopic examination of the symptomatic patients associated with the smear genetic test through GeneXpert MTB/Rif assay. So, two thirds of all selected patients were detected by the general practitioner due to specific symptomatology (passive way of case detection): 152 (73,7%) patients from SG and 52 (65,8%) patients from CG. One fifth of patients of both groups were detected by the specialist (pneumophtysiologist) and a fewer rate were detected otherwise (by transfer from other medical institutions, investigation by other specialists, detected in the frame of investigations performed for the work engagement).

Assessing laboratory features of pulmonary TB it was identified that one half of smokers were microscopic positive for acid-fast-bacilli and only a fewer part of the CG. So, the first criteria that defined the highest epidemiological danger of TB clusters was identified in one half of patients from SG. Infiltrates localized in both lungs were more frequently identified in SG [131 (63,6%) patients] comparing with infiltrates identified only in one lung, which were more frequently identified in CG 54 (26,2%). Evaluating radio-morphological features of pulmonary TB, were identified lung infiltrates complicated with destructions at 131 (63,6%) cases of SG and only at 18 (22,8%) patients from CG. Lung dissemination (through bronchogenic and lymphogenic ways) was established only in SG [28 (13,6%) patients]. Complications (such as hemoptysis, pneumothorax, pleurisy) occurred more often in the SG [59 (28,6%) cases] than in CG. Patients were informed about the fact that smoking cessation will improve treatment outcome, but no other psychological interventions and quitting replacement therapy were performed. A little rate of patients discontinued smoking due to increasing dyspnea. Treatment outcome convincingly established the impact of tobacco smoking on disease outcome. The highest rate of patients succesfully finished the standard treatment

Table 2

Case-management and pulmonary TB features

Characteristics n (%)		SG, n=206 n (%)	CG, n=79	P value
Case management	Lack of health insurance	162 (78,6)	45 (56,9)	**<0,001**
	Associated diseases	123 (59,7)	36 (45,6)	>0,05
	Late detected (>60 days)	131 (63,6)	28 (35,4)	**<0,001**
	Detected by general practitioner way	152 (73,7)	52 (65,8)	>0,05
	Detected by pneumophtysiologist	31 (15,0)	18 (22,7)	>0,05
	Other ways of detection	23 (11,1)	9 (11,4)	>0,05
Para-clinical features	Microscopic positive	121 (58,7)	12 (15,2)	**<0,001**
	1 lung involved	54 (26,2)	58 (73,4)	**<0,001**
	2 lungs involved	152 (73,7)	21 (26,6)	**<0,001**
	Lung destructions	131 (63,6)	18 (22,8)	**<0,001**
	Dissemination (bronchogenic, lymphogenic)	28 (13,6)	0	<0,001
	Complications	59 (28,6)	3 (3,8%)	**<0,001**

Tabel 3

Distribution of patients according to the demographic factors

Factors RR		Statistical indices		
		OR	AR%	
Demographic	Men	1,25 (1,04-1,53)	2,16 (1,22-3,7)	**20,8**
	Urban	1,38 (1,13-1,71)	2,78 (1,569-4,85)	**24,2**
	Low economical status	1,24 (1,03-1,5)	2,01 (1,16-3,51)	**19,9**
	Single person	1,32 (14-1,53)	2,84 (1,64-4,91)	**44,4**
	Poverty	1,47 (1,1-1,97)	2,17 (1,28-3,69)	**32,3**
	Alcohol abuse	1,94 (1,67-2,24)	36,6 (11,23-119,3)	**92,9**
Disease features	Lack of health insurance	1,35 (1,1-1,66)	2,61 (1,49 – 4,59)	**27,6**
	Microscopic positive	1,62 (1,39-1,89)	7,94 (4,06-15,59)	**74,1**
	2 lungs involved	1,8 (1,48-2,19)	7,63 (4,24-13,72)	**74,2**
	Lung destructions	1,56 (1,34-1,84)	5,69 (3,13-10,3)	**63,9**
	Dissemination	1,36 (1,23-1,51)	11,43 (1,53-85,5)	**92,3**
	Complications	1,43 (1,29-1,59)	9,96 (3,02-32,8)	**86,7**

according to WHO recommendations in CG: 76 (96,21%) *vs* 142 (68,9%) patients from SG. No deaths were registred in CG and 16 (7,67%) cases in SG. Patients that failed the standard treatment or those who were lost from follow-up predominated in patients from SG: 48 (23,31%) vs 3 (3,89%) patients of CG.

An important research outcome represents the relative risk (RR), odds ratio (OR) and attribuitable risk (AR) indices for identifying the priority interventions in the frame of specific subgroups. All indices demonstrated the risk impact of causal factor-tobacco smoking on TB development. There were selected only risk factors and features which exposed statistical differences between groups of patiens.

Calculating relative risk index it was established that all exposed conditions are associated with tobacco smoking. Odds ratio identified that major risk factors associated with tobacco smoking are alcohol abuse and TB-related characteristics: dissemination, complications due to TB, pathological process localised in both lungs, bacillary TB (smear positive for acid fast bacilli), lung destructions. It was establshed that preventive advantages of smoking cessation will be obtained especially on diminishing the rate of patients with lung dissemination and destructions, involvement of both lungs in the pathological process, associated complications (hemoptysis, pneumothorax, pleurisy), epidemiological danger (bacillary forms of pulmonary TB). In addition such associated determinants will be substantially reduced by smoking cessation: alcohol abuse and single civil state. A lower impact will be achieved by poverty-related features and residence.

Conclusions

Tuberculosis is a big challenge worldwide, in addition active smokers are the most widely expressed risk group for active disease.

Risk factors for the development of active tuberculosis at smokers are: poverty-related conditions, male sex, single matrimonial status, medico-biological conditions and alcohol addiction, low educational status, urban residence.

One half of smoking group with TB patients was established with positive bacillary status at smear microscopy.

Delayed case-management of active smokers with pulmonary TB was determined by the lack of health insurance in the frame of primary health care sector. Comorbidities and disease-related radio-morphological features (bilateral localization, lung destructions, dissemination, positive bacillary status) associated with enumerated risk factors contibute to low treatment outcome. Targeted interventions for smoking quitting in the frame of risk subgroups will diminish the rate of severe and complicated forms of TB and will increase the rate of treatment success, strenghthening TB control at the community level.

Raising awareness among smokers and their families about TB, emphasizing that the diagnosis and treatment is free of charge and independent regarding their social status will improve epidemiological state. Improvement of the socio-economical and hygienic conditions, associated with quitting drug therapy and psychological counseling will diminish the risk for TB development among smokers. Maintaining the active smokers as a part of high risk groups for the screenng to TB will diminish the rate of severe TB forms and the burden of smoking-related disease.

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Analysis of concomitant diseases of the transtibial amputation of lower limbs

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Abstract

Background: Medical rehabilitation of persons who have undergone unilateral transtibial amputees is a complex and multildimensional process. The presence of comorbidities and their complications increase mortality levels and slow down the process of rehabilitation.

Material and methods: 472 medical records of patients admitted during the years 2015 to 2016 were analyzed. 142 patients were selected because of unilateral transtibial amputations of diabetic complications with analysis of clinical diagnosis and concomitant pathologies. By examining clinical and functional, were evaluated dolor syndrome and goniometric knee joint of the amputated side. All patients received medical rehabilitation and orthopedic care in the hospital. Clinical and functional status was assessed in dynamics after treatment, and at 6 months.

Results: of somatic pathologies, cardiovascular diseases (hypertension – 88%, ischemic heart disease – 54%) are first mentioned in the concomitant diagnosis on admission, the most frequent pathologies associated with diabetes and in recitals average age of the study group. Dolor syndrome and functional status during rehabilitation treatment, improved significantly from 7.9$\pm$0.16 points, to 4.1$\pm$0.03 points, and knee extension deficit decreased on average by 4.69 degrees. After discharge home both indices did not support essential amendments.

Conclusions: To streamline the process of medical rehabilitation and improvement of the prosthetics of patients with amputations of lower limbs should be considered concomitant pathologies present and their long-term monitoring.

Key words: transtibial amputations, concomitant pathology, medical rehabilitation.

Introduction

Lower limb amputation is caused primarily by chronic vascular diseases, diabetes and trauma followed by installing a very high rate of disability and locomotor disabilities [1, 2, 3, 4]. The results presented by Transatlantic Inter-Society Consensus (TASC) show that the frequency of amputations of diverse etiology has increased considerably over the last 25 years and this number is expected doubling in the next 15 years [5]. For people under the age of 50 years and younger, trauma (accidents, labor etc.) is the main indication for amputation [6, 7, 8]. In Moldova in 2013, the rate of chronic conditions, complications that lead to amputations of limbs, was the following: for vascular diseases – 1560 cases, for trauma – 478 cases annually. Reported by gender (male / female) amputations are most commonly performed in men, the proportion is 3:1 [7, 8].

Personal and environmental factors are important in developing long-term functional capacity of a person who suffered amputation [9]. The goal of rehabilitation is considered reeducation mobility of people who have undergone an amputation. The study of disability by amputations of lower limb of these patients demonstrated that functional capabilities don't have a decisive role in assessing the quality of life [10].

Other factors impacting on the quality of life were proved to be high quality prosthesis, presence of comorbidities, phantom and residual pain in the stump [11,12]. The factors with the greatest impact on functional capacity demonstrated by a prospective study duration (2 weeks, 6 months and 12 months) were found to be: the duration and level of amputation, presence of concomitant pathologies and mental abilities [13].

The presence of comorbidities and their complications (e.g. kidney and cardiac failure, etc.) increases mortality and delays the rehabilitation process [13]. Of comorbidities first ranks diabetes, osteo-articular pathologies and cardiopulmonary [9].

Chronic pain can have a negative impact not only on the physical functionality, but on the emotional status, social and vocational. In a study of 437 people with amputations of lower limbs, Schans et al. [14] found that people who experienced phantom pain, and have worse quality of life than those who did not have phantom pain. Low back pain according to some studies as functional deficiencies can contribute to even more than the phantom pain or residual limb pain [15, 16].

Complex rehabilitation process of a patient with lower limb amputation should be focused both on functional recovery, as well as monitoring of concomitant diseases.

The purpose of the study: Estimating concomitant pathologies in patients with type II diabetes after unilateral transtibial amputees and their evolution in the medical rehabilitation complex.

Material and methods

The study was performed in Republican Experimental Centre for Prosthesis Orthopedics and Rehabilitation (CREPOR). At the first stage were analyzed 472 medical records of patients hospitalized in the Atypical Prosthetics ward and Complicated, during the years 2015-2016. There were selected records of 142 patients with unilateral transtibial amputations caused by diabetic pathology. The average age of patients was 60,31 years, 29 women and 113 men. All patients had degree of disability, confirmed by the National Council for Disability and Work Capacity determination. 60 persons received severe degree of disability, stressed (II) – 71 people and light degree (III) of disability – 11 people.

Phase two of the study was to assess clinicaly and functionaly 142 diabetic patients with unilateral transtibial amputees. All patients were underwent medical rehabilitation and orthopedic care (prosthesis type PNR3-12) in the hospital. Rehabilitation treatment comprised the application of passive methods (hand massage, thermotherapy, hydrotherapy, magnetotherapy) and active through the application of kinesiology for:

- reeducation of independent and assisted transfer with training to the new static and walking conditions.
- reeducation of standing balance.
- general and special physical development.
- increase of breathing capacity.
- stump preparation for applying provisional prosthesis.
- orthostatism and balance rehabilitation with provisional prosthesis.

Through the collection of historical data on admission were identified present concomitant diseases and the rehabilitation of functional capacity in the postoperative period (after amputation). Dolor syndrome evaluation was performed using the VAS scale and vicious stump by joint stiffness, using the goniometer. All indices were measured at admission (baseline) and after medical rehabilitation treatment at – discharge (1 month) and after 6 months. Data were analyzed by EXCEL, in calculating the coefficients Stiudent-derived indicators.

Results and discussion

Of the 142 patients admitted for medical rehabilitation and primary prosthesis, all were diagnosed with type II diabetes by about 13.03 years up to amputation, average serum glucose level during the last 6 months – 12,1 mmol/ l. Time from lower limb amputation, to consultation in CREPOR, constituted on average 9.38 months. Figure 1 shows that during this period only 41% of patients, who were consulted in CREPOR, underwent rehabilitation treatment. Because no patient was sent to specialized rehabilitation services, rehabilitation measures had a passive character followed by hygiene measures and local treatment of amputation stump, learning the technique of dressing. All the mentioned above measures were indicated by the surgeon.

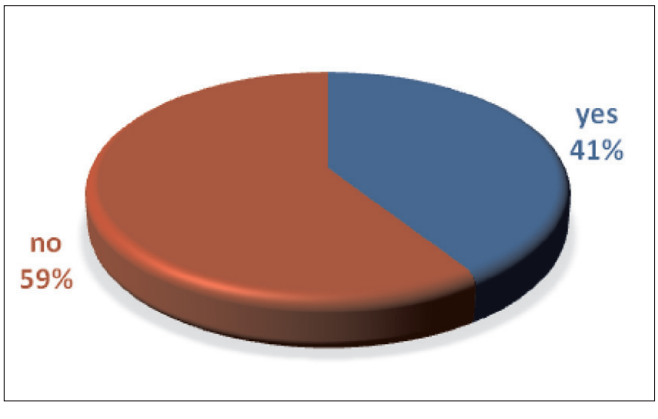

Fig. 1. Rehabilitation treatment previously conducted.

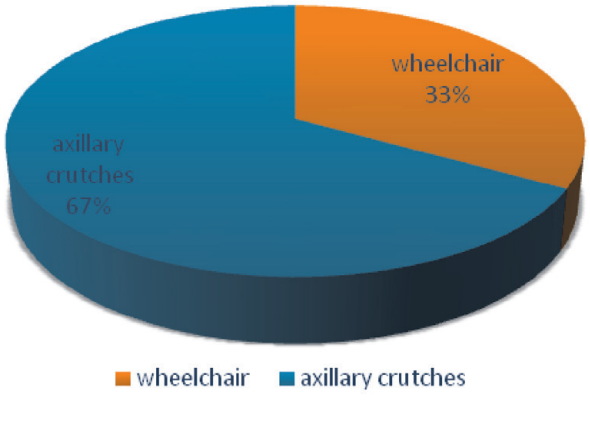

Fig. 2. Way Away.

Table 1

Feature comorbidities in diabetic transtibial amputations

Phantom pain		Other pain		Vicious stump		Hypertension	
Abs	%	Abs	%	Abs	%	Abs	%
132	92,95	138	97,18	68	47,88	125	88,02
Ischemic Heart Disease			**Obesity**			**Osteoarticular**	
Abs		%	Abs		%	Abs	%
77		54,22	52		36,51	79	55,63

An important functional criterion in the rehabilitation of patients after amputation is the outpatient capacity of patient, who underwent amputation. Also in surgical departments, patients were instructed in handling bilateral axillary crutches. Though walking, after unilateral transtibial amputees, is balanced against the thigh amputations and does not involve much effort and energy expenditure, however 33% of those hospitalized were traveling in a wheelchair (fig. 2). The large number of these people is determined by the presence of concomitant decompensated pathologies (hypertension, ischemic heart disease, etc.) or a patient fears to injure himself. The most frequent concomitant diseases diagnosed in hospitalization are shown in table 1.

Analyzing medical records, 97% of patients with diabetes after transtibial amputation, had different genesis pain (osteo-articular, muscular, neuropathic) caused by biomechanical disorders due to the absence of a segment. By the same cause, osteo-articular manifestations occur confirmed by X-rays. In reality these nosologies number is much higher, but it is not confirmed by laboratory tests to be established as a clinical diagnosis. Phantom pain present in 97.1% cases, confirming data from the literature showing installation phantom pain immediately after surgery, with their evolution throughout their lives. In most cases patients have both kinds of pain. No patients in the study group follow spec (Hypertension – 88%; Ischemic Heart Disease – 54%) are first mentioned in the concomitant diagnosis while on admission, the most frequent pathologies associated with Diabetes and in recitals average age of the study group. Not every patient has a Body Mass Index calculated, so diagnosis of Obesity is determined in only 36% of cases, which also does not represent the real situation.

Of all presented comorbidities on admission, vicious abutments and dolor syndrome by joint stiffness, proved to be influenced during medical rehabilitation. Dolor syndrome caused by local changes of the stump of another genesis during the implementation of means of medical rehabilitation in complex drug therapy (NSAIDs parenteral), yielded much from an average of 7.9±0.16 points to 4,1±0.03 (tab. 2). Over six months this metric has not changed much, modifying only 0.3 points after VAS. This stagnation is explained by the fact that patients at home, have not received supportive treatment and NSAIDs were administered on single occurrence of pain episodes. The intensity dolor syndrome that carries a moderate character and, in many cases, patients experienced pain without taking any action. On the other hand local dolor syndrome caused by prosthesis was declined by removing the causal factor (decreased prosthesis wearing time).

Table 2

Evolution of dolor syndrome in complex rehabilitation process by VAS

	Initial	1 month	6 months
Phantom pain	4,25±0,29	3,7±0,03	3,567±0,31
Other pain	5,905±0,16	4,155±0,03	3,805±0,33

Phantom pain patients originally presented with rather mild 7.9±0.16 points. There is a positive trend during medical rehabilitation, averaging 3.8 points. From discharge to 6 months, patients have not received specific phantom pain and do not maintain the results that were obtained at discharge. Dynamic results are insignificant, from 4.1±0.03 points to 3.8±0.33 points. The presence of joint stiffness vicious stump, was present in 68 people, which also represents 47.8% of all patients with unilateral transtibial amputees on admission (tab. 3).

Table 3

Evolution of goniometric measurements of the knee joint in the rehabilitation complex

	Initial	1 month	6 months
Flexion	96,58±0,05	103,67±0,03	106,76±0,07
Extension	10,38±0,39	5,69±0,16	4,52±0,52

Table 3 data show an increase in Angle indices, originally made for flexion from 96.58±0.05 degrees to 103.67±0,03 degrees recorded at discharge. More significantly changed goniometric data for knee extension, from 10.38±0.39 degrees to 5.69±0.16° after treatment. The results obtained for the extension deficit reduction are explained by the fact that the focus was on reeducation recovering knee exten-

sion. The prosthetic leg is influenced much more by scarcity extension, than limited knee flexion. Over the next five months this index practically has not changed for both flexion and extension, because all measures under home care were limited to hygienic care and not to increase functional capabilities.

Conclusions

1. Following evaluation and examination of the medical records of 142 patients with type II diabetes, after unilateral transtibial amputation, the most frequent comorbidities present at the primary consultation, proved to be dolor syndrome and joint stiffness vicious stump.

2. The first place of concomitant pathologies determined at admission, take cardiovascular pathologies (hypertension – 88%, Ischemic heart – 54.2%).

3. Reduced outpatient ability and vicious stump presence, is due to inadequate treatment of postoperative rehabilitation.

4. Insignificant evolution of Angle indices and dolor syndrome (assessed by VAS) in home conditions, is determined by the occasional administration of NSAIDs and absence of preventive rehabilitation programs.

5. To streamline the process of medical rehabilitation and improvement of the prosthetics of patients with amputations of lower limbs should be considered present concomitant pathologies and their long-term monitoring.

6. The rehabilitation care of persons who have undergone amputations of limbs, should be a continuous process with postoperative initiation, and continued after discharge in specialized departments, with secondary prevention programs.

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Curierul medical, October 2016, Vol. 59, No 5

The study of mechanisms of anti-inflammatory activity realization of a new malonic acid derivative – maldian

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Abstract

Background: The aim of this work was to study the implementation mechanisms established earlier, the anti-inflammatory activity of a new compound – di-(2,4-dimethyl) malonic acid anilide, code name – "Maldian".

Material and methods: The study was performed on nonlinear white male rats, weighing 220-250 g. The implementation mechanisms of maldian pharmacological action studied in terms of the effect of a new substance on the level of prostaglandin E and the effect on the activity of proteolytic enzymes of the kinin system in the blood of intact animals on the background of carragenine edema. Maldian antioxidant activity was assessed by the impact on the processes of lipid peroxidation in the membranes of liver mitochondria in rats. The role of adrenal system showing maldian anti-inflammatory effect was also studied.

Results: It is found that maldian at a dose of 7.3 mg/kg has a pronounced antioxidant activity reducing free radicals oxidation processes. There is an ability to inhibit kininogens, to inhibit the activity of the leading mediator of inflammation – kallikrein in the mechanism of anti-inflammatory maldian activity. Maldian significantly decreases the level of prostaglandin E on the background of acute inflammatory reaction. Anti-inflammatory maldian activity is implemented without any effects on the adrenal cortex.

Conclusions: Considering the results obtained, maldian – (di-(2,4-dimethyl) anilide malonic acid, is a promising compound for further pharmacological study and introduction into medical practice as a new modern drug with anti-inflammatory action.

Key words: derivatives of malonic acid, anti-inflammatory action mechanisms.

Introduction

Inflammation, as a typical pathological process, is the leading link of the pathogenesis of many diseases of a modern man. An inflammatory reaction is characterized by a symptom complex of functional, structural and metabolic abnormalities at the organ and cellular levels [1]. The main humoral factors of an inflammatory reaction on the stage of secondary alteration are: the activation of free radicals oxidation (FRO) due to the increased release of aggressive oxygen and oxygen-halogen radicals, and a significant decline in the capacity of endogenous antioxidant systems; the amplification by activated macrophages and endothelial cells synthesis of nitric oxide, which has potent non-specific cytotoxic effect; the release into the blood components of the complement system, in particular the membrano-atacking complex C5-C9, which violates the integrity of the cell membrane; the activation of hydrolytic enzymes of the lysosomes releasing when cells die; the increase of the synthesis and the release by activated macrophages and T-lymphocytes of tumor necrosis factor (TNF), the last can cause apoptosis and cell death, increases the generation of inflammation focus of the nitric oxide and activates the processes of the FRO.

The cellular factors of secondary alteration are neutrophils and macrophages [2]. It should also be noted that the most important mediator element of the inflammatory response are eicosanoids, which are the main producers in the inflammation of the monocytes and macrophages [3].

The predominant eicosanoids in the inflammation focus are considered as prostaglandin – PGE1 and PGE2, leukotriene – LTB4 and 5-hydro-peroxyisobutyrate acid. Thromboxane A2, prostacyclin I2 and leukotrienes LTS4, LTD4, LTE4 are produced in a smaller number [4].

A particularly important role in the development mechanism of inflammatory reactions is about prostaglandins, which, showing a powerful vasodilatation effect, increase hyperemia and exudation. PGE1 and PGE2 increase the sensitivity of afferent receptors to bradikinin and histamine; also they induce temperature increase [5].

Considering the above the activation of the FRO and the synthesis changes and the activity of prostaglandins play the key role in the modulation of the inflammatory response, so there is an urgent search and the development of a new drug with anti-inflammatory action, in implementation of which the leading targets are: the inhibition of FRO processes and the effect on the level of inflammatory mediators – kinins and prostaglandins E [6, 7, 8].

In this aspect a promising remedy can be a new compound di-(2,4-dimethyl) anilide malonic acid, synthesized by the scientists of the National University of Pharmacy (Kharkiv, Ukraune).

The aim of this work was to study the realization mechanisms of previously shown anti-inflammatory effect of di-(2,4-dimethyl) anilide malonic acid, from now on "Maldian" [9].

Material and methods

The study was performed on nonlinear white rats. The animals were kept in standard conditions of a vivarium in accordance with Good Laboratory Practics. The experiments were carried out in order to meet the requirements of European Community Council Directive on the protec-

tion of animals used for experimental and other scientific purposes [10]. The studies were carried out on 128 nonlinear male rats weighing 220-250 g. The animals were divided into groups of 8.

The anti-inflammatory maldian activity was studied on the model of carrageenan foot swelling in rats, which was modeled by subplanetary injection of 0.1 ml of 1% solution carrageenan. In accordance with methodical recommendations on the study of anti-inflammatory activity of new drugs maldian was injected intragastrically 30 min before modeling pathology at a dose of 7.3 mg/kg [11]. The acetylsalicylic acid at a dose of 98 mg/kg and voltaren at a dose of 8 mg/kg were used as reference drugs and were injected in accordance with the scheme which was similar.

The study of mechanisms of maldian anti-inflammatory activity was conducted through 3 stages (tab. 1).

Table 1

The studying stages of realization mechanisms of maldian anti-inflammatory activity

Stages	Studying model / Conditions	The index under study
Stage 1	Acute carrageenan of foot swelling in rats	The content of PGE1 in blood plasma
		Kallikrein and kallikreinogen in serum
Stage 2	Microsomal fraction of homogenate in rats liver	The concentration of malonic dialdehyde
Stage 3	Acute carrageenan of foot swelling in rats with preadrenalectomy	Antiexudative activity index

During the first stage under the conditions of reproduced carrageenan inflammation, 4 hours after carrageenan injection, blood sampling was conducted and examined whether PGE1 is contained as well as the level of kallikrein and kallikreinogen. The rats were decapitated under ether anesthesia to sample blood.

The level of prostaglandin E1 (PGE1) was determined in radioimmunology way using «Clinical Assay» (USA) reagents. The determination of PGE1 content in blood plasma was carried out on the background of the inflammatory response. Blood for the determination of PGE1 was sampled in plastic tubes in accordance with V. D. Pomognemo and co-authors' recommendations [12]. To prevent the processes of biosynthesis and metabolism PGE1, the transition from one series to another, the test tubes while sampling and processing blood were placed in ice. As an anticoagulant ethylenediaminetetraacetate (EDTA) at a concentration of 1 mg/ml of blood was used. To block the cascade of eicosanoids transformations by platelets in the tubes, the inhibitor prostaglandinsynthase –a solution of acetylsalicylic acid (0.01 ml of 0.4% solution of 1 ml of blood) was added to the plasma samples.

The plasma was separated by centrifugation at a temperature of 4 ° C. and 2000 rpm for 30 min. until complete precipitation of platelets and stored at -20 degrees C for 2-3 days. PGE1 extraction from plasma was performed using ethyl acetate and a preliminary removal of plasma neutral lipids using petroleum ether.

Kallikrein and kallikreinogen in the serum were determined spectrophotometrically by the rate of hydrolysis of the ethyl ester of N-benzoyl – L-arginine by the method of and T. S. Paskhina and A. V. Krinskaya [13].

During the second phase of the experiment the presence of antioxidant activity in the mechanism of maldian anti-inflammatory action was being studied.

The impact of a new compound on the intensity of lipid peroxidation (LPO) was studied in vitro using microsomal fraction of homogenate of rat's liver. The intensity of Fe2+ – ascorbate -induced by LPO of microsome membranes was determined according to the standard procedures. The intensity of NADPH-dependent of LPO of microsome membranes was determined in the medium of the following composition: 100 mmole of Tris-HCL buffer (pH 7.4), 1 mmole of NADPH, 4 mmole of ADP, 14 μmol of Mohr's salt. In ascorbinsaeure LPO the medium contained 100 mmole of Tris-HCL buffer (pH 7.4), 0.5 mmol of ascorbate, 12 μmol Mohr's salt. During some experiments, 4 mmole ADP (Sigma, USA) was additionally injected into the incubating medium. The concentration of microsome protein in the incubating mixture was 0.5-0.6 mg in 1 ml. Warmed up to 37 degrees air was constantly purged through the incubating mixture, providing the saturation of the medium with oxygen and mixing. The concentration of malonic dialdehyde (MDA) was determined spectrophotometrically by the reaction of thiobarbituric acid, using SF-16, after protein precipitation by trichloroacetic acid. Maldian was injected into the incubating medium at doses of 7.3 μm and 14.6 μm. As a reference drug voltaren at concentrations of 80 μm, 500 μm and 800 μm was selected [11].

The third phase of the research was devoted to the study of a possible involvement of the adrenal system in the mechanism of realization of maldian anti-inflammatory effect.

To ascertain the mechanism of maldian anti-inflammatory action of the adrenal system, the series of experiments with carrageenan swelling in rats with previously cut out adrenal glands were carried out. The adrenalectomy was performed bilaterally on the back under ethaminal-sodium anesthesia. 5 days after the surgery, the rats were simulated carrageenan swelling of the foot in accordance with the standard method described in methodical recommendations on the study of anti-inflammatory activity of new drugs [11].

The statistical processing of experiment results was done by common pharmacology methods determining the average arithmetic meanings (X) and a standard error (SE), the reliability of differences was determined using t-Student test at the significance level of 95% (p £ of 0.05) [14].

Results and discussion

Acute carrageenan swelling is characterized by a significant inflammatory reaction (table 2). It is found out that a new compound anti-inflammatory activity is at the level of a known drug with anti-inflammatory effect of voltaren. It gives us the grounds to study the implementation mechanisms of maldian anti-inflammatory activity in details.

Table 2

Antiexudative activity of maldian and voltaren under the condition of acute carrageenan swelling (n=8)

The conditions of the experiment	Dose mg kg	Antiexudative activity, % Time of inflammation			
		1 hour	2 hours	3 hours	4 hours
Maldian	7,3	26,3±0,84	35,7±1,72	48,8±2,12	56,9±0,97
Voltaren	8,0	24,0±2,10	33,0±2,70	46,2±2,20	55,0±2,30

Today, the leading role of prostaglandins E – lipid mediators of inflammation which has potent phlogogenic and pyrogenic effect of PGE1 is a scientific fact. [15]. The first phase of the experiment was devoted to the study of maldian influence on PGE1 content in the blood plasma in the acute inflammatory response (within 4 hours after Karenin injection). The results of the experiment are presented in table 3.

Table 3

The influence of maldian and reference drugs on the content PGE1 in the blood plasma of rats with carrageenan swelling (4 hours after carragenan injection) (n=8)

The conditions of the experiment	The content PGE1 in plasma	
	Nmol/l	% to intact control
Intact control	8,0±1,58	100
Control pathology	13,8±1,18 *	172
Maldian, of 7.3 mg/kg	0,68±0,39 * #	8,5
Acetylsalicylic acid, 98 mg/kg	0,24±0,08 * #	3,0
Voltaren, 8 mg/kg	1,17±0,38 * #	15

Notes: * – statistically significant differences relatively to the intact control group – p<0.05; # – statistically significant differences relatively to the control pathology group – p<0.001.

It is found out that rats of the control pathology group have acute inflammatory reaction (4 hours after Karenin injection) which is accompanied by a significant increase up to 72% level of PGE1 in plasma, relatively of intact animals.

Maldian injection is characterized by a pronounced anti-inflammatory effect, verified by a large-scale reduction in prostaglandin fractions on the background of acute inflammatory reaction. Maldian reduces the amount of studied prostaglandin by 20 times (p<0.001) relatively to the control group pathology.

It should be noted that the effect of a new compound on the level of prostaglandin E in terms of the inflammatory response, is at the level of reference drugs – acetylsalicylic acid and voltaren and slightly higher than the activity of the latter.

Taking into account the findings of previous studies [9] it is possible to note a high degree of the correlation between the anti-inflammatory effect of a new compound and its effect on the level of PGE1 in plasma.

Kinins are important modulators of the inflammation. Regardly to that, maldian effects on the activity of proteolytic enzymes of the kinin system in terms of carrageenan inflammation were studied. The results are shown in table 4.

Table 4

Maldian and acetylsalicylic acid influence on the content of kallikrein and kallikreinogen in the blood plasma of rats in the norm and on the background of carrageenan swelling (4 hours after Karenin injection) (n=8)

The conditions of the experiment	Kallikrein MED/ml	Kallikreinogen MED/ml
Intact control	84,6±2,2	240,5±5,5
Control pathology (carrageenan swelling)	128,4±3,8 *	327,6±14,3 *
Maldian, of 7.3 mg/kg	39,5±5,1 * # $	248,8±12,4 * # $
Carrageenan swelling + Maldian, of 7.3 mg/kg	44,5±3,9 * # $	336,6±15,4 * $
Acetylsalicylic acid, 98 mg/kg	66,3±4,3 * #	421,4±13,1 * #
Carrageenan swelling + Acetylsalicylic acid, 98 mg/kg	70,3±4,8 * #	422,3±11,4 * #

Notes: * – statistically significant differences relatively to the intact control group – p<0.01; # – statistically significant differences relatively to the control pathology group, p<0.01; $ – statistically significant differences relatively to the group of acetylsalicylic acid – p<0.01.

It was found out that in animals under the conditions of acute inflammatory response, induced by carrageenan, there has been a significant increase in the level of kallikrein up to 52% and kallikreinogen by 36%, relatively to the group of intact control.

While injecting maldian it was found out a significant reduction of kallikrein up to 47% relatively to the control pathology group (table 4), meanwhile maldian has no statistically significant effect on plasma levels of kallikreinogen.

Acetylsalicylic acid contributed to the increase of kallikreinogen content in the blood plasma of healthy animals up to 75% relatively to the intact control group; meanwhile

it significantly less pronouncedly reduced the concentrations of kallikrein relatively to maldian.

The results obtained show that the studied compound inhibits the release of one of the leading mediators of kallikrein inflammation.

Due to the fact that the inflammatory reaction triggers the cascade of FRO, the next step was the studying of the potential antioxidant maldian action on the model of induced LPO in the membranes of mitochondria of rat liver. Divalent iron ions and ascorbate were used as inductors (prooxidant). The results of the experiment are shown in table 5.

Table 5

The dynamics of changes in the concentration of malondialdehyde (MDA) in liver cells of rats under the conditions of Fe2+ – ascorbate dependent LPO and when added maldian and voltaren to the incubation medium

The conditions of the experiment/ the concentration of the introduced substances, μm	The accumulation of MDA whithin 5 min of incubation	
	nmol/l	% control
The study of the maldian effect		
Control (induction LPO)	24,4±0,40	100
Maldian, 3.6 μm	26,4±0,60	108
Maldian, of 7.3 μm	15,2±0,70 * #	62
Maldian, of 16.6 μm	11,5±0,73 * #	47
The study of voltaren effects		
Control (induction LPO)	27,5±0,40	100
Voltaren, 80 μm	33,0±0,68	120
Voltaren, 500 μm	16,5±0,50 * $	60
Voltaren, 800 μm	13,6±0,32 * $	9

Notes: * – statistically significant differences relatively to the control group (induction of LPO) – p<0,001; # – statistically significant differences relatively to maldian group at a dose of 3.6 μm – p<0.001; $ – statistically significant differences relatively to voltaren group at a dose of 80 μm – p<0.001.

In the groups, which caused the intensification of LPO processes due to the injection of prooxidant, the concentration of MDA (as a marker of LPO processes) was taken as 100 %.

Dose-dependent antioxidant maldian effect was found out. So, if you increase the dose of maldian from 3.6 μm to 7.3 μm, its ability to inhibit Fe2+ – ascorbinsaeure LPO in the mitochondria of rat liver is increased by 1.7 times and the subsequent doubling of the dose reduces pathological oxidation processes by 2,3 times (table 5).

Inhibitory effect of voltaren on the oxidation of membrane lipids of mitochondria was observed at concentrations of 500 μm and 800 μm, which accounted for 60% and 49%, respectively.

Analyzing the obtained results, it should be noted that voltaren has an inhibitory influence in experimental oxidative stress only at concentrations range of toxic doses, whereas the antioxidant maldian effect is manifested in low doses which effectiveness is of middle rate and ten times lower than those of voltaren.

Thus, the ability of maldian to reduce the level of the LPO in terms of inflammation is essential in the implementation of the anti-inflammatory action and its ability to normalize the destructive processes caused by the activation of the FRO.

In our study the mechanism of maldian anti-inflammatory action of adrenal system, its antiexudative activity on the model of carrageenan swelling in adrenalectomised animals has been examined. The results of the experiment are shown in table 6.

Table 6

Maldian antiexudative activity in the experiment on adrenalectomized and non-operated rats on the models of acute carrageenan swelling (n=8)

Antiexudative activity, %	Maldian at a dose of 7,3 mg/ kg	
	Adrenalectomized rats	Non-operated rats
1 hour of the experiment	24,3 ±2,50	26,6 ±2,70
2 hours of the experiment	33,8 ±3,10	36,0 ±3,09
3 hours of the experiment	46,3 ±2,70	49,1 ±2,65
4 hours of the experiment	54,9 ±3,01	57,3 ±3,49

The results obtained confirmed previously expressed antiexudative maldian activity [9], which peaks in 3-4 hours of the inflammatory response and indicates anticyclogenesis mechanism of the anti-inflammatory action of the new compound.

Analyzing the obtained data we can conclude that the dynamics of antiexudative maldian action of adrenalectomised animals does not differ from that which takes place while injecting the substances to non-operated rats (table 6.) Statistically significant differences between these groups were not established.

Thus, in the implementation of the maldian anti-inflammatory effect it's possible to exclude its influence on the adrenal cortex and the activation of the adrenal system.

Conclusions

The mechanisms of realization of the new compound – di-(2,4-dimethyl) malonic acid anilide and anti-inflammatory activity of the new compound, under the code name – "Maldian" were studied.

Anticyclogenesis mechanism of maldian antiexudative action at a dose of 7.3 mg/kg was verified by a significant decrease of prostaglandin E1 in the blood plasma of animals on the background of carrageenan swelling.

The effectiveness of the new compound exceeds the anti-inflammatory effect of voltaren at a dose of 8 mg/kg and acetylsalicylic acid at a dose of 98 mg/kg.

Maldian has a reliable inhibitory effect on kallikrein, reducing its content in the blood plasma up to 47% in terms of carrageenan swelling, meanwhile significantly exceeds the effect of acetylsalicylic acid at a dose of 98 mg/kg.

The antioxidant maldian activity as for the effect on lipid peroxidation at the level of voltaren at a dose of 8 mg/kg was found out.

Maldian has no inducing effect on the adrenal cortex, thus eliminating the activation of the adrenal system.

Maldian is a promising compound for further study and the introduction into medical practice as an effective new anti-inflammatory drug.

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Experience of Rottinger approach in hip replacement

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Abstract

Background: An important aspect in modern hip arthroplasty plays operative technique, namely the use of minimally invasive techniques and low-traumatic manipulation. Since the beginning of the development of minimally invasive technologies in orthopedics and increasing demands on the part of patients in the postoperative period there appeared a fast growing need to develop new minimally invasive approaches to achieve the objectives as opposed to the existing traditional techniques.

Material and methods: The analysis of 47 patients operated on traditional access (Harding) – control group (20 patients with osteoarthritis, 27 with a fracture of the femoral neck) and 42 patients undergoing surgery for Rottinger approach – the main group (20 – coxarthrosis, 22 – fracture of the femoral neck). A survey of patients and evaluation of Harris Hip Score were made.

Results: For evaluation of Harris Hip Score the following parameters were taken: the painful feelings when bearing load on the operated limb, the ability to walk different distances (unlimited, 30 minutes, 15 minutes, only indoors, impossible), the opportunity to wear socks or shoes, use stairs with no assistance, ability to perform daily activities and work, the need to use aids, limping, the ability to use public transport, sitting, operated joint mobility (in degrees). Grading for the Harris Hip Score: <70 – poor, 71-79 – fair, 80-89 – good, >90 – excellent. The overall result for the Harris Hip Score using Rottinger approach was 89.1 points, corresponding evaluation "good", and Harding method – 72.8 ("fair"). 6 weeks after surgery score for Rottinger approach was 95.3 points ("excellent"), Harding method – 82.4 points ("good").

Conclusions: Cosmetic effect by Rottinger approach length of incision is 8-10cm, without myotomy and violation of the fascia lata integrity, better visualization of the acetabulum, but worse is the proximal femur, the need for specialized tools. This operating technique provides a shorter period of hospitalization, reduces the need for rehabilitation and support aids, reduces the risk of complications from prolonged immobilization, and reduces the risk of dislocation by 4.15%.

Key words: hip replacement, mini-invasive Rottinger approach.

Introduction

According to the WHO expert group in 2012, 1 million 500 thousand hip joint arthroplasty are performed in the world. The number of operations over the last 5 years has increased in Europe by 80%, which is 175 thousand per year in only one Germany [1, 2, 4, 7]. World statistics shows that the average annual needs of hip replacement arthroplasty is 500 – 1000 injured patients per 1 million people, but considering the population of Ukraine in our country annually arthroplasty is required by 25-40 thousand sick and injured. Unfortunately, annually in Ukraine 10 times less operations are performed than the estimated number of joints replacement needed [5, 6]. Problem of hip replacement today is very relevant in connection with the need to perform this surgery for the elderly citizens because of femoral neck fractures, osteoarthritis and many other reasons. An important aspect in modern hip arthroplasty plays operative technique, namely the use of minimally invasive techniques and low-traumatic manipulation. Since the beginning of the development of minimally invasive technologies in orthopedics and increasing demands on the part of patients in the postoperative period there appeared a fast growing need to develop new minimally invasive approaches to achieve the objectives as opposed to the existing traditional techniques. Among the various surgical approaches in HJR best results are yielded by Rottinger approach. This method provides anatomical access to muscles without myotomy and violation of the fascia lata integrity. Anatomically performed access without or with minimal damage to anatomical structures ensures faster mobilization and shorter rehabilitation time compared to traditional techniques [8]. After HJR average duration of stay-in-bed days by traditional access lasts 7-14 days compared with mini-invasive access – 3-7 days [9].

Purpose of the study: To analyze the advantages and disadvantages of mini-invasive method of Rottinger approach with total hip replacement in retrospective study of patients.

Material and methods

The study was conducted at the orthopedic department of the 8th city clinical hospital in Lviv. The analysis of 47 patients operated on traditional access (Harding) – control group (20 patients with osteoarthritis, 27 with a fracture of the femoral neck) and 42 patients undergoing surgery for Rottinger approach – the main group (20 – coxarthrosis, 22 – fracture of the femoral neck). The average age of patients is 65 years (50-95 years). A survey of patients and evaluation of Harris Hip Score were made.

Table 1

The distribution of patients by disease, which resulted in need of hip replacement

	Osteoarthritis	Fracture of the femoral neck	Total number
Harding access	20	27	47
Rottinger approach	20	22	42

Surgery was performed in a position on the side with moving of ipsilateral part of the lower extremity. Auxiliary table bearing lower extremity limb position eases the processing of acetabulum. The surgeon should be located near the ventral part of the patient. The incision is performed from the top of the ventral part of the big spit and about two centimeters dorsal to the front-upper iliac spine. The average length of the section is 8-10 cm. After dissection of the fascia lata finger splits the gap between m. tensor fascia lata and m. gluteus medius at the height of the tops of the big spit, then cut is performed in the cranial direction. Lower limb is abducted and held in a bent position. Capsule is formed by two installed extra-capsular elevators type Homan. Lower limb is installed in external rotation for better visualization of the joint capsule. Neck resection is performed in two places to avoid dislocation of the femoral head. The first cut is made near the acetabulum with maximal external rotation. Next neck osteotomy is made distal according to the preoperative planning. The lower limb is held in the position of external rotation, 90 degree flexed knee, parallel to the table surface. Additionally, lower limb is displayed by assistant in adduction and hyperextension. Elevators installed around the top of big spit and opposite to the front wall of the acetabulum give a good look on acetabulum. Restrictions of visualization of the big spit are resolved by resection of the dorso-lateral part of a joint capsule. With specially curved chisel (right or left) channel in the spongy of the proximal part of the big spit is formed considering antetorsion. For riemmeration of the femoral canal using rasps is preferable with right or left handle. An important factor in the formation of the femoral canal is to prevent varus installation of the riemer. Endoprosthesis implantation is performed according to the manufacturer's recommendations. Mobilization can be made in the day of surgery or in the first day after surgery. From the beginning full axle load is allowed.

Results

Analysis of the arthroplasty by Rottinger approach effectiveness compared to the traditional method included the intraoperative and postoperative criteria. Comparative characteristics are given in the postoperative period and after 2 months.

Table 2

Comparative characteristics of surgical approaches in acute intra- and postoperative periods

Criteria	Harding access	Rottinger approach
Operating comfort for the surgeon	At least 2 assistants are needed	1 assistant is enough
Blood loss	250-1000 ml	150-400 ml
Analgesics in the postoperative period	2 narcotic and 1 non-narcotic analgesics	1 non-narcotic analgesic

Table 3

Evaluation of postoperative period using two methods

	Harding access	Rottinger approach
Pain	+++	+-
Mobility	Partial	Full
Patient's verticalization on the next day	60%	85%
The axle load on the 2nd day after surgery	Rarely possible full load	Often possible full load
The need to use aids	More than two months after discharge	In rare cases
The number of stay-in-bed days	7-14	3-7
The risk of recurrent dislocation	5,1%	0,95%

*Aids: crutches, four-legged walker.

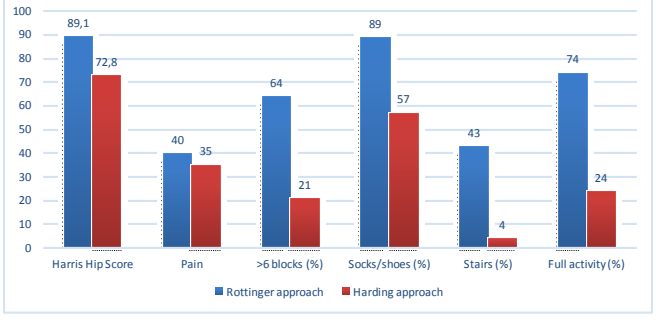

Fig. 1. Comparison of the measurement of Harris Hip Score in the early postoperative period (in points).

For evaluation of Harris Hip Score the following parameters were taken: the painful feelings when bearing load on the operated limb, the ability to walk different distances (unlimited, 30 minutes, 15 minutes, only indoors, impossible), the opportunity to wear socks or shoes, use stairs with no assistance, ability to perform daily activities and work, the need to use aids, limping, the ability to use public transport, sitting, operated joint mobility (in degrees). Grading for the Harris Hip Score: <70 – poor, 71-79 – fair, 80-89 – good, >90 – excellent. The overall result for the Harris Hip Score using Rottinger approach was 89.1 points, corresponding evaluation "good", the Harding method – 72.8 ("fair") (fig.1).

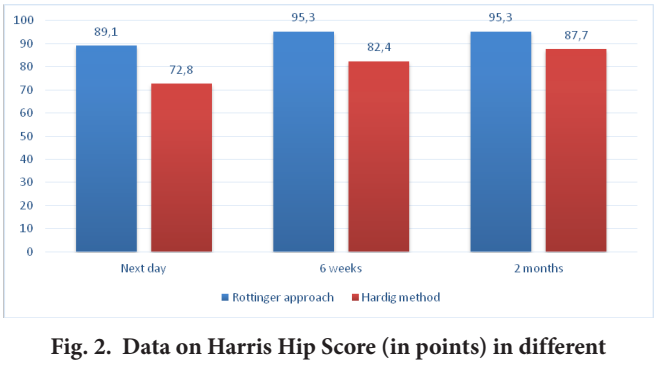

Fig. 2. Data on Harris Hip Score (in points) in different postoperative periods.

When comparing the investigated approaches dynamics on Harris Hip Score results is significantly different in the early postoperative period. 6 weeks after surgery score for Rottinger approach was 95.3 points («excellent»), Harding method – 82.4 points ("good"). Evaluation results of late postoperative period came close to the best results of using Rottinger approach (fig. 2).

Conclusions

1. Cosmetic effect by Rottinger approach length of incision is 8-10cm, without myotomy and violation of the fascia lata integrity, better visualization of the acetabulum, but worse is the proximal femur, the need for specialized tools.

2. This operating technique provides a shorter period of hospitalization, reduces the need for rehabilitation and support aids, reduces the risk of complications from prolonged immobilization, and reduces the risk of dislocation by 4.15%.

3. According to Harris hip score best results were observed after Rottinger approach in the early postoperative period (first 6 weeks), further functional outcome and pain drew to one level.

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Surveillance of quinolone generations in Emergency Medicine Institute

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Received October 17, 2016; accepted October 24, 2016

Abstract

Background: The main goal of the study was to evaluate the institutional representative data on quinolones antibacterial generations in accordance with WHO requirements, to determine the value of Defined Daily Doses per 1000 Occupied-Bed Days (DDD/1000) and cost in most important departments, comparing it with the same published data of international scientific journals.

Material and methods: For this study we used the data of a six-year (2009-2014) period in the Emergency Medicine Institute and their subdivisions with main consumption of antibiotics which shows the consumption dynamics of quinolone generations use in grams and value indexes.

Results: In the evaluated period, the medium yearly consumption of all quinolone generations recorded 63.03 DDD/1000 or a share of 11.14% from medium annual total of 566.02 DDD/1000 antibiotics. The same data in other international hospitals recorded 71.24 or 11.84% from total of 601.36 DDD/1000. In the end of the evaluated period, in IC departaments, the consumption of the first and the second generations registered 112.13 DDD/1000 and respectively the third and the fourth 6.02 DDD/1000 or a decrease by 2.27 and 13.85 times. In SSOT departments in the end of the evaluation the first and the second generations recorded 57.59 DDD/1000 or an increase by 40.25%. Medium annual cost per DDD/1000 for the first and the second generations of quinolone antibacterials in ICD recorded 4731.78 lei, the third and the fourth generations 6526.15 lei and respectively in SSOTD 365.78 lei and 149.20 lei.

Conclusions: In the end of the evaluated period in ICD of EMI quinolones of the first and the second generations represent 94.90% and the third and the fourth generations 5.10% from the total consumption. In SSOTD departments and in the entire EMI, the third and the fourth generations represent less than 1% of all consumption. This evaluation, as a part of multidisciplinary approach, serves as an important point for further survey of protocols and guides concerning the antibiotic consumption in one hospital.

Key words: quinolone antibacterials, generations, defined daily dose, consumption, rational use, hospitals.

Introduction

Since its discovery in the early 1960s, the quinolone antibacterial generations have considerably increased the clinical and scientific interest [1, 2]. A new four-generation classification of the quinolone drugs which have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favorable safety and tolerability profiles, takes into account the expanded antimicrobial spectrum and their clinical indications. With

the increasing number of available quinolone antibiotics, prescribing these drugs has become a challenge [3, 4, 5, 6, 7] and will likely gain more important indications in the future [8]. In some countries fluoroquinolones became the most commonly prescribed class of antibiotics to adults [9]. The adverse events in patients treated with quinolones are roughly similar to that observed in patients treated with other antibiotic classes [10, 11] and it is one more argument to be appreciated as first-line therapy [12]. Based on their antibacterial spectrum quinolones are divided into generations including many medical remedies [13]: first-generation (cinoxacin, flumequine, nalidixic acid, oxolinic acid, nemonoxacin, piromidic acid, pipemidic acid, rosoxacin), second-generation (ciprofloxacin, enoxacin, fleroxacin, omefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin), third-generation (balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin), fourth-generation (clinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin, prulifloxacin) [14, 15, 16, 17].

The main goal of the study was to evaluate the institutional representative data on quinolones antibacterial generations in accordance with World Health Organization (WHO) requirements to determine the value of Defined Daily Doses per 1000 Occupied-Bed Days (DDD/1000) and value cost in the dynamics per total institution and most important departments [18] compared with the same published data of international scientific journals.

Material and methods

The data of a six-year (2010-2014) period for this study were used. DDD/1000 consumption of quinolone antibacterial generations of Emergency Medicine Institute (EMI) shows the dynamics of consumption of antiinfectives for systemic use drugs indicated in grams and value indexes. Statistical, mathematical, analytical, logical, comparative and descriptive were used as the methods of study.

Results and discussion

For determining the number of DDD/1000, was used the data concerning the total annual consumption of quinolones generations and the statistics data concerning the number of treated patients (only patients with health insurance and other free treated by the state categories of citizens) in EMI, ICD (Reanimation, intensive Therapy and intensive Neurological "STROKE" departments) and SSOTD (Septic surgical and Septic orhtotraumotology departments) [19]. The evaluated period in the EMI is characterized by the use of parenteral (P) and enteral (E) forms of quinolones as following: first-generation: acidum pipemidicum DDD 0.8 E.P, second-generation: ofloxacinum DDD 0.4 E, ciprofloxacinum DDD 1.0 E. 0.5 P, third generation: gatifloxacinum DDD 0.4 E.P, fourth-generation: mofloxacin DDD 0.4 E.P. Total of the first and the second generations of quinolone antibacterial consumption in DDD/1000 during 2009-2014 is shown in figure 1.

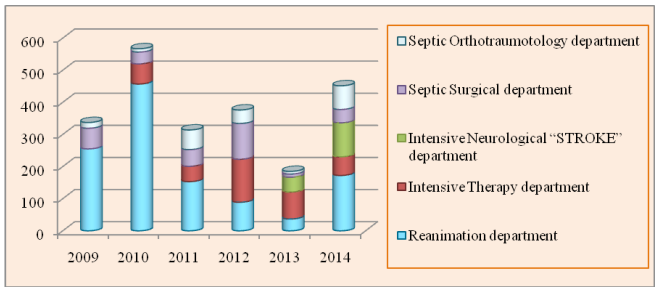

Fig. 1. Total of the first and the second generations of quinolone antibacterial consumption in DDD/1000 during 2009–2014.

As it could be mentioned from chart 1, in 2014 total departments consumption of the first and the second generations of quinolone antibacterials recorded 451.58 DDD/1000, which could be placed as following: first place – Reanimation department with 172.42 DDD/1000 or 38.18%, second – intensive Neurological "STROKE" department with 105.83 DDD/1000 or 23.44 %, third – septic Orhtotraumotology department with 73.62 DDD/1000 or 16.30%, fourth – intensive Therapy department with 58.15 DDD/1000 or 12.88% and septic Surgical department with 9.20 DDD/1000 or 9.20% on the fifth position. Since 2009 to 2014 a decrease in consumption by 32.43% recorded Reanimation department, by 35.43% septic surgical department and an increase by 4.14 times septic Orthotraumotology department. In figure 2, the consumption of parenteral forms of the first and the second generations of quinolone antibacterials in DDD/1000 during 2010-2014 is shown.

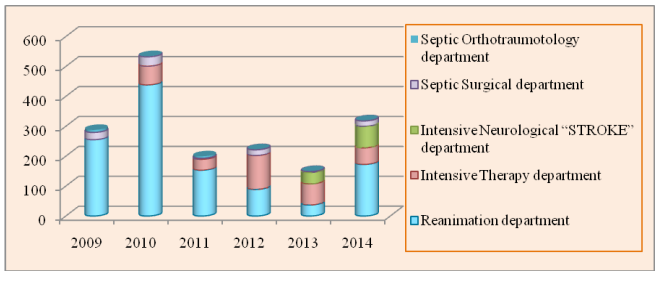

Fig. 2. Total of the first and the second generations of quinolone antibacterial consumption in DDD/1000 (parenteral forms).

In figure 2 parenteral forms of the first and the second generations quinolone antibacterial consumption are presented.

In 2014 parenteral forms represented 319.56 DDD/1000 or 70.76% from total consumption which could be placed as following: first place – Reanimation department with 172.42 DDD/1000 or 53.96%, second – intensive Neurological "STROKE" department with 72.08 DDD/1000 or 22.56%, third – intensive Therapy department with 55.49 DDD/1000 or 17.36%, septic Surgical department with

5.57 DDD/1000 or 5.57%, fourth – and septic Orhtotraumotology department with 1.78 DDD/1000 or 0.56% on the fifth position. Since 2009 to 2014 a decrease in consumption by 32.43% recorded Reanimation department, by 27.00% septic Surgical department and by 78.83% septic Orthotraumotology department. In figure 3, DDD/1000 of the first and the second generations of quinolone antibacterials (enteral forms) consumption during 2009-2014 is shown.

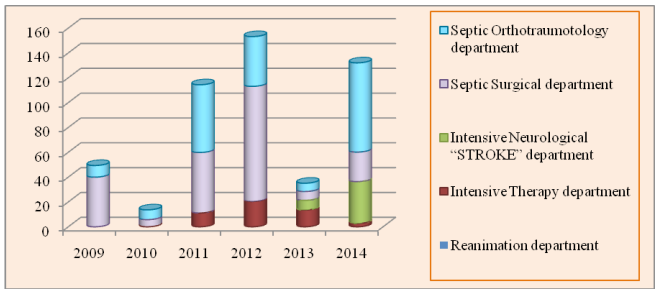

Fig. 3. Total of first and second generations of quinolone antibacterial consumption in DDD/1000 (enteral forms).

Figure 3 shows that in the evaluated period enteral forms of quinolone antibacterials recorded a considerable increment of consumption in all departments from 49.33 in 2009 to 132.02 DDD/1000 or by 2.68 times. In 2014 enteral forms represented 29.24% from total consumption, which could be placed as following: first place – septic Orhtotraumotology department with 71.84 DDD/1000 or 54.42%, second – intensive Neurological "STROKE" department with 33.75 DDD/1000 or 25.56%, third – septic Surgical department with 23.77 DDD/1000 or 18.00% and intensive Therapy department with 2.66 DDD/1000 or 2.01% on the fourth position. Since 2009 to 2014 septic Surgical department recorded a decrease in consumption by 40.56% and septic Orthotraumotology department registered an increase by 7.69 times.

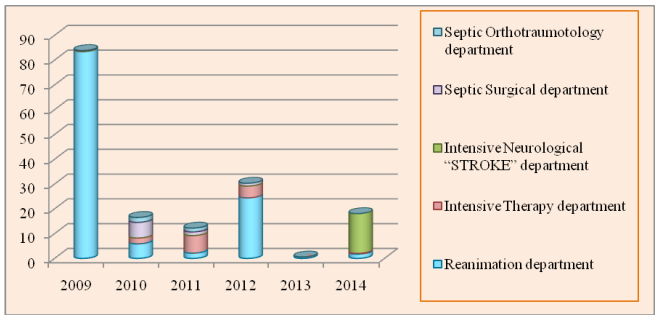

Fig. 4. Total of the third and the fourth generations of quinolone antibacterial consumption in DDD/1000 (parenteral forms).

The diagram from figure 4 proves a significant decrease of the third and the fourth generations of quinolone antibacterial consumption during the evaluated period from 83.86 to 18.07 DDD/1000 or by 78.45%. From all departments consumption in 2014, could be placed as following: first place – intensive Neurological "STROKE" department with 16.04 DDD/1000 or 88.77%, second – Reanimation department with 1.74 DDD/1000 or 9.63% and intensive Therapy department with 0.29 DDD/1000 or 1.60% on the third position.

Taking into consideration the situation that in the scientific journals published data about drugs consumption include the use of them in all intense care unites we determined medium consumption of DDD/1000 separately for ICD and SSOTD of EMI, for which was counted the total of DDD/1000 separately for ICD and SSOTD and divided by the number of these departments (3 and respectively 2). The results are shown in table 1.

Table1

The first, second, third and fourth generations of quinolone antibacterial consumption of DDD/1000 in ICD and SSOTD departments of EMI

The first and the second generations of quinolone antibacterials							
		2009	**2010**	**2011**	**2012**	**2013**	**2014**
ICD	Parenteral	255.17	250.52	94.87	101.22	48.56	100.00
	Enteral	0	9.37	5.56	10.2	7.11	12.14
	Total	255.17	259.89	100.43	111.42	55.67	112.13
SSOTD	Parenteral	16.39	16.75	4.92	10.28	2.15	9.79
	Enteral	24.67	6.82	51.63	66.39	6.88	47.81
	Total	41.06	23.57	56.55	76.67	9.02	57.59
EMI	Parenteral	41.7	25.6	62	14.3	6.4	14.3
	Enteral	49.2	22.6	39.1	38	33	31.9
	Total	86.9	46.46	87.94	50.5	39.13	45.97
The third and the fourth generations of quinolone antibacterials							
ICU	Total = Parenteral	83.43	4.12	4.62	14.6	0.19	6.02
SSOTD		0.22	4.15	1.50	0.57		
EMI		4.1	1.74	13.16	1.8	0.27	0.23

The data from table 1 shows that in the evaluated period consumption of the first and the second generations quinolone antibacterials in IC departments decreased by 56.06%, with P to E forms share from the yearly medium consumption in 2014 of 89.18% and 10.82% and vice versa in SSOTD increased by 40.28%, with P to E forms share of 17.00% and 83.00%, as well as the total EMI decreased by 49.2% and P to E forms share of 31.11% to 68.89%. Consumption in ICD comparatively to SSOTD departments in 2014 was (112.13:57.59) = 1.95 times more. Use of the third and the fourth generations of quinolone antibacterials registered only parenteral forms and represents from the total of 106.02 DDD/1000 quinolone antibacterials in 2014 in ICD a share of 5.68% and in SSOTD of 4.32%.

Calculated of all quinolone generations yearly medium consumption of 63.03 represents a share of 11.14% from 6 year medium annual total of 566.02 DDD/1000, [20]. The same data in large acute Australian public hospitals represents 49.54 or 5.29% from the medium total of

937.22 DDD/1000, [21, 22] and in all other international hospitals in different periods of time the yearly medium use was 71.24 or 11.84% from the medium total of 601.36 DDD/1000, [23, 24, 25, 26, 27, 28, 29, 30, 31, 32]. So, the yearly medium consumption of quinolone antibacterials in EMI is by 13.02% lower than presented data from other international hospitals and by 27.23% higher than recorded in large acute Australian public hospitals. The total value cost of four generations of quinolone antibacterial use per DDD/1000 in Reanimation department lei is presented in figure 5.

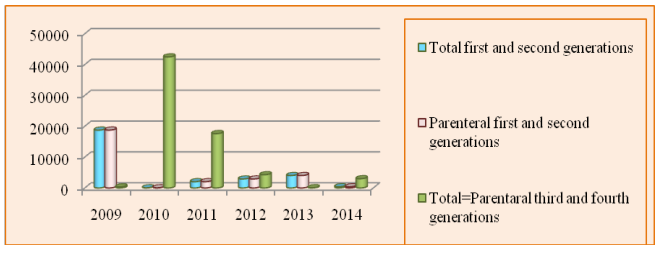

Fig. 5. Total value cost of quinolone antibacterial generations per DDD/1000 in lei in reanimation department.

From chart 5, it could be observed that the value cost per DDD/1000 in Reanimation department for the first and the second generations varied considerably during the evaluated period from 18746.33 lei in 2009 to 381.1 lei in 2014, as well as for the third and the fourth generations from 335.85 lei in 2009 to 42477.46 lei in 2010, to 17609.88 lei in 2011 and to 2985.5 lei in 2014.

Total value cost of quinolone antibacterials generations per DDD/1000 in lei in intensive Therapy department is shown in figure 6.

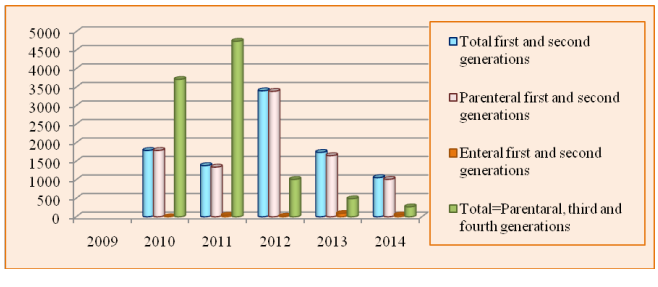

Fig. 6. Total value cost of quinolone antibacterial generations per DDD/1000 in lei in intensive therapy department.

As it could be observed from figure 6, the total cost of the first and the second generations of quinolone antibacterials in intensive Therapy department per DDD/1000 recorded a value of 1791,23 lei in 2010 and 1056.3 lei in 2014 from which the enteral forms of consumption represent a share from 0.41% to 4.48%. For the third and the fourth generations, the value cost per DDD/1000 in the same period decreased from 3710.08 lei to 267.38 lei. The total value cost of four generations of quinolone antibacterials use per DDD/1000 in intensive Neurological "STROKE" department in lei is presented in figure 7.

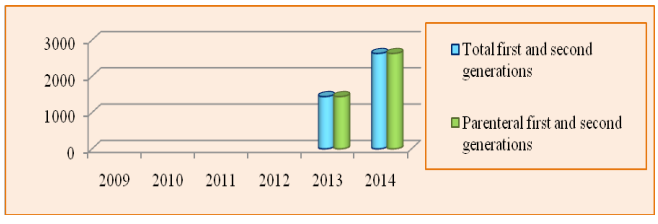

Fig. 7. Total value cost of quinolone antibacterial generations per DDD/1000 in lei in intensive neurological "STROKE" department.

From figure 7, it could be mentioned that the value cost per DDD/1000 of the first and the second quinolone antibacterials generations in intensive Neurological "STROKE" department varied from 1440.20 lei in 2013 to 2629.20 lei in 2014 or by 82.56%.

The total value cost of quinolone antibacterials generations use per DDD/1000 in septic Surgical department in lei is presented in figure 8.

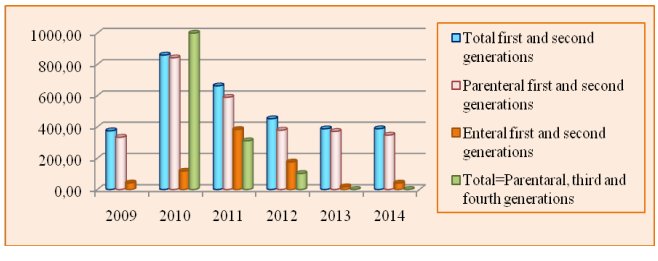

Fig. 8. Total value cost of quinolone antibacterial generations per DDD/1000 in lei in septic surgical department.

As it could be seen in figure 8 from the total value cost of the first and the second generations of quinolone antibacterials per DDD/1000 in 2014 share of enteral forms of use represents from the total cost 40,71 lei or 10.49%, with the higher records in 2011 of 383,47 lei or 57.90%. Value cost of the third and the fourth generations per DDD/1000 varied from 1018.5 to 999.49 lei.

The total value cost of four generations of quinolone antibacterials use per DDD/1000 in septic Orthotraumotology department in lei is presented in figure 9.

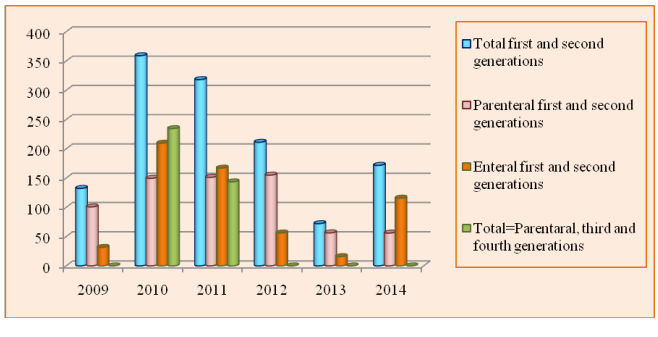

Fig. 9. Total value cost of four quinolone antibacterials per DDD/1000 in lei in septic orthotraumotology department.

Table 2

Medium cost of DDD/1000 in lei of quinolone antibacterial generations (parenteral and enteral forms) in EMI

Department	Structure of consumption	2009	2010	2011	2012	2013	2014
ICD	Parenteral first and second generations	18746.33	921.13	1678.183	3144.1	2370	1340.4
	Enteral first and second generations	0	0	41.75	13.95	89.49	45.28
	Total first and second generations	18746.33	921.13	1719.933	3158.1	2459.5	1385.7
	Total=Parentaral third and fourth generations	335.85	23093.77	11175.18	2646.2	279.47	1626.4
SSOTD	Parenteral first and second generations	217.19	495.68	370.45	266.95	213.57	201.68
	Enteral first and second generations	36.4	163.31	275.25	115.72	16.31	78.22
	Total first and second generations	253.6	609.24	490.3	331.74	229.87	279.9
	Total=Parentaral third and fourth generations	0	617.05	227.21	50.93	0	0

From chart 9, it could be mentioned that from the total value cost of the first and the second generations of quinolone antibacterials per DDD/1000 in 2014 share of enteral forms of use represents 40,71 lei or 10.49%, with the higher records in 2011 of 383,47 lei or 57.90%. Value cost of the third and the fourth quinolone antibacterial generations per DDD/1000 varied from 1018.5 to 999.49 lei.

To determine the medium cost of quinolone antibacterials in DDD/1000 separately for ICD and SSOTD was counted the total cost of DDD/1000 and divided by the number of these departments (3 and respectively 2) in the evaluated period.

As we can see from table 2, in the evaluated period total cost of DDD/1000 for the first and the second generations of quinolone antibacterials in ICD recorded a value from 18746.33 lei in 2009 to 1385.7 lei in 2014 from which enteral forms represent a share of 0.44% to 3.78% and respectively in SSOTD a value from 253.6 lei in 2009 to 279.9 lei in 2014 from which enteral forms represent a share of 7.10% to 56.14%. Total cost of DDD/1000 for the third and the fourth generations of quinolone antibacterials in ICD recorded a value from 335.85 lei in 2009 to 1626.4 lei in 2014.

Calculated medium annual cost per DDD/1000 for 6 evaluated years for the first and the second generations of quinolone antibacterials in ICD recorded 4731.78 lei, for the third and the fourth generations 6526.15 lei and respectively in SSOTD 365.78 lei and 149.20 lei or a share from ICD of 7.73% and 2.29%.

Conclusions

1. Annual consumption of all quinolone generations of 63.03 DDD/1000 in EMI represents a share of 88.47% from presented data of medium use 71.24 DDD/1000 recorded in others international hospitals and was by 27.23% higher than recorded 49.54 DDD/1000 in large acute Australian public hospitals.

2. Consumption of DDD/1000 in ICD departments of the first and the second generations quinolone antibacterials decreased by 56.06% during the evaluated period and in 2014 recorded 112.13 DDD/1000, with P to E forms share from of 89.18 and 10.82% and vice versa in SSOTD increased to 57.59 DDD/1000 or by 40.28%, with P to E forms share of 17.00 and 83.00%, as well as the total EMI decreased to 49.54 DDD/1000 or by 49.2% with a P to E forms share of 31.11 to 68.89%. Consumption in ICD comparatively to SSOTD departments in 2014 was by 1.95 times more. Use of the third and the fourth generations of quinolone antibacterials registered only parenteral forms and represents from the total 106.02 DDD/1000 quinolone antibacterials in 2014 in ICD a share of 5.68% and in SSOTD of 4.32%.

3. From the total departments consumption of 451.58 DDD/1000 in 2014 of the first and the second generations represents 94.90% and of all quinolone antibacterials in ICD could be placed as following: first place – Reanimation department with 172.42 DDD/1000 or 38.18%, second – intensive Neurological "STROKE" department with 105.83 DDD/1000 or 23.44 %, third – septic Orh-

totraumotology department with 73.62 DDD/1000 or 16.30%, fourth – intensive Therapy department with 58.15 DDD/1000 or 12.88% and septic Surgical department with 41.56 DDD/1000 or 9.20% on the fifth position. In SSOTD departments and in entire EMI the third and the fourth generations represent less than 1% of all consumption.

4. Medium annual cost per DDD/1000 recorded for the first and the second generations of quinolone antibacterials in ICD 4731.78 lei, for the third and the fourth generations 6526.15 lei, respectively in SSOTD 365.78 lei and 149.20 lei or a share from ICD of 7.73% and 2.29%.

5. Though this study has been limited to only EMI, the obtained data allows comparisons with a considerable number of international hospitals indicated by a big amount of differences in consumption, that can serve as a point for reviewing and optimisation of planning annual institutional necessities, as well as rationalisation the administration of quinolone antimicrobials on the one hand, and on the other hand can be as one of points for further survey of protocols and guide concerning the antibiotic consumption in one hospital.

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DISCUS COMPOSITUM

Abordarea bioregulatorie în patologiile coloanei vertebrale

-Heel
Healthcare designed by nature

Indicaţii terapeutice:

- Afecţiuni inflamatorii şi degenerative ale coloanei vertebrale.
- Osteocondroză vertebrală.
- Hernii și protruzii intervertebrale.
- Sindrom algic în regiunea vertebrală, ca urmare a unui proces displazic.

- Preparatul posedă acţiune metabolică complexă, regenerativă, analgezică, antiinflamatoare, spasmolitică şi sedativă.
- Îmbunătățește proprietățile elastice și hidrofile a discurilor intervertebrale.
- Acțiune trofică și de absorbție pe structura ligament-tendon a aparatului articular și pe țesutul conjunctiv al sacilor sinoviali.
- Inofensivitate maximă.
- Compatibil cu alte preparate medicamentoase.

REVIEW ARTICLES

Osteochondrosis: pathogenetic bioregulatory opportunities of using Discus compositum

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Abstract

Background: Osteochondrosis is a degenerative-dystrophic disc disease, characterized by a primary lesion of the intervertebral disc cartilage and reactive changes of the adjacent vertebral bodies. As a result of deterioration in metabolic processes in the intervertebral discs there occur in them degenerative-dystrophic processes, which lead to reduction in hydrophilicity and degradation of their dampening properties. There occurs the thinning of the fibrous ring, it cracks, and the displacement of the nucleus pulposus occurs, forming an outpouching- protrusion, and at rupture of the fibrous ring – the hernia. The affection of the intervertebral disc occurs due to its repeated injuries, metabolic disorders, endocrine changes, inadequate and protracted reactions of vascular, musculoskeletal and endocrine systems to stress. In osteochondrosis and accompanying pain syndromes, a wide range of drugs is applied: nonsteroidal anti-inflammatory drugs, analgesics, anesthetics, agents that enhance blood circulation, osteotropic agents, neuromuscular relaxants, etc. However, these groups of drugs have mainly temporary symptomatic effects and do not provide the necessary pathogenetic therapy.

Conclusions: Discus compositum is a base complex bioregulatory drug for the treatment of osteochondrosis and its complications. It acts on the main substrate of osteochondrosis, contributing to the improvement of the elastic properties of hydrophilicity of intervertebral discs. Discus compositum is well tolerated, including by children, and does not cause side effects characteristic for nonsteroidal anti-inflammatory drugs. It is used both as a monotherapy and in combination with other complex bioregulatory drugs and traditional medicines, thereby increasing the effectiveness of treatment, reducing its duration, avoiding surgery.

Key words: osteochondrosis, pathogenesis, bioregulation, Discus compositum.

Degenerative-dystrophic diseases of the spine and joints rank first in prevalence of diseases of the musculoskeletal system [1]. Among them, osteochondrosis is one of the most topical problems. Many clinical studies of domestic and foreign experts have shown that osteochondrosis is the disease of the whole body, and accordingly, the problem is interdisciplinary, relevant both for orthopedists and neurologists, and for family general practitioners [2]. The article provides a brief overview of the clinical studies that demonstrate the relevance of applying the bioregulatory approach and complex bioregulatory drugs, among which Discus compositum is a base complex bioregulatory drug for the treatment of vertebral osteochondrosis and its complications [3-5].

Osteochondrosis is a degenerative-dystrophic disc disease, characterized by a primary lesion of the intervertebral disc cartilage and reactive changes of the adjacent vertebral bodies. [6] As a result of deterioration in metabolic processes in the intervertebral discs there occur in them degenerative-dystrophic processes, which lead to reduction in hydrophilicity and degradation of their dampening properties. There occurs the thinning of the fibrous ring, it cracks, and the displacement of the nucleus pulposus occurs, forming an outpouching- protrusion, and at rupture of the fibrous ring – the hernia [6, 7]. The affection of the intervertebral disc occurs due to its repeated injuries, metabolic disorders, endocrine changes, inadequate and protracted reactions of vascular, musculoskeletal and endocrine systems to stress [6, 8].

In osteochondrosis and accompanying pain syndromes, a wide range of drugs is applied: nonsteroidal anti-inflammatory drugs, analgesics, anesthetics, agents that enhance blood circulation, osteotropic agents, neuromuscular relaxants, etc. [9]. However, these groups of drugs have mainly temporary symptomatic effects and do not provide the necessary pathogenetic therapy. Also, these drugs cause various side effects and upon long-term administration may be poorly tolerated. Similar disadvantages have the Cyclooxygenase-2 inhibitors in case of excess of their daily therapeutic dose. Also, the treatment is complicated by age restrictions and contraindications of drugs with comorbidity [9, 10]. Saturation of the body with chondroitin sulfates and glycosaminoglycans (building material) is not sufficient to restore the speed and efficiency of metabolic processes.

In this regard, the optimization of osteoarthritis therapy is topical by use of such approaches and drugs that have pathogenetic (structurally modifying) effect and can improve the efficiency and safety of the therapy, reduce the duration of drugs administration with undesirable side effects, and poorly tolerated.

One such approach, a decisive set of the above tasks is

bioregulatory. It is performed through the use of complex bioregulatory drugs [3-5]. Earlier in the literature of drugs there was used the term – antihomotoxic medications. Complex bioregulatory drugs contain ultra-low doses of the active ingredients that help to restore self-regulation and detoxification processes in the body. This in turn leads to the activation of regeneration / repair processes. An important property of complex bioregulatory drugs is the lack of pharmacokinetics, as ultra-low doses are not metabolized in the body. They do not require additional energy; do not have a pharmacological stress on the body [3-5].

Basic complex bioregulatory drug for pathogenetic therapy of osteoarthritis – Discus compositum (solution of 2.2 ml injections), contains 37 components in ultra-low doses, which act on the main substrate of osteoarthritis, contributing to the improvement of the elastic properties and hydrophilicity of intervertebral discs. The drug also has a trophic, metabolic, regenerative, analgesic, anti-inflammatory and resolving action on the ligament-tendon unit [7, 11].

The efficacy and the favorable safety profile of the complex bioregulatory drug Discus compositum is confirmed by numerous clinical studies [1, 2, 4-14].

Thus, the State University of Medicine and Pharmacy "N.Testemitanu" (Chisinau, Moldova) held a three-dimensional clinical randomized trial "Antihomotoxic therapy for lumbar pain in children and teenagers" (Savga N.G. et al, 2009). Within it there was investigated the clinical application of complex bioregulatory drug Discus compositum, Traumeel S (has an anti-inflammatory, analgesic, decongestant, immunomodulatory effect), Zeel T (has a chondroprotective, regenerative, anti-inflammatory, analgesic effect) in the complex of therapeutic measures in children with pain syndrome in the lumbar region, caused by dysplasia.

There were 524 patients under supervision aged 9-17 years with various dysplastic vertebral processes: dysplasia of intervertebral discs, arch laminae of vertebral body, fibrous rings (protrusion, disc herniation), tropism anomalies; lesion of the vertebral bodies; arthrosis of zygapophysial joints; scoliotic spinal deformation (congenital, dysplastic, post-traumatic, neurological, etc.); instability in the vertebral segments.

The intensity of pain syndrome in all patients was determined by a visual analog scale. The spinal function was investigated clinically. It was paid attention to posture, configuration of the spine, the presence and extent of its deformation, limit of the bends in one direction or another.

In order to assess the neurological status there was determined, above all, the severity of Lassegue symptom, as well as knee and Achilles reflexes.

Paraclinical examination was intended to determine the characteristics of the dysplastic process, manifested by pain syndrome. It included modern methods of instrumental examination: Computer tomography, 3D-computer tomography, MR-imaging, ultra-sound study of the spine, spinal thermography, laser Doppler – flowmetry and scintigraphy, histomorphological study.

An indicator of the effectiveness of the treatment was to assess the quality of life of patients. Patients were divided into two groups: I – the main group, which underwent an experimental treatment, offered by the authors of the study; II – the control group with conventional treatment. Both groups were relatively identical, with no significant differences in age, sex and the basic parameters of the disease.

The main group included 209 children who received as a course of therapy a treatment complex including antihomotoxic therapy (Discus compositum, Zeel T, Traumeel S etc., injected subcutaneously paravertebrally in the maximum pain sensitivity zone), manual and "Detenzor" – therapy.

The control group consisted of 315 children, who received traditional physio-functional treatment: modern kinetotherapy techniques, physiotherapy, physical therapy procedures, paravertebral blocks, stretching method, medication.

The results demonstrated that in the combined therapy with antihomotoxic drugs, the effect of treatment is significantly higher than that in the group of patients who underwent standard treatment. Significant improvements were confirmed by subjective indicators in patients of the main group (reduction in the intensity of pain syndrome, reduction of pain points at paravertebral palpation, disappearance of the feeling of squeezing in the spine and the tension of the back muscles, increase of range of motion in joints, sleep normalization, reduction of asthenic syndrome) have been observed immediately after the end of treatment and long-term periods.

It has been found that the use of complex antihomotoxic medications as basic medication provides a single organ-tissue therapeutic component, which is performed at the level of the bone, muscle and cartilage structures of the spinal column. Discus compositum, Zeel T, Traumeel S were included in the treatment complex of dysplastic process of the spinal column due to their pronounced well-known properties (anti-inflammatory, antiedemic, analgesic, chondroprotective and hondrostimulatory etc.). These drugs have a therapeutic effect on the entire spectrum of disorders (degenerative, trophic, immune, etc.), characteristic to the dysplastic process. Moreover, the above-mentioned antihomotoxic drugs practically do not cause allergic reactions, side effects and are well tolerated by children. Due to this, antihomotoxic drugs allow receiving a pronounced clinical effect and are comparable to traditional medical treatment [14].

For drugs an important characteristic is also the safety profile, especially for patients with concomitant diseases,

pregnant and breastfeeding women, children. In the clinical study "Therapeutic effect of homeo-siniatry in patients with combined pathology of the spine and of the digestive system" (Komlevf N.E. et. al, 2005) there was investigated the effectiveness of complex bioregulatory drugs both in relation to osteochondrosis and their impact on associated diseases of the digestive tract. The patients of the main group were injected with Discus compositum, Traumeel S and other complex bioregulatory drugs, and in the control group, patients received conventional treatment (nonsteroidal anti-inflammatory drugs, etc.). Results: in the main group there was a significant and stable positive dynamics, both of osteochondrosis, and of digestive system (confirmed by Gastroscopy). The patients of the control group did not reach the desired effect in the treatment of osteochondrosis and in gastro-intestinal tract was registered a slight deterioration [13].

In the clinical study "Herniated intervertebral disc of the lumbar spine and their biological therapy" (Rolik I.S. et al, 1999) there was investigated the therapeutic efficacy of complex bioregulatory drugs Discus compositum and Traumeel S (elimination of circulatory disorders in the disc, the stimulation of repair processes) at osteochondrosis of spine, complicated with intervertebral hernia and protrusions. The patients of the main group were treated with complex bioregulatory drugs, and of the control group – with traditional drugs. As a result of a year-long cycle of treatment, according to the instrumental examinations, a more pronounced regression of pathological changes of the spine was found in the main group. Conclusion – the use of complex bioregulatory drugs in the treatment of osteochondrosis complicated by herniated disc and protrusions is highly effective, the drugs have a high safety profile, and their use is economically feasible and advantageous in comparison with other methods of treatment, including the cost of treatment of side effects from the use of traditional medicines. It is noted that complex bioregulatory drugs therapy allows delaying or in many cases, avoiding surgery [7].

Ukrainian colleagues from the Lviv National Medical University "D. Galitsky" (Jackiewicz J.E. et al., 2005) have developed guidelines of Ministry of Health of Ukraine "Pathogenetically directed drug therapy of destructive-dystrophic diseases of the spine and joints". They describe the range of modern treatment methods and drugs used for diseases of the joints and spine, including osteochondrosis. Recommendations are made on the use of Discus compositum, Traumeel S, Zeel T, which make it possible to significantly improve the results of treatment, reduce the dosage of some allopathic remedies, and in some cases, cancel them [12].

An important pathogenetic mechanism of aggravation of vertebral osteochondrosis is aseptic inflammation of connective tissue formations in the area of degenerative-dystrophically changed spine area. Local inflammation process causes tissue swelling and additional compression of spinal roots, which clinically is manifested by long and persistent pain syndrome and a positive symptom of "cough impulse". Currently, the most informative indicator describing the presence and intensity of inflammation is the concentration of C-reactive protein of blood serum. Increase in osteochondrosis of level of C-reactive protein up to 3-7

Table 1

Recommendations for use of complex bioregulatory drugs in osteochondrosis

	Acute and subacute period	**Completion of the course of treatment (3-6 weeks or more)**
Basic complex bioregulatory drug in osteochondrosis		
Discus compositum	2.2 ml i/m, s/c, i/c every other day No 5	then 2 times/week No 5-10
For C-reactive protein **3-7 mg/L** to add in the scheme:		
+ Traumeel S	2.2 ml i/m, s/c, i/c every day No 3-5	then 1 tablet 3 times/day (until C-reactive protein is reduced below mg/L)
	ointment: easily embrocate / apply a bandage on the area of affected segment on the first day – 5-6 times, then 3 times / day	ointment: easily embrocate 2-3 times/day, including massage; or daily administer phonophoresis No 10
For **spondyloarthrosis** to add in the scheme:		
+ Zeel T	2 ml i/m, s/c, i/c every other day No 5	1 tablet sublingual 3 times/day
	ointment: apply on the skin on the area of affected joints up to 5 times/day	ointment: apply on the skin on the area of affected joints 2-3 times/day

An anti-relapsing treatment course in osteochondrosis is recommended twice a year.

mg/L indicates a local inflammation and serves a criterion to be included in the treatment regimen with the complex regulatory drug Traumeel S [17]. Intramuscularly or by biopunktury daily 3-5 days Traumeel S is administered in combination with Discus compositum. After that, a transition is made to Traumeel S in the form of tablets. Criterion for stopping taking the tablets Traumeel S is the reduction in C-reactive protein levels below 3 mg/L (table 1.) [17].

The studies have shown an increase of effectiveness of therapy of osteochondrosis with a combination of injected complex bioregulatory drugs Traumeel S and Zeel T with ointment and tablet forms of these drugs. At the beginning of treatment (acute phase / aggravation) for course of injection, it is recommended to use locally the ointment Traumeel S and Zeel T. With the purpose of prolonging and consolidating the effect of treatment, achieving a more long-term remission after a course of injections (on outpatient stage) it should not less than 3-6 weeks continue applying ointments Traumeel S and / or Zeel T in combination with the tablet forms of the complex bioregulatory drugs [12, 14]. Recommended dosages of complex bioregulatory drugs in combined use are listed in table 1.

Conclusions

Discus compositum is a base complex bioregulatory drug for the treatment of osteochondrosis and its complications. It acts on the main substrate of osteochondrosis, contributing to the improvement of the elastic properties of hydrophilicity of intervertebral discs. Discus compositum is well tolerated, including by children, and does not cause side effects characteristic for nonsteroidal anti-inflammatory drugs. It is used both as a monotherapy and in combination with other complex bioregulatory drugs and traditional medicines, thereby increasing the effectiveness of treatment, reducing its duration, avoiding surgery (!) [1,2,6-16].

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BOOK REVIEW

Monograph "The heterogeneity of histological types of breast cancer: sources, reasons and practical application"

The author – Veaceslav FULGA, MD, PhD, Associated professor

Nicolae Testemitsanu State University of Medicine and Pharmacy, the Republic of Moldova
Publishing company Impressum, Chisinau, 2016, 178 pages

Breast cancer is the most common cancer in women worldwide. It is described as a group of heterogeneous diseases, different in clinical course, pathological aspects and therapeutic sensibility.

In the present study the author debated in details the origin of breast cancer, by specifying cellular components of ductal and lobular segments of normal mammary gland. The author skillfully described the role of different intrinsic and extrinsic factors during mammary epithelium differentiation, and performed a parallel connection with pathology as well.

The author demonstrated in details that previous classification of breast cancer, the histological one, has not a practical application. Dr. Fulga simultaneously reviews new methods, much more refined, based on the interpretation of genes expression and hormone receptor status. The author related also to his own results concerning estrogen, progesterone, androgen, HER2, Ki67, p53, BCL2, E-cadherin, EGFR receptors expression in invasive lobular and ductal breast cancer of NOS type. All data were grouped in molecular subtypes, accepted in contemporary oncology and those which are scientifically still deliberated.

The main, dominating idea developed in this study, is that a single histological type of breast cancer in fact includes all molecular characteristics, described initially by Perou et al. (2000) as intrinsic subtypes. The author demonstrated that ductal carcinomas of different grade of differentiation are in fact particular pathologies, with distinct genetical, immunohistochemical features. The Luminal group was the most often determined type of cancer, characterized with a high rate of proliferation.

This study was devised in 8 chapters, 43 subchapters, provided with 11 tables, 35 schemes and pictures, with a long list of 375 references.

The monograph starts with **Introduction** where the author stated clearly the background and purpose of the study.

Chapter I. **Material and methods.** The author described types of breast cancer and methods included in the monograph.

Chapter II. **Mammary gland in norm – the organ with dynamic structure**. The author described the cellular components, mainly epithelial one, in accordance with the stage of development: prenatal and postnatal, highlighting the changes of structure during puberty, pregnancy and menopause.

Chapter III. **From theory to practice, from the norm to pathology.** Here the author described the expression of receptors for estrogen, progesteron, androgen, HER2, EGFR, Ki67, CK5, p53, BCL2 and E-cadherin during mammary epithelium differentiation.

Chapter IV. **Morphological and immunohistochemical heterogeneity of breast cancer.** In this chapter Dr. Fulga evaluated the importance of morphology and immunohistochemistry in prognosis and prediction.

Chapter V. **Molecular classification of breast cancer.** An extensive characteristic of molecular subtypes accepted in contemporary oncology and those which are still genetically, immunohistochemically debated.

Chapter VI. **The origin of breast cancer.** Here the author discussed about theories, hypothesis concerning cellular origin of breast cancer.

Chapter VII. **The epidemiology of resistance to chemotherapy.** The author described the possible mechanisms of resistance to hormonal, immune and chemo-therapy, plus highlighted the possible pathways of development of personalized treatment.

Chapter VIII. **Microambiance and carcinogenesis.** It's a short review of the role of cellular neighborhood in carcinogenesis.

The monograph finalizes with Conclusions and References.

Conclusion: "The heterogeneity of histological types of breast cancer: sources, reasons and practical application" is a nice, well-done and useful study which must be printed as a monograph, because practitioners of pathology, oncology and those who seek to understand the breast cancer development will find outstanding practical guidance and clinical findings in this book.

Eugen MELNIC, MD, PhD, Associate Professor
Head of the Morphopathology Department
Nicolae Testemitsanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

IN MEMORIAM

Illarion Postolachi
to the 80th anniversary since the birth

By Alexander Postolachi

Illarion Postolachi Department of Orthopedic Stomatology
Nicolae Testemitsanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

Fig. 1. Illarion Postolachi, MD, PhD, Professor, Honored man of science of the Republic of Moldova.

Postolachi Illarion Ivanovich, was born on October 20, 1936 in the village New Kureshnitsa, district Soroca in a peasant's family (father is Ivan Yakovlevich, 24.06.1911–24.11.1979, mother is Anna Aleksandrovna, 15.08.1911–16.06.1985) (fig. 1, 2).

The main dates of biography:

1944-1951 – the pupil of seven-year school in the village Sholkan, district Soroca.

1951 – high school №1, Soroca.

1954–1959 – continues study in the Kharkiv State Medical Stomatologic institute (Kharkiv, Ukraine) (fig. 3).

1959-1960 – the military dentist of the Pacific navy in Vladivostok. Then he is transferred to the 26th infirmary in the village De-Castri of Khabarovsk Krai.

1961 – the divisional dentist in Grozny.

1962-1963 – the clinical intern of department of the Orthopedic Dentistry of the Bogomolets National Medical University in Kiev.

1963-1969 – the assistant to department of the Orthopedic Dentistry of the Chisinau state medical institute.

1967 – defended the dissertation for a degree of the candidate of medical sciences, on the subject: "Clinical features and treatment of a deep occlusion at children (clinical and experimental investigation)". The research supervisor of the thesis – the Doctor of medical sciences, professor A. I. Betelman (the department of orthopedic odontology of the Kiev state medical institute of A. A. Bogomolets). Studying of histological microscopic sections of functionally loaded teeth showed that in tissues of periodont take

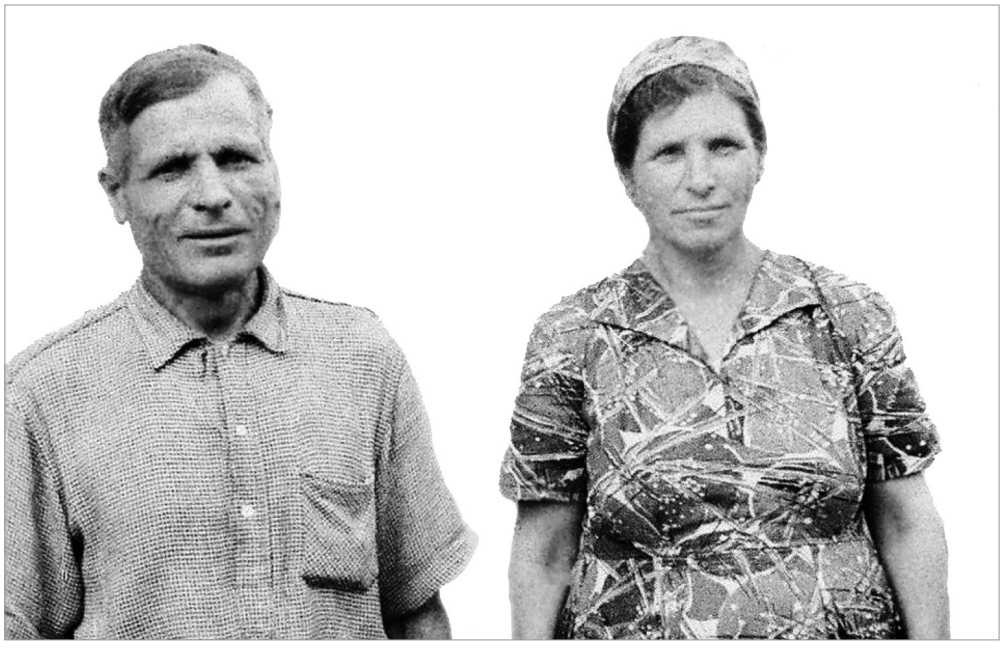


Fig. 2. Parents of Illarion Postolachi.

place deep morphological changes. In all cases was observed edema of tissues of a gingiva, narrow periodontal cleft in the direction to apexes of roots, squeezing of a periodontium and resorption of a bone tissue. It was established that tissue transformations of alveolar processes both in the field of functionally loaded, and in the unloaded teeth are the cornerstone of the mechanism of treatment of a deep occlusion.

1972 – the scientific status of the associate professor is given.

1969-2007 – the head of the department of the orthopedic odontology of the Chisinau State Medical Institute.

1971-1982 and 1992-2001 – the dean of Stomatologic faculty.

1979-1999 – the chief dentist of the Ministry of Health and the Chairman of Certifying commission of dentists of the Republic of Moldova.

1980-1988 – the head of the first epidemiological inspection of the population of the Moldavian SSR for the purpose of studying the structure of orthopedic dental diseases and establishing types of necessary medical care.

1983 – implemented in practice of dental health care of Moldova a method of the production of artificial porcelain crowns, which allow to increase the functional and esthetic value of prosthetic works for frontal teeth.

1983 – defended the doctoral dissertation on the subject: "Patterns of protective and compensatory reaction in tooth tissues and a possibility of its stimulation at orthopedic interventions. Experimental clinical trial" (Kiev, 06.01.1983). Subsequently, results of the long-term work formed the basis of the monograph "Artificial Tooth Crowns" (1985).

1986 – the academic status of professor is given.

1976-1990 – the coauthor in 10 scientific articles published in the central medical magazine of the USSR "Stomatology" (Moscow).

1976-2011 – the board member and the vice-chairman of scientific organization of dentists in the Republic of Moldova.

1979 – results of his own scientific research and achievements are noted in the encyclopedic reference book "Moldavian Soviet Socialist Republic" (page 376).

1984-1990 – the member of Editorial board of the journal "Medical Care of Moldova".

1985 – the monograph "Artificial Tooth Crowns" is published /under edition E. L. Kiriyak/. – Chisinau: "Știința", 1985. – 85 pages.

987 – takes advanced training courses for professors in orthopedic odontology at the Moscow medical stomatologic institute of N. A. Semashko.

1987-1990 – the board member of Association of stomatologists of USSR.

1988 – together with the candidate of medical sciences I. Sheptelich and the associate professor E. Kiriyak completed methodical references on "Selective Grinding of Teeth as a Method of Orthopedic Treatment". – Chisinau: "Știința", 1988. – 15 pages.

1988 – together with the group of authors (prof. M. G. Bushan /Kishinev/, prof. Z. S. Vasilenko /Kiev/, prof. L. S. Velichko /Minsk/, prof. G. Yu. Pakalns /Riga/, Dr. of medical sciences D. M. Karalnik /Moskva/, candidate of medical sciences I. Inzhiyants/Pyatigorsk/, I. Poyurovskaya /Moscow/) worked on the creation of the refer-

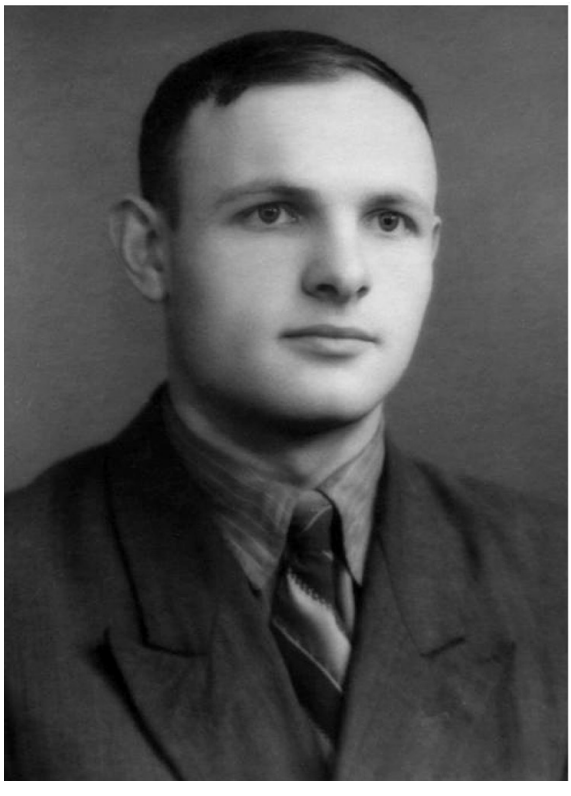


Fig. 3. A graduate of the faculty of dentistry.

ence book which included the questions connected with inspection of orthopedic patients, pre-prosthetic therapy and surgery, a maxillofacial prosthetic repair, the most often found mistakes and complications at different stages of manufacturing of dentures: "Reference book of a prosthodontist" – Chisinau: "Cartea Moldoveneasca", – 1988. – 428 pages.

1989 – published the education guidance "Orthodontic and orthopedic treatment of the anomalies of a bite caused by a congenital facial cleft" / F. Horoshilkina, G. N. Granchuk, I. I. Postolachi; under edition of P. D. Godorozha; – Chisinau: "Știința", 1989. – 144 pages.

1990 – one of the authors, together with associate professors S. Syrbu, I. Sheptelich, of the Moldova's first terminological dictionary on orthopedic and therapeutic stomatology for students and dentists "Dictionary of prosthethic and therapeutic stomatology terminology". – Chisinau: "Știința", publishing house, 1990. – 38 pages.

1991 – Together with the candidate of medical sciences, associate professor G. G. Birsa, completed methodical references on the subject "Improvement of clinical and technological processes in manufacturing of metal-ceramic tooth prostheses"– Chisinau: "Știința" publishing house, 1990. – 47 pages. It describes the basic clinical principles and technological processes of production of metal-ceramic tooth prostheses, and established the role of the certain factors influencing their quality.

1993 – Together with associate professors I. Sheptelich and G. Nikolau completed methodical references of "Aplication of implants in stomatology", 28 pages.

1995-2001 – the member of Consortium of deans of stomatologic faculties of Romania and the Balkan countries.

1982-1992 – the Chairman of the methodical Commission of stomatologic faculty.

1992 – For big merits in the field of medicine the title "Honored Man of Science of the Republic of Moldova" is awarded.

1993-2009 – the member of the Academic Council on presenting of theses.

1993 – the textbook for students is published: Postolachi I. and coauthors. "Prosthodontics". – 446 pages.

1994 – the textbook for students is published: Bârsa Gh., Postolachi I. "Techniques of dentures creation". – 399 pages.

1995 –the medal "Civil Merit" (for merits in favour of civil society) is awarded.

1999-2003 – participated in the organization and development of National congresses of dentists of the Republic of Moldova (X–1999; XI–2001; XII–2003).

2006 – is awarded medal "Nicolae Testemițanu".

2006 – is named "the Person of the Year", is awarded the medal "The World of Freedom" according to ABI of the USA.

2006-2011 – the member of Editorial board of the journal "Dental Medicine" in the Republic of Moldova.

On October 20, 2016, is the 80th anniversary since the birth of Illarion Ivanovich Postolachi, who bore the title "The Honored man of science of the Republic of Moldova". He was the doctor of medical sciences, professor, the founder of national school of orthopedic stomatology and the founder of its bioethical direction, for many years he was the head of the department of Orthopedic stomatology of the USMF "Nicolae Testemitanu" in Chisinau. Results of its long-term clinical and experimental studies formed the basis of the doctoral dissertation on "Patterns of protective and compensatory reactions in tooth tissues and a possibility of their stimulation at orthopedic interventions. Experimental and clinical probe" (Kiev, 06.01.1983, Ukraine) which allowed to make one of the major practical conclusions that simultaneous deep preparation of a large number of teeth is doubtful and unsafe because of creating a huge "wound surface" of solid tissues, that demands the corresponding protection. Having carried out careful generalization and the complex analysis of own research and the latest scientific facts, I. I. Postolachi has formulated a number of definite patterns, and chronology of development of pathophysiological reactions and morphological changes in hard tissues, has defined the main protective and preventive actions after teeth preparation. He has proved the necessity of the sparing method of

preparation both protective and preventive measures after orthopedic interventions on solid tissues of teeth, which included independently developed methods on the basis of available medical supplies in practical activities of dentists. For stimulation of protective and compensatory reaction in tissues of the prepared teeth, especially when teeth are completely deprived of enamel, alongside with the use of mechanical means of protection professor I. I. Postolachi recommends to use medicines that contain calcium, phosphorus, and also specially developed stimulating paste by his own recipe.

Thus, I. I. Postolachi on the basis of own research has developed a sequence of recommendations for orthopedic treatment of dental patients: 1) technique of the sparing preparation of teeth with continuous water irrigation; 2) protective and preventive measures that reduce inevitably arising pathological phenomena in tooth after preparation; 3) actions providing activation of reparative processes in hard tissues.

Later results of researches were published in the monograph "Artificial Tooth Crowns" (1985). Many highlighted issues are fundamental for theoretical and practical stomatology, and remain actual in science and practice of the present days.

Without any doubt, the fixed denture requires obligatory preparing of a layer of solid tissues of teeth. As professor I. I. Postolaki notes, such operative measure negatively influences, first of all, on tooth tissues and can become the reason of a series of the close and remote complications. Quite often preparing of teeth is performed without following the proper technique and appropriate air and water cooling, the fact that enlarges the risk of various complications.

Professor I. I. Postolachi underlined that, without having necessary data about the histomorphological changes and features of pathophysiological reactions in tooth tissues in response to a mechanical intervention, prosthodontists as a rule, dissect teeth, without keeping to the appropriate measures for activation of protective processes and prophylaxis of possible complications. Such approach to process of preparation of teeth under crowns is not justified from the biological point of view because preparing of tooth should be considered as a type of the surgical intervention, demanding the corresponding protective measures referred to creation of optimum conditions for implication of protective reactions. It is fair from those positions that at destruction of enamel-dentinal border dentinal canaliculi become open and pulp elements – protoplasmic processes of odontoblasts are damaged. Therefore, because of such manipulation the "wound" surface of a dentine and a wound surface of a pulp are formed. Considering specific structure and biological properties of solid tissues of teeth, by numerous observations it was established that in the next several days after preparing there are no accurate morphological changes. They become visible only in a pulp of teeth several hours after an operative measure thanks to features of its structure and functions. Proceeding from the above stated, one of fundamental conclusions, which has to become the rule for all prosthodontists, is the following: while preparing teeth under crowns, the doctor is obliged to take preventive measures for conservation of viability of tissues of teeth, and after its completion must undertake the appropriate protective measures.

The subsequent results of researches of Professor I. I. Postolachi showed that in the course of preparation of teeth it is necessary to consider existence of certain protective barriers in tissues of teeth to caries, wedge-shaped defects, pathological erasability and other diseases, and their absence at intact teeth, which preparation is inevitable when designing bridges. Besides, while making an obturation only a limited site of a surface of tooth serves as an operational field, while preparation under artificial crowns requires the whole crown as an operational field.

Fundamental scientific and practical regulations on protective and compensatory mechanisms in tooth tissues caused by deep preparation for artificial crowns Reaction of tooth tissues to deep preparation according to I. I. Postolachi (1982).

1 day later:

1. Growth of blood filling of pulp vessels;
2. Centers of large size hemorrhage in pulp (fig. 4);
3. More considerable vacuolization of odontoblast and other zones of pulp;
4. Growth of macrophages quantity – the phenomenon of protective character.

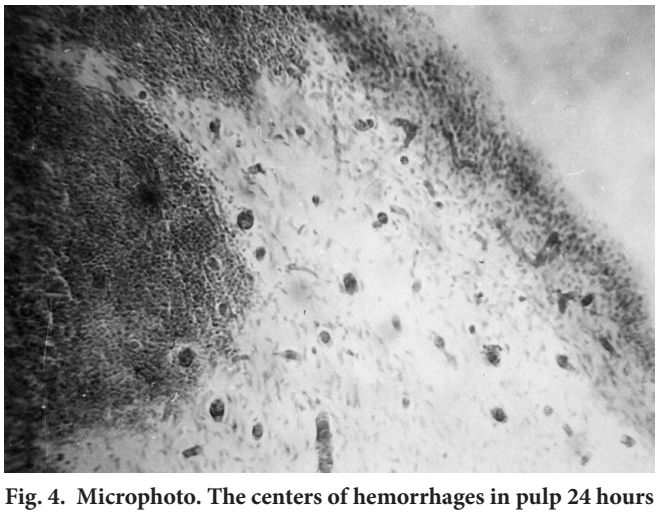


Fig. 4. Microphoto. The centers of hemorrhages in pulp 24 hours after preparation of tooth with a dentine exposure. Hematoxylin and eosin stain.

30 days later:

1. Blood filling of pulp vessels is less expressed, however, the phenomenon of a mesh atrophy is observed, the sign of dystrophic character leading to the death of odontoblasts;

2. Quantity and the size of a vacuole decrease;

3. Formation of tertiary dentine in a peripheral layer of pulp.

90 and 180 days later:

1. The beginning of normalization of vascular reaction, but dystrophic process (a mesh atrophy) progresses;

2. In a layer of odontoblast small vacuoles are noticed;

3. In the dentine is found disintegration of contents of the opened tubules. When air and microorganisms get into them, they form, so-called, "dead ways" which stretch in the form of dark strips towards the pulp chamber;

4. From the site of pulp chamber is seen the formation of a layer of secondary dentine which is poorly canalized, and the available dentine tubules are located chaotically (fig. 5, 7).

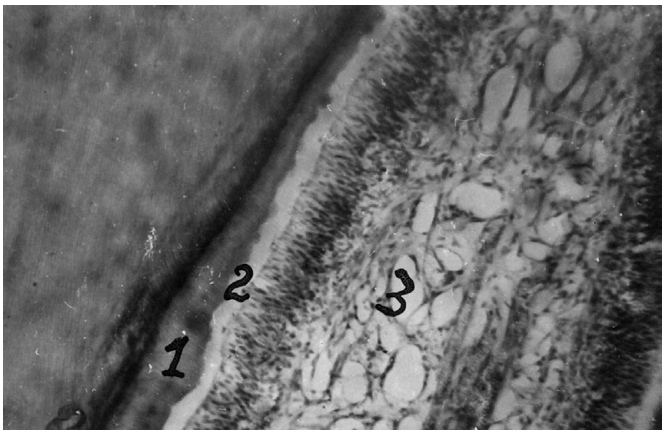


Fig. 5. Strips of secondary dentine (1), predentin (2) and pulp (3)180 days after preparation of tooth with a dentine exposure. Microphoto. Hematoxylin and eosin stain.

Features of reparative regeneration of dentine according to I. I. Postolachi (1982)

1. After preparation of teeth with an exposure of dentine its morphological reorganization leads finally to formation of the protective capsule around this site. It blocks penetration of disintegrated content of the opened tubules deep into blood vessels of pulp and, therefore, in the whole organism.

2. It is established that preparation of teeth with destruction of enamel-dentine border violates formation of a zone of sclerotized dentine ("dead ways"). It is noted that in certain cases, even ten years after covering of teeth with a crown, there are no signs of mineralization of the main substance of dentine and formation on its surface of a sclerotized layer.

3. It is proved that the peripheral strip of sclerotized dentine (60–80 microns) is formed within the first three years. Speed and width of its formation are in direct dependence on depth of preparation of enamel and age of patients. Further, its size increases much more slowly (fig. 6).

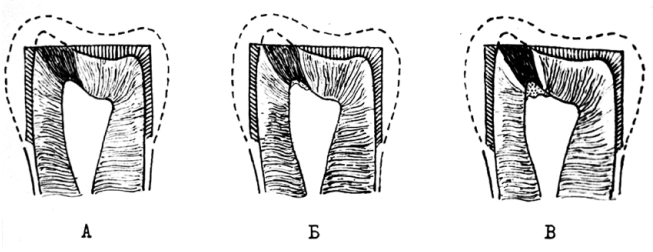
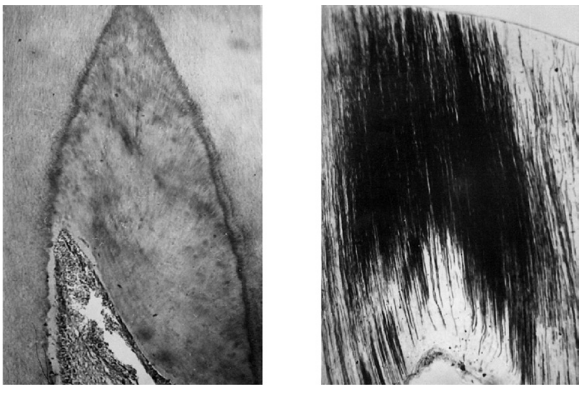


Fig. 6. The scheme of dynamics of encapsulation of the pathological process which has resulted from opening of dentinal tubules: A – right after preparation; B, C – 3 and more years later.

An attentive study of the main conclusions of the dissertation work and the monograph of I. I. Postolachi reveals their potential for practical activities of dentists that could bring considerable benefit to many patients with defects of solid tissues of vital teeth as well as for those with partial edentations.



a b

Fig. 7. Protective and compensatory reactions in dentine after preparation: a) Formation of a layer of secondary dentine according to the site of naked dentine 180 days after preparation of a tooth. Microphoto. Hematoxylin and eosin stain; b) The protective capsule around the opened dentine tubules 9 years after covering a tooth with an artificial crown.

It is necessary to emphasize that established facts, regularities and practical recommendations for dentists developed by Professor I. I. Postolachi get special value in the context of the latest developments, both in orthopedic and therapeutic stomatology. Thus, results of extensive scientific research and the reasoned practical recommendations of Professor I. I. Postolachi support the main tendency in modern stomatology of the 21st century and all world medicine directed to minimum invasive instrumental intervention in tissues of a human body.

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3. The abstract should be written on the title page in English and be limited trom 220 to 240 words. The abstract should end with 3 to 6 key words.

4. The text of clinical or experimental articles (has to be less than 16 pages long) should consist of an Introduction, Material and Methods, Results, Discussion, Conclusions and be followed by no more than 40 References. The **review articles** must not exceed 25 pages and contain no more than 100 references.

5. The tables and figures must be typed, consecutively numbered and followed by an explanatory text. The figures that have to emphasize a comparison or details are published in colour. If coloured figures are to be placed, the author must pay an additional fee of €100 per page (1-8 figures on a page).

6. The references are to be listed in order of their appearance in the text, and the appropriate numbers are to be inserted in the text [in square brackets] in proper places. The references must comply with the general format outlined in the Uniform Requirements for the Manuscripts Submitted to Biomedical Journals developed by the International Committee of Medical Journal Editors (www.icmje.org), chapter IV.A.9. The references in the Cyrillic script should be transliterated into Latin script as follows: А–A, Б–B, В–V, Г–G, Д–D, Е–E, Ё–E, Ж–ZH, З–Z, И–I, Й–Y, К–K, Л–L, М–M, Н–N, О–O, П–P, Р–R, С–S, Т–T, У–U, Ф–F, Х–KH, Ц–TS, Ч–CH, Ш–SH, Щ–SCH, Ы–Y, Э–E, Ю–YU, Я–YA, Ь and Ъ are omitted. Immediately after the transliteration the translation of the title in English [in the square brackets] should follow. For example: Ivanov IV, Sidorov VM, Kozlov NF. Transplantatsiya organov i tkaney [Transplantation of organs and tissues]. Vestnik Khirurgii [Messenger of Surgery]. 2010; 26(6):45-49.

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1. Articolele se imprimă în formatul A4, Times New Roman 12, în Microsoft Word la intervalul 1,5, cu câmpurile de 2 cm.

2. Foaia de titlu conține prenumele și numele autorilor, titlul și gradul științific, instituția, numărul de telefon și adresa electronică a autorului corespondent.

3. Rezumatul în limba engleză (220-240 cuvinte) se expune consecutiv pe foaia de titlu, inclusiv cuvintecheie, de la 3 până la 6. În rezumat este obligat să fie expus scopul cercetării (dacă nu este clar din titlu), metodologia studiului, rezultatele obținute și concluziile.

4. Textul articolelor clinice, experimentale (până la 15 pagini) cuprinde: Introducere; Material și metode; Rezultate obținute; Discuții; Concluzii și Bibliografie până la 40 de referințe. Altă structură se acceptă, dacă aceasta corespunde conținutului materialului. **Articolele de sinteză** nu vor depăși 25 de pagini și bibliografia până la 100 de surse.

5. Tabelele și figurile trebuie să fie enumerate și însoțite de legendă. Figurile care necesită contrastare sau evidențierea detaliilor sunt executate color. Figurile color se publică din sursele autorului – 100 €, 1-8 figuri pe pagină.

6. Referințele, în conformitate cu cerințele Comitetului Internațional al Editorilor Revistelor Biomedicale (www.icmje.org, capitolul IV.A.9), se expun în ordinea apariției în text. În lista referințelor titlul articolului, se traduce în limba engleză, poziționându-se în paranteze pătrate. Referințele bibliografice prezentate în grafie chirilică sunt transliterate în grafie latină, utilizând următoarele semne grafice: А–A, Б–B, В–V, Г–G, Д–D, Е–E, Ё–E, Ж–ZH, З–Z, И–I, Й–Y, К–K, Л–L, М–M, Н–N, О–O, П–P, Р–R, С–S, Т–T, У–U, Ф–F, Х–KH, Ц–TS, Ч–CH, Ш–SH, Щ–SCH, Ы–Y, Э–E, Ю–YU, Я–YA; Ь și Ъ se omit. Imediat după transliterare, în paranteze pătrate, se prezintă traducerea titlului articolului în limba engleză. De exemplu: Ivanov IV, Sidorov VM, Kozlov NF. Transplantatsiya organov i tkaney [Transplantation of organs and tissues]. Vestnik Khirurgii [Messenger of Surgery]. 2010; 26(6):45-49.

ГИД ДЛЯ АВТОРОВ

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