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Original article

COMPLICATIONS ASSOCIATED WITH ACUTE PULMONARY EMBOLISM – DATA FROM THE REGISTRY OF PATIENTS WITH VENOUS THROMBEMBOLISM

КОМПЛИКАЦИИ АСОЦИРАНИ СО АКУТНА ПУЛМОНАЛНА ЕМБОЛИЈА – ИСКУСТВА ОД РЕГИСТЕРОТ НА ПАЦИНТИ СО ВЕНСКИ ТРОМБЕМБОЛИЗАМ

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Abstract

Correct estimation of the severity, mortality, and complication risk are crucial for effective treatment of pulmonary embolism (PE). A total of 162 patients hospitalized with acute PE, treated either with standard treatment with heparin and vitamin K antagonists (VKA) or heparins, followed by direct oral anticoagulants (DOAC) were followed for a 90-days period. Demography, clinical and radiologic presentation, smoking status and concomitant comorbidities were analyzed. The mortality risk was estimated by calculating PESI and sPESI score. The results showed uneven utilization of both treatment modalities (93.8% treated with VKA *versus* 6.17% with DOAC). Smoking as an independent factor was detected in 55.56% of patients, and is greater than the overall smoking prevalence in Macedonia. Central propagation of PE was found in 57.79% of cases and together with the presence of pleural effusion was associated with a greater risk for complications. Estimation of 30-day mortality risk with PESI and sPESI showed their high predictive value, with an advantage of sPESI, in terms of better accuracy and simplicity of performance. Correct estimation of risk for complications and mortality is important for improving the overall safety of patients with PE and has a positive „cost-benefit" effect for organization of the treatment.

Keywords: pulmonary embolism, mortality, complications

Апстракт

Правилната процена на тежиата и ризикот од компликации и смртен исход се клучни за ефикасен третман на пулмоналната емболија (ПЕ).

Во тек на 90 дена се следени 162 болни, хоспитализирани поради акутна ПЕ, третирани со стандардна терапија со хепарини и антагонисти на витамин К (ВКА) или со хепарини и консекутивна долгорочна терапија со директни орални антикоагулантни лекови (ДОАК). Анализирани се демографските карактеритики, пушачкиот статус, стратифицирана е клиничката и радиолошката презентација и присуството на коморбидитети. Ризикот од морталитет е проценет со помош на ПЕСИ и сПЕСИ скор. Резултатите покажаа нееднаква примена на двата модалитети на терапија (93.82% третирани со ВКА и 6.17% со ДОАК). Пушењето како независен ризик фактор е детектирано кај 55.56% од болните, што претставува поголема застапеност од општата популација во Македонија. Централна локација на ПЕ е најдена кај 57.79% од испитаниците и заедно со присуството на плеврален излив е поврзана со поголем ризик за компликации. Проценатa на 30-дневниот ризик за морталитет со ПЕСИ и сПЕСИ скоровите ја потврди новната висока предиктивна вредност, со предност на сПЕСИ скорот во смисол на поголема точност и едоставност за примена. Точната процена на ризикот од компликации и смртност ја подобрува безбедноста на болните и има поволен „cost-benefit " ефект при организација на лекувањето.

Клучни зборови: пулмонална емболија, морталитет, компликации

Introduction

Pulmonary embolism (PE) is one of the modes of presentation of venous thromboembolism (VTE) and is a frequent cause of morbidity and mortality in the population. The incidence of PE is approximately 60 to 70 per 100,000; its management remains a serious health problem [1]. PE represents the third most common cause of cardiovascular death, after myocardial infarction and cerebrovascular insults [2], and is a leading preven-

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table cause of death among hospitalized patients [3]. The presenting signs and symptoms of PE are non-specific and with variable intensity, ranging from complete asymptomatic to extensive alteration of the general condition of the patient, acute circulatory and respiratory insufficiency and shock. This often leads to misinterpretation and incorrect initial estimation of the seriousness of the situation, resulting in delayed diagnosis and inadequate treatment. As for illustration, in a study of Beckman *et al*. diagnosis was confirmed in only one third of the patients with clinical suspicion for PE, and in about 25% of the autopsies PE was detected as an incidental finding. The implication of this diagnostic problem is that if all patients with clinical suspicion of PE are treated, more than two thirds of the patients would receive unnecessary anticoagulation. On the other hand, without adequate and timely treatment, the acute mortality rate of PE would be 15%, and additional 26-33% would experience recurrent, potentially fatal episodes of PE [4].

For didactical reasons and more efficient analysis, the treatment of VTE and PE is often presented as treatment of the acute phase, usually encompassing the first 5-10 days of treatment after initial diagnosis, followed by a period of long-term maintenance therapy, which, depending on the provoking factors and the circumstances of the incident, could last 3, 6, or more than 12 months after the acute embolic incident [5,6]. The exact duration of the long-term treatment is estimated individually, for each patient, according to the contemporary guidelines. There are still numerous dilemmas concerning the period of long-term treatment, and it is still subject to debates, despite the issues of the most contemporary recommendations [7,8].

In the past decade, the protocols for treatment of acute PE have undergone substantial changes, as a result of the emerging studies which analyze the rate of recurrence and complications associated with the standard treatment, and especially after the introduction and approval of the direct oral anticoagulant medications (DOAC) [9-12]. DOACs are known as "target-specific" (TSOAC) or "novel" oral anticoagulants (NOAC). This group encompasses rivaroxaban (registered for the treatment of VTE since 2012), apixaban, edoxaban and dabigatran [13]. All aforementioned DOACs are at least „non-inferior" to warfarin, but their advantage is in the standard dosing and there is no need of routine monitoring of the blood level and their efficiency. The treatment with DOACs can often be commenced since the very moment of initial diagnosis of VTE, unlike the oral vitamin K antagonists (VKA) which need to be "bridged" with heparin preparations. Still, the dilemmas concerning the utilization of the DOACs arise from the concern that specific antidotes are not readily available, as well as the referrals for "non-responders" to initial treatment with DOACs [14]. An additional problem with the usage of DOACs in Macedonia is the fact that they are not covered by the public health insurance, which makes the experience with their application for acute and long-term treatment of PE and deep venous thrombosis (DVT) scarce.

International as well as local studies are necessary to clear the aforementioned dilemmas concerning the efficiency, safety and adequate choice of the available treatment regimens for PE. We need exact definition and selection of patients, their characteristics and clinical presentation of the VTE, in which heparins, VKAs or DOACs would be preferred.

Estimation of the risk for early mortality is an additional problem of the decision and choice of adequate treatment. A series of scoring systems are proposed for this purpose [15]. PESI (Pulmonary Embolism Severity Index) and sPESI (Simplified Pulmonary Embolism Severity Index) scores are the most frequently used, especially the sPESI, which is proposed in the most recent guidelines, because of its simplicity, accessibility of the required parameters, short application time and the confirmed accuracy of the obtained results [16,17].

Aim of the study

The primary aim of this study was to estimate the characteristics of the patients, hospitalized at the Clinic of Pulmology and Allergy in Skopje, because of acute PE, with or without DVT, analyzing the presentation of PE (clinical and radiologic), estimation of the severity, as well as the relative risk for early mortality. The secondary outcome was to estimate the bleeding risk associated with the applied treatment.

Material and methods

Material

All patients aged over 18 years hospitalized at the Clinic of Pulmology and Allergy in Skopje in the period from October 2011 until December 2017, with diagnosed PE, with or without DVT, were included in the study. Patients were registered in the Registry for thromboembolic incidents - RIETE, Center Number 04, active at the Clinic since October 2011. All patients had signed the dedicated Informed Consent form, allowing inclusion of their disease data into the Registry. Patients were included in RIETE prospectively, consecutively, depending on the date of their hospitalization at the Clinic of Pulmology and Allergy. Patients were treated according to the recommendations of the contemporary international and local guidelines, with heparins + VKA (non-fractionated heparin, or low molecular weight heparin – LMWH simultaneously with vitamin K antagonist), titrating the dose until INR 2-3, continuing the VKA as a long-term therapy, or heparins in the first days after diagnosis, followed by DOACs as a long-term treatment.

Inclusion criteria
Patients aged 18 or more, with diagnosed PE, with or without DVT. Valid diagnosis was considered if PE was confirmed with objective imaging tests, such as computerized contrast tomography of the lungs by the standard protocol for pulmonary angiography – CT angiography.

Exclusion criteria
Patients with severe or fatal comorbid conditions which represent independent cause for imminent lethal outcome or bleeding (patients with terminal stage of malignant disease, acute myocardial infarction, acute cerebrovascular incident - CVI, impairment of the coagulation associated with bleeding, not related to anticoagulant therapy), severe psychiatric patients, pregnant women and patients who did not give, or had withdrawn their consent to the study.

Followed variables - demographic characteristics, smoking status, presence of comorbidities, chest CT characteristics, routine blood analyses, PESI and sPESI scores, blood gas analyses, length of hospitalization, INR (for patients on VKAs), mortality and incidence of bleeding registered in the period of 90 days after initial diagnosis of PE.

Method of work
General methodologic approach

This is an observational, retrospective epidemiological study with prospective approach. We analyzed parameters from the medical history of the patients, data from the outpatients follow-up, whereas the researcher did not influence the decisions for treatment of the ordinating pulmonologist. An especially dedicated instrument - questionnaire for data collection was designed according to the needs of the RIETE Registry and the study. Data were collected combining the interview with the patient, medical history, routine controls and telephone contact after hospitalization.

Clinical method
The following parameters were analyzed
Demographic characteristics at the moment of initial diagnosis – gender, age, height and weight. Smoking status was defined as “smoker”, “non-smoker”, “ex-smoker”, and “unknown smoking status”.
Imaging methods - results and radiologic presentation from the chest CT angiography obtained at initial diagnosis were analyzed and grouped as follows:
- Massive (multiple) PE, central (PE in *truncus pulmonalis*), PE in main pulmonary arteries, lobar, segmental, and subsegmental;
- Unilateral or bilateral;
- With or without pleural effusion;
- With or without pulmonary infarction.

Clinical presentation
- Initial symptoms (hemoptysis, chest pain, dyspnea, syncope, body temperature, pain/swelling of extremities);
- Clinical parameters (heart and respiratory frequency, arterial pressure, blood saturation and partial pressure of oxygen and carbon dioxide);
- PESI and sPESI scores with estimation of a 30-day mortality risk - low, intermediate and high risk;
- Presence of comorbid conditions.

Incidence of bleeding, graduated as minimal (self-limiting, which did not require change of treatment), moderate (followed by temporary change of treatment and solved without consequences), and severe (requiring cessation of anticoagulation treatment, transfusion of blood elements and/or surgical intervention, or resulting in severe health consequences or death). Time of incidence of bleeding since initializing the treatment was calculated.

Biochemical, laboratory analyses
Values of INR at the moment of bleeding incidents

Survival during the follow-up period of 90 days. The incidence of all-cause mortality was analyzed as early death, occurring in the first 7 days, death during the acute treatment (in the period of 8-30 days) and death within 31 to 90 days from the PE incident.

Statistical method

Basic statistical analysis, demographic statistics, calculation of frequencies and relative risk determination were calculated using Microsoft Excel.

Results

A total of 162 patients were included in this study. 152 (93.82) of them were initially treated with heparins + VKA (treating dose of LMWH or non-fractionated heparin in 24 hours continuous infusion and acenocoumarol, titrating the dose to INR ranging 2-3), according to the actual guidelines of the European Society of Cardiology (ESC). Ten patients (6.17%) were treated with DOACs after the initial acute phase treatment.
Demographic characteristics: 84(51.85%) of all patients in the study were male, and 78 (48.15%) were female. The average age of patients was 52.3 (ranging from 18 to 87 years). The dominating age was 31-70 years, with a tendency towards younger age in the group treated with DOACs. The distribution of patients by age is presented in Table 1.

Table 1. Distribution of patients by age groups

Age rage	Heparin+VKAs	Heparin + DOACs	Total
18-30	11(7.2%)	0(0%)	11(6.7%)
31-50	43(28.2%)	4(40%)	47(29.01%
51-60	40(26.3%)	4(40%)	44(27.1%)
61-70	34(22.5%)	1(10%)	35(21.6%)
>71	24(15.7%)	1(10%)	25(15.4%)
Total	152	10	162

The average weight of patients was 81.04 +/- 29.04 kg. Our results showed that according to the smoking status, only 71 patients (43.82%) were non-smokers, 74 (45.68%) were active smokers and 16 (9.88%) were ex-smokers. There was an evident domination of current and ex-smokers compared to the non-smokers, with a total of 55.56%. The distribution by smoking status is presented in Table 2.

Table 2. Distribution of patients by smoking status

Smoking status	Heparin+VKAs	Heparin + DOACs	Total
Non-smokers	66(43.42%)	5(50.00%)	71(43.82%)
Current smokers	69(45.39%)	5(50.0%)	74(45.68%)
Ex-smokers	16(10.52%)	0(0.00%)	16(9.88%)
Unknown	1(0.66%)	0(0.00%)	1(0.62%)
Total	152	10	162

The analysis of the radiologic presentation of the chest CT showed that massive PE was found in 5 (3.08%) patients, central PE in 7(4.32%) patients, main pulmonary arteries were targeted in 42 (25.92%), lobar arteries in 34 (20.98%), segmental in 44 (28.9%) and subsegmental PE was detected in 30 (19.7%) patients. Ninety-two (60.52%) of the total of 162 patients had unilateral PE and 70 (46.05%) had bilateral presentation. In 80 (52.63%) patients pleural effusion was detected on CT or ultrasound, and infarction was documented in 65 (42.76%) from the analyzed cases. Interestingly, 90% of patients treated with DOACs did not have a pleural effusion and 50% did not present with parenchymal infarctions.

The most frequent symptoms were chest pain and dyspnea, 142(87.65%) and 156(96.29%), respectively; 48 patients had hemoptysis (29.62%), and the least frequent findings were syncope in 12(7.41%) and significant hypotension (arterial pressure below 90 mmHg) in (2.47%) cases. The results from the blood gas analyses showed that a significant oxygen hypo-saturation (<90%) was detected in 20 (12.34%) patients, hypo-saturation in the range from 91 to 95.9% in 84(51.85%), and normal saturation was found in 51(31.48%) patients. Hypocapnia was registered in 32(19.75%) cases.

Concomitant DVT was found in 29 (17.90%) patients. Only one of the patients had DVT of an upper extremity.

Presence of comorbidities was found in 111 (68.52%) patients, and coexistence of multiple diseases was present in 46(28.39%). We found domination of cardiologic entities, present in 40 patients (24.69%), malignant diseases in 24(14.81%), and respiratory pathology in 20(12.3%). The lowest frequencies were registered for past CVI 6(3.70%), psychiatric conditions 10(61.72%), chronic renal and hepatic insufficiency 9(5.56%), and diabetes 8(4.93%).

Bleeding associated to the applied treatment was found in 9 (5.92%) patients treated with heparins + VKAs and 2 patients treated with heparins + DOACs. The total count of bleeding incidents was 11 (6.79%). The intensity of bleeding was minor in 5 patients on VKAs and 2 on DOACs, moderate in 3 patients treated with VKAs and severe bleeding was registered in only one patient on VKAs. In 4 of the patients treated with VKAs, the values of INR were higher than 3 at the moment of the incident. INR was not tested in patients treated with DOACs.

The total number of patients with lethal outcome was 16 (9.87%), all from the group of patients treated with VKA. Death in the first 7 days occurred in 2 patients, aged from 61 to 70 years. In the period from 8-30 days, we lost 6 patients (3 aged 31-50, 2 from 61-70 and 1 older than 71 year), and up to 90 days death occurred in 8 patients (one 27-year-old patient, 3 from the age group 51-60, 2 from 61-70 years and 2 older than 71 year). Concerning the combined incidence of comorbidities among the patients with lethal outcome, 6 of them had joint incidence of malignant disease, 3 had previous CVI, and 2 had coexistent renal, liver or respiratory failure.

The estimation of severity of the PE and relative risk for early death with PESI and sPESI showed divergence in the obtained results. The results from PESI score are presented I and II - low risk, and III, IV and V as high risk for 30-days mortality. For sPESI, score of 1.1% means low risk and 8.9% high risk for early mortality and severity of complications. The results from PESI and sPESI are presented in Table 3. In 4 patients, the scores were not calculated because of the lack of information about the oxygen saturation.

Table 3. Distribution of PESI and sPESI in the analyzed subjects

PESI score				sPESI score			
Score	**Heparin + VKA (152)**	**Heparin + DOAC (10)**	**Total (162)**	**Score**	**Heparin + VKA (152)**	**Heparin + DOAC (10)**	**Total (162)**
I	60(39.47%)	6(60.00%)	66(40.7%)	Low 1.1	78(51.31%)	8(80.00%)	86(53.08%)
II	41(26.97%)	1(10.00%)	42(25.92%)	High 8.9	69(45.39%)	1(10.00%)	70(43.21%)
III	29(19.07%)	2(20.00%)	31(19.13%)				
IV	14(9.21%)	0	14(8.64%)				
V	3(1.97%)	0	3(1.85%)				

Grouping of the results from the PESI score as low and high risk showed that 108 (66.67%) patients had scored I and II, while 48 (29.62%) had III, IV and V, representing a high risk. This was not analogue to the estimation obtained with sPESI, where 86 patients (53.08%) had low and 70 (43.21%) patients had a high risk for 30-days mortality. The analysis and correlation of both scores with the lethal incidents showed that lethal outcome was predicted in 15 (93.75%) with sPESI and in 12 patients (75.00%) using the PESI score. sPESI did not predict the lethal outcome in only one patient. A more detailed analysis showed that from 4 patients with PESI I and II, 3 had sPESI 8.9%, pointing to a high risk, but death did not occur within the first 30 days. One of the four patients with PESI III score died within 30 days from established diagnosis of PE.

Table 4. Distribution of PESI and sPESI scores in the 16 patients with lethal outcome

PESI score		sPESI score	
Score I and II	4(25.00%)	Low 1.1%	1(6.25%)
Score III	4(25.00%)	High 8.9%	15(93,75%)
Score IV and V	8(50.00%)		

Discussion

In spite of the vast research and published guidelines, there are still many unresolved moments in the decision process for acute and long-term treatment of PE. Individualized approach, the choice of adequate treatment, estimation of the necessity of hospitalization or possibility of home treatment, incidence of associated complications of the treatment or the disease itself, and the risk of lethal outcome are still current topics for discussion [5-7,18].

Perceiving the non-inferiority of the DOACs, referred in the recent studies, the recent ESC and ERS guidelines for the diagnosis and management of acute pulmonary embolism issued in 2019, give priority to the DOACs in the treatment of PE with low and moderate risk from early death and complications. DOACs are listed as treatment of choice for long-term treatment and prevention of recurrent PE, but also in the acute phase, when treatment with oral anticoagulants is indicated (evidence level A) [8,19,20]. Low molecular weight heparins remain the first line treatment in patients with PE with a more severe clinical presentation [21]. In our study, 152(93.82%) patients were treated with heparins + VKE (non-fractionated heparin, or low molecular weight heparin - LMWH simultaneously with vitamin K antagonist), titrating the dose until INR 2-3, continuing the VKE as a long-term therapy, whilst 10 (6.17%) received direct oral anticoagulants after initial LMWH in the acute phase. The analyzed material was obtained from the data of the patients Registered in the RIETE registry, center 04, included in the period from October 2011 until December 2017, when DOACs were just recently registered for medical use in Macedonia. Hence, they were not easily available and there was general "fear from their prescription and possible complications (bleeding)" because of the lack of availability of antidotes and specific test for their efficiency and therapeutic range. The great difference in the frequency between the groups of patients with both treatment modalities makes comparative analysis and extrapolation of relevant results difficult. The authors are looking forward to analysis of the more recent material from the Registry, when the prescriptiton of DOACs has become more frequent.

Smoking as an independent risk factor for PE is associated with increase of the absolute risk of PE in 24.3 (95% CI 15.4-26.7) from 100 cases [22]. Still, a direct association of smoking with thrombus formation has still not been confirmed [23]. In our material, 45.68% of patients were current smokers and additional 9.88% were ex-smokers, which was a larger percentage than the referred average incidence of smokers in Macedonia, which was estimated to 36.1% (46.6% male and 26.8% female smokers). This fact might confirm the association of PE with the smoking status. The gender distribution (62.27% males and 32.23% females), follows the global gender distribution of smoking in Macedonia [24].

According to the radiological presentation, in 57.79% of the analyzed subjects with PE, involvement of the central and great (main and lobar) pulmonary arteries was detected, and in 42.21% peripheral distribution of the emboli was found. Similarly, Martinez *et al.* [25] described central presentation of PE in 48.11% of their

analyzed subjects, associated with a significantly higher risk of lethal outcome, with an odds ratio (OR) of 1.81. According to Kiris, the presence of pleural effusion was associated with increased 30-days, as well as long term mortality risk, in patients with PE [26,27]. Pleural effusion was present in 80(52.63%) patients in our study, 79 of which treated with VKAs. From the patients treated with DOACs, 90% did not have pleural effusion, and in 50% parenchymal infarction was not detected. As previously stated, drawing comparative conclusions is not possible because of the uneven distribution, but a tendency can be anticipated.

It is commonly accepted that the incidence of VTE and PE as well as their prognosis are a result of the interaction between the patient-associated risk factors, which are often persistent, and environmental risk factors, which are ussualy transient. Extensive trauma, sugical interventions, fractures of the lower extremities, and spinal trauma are strong risk factors for PE. Coexsistence of neoplasia not only represents a significant risk factor, but also an independent predisposing factor for acute episodes of VTE [28]. In this study, coexsistence with malignat diseases was found in 24(14.81%) cases, six of which had lethal outcome during the observation period.

Cohen *et al*. presented that in 2004, from the total population of 6 European countries, more than 370,000 deaths were due to VTE. 34% of those cases had abrupt death, within several hours from the onset of symptoms, without even a chance to start an adequate treatment. From the other patients, PE as a cause of death was found post mortem in 59%, and only in 7% PE was diagnosed on time [29]. According to Bělohlávek, the total mortality rate in the case of first acute incident of PE was 11.4% in the first 2 weeks, and it increased to 17.4% in the long-term follow-up of patients [1]. These percentages increased from 18 to 65%, depending on the extensivenes of the incident, rangng from 20% in treated PE, 25-30% in PE with cardiogenic shock, and 5-25% in submassive PE.

In our study, mortality was analyzed in three periods, as early, all-cause mortality within the first 7 days after the thrombotic incident, death from 8 to 30 days since establishing of diagnosis of PE, and death from 31 to 90 days from the actuel incident. The total number of patients with lethal outcome was 16 or 9.87% from the total analyzed subjects, all of them treated with heparins + VKAs. Death in the first 7 days occurred in 2 subjects, from 61 to 70 years old. In the period from 8-30 days, death was registerd in 6 patients (3 aged 31-50, 2 from 61-70 and 1 older than 71 year). In the period from 31 to 90 days, death occurred in 8 patients (one 27-year-old patient, 3 from the age group 51-60, 2 from 61-70 years and 2 older than 71 year). Concerning the combined incidence of comorbidities among the patients with lethal outcome, 6 of them had joint incidence of malignant diseases, 3 had previous CVI, and 2 had coexistent renal, liver or respiratory failure. Our results are comparable with the some cited in the literature [30]. Apart from the clinical, radiologic and laboratory parameters, when calculating the mortality risk it is necessary to include parameters for the presence of possible aggravating factors and comorbiditties. The combibnation of these parameters is included into the predictiuve calculators, such as PESI and sPESI, which are most commonly utilized, although more advanced methods have been metioned in the recent literature [31]. The greatest value of the PESI scores is their accuracy in detection of the low-risk patients, which would be candidates for outpatient treatment [32]. The analysis of the results obtained with PESI and simplified PESI scores in our material showed a certain divergence concerning the capacity for correct estimation of the severity and moratlity risk. Grouping the results from the PESI scores to low and high risk showed that sPESI had a better predictive capacity to estimate the early, 30-days and late mortality than the traditional PESI score. Utilizing the sPESI score, lethal outcome was predicted in 15(93.75%) cases, and failed to predict only one death incident. On the contrary, PESI mannaged to predict lethal outcome in 12(75.00%) patients; 3 of the 4 patients with PESI I or II had sPESI score pointing to high risk, but in none of them death did not occur in the first 30 days. One of the four patients with PESI score III died within 3 days of initial diagosis of PE. The limitation of this study is in the small absolute number of patients with lethal outcome, which makes detailed statistical analysis inacurrate.

The contemporary tendencies for management of PE and the increasing experience with the utilisation of DOACs open a new possibility of patients' selection for home treatment of PE. Dentali *et al.* treated 53% of their patients with DVT and 17% of their patients with PE as outpatients, and the hospitalization for PE was shorter than 5 days [33]. The rigorous selection of patients with PE suited for this mode of treatment, determining the follow-up strategy and planning their surveilance as part of the challenges confronting the contemporary medicine.

Conclusion

This study has pointed out the importance and necessity of detailed assessment of patients with acute pulmonary embolism in order to obtain efficient, contemporary and, most of all, individualized approach to their management. The exact estimation of the risk of complications and mortality improves the safety of patients and has a favorable „cost-benefit" in the organization of the treatment.

Conflict of interest statement. None declared.

References

1. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Exp Clin Cardiol* 2013; 18: 129-138.
2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012; 379: 1835-1846.
3. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol* 2008; 28: 370-372.
4. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med* 2010; 38(4 Suppl): S495-S501.
5. Streiff MB, Agnelli G, Connors JM, *et al*. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis* 2016; 41: 32-67.
6. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *JAMA* 2014; 311(7): 717-728.
7. Konstantinides SV, Torbicki A, Agnelli G, *et al*. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35(43): 3033-3069.
8. Konstantinides SV, Meyer G, Becattini C, *et al*. ESC Scientific Document Group, 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *European Heart Journal* 2020; 41(4): 543-603.
9. Levine GN. Cardiology Secrets. *Fifth Edition, Elsevier* 2018; 522-533.
10. Lobo JL, Jiménez D, Teresa Orue M, *et al*. Recurrent venous thromboembolism during coumarin therapy. Data from the computerised registry of patients with venous thromboembolism. *British Journal of Haematology* 2007; 138: 400-403.
11. Borjas Howard J, Ruiz-Sada P, de Leeuw K, *et al*. Risk of recurrent venous thromboembolism in patients with autoimmune diseases: data from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry. *British Journal of Haematology* 2021; 194(1): 195-199.
12. Tafur A, Bikdeli B, Weinberg I, *et al*. Real-Time Dissemination of Aggregate Data on Presentation and Outcomes of Patients With Venous Thromboembolism: The RIETE Infographics Project. *Clinical and Applied Thrombosis/Hemostasis*. January 2020.
13. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism TA 287 Guidance NICE". www.nice.org.uk. Published 26 June 2013, Retrieved 1 October 2021.
14. Houghton D, Key NS, Direct Oral Anticoagulants, International Encyclopedia of Public Health (Second Edition), 2017; 330-336.
15. Marshall PS, Mathews KS, Siegel MD, *et al*. Diagnosis and management of life-threatening pulmonary embolism. *J Intensive Care Med* 2011; 26(5): 275-294.
16. Donze J, Le Gal G, Fine MJ, *et al*. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost* 2008; 100: 943-948.
17. Elias A, Mallett S, Daoud-Elias M, *et al*. Prognostic models in acute pulmonary embolism: a systematic review and meta-analysis. *BMJ Open* 2016; 6: e010324.
18. Torbicki A, Perrier A, Konstantinides S, *et al*. Authors/Task Force Members. Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008; 29(18): 2276-2315.
19. van Es N, Coppens M, Schulman S, *et al*. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014; 124: 1968-1975.
20. van der Hulle T, Kooiman J, den Exter PL, *et al*. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost* 2014; 12: 320-328.
21. Steffel J, Verhamme P, Potpara TS, *et al*. ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018; 39: 1330-1393.
22. Yun-Jiu C, Zhi-Hao L, Feng-Juan Y, *et al*. Current and Former Smoking and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis. *PLoS Med* 2013; 10(9): e1001515.
23. Enga KF, Braekkan SK, Hansen-Krone IJ, *et al*. Cigarette smoking and the risk of venous thromboembolism: the Tromsø Study. *J Thromb Haemost* 2012; 10(10): 2068-2074.
24. "FYR Macedonia. "The Tobacco Atlas. Available at: http://www.tobaccoatlas.org/country-data/fyr-macedonia/. Accessed November 2021.
25. Alonso Martinez JL, Anniccherico Sánchez FJ, Urbieta Echezarreta MA, *et al*. Central Versus Peripheral Pulmonary Embolism: Analysis of the Impact on the Physiological Parameters and Long-term Survival. *North American journal of medical sciences* 2016; 8(3): 134-142.
26. Kiris T, Yazıcı S, Koc A, *et al*. Prognostic impact of pleural effusion in acute pulmonary embolism. *Acta Radiol* 2017; 58(7): 816-824.
27. Yıldızeli SO, Kasapoğlu US, Arıkan H, *et al*. Pleural effusion as an indicator of short term mortality in acute pulmonary embolism. *Tuberk Toraks* 2018; 66(3): 185-196.
28. Gussoni G, Frasson S, La Regina M, *et al*. RIETE Investigators.Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. *Thromb Res* 2013; 131: 24-30.
29. Cohen AT, Agnelli G, Anderson FA, *et al*. VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; 98: 756-764.
30. Martin KA, Molsberry R, Cuttica MJ, *et al*. Time Trends in Pulmonary Embolism Mortality Rates in the United States, 1999 to 2018. *J Am Heart Assoc* 2020; 9:e016784.
31. Barnes GD, Muzikansky A, Cameron S, *et al*. Comparison of 4 Acute Pulmonary Embolism Mortality Risk Scores in Patients Evaluated by Pulmonary Embolism Response Teams. *JAMA Netw Open* 2020; 3(8): e2010779.
32. Aujesky D, Roy PM, Verschuren F, *et al*. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, openlabel, randomised, noninferiority trial. *Lancet* 2011; 378: 41-48.
33. Dentali F, Di Micco G, Giorgi Pierfranceschi M, *et al*. Rate and duration of hospitalization for deep vein thrombosis and pulmonary embolism in real-world clinical practice *Ann Med* 2015; 47(7): 546-554.

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ММР

Original article

DEMOGRAPHIC DATA, PATIENT CHARACTERISTICS, AND ETIOLOGY OF LIVER CIRRHOSIS

ДЕМОГРАФСКИ ПОДАТОЦИ, КАРАКТОРИСТИКИ НА ПАЦИЕНТИТЕ И ЕТИОЛОГИЈА НА ЦРНОДРОБНАТА ЦИРОЗА

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Abstract

Introduction. Despite all significant therapeutic advances in recent years, liver cirrhosis is still related to significant healthcare burden worldwile. The aim of the study was to review the demographic data, patient characteristics and the prevalence of different etiological entities in cirrhotic patients.
Methods. In 71 patients with liver cirrhosis, we evaluated the demographic data, clinical features and etiology of liver disease and we analyzed the data in relation to the presence of acute decompensation (AD).
Results. AD was diagnosed in 39 (54.93%) patients, with no statistically significant percentage difference among both groups (p=0.2417). The analysis showed a significant male predominance (p=0.0001) and significantly older age in female patients (p=0.0211). Regarding AD, the analysis neither confirmed a significant association between AD and gender (p=0.6567), nor a significant age difference between patients in both groups (p=0.9817). Alcoholic liver disease was the most prevalent etiology, without significant association between the etiology and the presence of AD (p=0.1241). The analysis confirmed significantly more decompensated than compensated patients according to the Baveno classification (p=0.0001) and most patients, 44(61.97%), were classified in Baveno class 3.
Conclusion. Despite demographic data, etiology and stage of disease, it seems that the presence of AD has also a significant impact on the course of the disease and the prognosis in cirrhotic patients.

Keywords: liver cirrhosis, demografic data, etiology, acute decompensation

Апстракт

Вовед. И покрј сите значајни тераписки достигнувања во изминатите години, црнодробната цироза сеуште претставува значително оптоварување на здравствениот систем на светско ниво. Цел на студијата беше да се направи преглед на демографските податоци, карактеристиките на пациентите и на застапеноста на различни етиолошки причинители кај пациентите со црнодробна цироза.
Методи. Кај 71 пациент со црнодробна цироза ги евалуиравме демографските податоци, клиничките карактеристики, и етиолошките причинители по што податоците ги анализиравме во однос на присуството на акутна декомпензација (АД).
Резултати. АД беше дијагностицирана кај 39(54.93%) пациенти, без присуство на статистички сигнификантна разлика во процентуалната застапеност помеѓу двете групи (p=0.2417). Анализата утврди сигнификанта предоминација на машкиот пол (p=0.0001) и сигнификантно повисока возраст кај пациентите од женски пол (p=0.0211). Во врска со АД, анализата ниту потврди сигнификантна асоцираност помеѓу АД и полот (p=0.6567), ниту сигнификантна возрасна разлика помеѓу пациентите во двете групи (p=0.9817). Алкохолната црнодробна болест беше најзастапниот етиолошки причинител, но без присуство на сигнификантна асоцираност помеѓу етиологијата и присуството на АД (p=0.1241). Анализата потврди сигнификантно повеќе декомензирани отколку компензирани пациенти според Baveno класификацијата (p=0.0001), а најголем дел од пациентите 44 (61.97%), беа класифицирани во Baveno класа 3.
Заклучок. Освен демографските карактеристики, етиологијата и стадиумот на болеста, се чини дека и присуството на АД има значајно влијание врз текот на болеста и прогнозата кај пациентите со црнодробна цироза.

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Клучни зборови: црнодробна цироза, демографски податоци, етиологија, акутна декомпензација

Introduction

Despite all the significant therapeutic advances and achievements in recent years, chronic liver disease is still related to a significant healthcare burden. According to some data, liver cirrhosis is present in approximately 0.1% of the European population. More than 170,000 cirrhosis-related deaths are reported in Europe each year, making it the fifth most common cause of death in Europe [1,2], with one-year mortality varying significantly between 1% and 57% [3]. A large population study involving 4,010 patients with liver cirrhosis found an incidence of 33/100,000 inhabitants per year (95% CI 28-40) and five-year mortality of 62% (95% CI 59-65) [4]. Acute decompensation (AD) is a heterogeneous entity characterized by the development of one or more complications of chronic liver disease and it is associated with increased mortality in cirrhotic patients [5-7]. The aim of the study was to review the demographic data, patient characteristics and the prevalence of different etiological entities in patients with liver cirrhosis.

Material and methods

In this cross-sectional study, we enrolled 71 patients with liver cirrhosis. The diagnosis was made according to the specific clinical, morphological, and laboratory data. According to the presence of AD, patients were divided into two groups. During enrolment, we Registered demographic data and some of the relevant features of chronic liver disease. In order to define the etiology of liver disease we obtained data regarding daily alcohol intake; we performed serology for heaptitis B and hepatitis C; we measured several autoimmune markers (anti-nuclear antibodies, anti-mitochondrial antibodies, anti-soluble-liver-antigen antibodies, liver-kidney microsomal antibodies) and we performed additional analyses when needed. In all patients, we performed clinical examinations, abdominal ultrasound, complete blood count, biochemical analysis of blood sample, prothrombin time (PT), international normalized ratio (INR), and gas analysis from capillary blood. Afterwards, we calculated the scoring systems that are currently used in cirrhotic patients (CTP, MELD, SOFA, and SAPS II score) and according to the Baveno classification we classified patients into 4 classes.

In this study we analyzed the demographic data of patients and some relevant features of chronic liver disease and portal hypertension mainly in relation to the presence of AD. The analysis of the qualitative series was performed by determining the coefficient of relations, proportions, and rates, and they were presented as absolute and relative numbers. The quantitative series were analyzed by using the measures of central tendency (average, median, minimum values, maximum values, and interactive ranks) and dispersion measures (standard deviation, standard error). Pearson Chi-square test and Fisher Freeman Halton exact test were used in order to determine the association between certain attributive dichotomous features. Difference test was used to compare the proportions. T-test was used to determine the significance of the difference between the means of two samples. A significance level of $p < 0.05$ was used to determine the statistical significance. All patients signed an informed consent for participation in the study. The study protocol was in line with the ethical principles of the Helsinki Declaration and it was approved by the Ethics Committee of the Faculty of Medicine at Ss. Cyril and Methodius University in Skopje.

Results

According to the presence of AD, patients were divided in two groups. AD was diagnosed in 39 (54.93%) patients, with no statistically significant percentage difference among the groups {Difference test: 9.86% [(-6.43-25.45) CI 95%]; Chi-square=1.371; df=1; p=0.2417}. The analysis showed a significant male predominance in the study group {56 (78.87%) males *vs.* 15 (21.13%) females (gender ratio 3.73:1); {Difference test: 57.74% [(42.39-68.89) CI 95%]; Chi-square=47.008; df=1; p= 0.0001}. In patients without AD, there were 9 (23.1%) females *vs.* 30 (76.92 %) males, while in AD patients there were 6 (18.7%) females *vs.* 26 (81.2%) males. The analysis did not confirm a significant association between gender and AD (p=0.6567) (Table 1, Figure 1). The mean age in the sample was 58.8 ± 10.7 [95%

Table 1. Sample distribution according to gender and AD

Gender		AD[1] (N=71) No	Yes	Total	P
Female	**N**	9	6	15	Pearson Chi-square test=0.1975; df=2; p=0.6567
	%	23.08%	18.75%	21.13%	
Male	**N**	30	26	56	
	%	76.92%	81.25%	78.87%	
Total	**N**	39	32	71	
	%	54.93%	45.07%	100%	

[1]acute decompensation, *significant for p<0.05

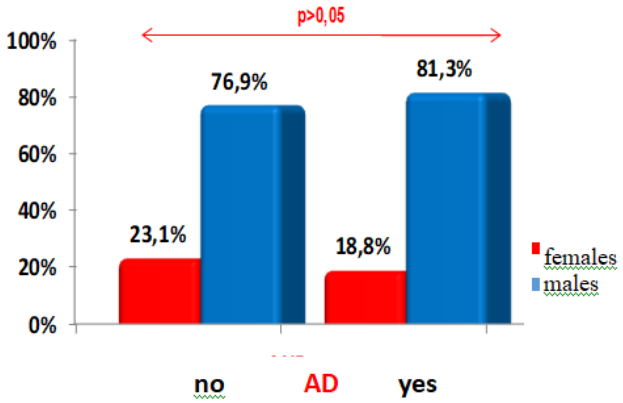

Fig. 1. Sample analysis according to gender and AD

Table 2. Age analysis according to gender and AD

	Parameters	Number (N)	Mean	Standard deviation	Min	Max	Median	95% CI of mean	
								Lower	Upper
Gender	**Female**	15	62.47	8.47	48.00	77.00	61.00	58.10	66.93
	Male	56	55.34	10.83	31.00	84.00	55.50	52.53	58.05
	Total	71	56.84	10.73	31.00	84.00	58.00	54.39	59.14
	t-test (69)=-2.359; p=0.0211*								
AD	**No**	39	56.87	11.31	31.00	77.00	58.00	53.51	60.50
	Yes	32	56.81	10.14	34.00	84.00	58.00	53.39	60.52
	Total	71	56.84	10.73	31.00	84.00	58.00	54.51	59.28

t-test (69)=0.023; p=0.9817, *significant for p<0.05

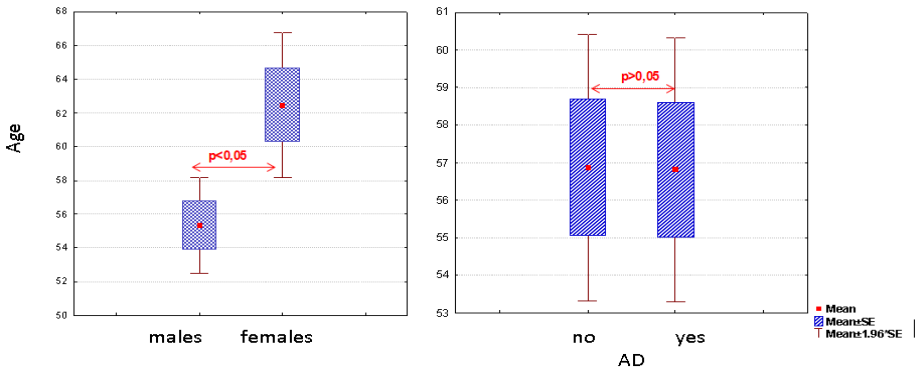

Fig. 2. Age analysis according to gender and AD

Table 3. Etiology of liver cirrhosis according to AD

Etiology		AD (N=71)		
		No	Yes	Total
Alcoholic liver disease	**Number**	14	22	36
	%	35.90%	68.75%	50.70%
Chronic hepatitis B	**Number**	9	3	12
	%	23.08%	9.38%	16.90%
Chronic hepatitis C	**Number**	3	2	5
	%	7.69%	6.25%	7.04%
Primary biliary cholangitis	**Number**	1	0	1
	%	2.56%	0%	1.41%
Cryptogenic	**Number**	7	3	10
	%	17.95%	9.38%	14.08%
Autoimmune hepatitis	**Number**	5	1	6
	%	12.82%	3.13%	8.45%
Nonalcoholic fatty liver disease	**Number**	0	1	1
	%	0%	3.13%	1.41%

Fisher Freeman Halton exact test: p=0.1241, *significant for p<0.05

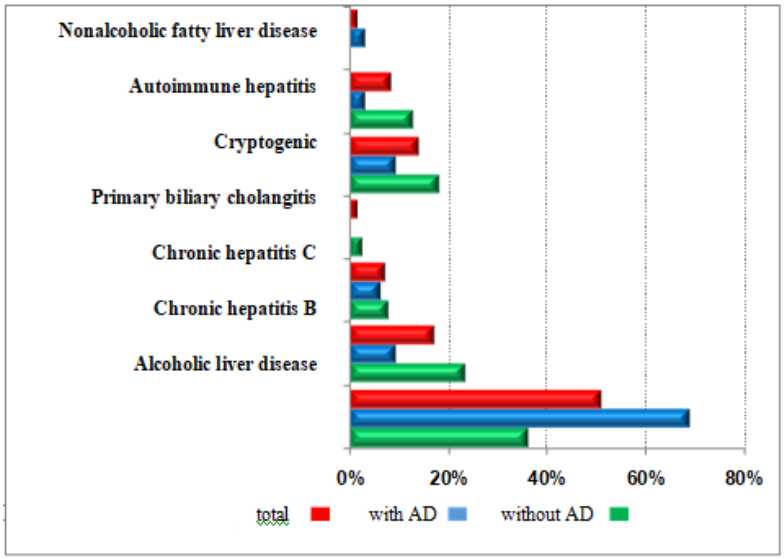

Fig. 3. Etiology of liver cirrhosis according to AD

Table 4. Sample analysis according to Baveno classification

Baveno classification		Total	Group
Baveno class 1	**Number**	4	
	%	5.63%	**Compensated**
Baveno class 2	**Number**	7	**11 (15.5%)**
	%	9.86%	
Baveno class 3	**Number**	44	
	%	61.97%	**Decompensated**
Baveno class 4	**Number**	16	**60 (84.5%)**
	%	22.54%	

CI (54.4-59.1)]. The mean age of female patients was 62.5±8.5 [95% CI (58.1-66.9)], while the mean age of male patients was 55.3±10.8 [95% CI (52.5-58.0)]. The analysis confirmed a significantly older age in female patients (p=0.0211), (Table 2, Figure 2). The mean age of patients without AD was 56.9±11.3 [95% CI (58.1–60.5)] years, while the mean age of patients with AD was 56.8.±10.1 [95% CI (53.4-60.6)] years. The analysis did not confirm a significant age difference between patients in both groups (p=0.9817) (Table 2, Figure 2).
The case distribution showed that alcoholic liver disease was the most prevalent etiology among patients in both groups [14 (35.9%) without AD *vs*. 22(68.7%) with AD] but there was no significant association between the etiology and the presence of AD (p=0.1241) (Table 3, Figure 3). In order to define the stage of the disease, we calculated several scoring systems. The frequency distribution test showed irregular distribution regarding CTP, MELD, SOFA and SAPS II score (Shapiro-Wilk: W=0.9342, p=0.0011 *vs.* W=0.9179, p=0.0001 *vs*. W=0.9418, p=0.0025 and W=0.8757, p=0.00001**,** respectively). The mean CTP score was 8.9±2.9, the mean MELD score was19.7±9.9, the mean SOFA score was 4.7±2.6 and the mean SAPS II score was 20.6±10.2. Regarding the Baveno classification, 60 (84.5%) patients were defined as decompensated [most patients, 44(62%) were classified in Baveno class 3, followed by 16(22.5%) in Baveno class 4]. There were 11(15.5%) compensated patients [4(5.6%) in Baveno class 1 and 7 (9.8%) in Baveno class 2]. The sample analysis confirmed a significantly higher percentage of decompensated patients {Difference test: 69% [(54.63-78.36) CI 95%]; p=0.0001}, (Table 4)}.

Discussion

The results obtained in our study opened several important issues. Regarding demographic data, the results confirmed a significant male predominance among cirrhotic patients and significantly older age in female patients. Regarding AD, the study confirmed its presence in 54.93% of patients, but did not confirm a significant association between AD and the etiology of liver cirrhosis. Also, the study neither confirmed a significant association between AD and gender nor significant age difference between patients in both groups.
Regarding the etiology distribution in the study group, we came across some interesting data. Being present in half of the patients, alcoholic liver disease (ALD) was the most prevalent etiology among cirrhotic patients in both groups. According to the literature, there are variations in the etiological distribution in patients with chronic liver disease depending on the geographic region and the prevalence of chronic hepatitis B and chronic hepatitis C [8]. In one population-based cohort study [4], ALD was also the most prevalent entity

(79%), followed by chronic hepatitis C (5%), chronic hepatitis B (1%), autoimmune hepatitis (2%), primary biliary cholangitis (2%), primary sclerosing cholangitis (0.41%), haemochromatosis (2%), alpha-1 antitrypsin deficiency (1%), non-alcoholic fatty liver disease (NAFLD) (0.3%), cryptogenic cirrhosis (9%) and other causes (0.2%) [4]. Remarkably, we registered only one patient with NAFLD, and the etiology of liver disease remained unknown in 14.08%, which is relatively high percentage in comparison to other research [4]. In recent decades, non-alcoholic steatohepatitis (NASH) is an increasingly recognized entity underlying chronic liver disease, and according to some studies, a significant percentage of cryptogenic cases belong to NAFLD/ NASH [9]. In a survey of 2,000 liver biopsies, NAFLD/ NASH comprised 22.5% of the biopsies between the years 2003-2006 [8], as compared to 5% between the years 1990-1995 [10]. This means that patients with diabetes, dyslipidemia, and metabolic syndrome, in general, should be more carefully observed and monitored in the context of early and appropriate detection of NAFLD as a possible cause of chronic liver disease. The low detection rate of haemochromatosis and alpha-1 antitrypsin deficiency could be partially explained by the necessity of confirming the entities by a specific genetic analysis. Nevertheless, it seems that the low clinical awareness and suspicion for these entities could be responsible for the low diagnostic rate among cirrhotic patients. Defining the specific etiology that underlies the chronic liver disease is important not only for providing specific etiological treatment and slowing down the disease progression, but also for a better natural course and risk assessment. Moreover, according to some research, ALD and cryptogenic cirrhosis are associated with worse prognosis [4,11]. Still, the small number of patients in our group disabled us from performing a more precise analysis regarding etiology.

AD is a complex and heterogenous entety [6,12-16] that not only modifies the natural course of chronic liver disease, but also poses an important prognostic role in cirrhotic patients. AD occurs more frequently in decompensated and in patients with advanced disease and the presence of AD is related to an increased hospital mortality [6]. Also, according to some research the history of previous acute decompensation may also have negative prognostic impact [17]. Taking into account the important prognostic role of AD, patients in our study were initially divided in two groups. Our study neither confirmed a significant association between AD and the analyzed demographic data (gender and age), nor between AD and the etiology of liver disease. This is partially in line with the literature data suggesting that AD is mainly associated with the presence and degree of portal hypertension. Also, according to some studies, infection and sepsis are the most common precipitating causes of AD [18]. Recent data also suggest that it is not only important to define the presence of AD, but it seems that the degree of AD also plays a role from the prognostic point of view [19]. This is the reason why many researchers have worked on defining relevant and useful scores for detecting and quantifying AD in cirrhotic patients [19].

In conclusion, in order to make a proper assessment of the natural course of chronic liver disease and to predict the prognosis more accurately, it is important to properly obtain data regarding the etiology and stage of liver disease, the presence and degree of portal hypertension, and also to define and quantify the presence of acute decompensation.

Conflict of interest statement. None declared.

References

1. Blachier M, Leleu H, Peck-Radosavljevic M, *et al*. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; 58: 593-608.
2. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet* 2006; 367: 52-56.
3. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44(1): 217-231.
4. Dam Fialla A, Schaffalitzky de Muckadell OB, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: a population-based cohort study. *Scand J Gastroenterol* 2012; 47(6): 702-709.
5. Alexopoulou A, Vasilieva L, Mani I, *et al*. Single center validation of mortality scores in patients with acute decompensation of cirrhosis with and without acute-on-chronic liver failure. *Scand J Gastroenterol* 2017; 52(12): 1385-1390.
6. Arvaniti V, D'Amico G, Fede G, *et al*. Infections in patients with cirrhosis increase mortality four-fold and should be used in deter- mining prognosis. *Gastroenterology* 2010; 139: 1246-1256.
7. Fayad L, Narciso-Schiavon JL, Lazzarotto C, *et al*. The performance of prognostic models as predictors of mortality in patients with acute decompensation of cirrhosis. *Ann Hepatol* 2015; 14(1): 83-92.
8. Samonakis DN, Koulentaki M, Coucoutsi C, *et al*. Clinical outcomes of compensated and decompensated cirrhosis: A long term study. *World J Hepatol* 2014; 6(7): 504-512.
9. Liou I, Kowdley KV. Natural history of nonalcoholic steatohepatitis. *J ClinGastroenterol* 2006; 40 Suppl 1: S11-S16.
10. Avgerinos A, Koulentaki M, Tzardi M, *et al*. Increased incidence of steato- hepatitis during the last sixteen years in Crete. EASL special conference on NASH/NAFLD. Bologna, Italy, 2009.
11. Ferreira LG, Anastácio LR, Lima AS, Touslon Davisson Correia MI. Predictors of mortality in patients on the waiting list for liver transplantation. *Nutr Hosp* 2013; 28(3): 914-919.
12. Moore KP, Wong F, Gines P, *et al*. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003; 38: 258-266.
13. Blei AT, Córdoba J. Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. *Am J Gastroenterol* 2001; 96: 1968-1976.

14. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med* 2010; 362: 823-832.
15. Gustot T, Durand F, Lebrec D, *et al*. Severe sepsis in cirrhosis. *Hepatology* 2009; 50: 2022-2033.
16. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009; 3(1): 269-282.
17. Lee M, Lee JH, Oh S, *et al*. CLIF-SOFA scoring system accurately predicts short-term mortality in acutely decompensated patients with alcoholic cirrhosis: a retrospective analysis. *Liver Int* 2015; 35(1): 46-57.
18. Dhiman RK, Agrawal S, Gupta T, *et al*. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. *World J Gastroenterol* 2014; 20(40): 14934-1441.
19. Jalan R, Pavesi M, Saliba F, *et al*. CANONIC Study Investigators; EASL-CLIF Consortium. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol* 2015; 62(4): 831-840.

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Original article

POSTOPERATIVE PAIN AND QUALITY OF LIFE IN PATIENTS WITH FEMORAL NECK FRACTURES TREATED WITH OSTEOSYNTHESIS AND ARTHROPLASTY

ПОСТОПЕРАТИВНА БОЛКА И КВАЛИТЕТ НА ЖИВОТ КАЈ ПАЦИЕНТИ СО ФРАКТУРИ НА ВРАТ НА БУТНА КОСКА ТРЕТИРАНИ СО ОСТЕОСИНТЕЗА И АРТРОПЛАСТИКА

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Abstract

Introduction. Femoral neck fractures in our country and worldwide take epidemiological proportions. According to numerous publications and papers, hip fractures take about 25-35% of the hospital capacity of orthopedic-traumatic institutions. One of the most important causes of mortality and morbidity in the elderly population are these fractures. In almost all cases, these fractures lead to exacerbation of the existing chronic diseases resulting in deterioration, i.e., reduced function of the locomotor system and failure of other organ systems, which often lead to death. They are not only a hospital and health problem, but also a socioeconomic and financial problem as for their treatment significant financial resources are spent that additionally burden the health funds. A femoral neck fracture can be a trigger for a series of health problems that require different levels of care [1,2].
Aim. Evaluation of the postoperative pain and quality of life in patients after femoral neck fractures threated with osteosynthesis and arthroplasty.
Methods. This study was conducted at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre at the Faculty of Medicine in Skopje. According to its design, this was a clinical intervention study. It evaluated 27 patients with a femoral neck fracture who were divided into two groups: 15 treated with osteosynthesis (screws) and 12 with arthroplasty.
Results. The analysis of the quality of life of patients from both groups one month after the intervention showed that the SF score for all 6 scales was not signifycantly different between patients in the osteosynthesis group and the arthroplasty group. Patients operated on with the arthroplasty method rated the quality of life in terms of physical function, physical pain, general health, vitality, mental health and social functioning with a slightly higher score, i.e., better. Pain score on the VAS scale was higher in the osteosynthesis group, with greater statistical significance immediately postoperatively. Patients operated on with the method of osteosynthesis had a significantly stronger postoperative pain than patients operated on using the method of arthroplasty.
Conclusion. Surgical treatment of femoral neck fractures is a method of choice and it is accepted by international consensus both in our country and worldwide. Today, there is no place for conservative treatment of this type of injury. Postoperative pain was greater in patients treated with osteosynthesis than in patients treated with arthroplasty.

Key words: osteosynthesis, arthroplasty, quality of life

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Апстракт

Вовед. Повредите на вратот на бутната коска во нашата држава и низ светот се епидемиолошки пропорционални. Според различни студии, за фрактури на колк е употребен 25-35% од капацитетот на институците за траума. Најголеми причини за морталитет и морбидитет во старата популација се овие фрактури на колк. Најчесто, фрактурите на колк кај повозрасни лица водат кон влошување на постоечките хронични заболувања, пример намалената функција на локомоторен систем води кон детериоризација на функцијата и на други органи и често кон смрт. Постојат проблеми и од социоекономски и финансиски аспект поради долготрајното и скапо лечење кое доведува до оптеретување на здравствениот фонд. Фрактира на врат на колк може да предизвика различни здравствени проблеми кои ке им треба различен степен на нега.
Цел. Евалуација на постоперативна болка и квалитет на живот кај пациенти со скршеница на вратот на бутната коска.

Методи. Студијата беше клиничка интервентна, спроведена на Универзитетската клиника за ТОАРИЛУЦ, а во истата беа евалуирани вкупно 27 пациенти со скршеница на вратот на бутната коска поделени во две групи и тоа 15 третирани со остеосинтеза и 12 со артропластика (ендопротеза).

Резутати. Анализата на квалитетот на живот од двете групи, еден месец по интервенцијата не покажа значителна статистичка сигнификантост во сите 6 елементи кај пациентите во обете групи со остеосинтеза и артропластика. Пациентите оперирани со ендопротеза квалитетот на живот по однос на физичка функционалност, физичка болка, генерално здравје, виталност, ментално здравје и социјално функционирање покажаа малку повисоки вредности. Постоперативната болка, мерена со ВАС скалата беше поголема кај пациентите третирани со остеосинтеза.

Заклучок. Хируршкиот третман кај скршениците на вратот на бутната коска е метод на избор не само кај нас туку и ширум светот со интернационален консензус. Нема место за конзервативен третман кај ваквиот тип на скршеници. Постоперативната болка беше повисока кај пацинетите третирани со остеосинтеза отколку кај пациентите третирани со ендопротеза.

Клучни зборови: остеосинтеза, артропластика, квалитет на живот

Introduction

Femoral neck fractures in our country and worldwide take epidemiological proportions. According to numerous publications and papers, hip fractures take about 25-35% of the hospital capacity of orthopedic-traumatic institutions. One of the most important causes of mortality and morbidity in the elderly population are these fractures. In almost all cases, these fractures lead to exacerbation of the existing chronic diseases resulting in deterioration, i.e., reduced function of the locomotor system and failure of other organ systems, which often lead to death. They are not only a hospital and health problem, but also a socioeconomic and financial problem as for their treatment significant financial resources are spent that additionally burden the health funds. A femoral neck fracture can be a trigger for a series of health problems that require different levels of care [1,2].

Intracapsular femoral neck fractures are most common in the elderly population and are most often the result of a trivial trauma. However, such fractures are rare in the younger population (under 50 years) and come as a result of a severe trauma such as: fall from height, car accidents and less often sports activities [2-4]. They take about 2-3% of the total number of femoral neck fractures [2-5]. Complications in their treatment are still present in a larger percentage [6]. It is common knowledge that this type of fracture in the younger population is not associated with a high mortality rate, which is not the case in the elderly population [7].

Material and methods

This study was conducted at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre at the Faculty of Medicine in Skopje. According to its design, this was a clinical intervention study. It evaluated 27 patients with a femoral neck fracture who were divided into two groups: 15 treated with osteosynthesis (screws) and 12 with total endoprosthesis implantation.

In all patients, fractures were evaluated according to the Garden and Powels classifications.

Quality of life was analyzed in each patient 1 month postoperatively with the short form of the SF-36 questionnaire, which consists of 36 items measuring 8 physical and mental dimensions of health (physical functioning, physical limitation, physical pain, general health, vitality, emotional limitation, mental health, social functioning). The results of this scale range from 0 to 100, where a score of 100 indicates the highest score for quality of life.

Pain intensity was quantified by the VAS scale, one of the first pain measurements used in 1921 by Hayes and Patterson. It is often used in clinical trials to measure the intensity of various symptoms such as the degree of pain a patient is experiencing. It is one-dimensional measure of pain progression and serves to compare the degree of pain in patients with different etiological causes of the disease. The range is from 1 to 10 and the degree of pain is directly proportional to the size of the figure (10 indicating the largest pain) [30].

The obtained data were statistically analyzed with the SPSS - statistical program for Windows 17.0. Category data is represented by absolute numbers, whereas quantitative data by a mean (SD). The Shapiro-Wilk's W test was used to test the normality of the data. To compare the two groups of patients depending on the distribution of data, parametric and non-parametric tests for independent samples were used (Fisher exact test, Mann-Whitney U-test; Student t-test). The validity of the questionnaire was determined by calculating Cronbach-alpha. The values of $p<0.05$ were taken as statistically significant.

Results

Out of a total of 27 patients with femoral neck fracture, 15 were surgically treated with the method of osteosynthesis (screws), and 12 patients with endoprosthesis. Both groups were homogeneous in terms of gender, with a higher prevalence of female patients - 9 in the group with osteosynthesis and 8 in the group with endo-

prosthesis (p=1.0). The average age in the first group was 52±9.8, while in the second group 60± 12.3 years. Garden type 1 and 2 fracture was significantly more common in the group with 14 *vs*. 1 osteosynthesis, and Garden type 3 and 4 in the group with endoprosthesis 10 *vs.* 2. Five patients of the osteosynthesis group were with a history of comorbidity and 6 of the endoprosthesis group. Patients in the osteosynthesis group had a significantly shorter length of hospital stay than patients in the endoprosthesis group (3.1±2.0 *vs*. 5.9±4.3; p=0.001).

Table 1. General characteristics of the patients in the two groups

Patient data		Group 1 Osteosynthesis (screws) n = 15	Group 2 Endoprosthesis n = 12	P = value
Sex	Male	6	4	[a]p=1.0 NS
	Female	9	8	
Age		52 ± 9.8	60 ± 12.3	[b]p = 0.0016 SIG
Fracture type	Garden 1 and 2	14	2	[a]p= 0.001 SIG
	Garden 3 and 4	1	10	
Presence of comorbidities	Yes	5	6	[a]p = 0.45 NS
	No	10	6	
	Days of hospitalization	3.1 ± 2.0	5.9 ± 4.3	[c]p = 0.001 SIG

Data are shown in absolute numbers or with mean ±SD, [a]p (Fisher exact, two-tailed test); [b]p (t-test); [c]p (Mann-Whitney test)

Pain intensity in both groups of patients was analyzed at three time points: the first and the second day postoperatively, and 2 weeks postoperatively.
At all three time points, the mean score on the VAS scale was higher in the osteosynthesis group, with greater statistical significance immediately postoperatively. Patients operated on with the method of osteosynthesis had a significantly stronger postoperative pain than patients operated on using the method of endoprosthesis.

Table 2. VAS scale for postoperative pain

VAS scale	Osteosynthesis (screws) n = 15	Endoprosthesis n = 12	P = value
1 day postoperatively	8.7±5.3	6.1±4.0	p=0.17 NS
2 days postoperatively	7.19±5.8	5.2±3.9	p=0.18 NS
2 weeks post-operatively	3.8±2.2	2.3±1.6	p=0.06 NS

Data are shown with mean ±SD, p (Mann-Whitney test)

The analysis of the quality of life of patients from both groups one month after the intervention showed that the SF score for all 6 scales was not significantly different between patients in the osteosynthesis group and the endoprosthesis group. Patients operated on with the endoprosthesis method rated the quality of life in terms of physical function, physical pain, general health, vitality, mental health and social functioning with a slightly higher score, i.e., better.

Table 3. SF-36 score for quality of life

SF-36	Osteosynthesis (screws) n = 15	Endoprosthesis n = 12	P = value
physical functionality	58.8±28.56	59.8±29.60	0.35 NS
physical limitation	49.2±42.01	49.8±32.43	0.49 NS
physical pain	51.0±21.79	53.0±23.65	0.49 NS
general health	65.5±26.06	66.8±21.16	0.28 NS
vitality	51.0±21.79	53.0±19.89	0.23 NS
emotional limitation	73.5±40.51	72.9±35.19	0.44 NS
mental health	57.1±27.89	59.±23.29	0.46 NS
social functionality	62.9±30.53	65.9±31.81	0.34 NS

Data are shown with mean ±SD, p (Mann-Whitney test)

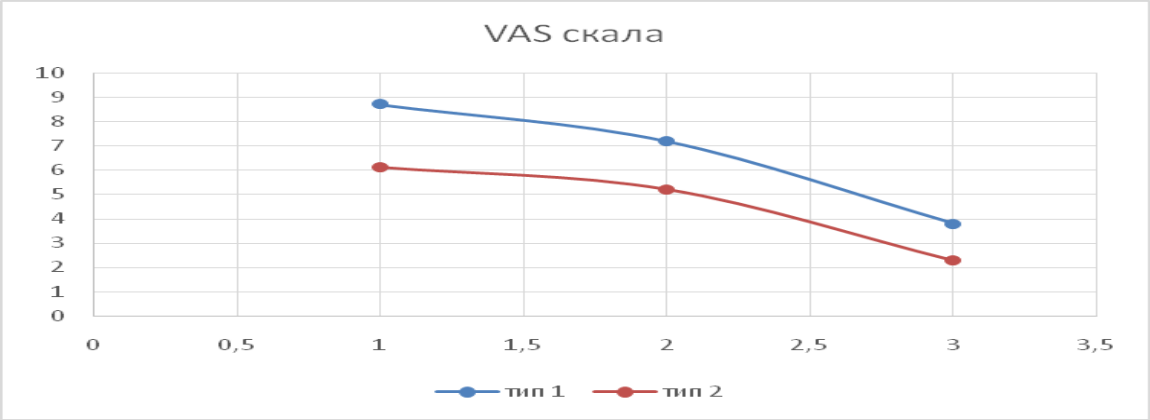

Fig. 3. VAS scale for postoperative pain

Discussion

To evaluate and surgically treat patients with femoral neck fractures, it is important to understand the differences between the younger and elderly population. Specific differences between them are as follows: bone and vascular anatomy, mechanism of injury, joint injuries, fracture morphology, and type of treatment. In all the controversy regarding surgical treatment today, there is a general consensus that femoral neck fractures should be treated surgically. There is no place for conservative treatment in the treatment of neck fractures of the femur with long bed rest [8-12]. Femoral neck fractures in the young population are associated with a high percentage of complications such as osteonecrosis [4,8,9,21] and non-healing [4,8]. The percentage of these complications in the literature ranges from 12 to 86% [4,10,14]. Surgeries performed to save the femoral head, such as a valging osteotomy do not provide best results [15-18]. Arthroplasty surgical procedures, on the other hand, are not an ideal choice as the primary procedure in the treatment of young people seeking high levels of activity [11]. Today, key factors in surgical treatment with this population are: early surgery, anatomical repositioning and stable fixation. Anatomical repositioning and stable fixation are accepted as imperatives [3,4,5,10] in the treatment of femoral neck fractures along with the time of surgery [19], while the role of decompression capsulotomy and open repositioning is still debatable. [12,20-24]

Thigh bone fractures, on the other hand, in the elderly population are very different from the younger population in the mechanism of injury (in the elderly population it is a trivial trauma), poor bone quality and osteoporosis that changes the morphology of the fracture. Transferral, subcapital fractures with impact of fragments are most common in this population. In young population, good bone quality and severe trauma result in a more basicervical fracture located in the distal part of the neck, and the fracture line is vertical and biomechanically much more unstable [25-27] and is often accompanied by posterior comminution of the neck which changes the type of surgical treatment, too [28,29]. Such features of femoral neck fractures have important implications on the decision to choose a surgical treatment in order to achieve normal fracture healing. The concept of choosing a surgical treatment for the elderly is different from that for the young population. With the elderly population, the goal of treatment includes: mobility, removal and prevention of complications as a result of prolonged bed rest. To achieve this goal there are several options for surgery: repositioning and stable fixation, hemiarthroplasty, and total hip arthroplasty depending on the type of fracture. The purpose of the surgical treatment in young people is: to preserve the head, to avoid complications (osteonecrosis and non-healing) and to restore all the activities of the patient as before the injury. Arthroplasty as a first option in young patients has not been shown to be ideal for achieving high levels of functional activity. Anatomical repositioning and stable fixation are imposed as a consensual imperative in surgical treatment in the young population.

Conclusion

Surgical treatment of femoral neck fractures is a method of choice and it is accepted by international consensus both in our country and worldwide. Today, there is no place for conservative treatment of this type of injury. The conservative treatment is accompanied by prolonged bed rest; the patient is usually in traction or in plaster corset, splints that generate complications such as: pressure ulcers, comorbidities, lung complications, infections that lead to deteriorated health and eventual death. The results obtained from the measurement of the quality of life with PCS and MCS as well as the measurement of YOU scale have led to the conclusion that the type of repositioning is the most important factor for a good postoperative course. The results obtained in our study clearly demonstrated that in patients with good and excellent reposition, there was a progressive increase in values for PCS and MCS, and thus a better quality of life, which was not

the case in patients with poor fracture reposition. Post-operative pain was greater in patients treated with osteo-synthesis than in patients treated with endoprosthesis.
Over the years, the outcome of surgical treatment has improved significantly, mainly due to innovations in osteosynthetic material, endoprosthetics, surgical techniques, and active patient rehabilitation. A large number of patients with femoral neck fractures will return to their homes and to their daily activities just as they did before the injury.

Conflict of interest statement. None declared.

References:

1. Oden A, Dawson A, Dere W, *et al*. Lifetime risk of hip fractures is underestimated. *Osteoporosis Int* 1998; 8: 599-603.
2. Robinsom CM, Court-Brown CM, McQueen MM, Christie J. HIP Fractures in Adults younger than 50 years of age: Epidemiology and Results. *Clin Orthop Relat Res* 1995; 312: 238-246.
3. Askin SR, Bryan R. Femoral Neck fractures in young adults. *Clin Orthop Relat Res* 1976; 114: 259-264.
4. Protzman RR, Burkhalter WE. Femoral Neck fractures in young adults. *J Bone Joint Surgery Am* 1976; 58: 689-695.
5. Zetterberg CH, Elmerson S, Andresson GB. Epidemiology of hip fractures in Goteborg, Sweden, 1940-1983. *Clin Orthop Relat Res* 1984; 191: 43-52.
6. Berglung-Róden M, Swiestra BA, Wingstrand H, Thorngren K-G. Prosprective comparison of hip fracture treatment, 956 cases followed for 4 months in the Netherlands and Sweden. *Acta Orthop Scand* 1994; 65: 287-294.
7. Lu-Yao GL, Keller RB, Littenberg B, Wennberg JE. Outcomes after displaced fractured of the femoral neck: A meta-data analysis of one hundred and six published reports. *J bone Joint Surg Am* 1994; 76: 15-25.
8. Dedrick DK, Mackenze JR, Burney RE. Complication of femoral neck fracures in young adults. *J Trauma* 1986; 26: 932-937.
9. Haidukewuch GJ, Rothwell WS, Jacofsky DJ, *et al*. Operative treatment of femoral neck fractures in patients between the age of fifteen and fifty years. *J Bone Joint Surg Am* 2004; 86: 1711-1716.
10. Swiontkowski MF, Winquist RA, Hansen ST. Fractures of the femoral neck in patients betewwn twelve and forty-nine years. *J Bone Surg Am* 1984; 66: 837-846.
11. Chandler HP, Reineck FT, Wixson RL, McCarthy JC. Total hip replacement in patients younger than 30 years old. *J Bone Joint Surg Am* 1981; 63: 1426-1434.
12. Keller GS, Laros GS. Indication for open reduction of femoral neck fractures. *Clin Orthop Relat Res* 1980; 152: 131-137.
13. Claffey TJ. Avascular necrosis of the femoral head: An anatomic study. *J Bone Joint Surg Br* 1960; 42: 802-809.
14. Arnoldi CC, Lemperg RK. Fracture of the femoral neck: II, Relative importance of primary vascular damage and surgical procedure for the development of necrosis of the femoral head. *Clin Orthop Relat Res* 1977; 139: 217-22.
15. Mishra US. Intertrochanteric displacement osteotomy in the treatment of femoral neck fractures. *Injury* 1979; 10: 183-189.
16. Fontanesi G, Costa P, Giancecchi F, Tartaglia I. Intratrochanteric valgus osteotomy and sliding compression hip screw fractures of the femoral neck. *Ital J Orthop Traumatol* 1991; 17: 293-304.
17. Marti RK, Schuller HM, Raaymakers EL. Intertrochanteric osteotomu for non-union of the femoral neck. *J Bone Surg Br* 1989; 71: 782-787.
18. Anglen JO. Intertrochanteric osteotomy for failed internal fixation of femoral neck fractures. *Clin Orthop Relat Res* 1997; 341: 175-182.
19. Mannineger J, Kazar GY, Fekete GY, *et al*. Avoidance of avascular necrosis of the femoral head following fractures of the femoral neck, by early reduction and internal fixation. *Injury* 1985; 16: 437-448.
20. Maruenda JI, Barrios C, Gomar-Sancho F. Intracapsular hip pressure after femoral neck fracture. *Clin Orthop Relat Res* 1997; 340: 172-180.
21. Woodhouse CF. Dynamic influence of vascular occlusion affecting the development of vascular necrosis of the femoral head. *Clin Orthop Relat Res* 1962; 32: 119-129.
22. Bonnaire F, Schaefer DJ, Kuner EH. Hemathrosis and hip joint pressure in femoral neck fractures. *Clin Orthop Relat Res* 1998; 353: 148-155.
23. Holmberg S, Dalen N. Intracapsular pressure and caput circulation in nondisplaced femoral neck fractures. *Clin Orthop Relat Res* 1987; 219: 124-126.
24. Crawfurd EJ, Emery RJ, Hansell DM, *et al*. Capsular distension and intracapsular pressure in subcapital fractures of the femur. *J Bone Joint Surg Br* 1988; 70: 195-198.
25. Bartonickek J. Pauwels' classification of femoral neck fractures: Correct interpretation of the original. *J Orthop Trauma* 2001; 15: 358-360.
26. Broos PL, Vercruysse R. Fourneau I, *et al*. Unstable femoral neck fractures in young adults: Treatment with the AO 10-degree blade plate. *J Orthop Trauma* 1998; 12: 235-239.
27. Baitrer AC, Maurer SG, Hickey DG, *et al*. Vertical shear-fractures of the femoral neck. *Clin Orthop Relat Res* 1999; 367: 300-305.
28. Kauffman JI, Simon JA, Kummer FJ, *et al*. Internal fixation of femoral neck fractures with posterior comminution: A bimochenical study. *J Orthop Trauma* 1999; 13: 155-159.
29. Holmes CA, Edwards WT, Myers ER, *et al*. Biomechanics of pin and screw fixation of femoral neck fractures. *J Orthop Trauma* 1993; 7: 242-247.

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Original article

IMPORTANCE OF MAGNETIC RESONANCE IN DETECTION OF LIVER METASTASIS WITH PERIPHERAL DESMOPLASTIC REACTION

ВАЖНОСТА НА МАГНЕТНА РЕЗОНАНЦА ВО ДЕТЕКЦИЈА НА ХЕПТАЛНИ МЕТАСТАЗИ СО ПЕРИФЕРНА ДЕЗМОПЛАСТИЧНА РЕАКЦИЈА

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Abstract

Introduction. The most common malignant lesion of liver are metastases and they can be seen 18 to 40 time more often than primary liver malignant lesion [1]. Therefore, the complete surgical resection of liver metastases is related with increase of survival rate in patients with malignant disease. Defining the size, location and involvement of residual liver parenchyma has crucial importance in selecting potential patients for surgical resection [2].

Methods. This study comprised 23 patients ranging in age from 40 to 75 years, 15 females and 8 males with previously detected malignant diseases. Eleven of them had breast surgery, and had also previously received cytostatic therapy; another 2 were with ovarian cancer and two with colon cancer. Five men have had colon surgery for colon cancer and 3 had pancreatic cancer. All of these patients underwent MRI of the upper abdomen and liver in native series. While performing the MRI, controlled breathing was assured and series were made after the intravenous application of contrast for MRI with magnitude of the magnetic field of 1,5 Tesla. In the examination and MR evaluation, the following sequences were included -standard spin-echo (SE) T1-weighted (T1W) and T2-weighted (T2W) single breath-hold, as well as the sequences with intravenous application of gadolinium dimeglumine.

Results. Eleven patients underwent breast surgery, two had ovarian cancer; in total 24 metastasis were detected, of which 20 were hypovascularized with continuous irregular peripheral ring enhancement. Four of them had benign presentation, resembling hemangiomas. In 7 patients with colon cancer, 17 metastases were detected with different diameter, that were hypervascularized with maximum diameter of 23 mm and significant 7 mm ring enhancement.

Conclusion. Regarding MRI characteristics of the ring enhancement, surgical resection of the metastasis should be taken into account in terms of assessment of the malignant potentials of the recurrent lesions.

Key words: metastases, liver, desmoplastic rings, surgical resection, malignant diseases, MRI

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Абстракт

Вовед. Најчести малигни лезии на црн дроб се метастазите и се среќаваат 18 до 40 пати почесто од примарните лезии на црн дроб. Токму поради тоа е неопходна соодветна дијагностика која има многу важна улога во комплетна ресекција на метастазите на црн дроб со директно влијание на покачување на ратата на преживување кај пациенти со малигни заболувања. Дефинирање на нивната големина, локација и волумен на резидуален паренхим на црн дроб се со висок степен на важност во селекција на потенцијални пациенти за хируршка ресекција на метастази.

Методи. Оваа студија е ретроспективна клиничка студија во која се вклучени 23 пациенти на возраст од 40 до 75 години од обата пола со претходно дијагностицирано малигно заболување. Единаесет пациентки биле со тотална мастектомија и примиле цистостатска терапија, две биле оперирани од оваријален канцер, две од колоректален канцер. Пет пациенти од машки пол биле со колоректален канцер третирани хируршки а тројца од нив биле третирани за панкреатичен канцер.

Сите пациенти биле испитувани со магнетнатна резонанца во нативна серија и серија со интравенска апликација на контраст во секвенци со контрола на дишење.

Резултати. Кај единаесет пациентки со рак на дојка, две со оваријален канцер биле детектирани 24 метастази од кои 20 се со хиповаскуларизација и со континуиран ирегуларен периферен прстенест сигнал. Четири од нив имаа бенигна презентација во прилог на хенагиоми. Кај седум пациенти со колоректален карцином биле детектирани 17 мета-

стази со различна големина, хиперваскуларизирани со максимален дијаметар до 223 мм и со сигнификантен периферен прстен на дезмопластична околна реакција.
Заклучок. Магнетна резонанца ги карактеризира периферните околни реакции на хепатален паренхим на самите метастази како дезмопластична реакција која може да има висок малиген потенцијал за рецидивирање на лезиите.

Клучни зборови: Метастази, црн дроб, дезмопластична реакција, хируршка ресекција, малигни заболувања, магнетна резонанца

Introduction

The most common malignant lesion of liver are metastases and they can be seen 18 to 40 time more often than primary liver malignant lesion [1]. Therefore, the complete surgical resection of liver metastases is related with increase of survival rate in patients with malignant disease. Defining the size, location and involvement of residual liver parenchyma has crucial importance in selecting potential patients for surgical resection [2].
Today, a few radiology methods such as abdomen ultrasound have an important place in detecting of liver metastases as well as in specifying their size and location. On the other hand, as far as this method of ultrasound is useful, since the surgical process is prolonged, it has technical limitation in differentiation of malignant from benign lesions [3].
Contrast computed tomography of liver performed in three phases has a higher sensitivity than abdominal ultrasound, still with limitation compared to magnetic resonance of liver, due to radiation exposure of patients, specification and characterization of liver focal changes [4-6].
The characteristics of liver metastases are closely connected with those of the primary malignant lesion from which they originated. Therefore, they have different specification in presentation with magnetic resonance examination. This has been the reason for developing and including different kind of techniques that give possibilities in exact differentiation in terms of proper treatment.
Magnetic resonance has been emphasized as the state of art radiology non-invasive examination of liver metastases due to its possibilities of characterization and differentiation of tissue level as well as due to absence of radiation exposure of the patient.
Magnetic resonance examination is starting with general sequences like standard spin-echo (SE) T1-weighted (T1W) and T2-weighted (T2W) as well as long time sequences in wide range. Quality of examination completely depends on communication and cooperation with the patients [7]. Inclusion of sequences with holding breath and short time necessary for the examination gives possibility of avoiding artefacts.
Different kind of metastases has different MRI presentation, hypo- to isointense on T1 sequences, iso- to hyperintense on T2 sequences. Intravenous application of contrast medium gives data on vascularization of metastases, so they can be less vascularized or more vascularized. Colon carcinoma, lung carcinoma, breast carcinoma and stomach carcinoma present with less vascularized metastases with ring like perilesional enhancement.
Neuroendocrine tumors due to content of carcinoid or islet cells, renal carcinoma, melanoma as well as thyroid carcinoma mostly have hypovascularized liver metastases with variable ring perilesional enhancement due to "wash in" and "wash out" phases of contrast medium.
The basic principle of magnetic resonance is the magnetic field that is stimulating hydogenium jones in the segment of body that is examined and trough different softer applications, electromagnetic signal is being transformed into an image.
Thus, information is obtained on physiology or pathology of the tissue or organ of interest. This condition can be verified by application of a contrast medium such as gadopenetate dimeglumine.

Materials and methods

This study comprised 23 patients ranging in age from 40 to 75 years, 15 females and 8 males with previously detected malignant diseases.
Eleven of them had breast surgery, and had also previously received cytostatic therapy; another 2 were with ovarian cancer and two with colon cancer. Five men have had colon surgery for colon cancer and 3 had pancreatic cancer. All of these patients underwent MRI of the upper abdomen and liver in native series. While performing the MRI, controlled breathing was assured and series were made after the intravenous application of contrast for MRI with magnitude of the magnetic field of 1,5 Tesla. In the examination and MR evaluation, the following sequences were included -standard spin-echo (SE) T1-weighted (T1W) and T2-weighted (T2W) single breath-hold, as well as the sequences with intravenous application of gadolinium dimeglumine.
State-of-the-art MRI techniques give opportunity for shorter acquisitions of sequences during one respiratory cycle with using T1W fast spoiled gradient echo (SGE) sequences. This sequence is selective in terms acquisition of a single slice short time with the central k-space data acquired over a fraction of that time. As the image contrast is derived from central k-space, single shot techniques are remarkably motion insensitive, and they are breathing-independent. Therefore they can be

useful with difficult patients. T1W gradient echo and two-dimensional (2D) has decreased artefacts lines.
This advanced combination of examination helps in better evaluation of liver anatomy and gives enough volumetric data for multiplanar recontractions.

Results

Eleven patients underwent breast surgery, two had ovarian cancer; in total 24 metastasis were detected, of which 20 were hypovascularized with continuous iregular peripheral ring enhancement. Four of them had benign presentation, resembling hemangiomas (Table 1).
In 7 patients with colon cancer, 17 metastases were detec ted with different diameter, that were hypervascularized with maximum diameter of 23 mm and significant 7 mm ring enhancement.
Three patients diagnosed with pancreatic cancer were detected with 12 metastases with mixed vascularization with significant ring enhancement, due to desmoplastic reaction.

Table 1. Desmoplastic reaction in liver metastases

Primary malignancy	Ca breast 11 patients	Ovarian Ca 2 patients	Colon Ca 7 patients	Pancreatic ca 3 patients
Number of liver metastases MRI detected	17	3	17	3
Anatomic localization	V , VI VII	IV , V, VII , VII	VII, VIII, II, V	V, VI,VII,
Size	20 mm - 9 mm	23 mm -10 mm	23 mm- 9 mm	40 mm – 9 mm
Vascularization	Hypovascular	Hypovascular	Hypervascular	Mixed vascularity
Parenchymal ring	Continual hypersignal ring 3 mm	Continual hypersignal ring 6 mm	Continual hypersignal ring 7 mm	Discontinuous hypersignal ring 3 mm

Discussion

Liver metastases present with variable intensity of signal on T1 and T2 sequences, hypo- to isointense signal on T1W, iso- to hyperintense on T2W [7]. They have tendency to lose signal intensity on prolonged T2W (TE > 160), which is different from focal lesion with blood of high protein content which can be seen in hemangioma or liver cysts. Different types of liver metastases originating from sarcoma, melanoma (Figure 1) or neuroendocrine tumors due to central liquefaction necrosis present with central hypersignal intensity [8].
In 25% of metastases originating from colorectal carcinoma also hypersignal peripheral zone can be seen, which is a signal from viable tumor tissue with central hypointense signal due to necrosis [9]. This can be presented with two types of signs - "doughnut sign" on T1 sequences or "target sign" on T2 sequence [10].
The doughnut sign presents hypointense peripheral ring zone with central even more hypointense signal. The target sign is hyperintense center of necrosis or fibrosis with hyperintense peripheral ring zone due to a viable malignant tissue.
There are some cases where metastases present hyperintense signal on T2 sequences in the central part or like peripheral ring, but sometimes due to paramagnetic content metastases can be hyperintense completely [11]. High intensity on T2 sequences can be seen in melanoma metastases due to melanin content in the cells or in colorectal carcinoma due to extracellular methemoglobin released due to bleeding; ovarian carcinoma metastases have a high T1 intensity due to mucinous content [12].
One more specific sequence is diffusion weighted MR imaging (DWI), which is based on Brown movement of water molecules. Koh *et al*. [13] in a study of 40 patients with liver metastases from colorectal carcinoma presented a relevant coefficient of diffusion map (ADC) higher than the liver background.
The intravenous contrast is extracellular agent that shortens the time of T1 sequences and presents increasing of signal intensity. The liver has a unique double vascularization, approximately 70 to 80% from the central portal veins and the remaining vascularization is from the hepatic vein. Hepatic metastases develop similar vascularization with the primary malignancy. Therefore, they can be classified as hypovascular, hy-

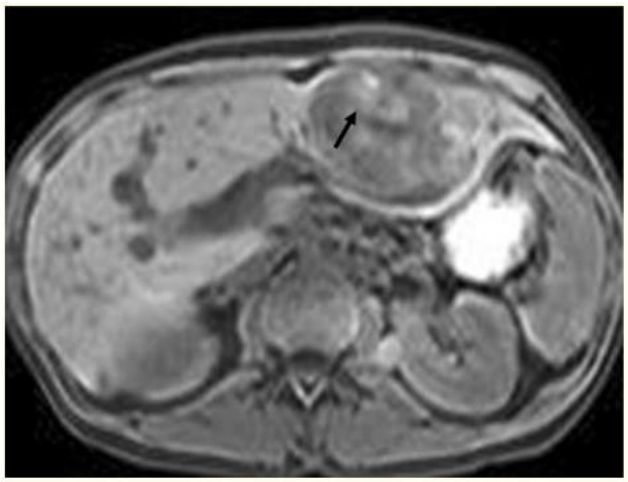

Fig. 1. Melanin metastases of liver with hyperintense signal on T1 sequences

pervascular or sometimes a mixed signal of vascularization. Metastases that are vascularized from heaptic vein are hypervascular (Figure 2), opposite to those

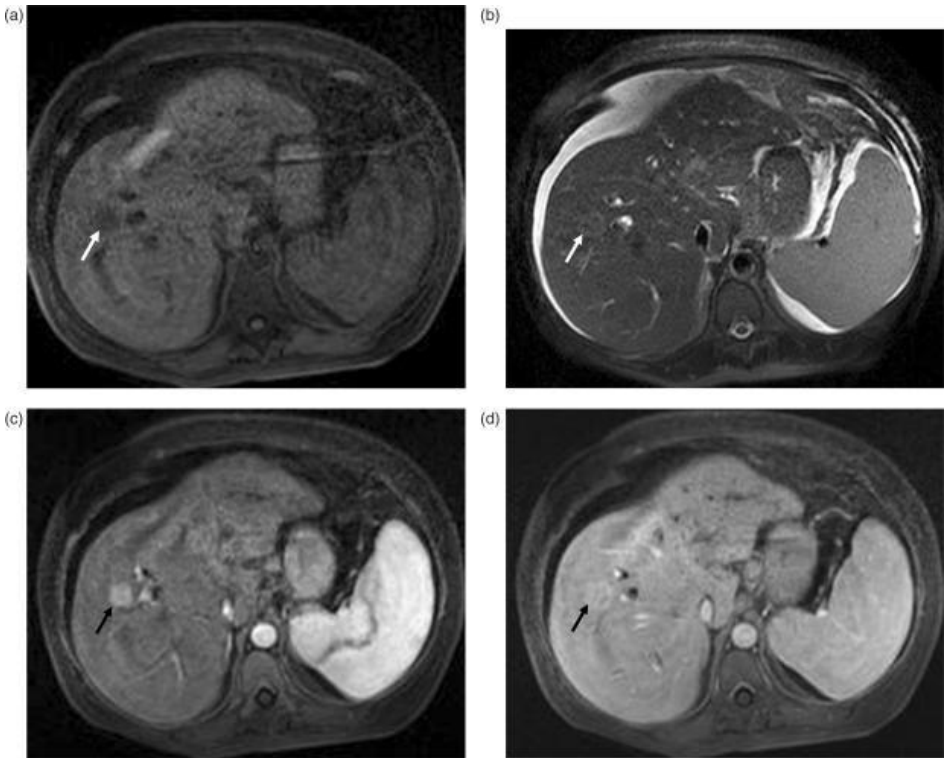

Fig. 2. Hypervascular metastases from breast carcinoma

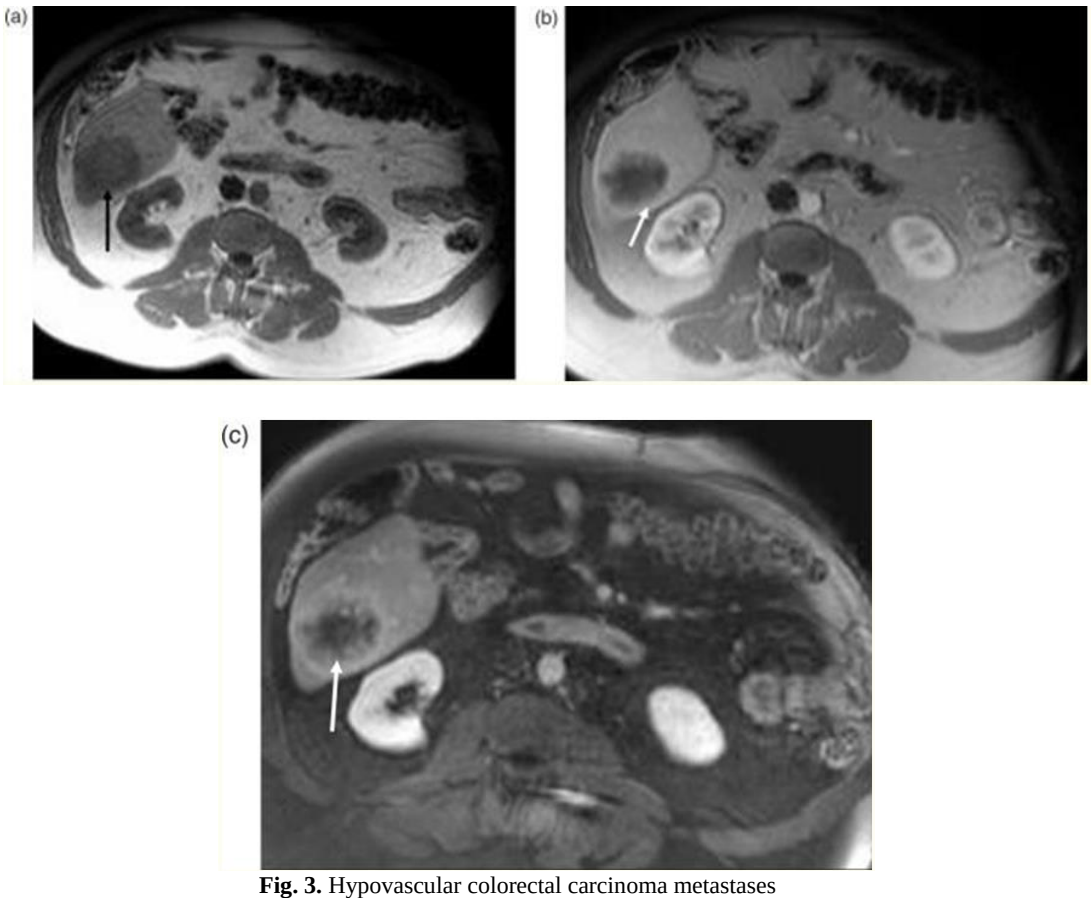

Fig. 3. Hypovascular colorectal carcinoma metastases

which are vascularized from portal vein and present hypervascularity (Figure 3). Hypervascular metastases are with high intensity in the arterial phase, and hypovascular in portal venous phase. This is why it is necessary to perform MRI in 2 phases with the differrence between dynamic injection of contrast and initiation of sequence with delay of 30 seconds. The time difference depends on patients' ejection heart fraction. We can detect arterial phase even visually when portal vein is visible, and hepatic vein is not visible [14- 16]. Optimum venous phase is 55 to 70 seconds after dynamic application of contrast. Late phase is after 2 to 4 minutes.
Semelka *et al*. presented in their study hepatic metastases that were with transitory peripheral continuous ring enhancement which was due to a viable tumor tissue. Central signal was deep hypotensive due to necrosis in the metastases [17]. Advanced histological analysis has shown that external lesion ring is desmoplastic reaction due to inflammation or vascular proliferation, but it is not clear if there is potentiality for malignant recidivism [18]. This desmoplastic reaction and assessment of its malignant potentiality can change the approach in surgical resection and treatment of metastases [19].

Conclusion

The technical capacity of magnetic resonance performed in different sequences provides proper information at tissue level of focal liver changes. MRI presents their nature, anatomical localization, vascularization and infiltrative potential especially in presentation and analyses of peripheral ring signal intensity types.
Regarding MRI characteristics of the ring enhancement, surgical resection of the metastasis should be taken into account in terms of assessment of the malignant potentials of the recurrent lesions.
Another important fact about MRI characteristics of the ring enhancement is in terms of differentiation metastasis from hemangiomas, that also can present with nodular or discontinuity of ring enhancement.

Conflict of interest statement. None declared.

References

1. Imam K, Bluemke DA. MR imaging in the evaluation of hepatic metastases. *Magn Reson Imaging Clin N Am* 2000; 8: 741-756.
2. Ward J. New MR techniques for the detection of liver metastases. *Cancer Imaging* 2006; 6: 33-42.
3. Rummeny EJ, Marchal G. Liver imaging. Clinical applications and future perspectives. *Acta Radiol* 1997; 38: 626-630.
4. Semelka RC, Cance WG, Marcos HB, Mauro MA. Liver metastases: comparison of current MR techniques and spiral CT during arterial portography for detection in 20 surgically staged cases. *Radiology* 1999; 213: 86-91.
5. Soyer P, Levesque M, Caudron C, *et al*. MRI of liver metastases from colorectal cancer vs. CT during arterial portography. *J Comput Assist Tomogr* 1993; 17: 67-74.
6. Schima W, Kulinna C, Langenberger H, Ba-Ssalamah A. Liver metastases of colorectal cancer: US, CT or MR? *Cancer Imaging* 2005; 5A: S149-S156.
7. Saini S, Nelson RC. Technique for MR imaging of the liver. *Radiology* 1995; 197: 575-577.
8. Martin DR, Danrad R, Hussain SM. MR imaging of the liver. *Radiol Clin North Am* 2005; 43: 861-886.
9. Martin DR, Friel HT, Danrad R, *et al*. Approach to abdominal imaging at 1.5 Tesla and optimization at 3 Tesla. *Magn Reson Imaging Clin N Am* 2005; 13: 241-254. v–vi.
10. Hahn PF, Saini S. Liver-specific MR imaging contrast agents. *Radiol Clin North Am* 1998; 36: 287-297.
11. Ji H, Ros PR. Magnetic resonance imaging. Liver-specific contrast agents. *Clin Liver Dis* 2002; 6: 73-90.
12. Bellin MF, Zaim S, Auberton E, *et al*. Liver metastases: safety and efficacy of detection with superparamagnetic iron oxide in MR imaging. *Radiology* 1994; 193: 657-663.
13. Koh DM, Scurr E, Collins DJ, *et al*. Colorectal hepatic metastases: quantitative measurements using single-shot echo-planar diffusion-weighted MR imaging. *Eur Radiol* 2006; 16: 1898-1905.
14. Vogl TJ, Hammerstingl R, Schwarz W, *et al*. Superparamagnetic iron oxide-enhanced versus gadolinium-enhanced MR imaging for differential diagnosis of focal liver lesions. *Radiology* 1996; 198: 881-887.
15. Sica GT, Ji H, Ros PR. Computed tomography and magnetic resonance imaging of hepatic metastases. *Clin Liver Dis* 2002; 6: 165-179. vii.
16. Wittenberg J, Stark DD, Forman BH, *et al*. Differentiation of hepatic metastases from hepatic hemangiomas and cysts by using MR imaging. *AJR Am J Roentgenol* 1988; 151: 79-84.
17. Kelekis NL, Semelka RC, Woosley JT. Malignant lesions of the liver with high signal intensity on T1-weighted MR images. *J Magn Reson Imaging* 1996; 6: 291-294.
18. Semelka RC, Hussain SM, Marcos HB, Woosley JT. Perilesional enhancement of hepatic metastases: correlation between MR imaging and histopathologic findings-initial observations. *Radiology* 2000; 215: 89-94.
19. Yu JS, Rofsky NM. Hepatic metastases: perilesional enhancement on dynamic MRI. *AJR Am J Roentgenol* 2006; 186: 1051-1058.
20. Soyer P, Gueye C, Somveille E, *et al*. MR diagnosis of hepatic metastases from neuroendocrine tumors versus hemangiomas: relative merits of dynamic gadolinium chelate-enhanced gradient-recalled echo and unenhanced spin-echo images. *AJR Am J Roentgenol* 1995; 165: 1407-1413.

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Original article

EVALUATION OF FUNCTIONAL RESULTS IN PATIENTS AFTER TOTAL HIP ARTHROPLASTY SURGICALLY TREATED WITH MODIFIED ANTEROLATERAL APPROACH BY WATSON JONES

ЕВАЛУАЦИЈА НА ФУНКЦИОНАЛНИ РЕЗУЛТАТИ КАЈ ПАЦИЕНТИ ПОСЛЕ ТОТАЛНА АРТРОПЛАСТИКА НА КОЛКОТ, ХИРУРШКИ ТРЕТИРАНИ СО ПРИМЕНА НА МОДИФИЦИРАН АНТЕРО-ЛАТЕРАЛЕН ПРИСТАП ПО WATSON JONES

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Abstract

Introduction. Degenerative hip diseases are among the most common musculoskeletal disorders. Approximately 28% of the population over the age of 45 suffers from osteoarthritis of the hip and its prevalence is expected to increase in the coming decades.
Aim. Evaluation of functional results in patients after total hip arthroplasty surgically treated with modified anterolateral approach by Watson Jones.
Methods. This retrospective study was performed at the University Clinic for Orthopedic Diseases, and included 30 patients diagnosed with degenerative hip disease, surgically treated with a modified anterolateral approach by Watson Jones with total hip artrhroplasty in the period 2018-2019. For the purposes of the study, patients were analyzed with the Harris Hip Score preoperatively.
Results. One day before the intervention, all patients had Harris Hip score lower than 70, which indicated a poor result. Thirty days post-surgery, the value of Harris Hip score ranged from 70.95 to 75.2, the average value of the Harris Hip score was 72.34±1.5. After 6 months of the performed surgery, the Harris Hip score was 90.05 to 92.2, the mean value of the Harris Hip score was 91.60±0.9. One year after surgery, patients had a Harris Hip score of 93.7 to 95.4, mean 95.08±0.4. All patients operated on with the anterolateral approach, one year after the intervention, had an excellent result; Harris Hip score between 90 and 100.
Conclusion. There is no consensus regarding the best approach for primary total hip arthroplasty. The benefits and understanding of each approach are well documented and the choice of which approach to use depends largely on surgeon's preferences.

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Keywords: modified anterolateral approach, hip osteoarthritis, Harris Hip Score

Апстракт

Вовед. Дегенеративните заболувања на колкот се меѓу најчестите мускулно-скелетни нарушувања. Приближно 28% од популацијата на возраст над 45 години страда од остеоартритис на колкот и се очекува неговата преваленца да се зголеми во наредните децении.
Цел. Евалуација на функционалните резултати кај пациенти по тотална артропластика на колкот хируршки третирани со модифициран антеролатерален пристап по Watson Jones.
Методи. Студијата се спроведе на Универзитетската клиника за Ортопедски болести, таа е од ретроспективен карактер и опфати 30 пациенти со дијагноза на дегенеративно заболување на колкот, хируршки третирани со модифициран антеролатерален пристап по Watson Jones во периодот 2018-2019 година со тотална артропластика на колкот. Во интерес на студијата, пациентите беа испитувани со Harris Hip Score предоперативно.
Резултати. Сите пациенти еден ден пред интервенцијата имале оцена на Harris Hip Score помал од 70, што укажува на лош резултат. По 30 дена од операцијата, вредноста на Harris Hip Score се движеше од 70,95 до 75,2, просечната вредност за Harris Hip Score беше 72,34. 1.5. По 6 месеци од извршената операција, Harris Hip Score беше 90,05 до 92,2, средната вредност за Harris Hip Score беше 91,60±0,9. На следење една година по операцијата, пациентите имаа оцена на Harris Hip од 93,7 до 95,4, што значи 95,08±0,4. Сите пациенти оперирани со антеролатерален пристап, по една година интервенција, имаа одличен резултат, Harris Hip Score помеѓу 90 и 100.

Заклучок. Не постои консензус за тоа кој пристап е најдобар за примарна тотална артропластика на колкот. Придобивките и разбирањето на секој пристап се добро документирани и изборот на кој пристап да се користи во голема мера зависи од преференциите на хирургот.

Клучни зборови: модифициран антеролатерален пристап, коксартроза, Harris Hip Score

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Introduction

Degenerative hip diseases are among the most common musculoskeletal disorders [1,2]. Approximately 28% of the population over the age of 45 suffers from osteoarthritis of the hip and its prevalence is expected to increase in the coming decades [3-5]. The founder of modern total hip arthroplasty (THA) was Charnley in 1950 [6,7]. After decades of progress and development, this surgery has become one of the most frequently performed surgical interventions in orthopedics. In 2010 in the United States, approximately 2.5 million patients living with artificial hips were registered, and approximately 332,000 interventions were performed annually [8.9]. This number is expected to grow significantly in the coming years [10,11].

The adult standardized prevalence of symptomatic radiographically verified osteoarthritis of the hip varies from 1% to 10% in larger population-based prevalence studies [12-16]. Differences in research results may be due to differences in risk factor profiles between the populations in which the analysis was performed. The two largest studies conducted in the United States, the Osteoarthritis Project in Johnston [16] and Framingham [14], showed prevalence rates of 10% and 4.2%, respectively. The higher prevalence in the Johnston study is thought to be due to the rural population, which is predominantly represented by farmers and African Americans, who are independent factors in osteoarthritis of the hip [16]. In contrast to this study, the Framingham study includes a predominantly urban, Caucasian population.

On the other hand, a study conducted in Beijing, reports a prevalence of hip osteoarthritis of about 1% which suggests a significantly lower risk of hip osteoarthritis in Asian ethnicities [12]. It is particularly important to note that the prevalence of hip osteoarthritis is much higher when verified on the basis of symptomatology or radiography in isolation [12-16].

Hip osteoarthritis can only be diagnosed with a clinical picture, although radiographic examinations may be useful to confirm the diagnosis and to monitor disease progression. Following a well-established history that includes data on possible risk factors for generative hip disease, the physician should perform a detailed clinical examination. The examination itself should include inspection and comparison of the length of the affected and healthy leg, evaluation of body weight, presence or absence of deformity, as well as range of motion in the hip and neurovascular status.

In 1957, Kellgren and Lawrence [17] published a scale for the assessment of radiological assessment of hip osteoarthritis which still remains the most widely used classification system, but this scale is not specific for the assessment of degenerative hip disease. In 1963, Kellgren described four degrees of osteoarthritis of the hip based on the degree of joint narrowing, osteophyte formation, arthritic changes affecting the bone margins, and gross deformity as follows: Grade 1 - suspected hip osteoarthritis with possible joint narrowing space, medial and subtle osteophyte formation around the femoral head; Grade 2 - mild hip osteoarthritis with some narrowing of the joint space with definite formation of osteophytes and mild subchondral sclerosis; Grade 3 - moderate hip osteoarthritis with significant narrowing of the joint space, small osteophytes, sclerosis and cyst formation and deformity of the femoral head and acetabulum; Grade 4 - wiped joint space with features seen in grades 1 to 3, large osteophytes, and gross deformity of the femoral head and acetabulum [18,19].

Other imaging studies such as computed tomography and magnetic resonance imaging are not required for diagnosis and are usually reserved for the identification of secondary causes. A laboratory kit may be performed to confirm the diagnosis and rule out inflammatory conditions such as rheumatoid arthritis, especially if joint symptoms are associated with morning stiffness and synovial inflammatory changes.

It is important to note that there may be a significant contrast between symptoms and radiographic findings. Thus, patients with marked radiographic changes might not show severe correlated clinical symptoms and *vice versa*.

Materials and methods

The study was performed at the University Clinic for Orthopedic Diseases; it was of retrospective character and included 30 patients diagnosed with degenerative hip disease, surgically treated with a modified anterolateral approach by Watson Jones with total hip artrhroplasty in the period 2018-2019. For the purposes of the study, patients were analyzed with the Harris Hip Score preoperatively. Follow-up of the patients after discharge was scheduled at 30 days postoperatively, and at 6 and 12 months. We examined Harris Hip score in all control time points.

Surgical approach

The patient is introduced to spinal anesthesia. He/she is placed in a supination position. The operating field is cleaned and garnished according to the protocol. The skin incision is made 3-4 cm laterally from the

spina iliaca anterior superior and extends to the base of the large trochanter. It is prepared in layers of skin, subcutaneous tissue, *fascia lata* and muscles, after which the joint capsule is reached, and whether a capsulotomy will be performed depends on the decision of the surgeon. After capsulotomy, the neck of the femur is reached, where an osteotomy is performed and the head of the femur is removed from the acetabulum. The acetabulum rhymes and the acetabular component is placed. The leg is placed in a corrective position, during which the intramedullary canal of the thigh is rhymed, and then the stem is placed in the intramedullary canal of the thigh; an artificial head is placed on it, and then the head is repositioned in the acetabulum.

Results

Patients treated surgically with a modified anterolateral approach by Watson Jones had a mean age of 64.0 ±6.2 years. Their mean age was between 60-70 years. The body mass index was 19.7 and 29.3 kg/m2; The average BMI was 24.94±3.1 kg/m2. Patients with normal weight and overweight were equally represented. The minimum length of the operative skin incision was 7 cm, and was measured in 7 patients; the maximum length of 10 cm was measured in 5 patients. The average length of the surgical incision was 8.4±1.1 cm. The day before the surgery, the values of the Harris Hip score ranged from 6.8 to 48.8; average 22.72± 12.3. The median value of the Harris Hip score was 19.2. One day before the intervention, all patients had Harris Hip score lower than 70, which indicated a poor result. Thirty days after surgery, the value of Harris Hip score ranged from 70.95 to 75.2; average value being 72.34±1.5. After 6 months of the performed surgery, the Harris Hip score was 90.05 to 92.2; the mean value was 91.60±0.9. On follow-up one year after surgery, patients had a Harris Hip score of 93.7 to 95.4, mean 95.08±0.4. All patients operated on with anterolateral approach, after one year of the intervenetion, had an excellent result; the Harris Hip score was between 90 and 100. Postoperatively, at 30 days, 6 and 12 months, female and male patients operated on with anterolateral approach did not differ significantly regarding the Harris Hip score ($p=0.33$, $p=0.55$ and $p= 0.95$, respectively at the time points analyzed). The mean score was similar in both sexes: about 72 after one month of intervention, about 91 after 6 months, and about 95 after 12 months. A significant correlation was confirmed between age and the Harris Hip score, 30 days postoperatively ($p=0.016$) and 6 months postoperatively ($p<0.0001$), while the correlation 12 months postoperatively was on the verge of significance ($p=0.056$). All correlations were negative or indirect, which showed that with increasing age of patients operated on with the anterolateral approach, a decrease was registered. The value of the Harris Hip score was r =-0.435; r=-0.611 and r=-0.352, respectively in the three consecutive post-intervention time points. The average verticalization time was 2.2 ± 0.4 days.

Discussion

The advantages of the anterolateral approach are a reduced incidence of dislocations [20,21] and provision of good acetabular exposure [22]. However, there are obvious drawbacks. The anterior *gluteus medius* may restrict proximal femoral exposure, requiring tenotomy of these fibers [20]. The lower branch of the superior gluteal nerve is also vulnerable to damage [23,24].

Wang Gang *et al*. in their study published their results from the use of anterolateral implants in patients treated surgically for femoral neck fractures and considered that minimally invasive surgery through an anterolateral approach potentially leads to a reduction in operative trauma, less blood loss, less soft tissue damage, a reduction in postoperative pain, and faster verticalization of patients. Theoretically, these improvements could result in shorter hospital stays, verticalization, and rehabilitation periods, as well as better cosmetic results through smaller skin incisions and wound closure [25-33]. The long-term outcome of total hip arthroplasty may be influenced by the positioning of the components. Improper placement can lead to reduced implant longevity and other debilitating complications such as recurrent dislocations.

Reducing pain and improving function after total hip arthroplasty is measured with instruments such as the Harris Hip Scale (HHS) [34]. HHS is the most commonly used instrument for assessing the outcome of total hip arthroplasty [35]. HHS is valid and reliable [36-39] and is often used as the reference/gold standard for assessing the constructive validity of other patient outcome measures reported for hip surgery outcomes [40]. HHS is joint-specific, hip surgery and is widely available. A surgeon or healthcare professional conducts HHS.

To our knowledge, despite its widespread use, there are no published data on what is clinically significant difference in HHS or whether HHS results are predictable for the risk of future revision surgery. If HHS can predict the risk of revision surgery, future studies could evaluate its usefulness as a screening tool for implant failure after total hip arthroplasty.

Jasvinder A Singh *et al*. published a study examining the ability of HHS to predict the risk of needing revision surgery after primary total hip arthroplasty. In conclusion, they found that in patients who underwent primary hip arthroplasty, HHS responded to changes and predicted the risk of revision after primary total arthroplasty. Clinically significant improvement thresholds for minimal and moderate clinically significant improvements in HHS have been defined in this study so that they can now be used in clinical trials in arthro-

plasty and clinical care. This study also established the additional usefulness of HHS in predicting the need for early revision surgery for total hip arthroplasty [41].

Harris (1969) designed 100-point grading scale and with domains of pain, function, activity, deformity, and movement. It is designed for use in young men with often long-lasting severe secondary osteoarthritis following an acetabular fracture that has been surgically treated with arthroplasty. Although not originally designed for patients with hip arthroplasty, it is widely used in this population. Since its introduction, several authors have reported that the result is a valid measure of the outcome for total hip arthroplasty based solely on the validity of good construction [42-44]. Although the validity of the design is important, it is not the only factor in assessing the overall validity of the outcome questionnaire. Confidentiality, internal consistency, content validity and accountability are also important. The questionnaire is suitable only when all 5 psychometric properties are of sufficient quality [45]. This scale is a measure of dysfunction, so the higher the score the better the outcome for the patient. Results can be calculated and recorded online. The maximum possible result is 100, and the results are interpreted as follows: <70 = poor result; 70-80 = fair, 80-90 = good and 90-100 = excellent.

Conclusion

The question which surgical approach to the hip is to be used for implantation of a total hip endoprosthesis has been widely debated. Despite this, there is no consensus which approach is the best regarding primary total hip arthroplasty. The benefits and understanding of each approach are well documented and the choice of which approach to use depends largely on surgeon's preferences, which in turn reflects the surgeon's training and experience.

Conflict of interest statement. None declared.

References:

1. Felson DT, Lawrence RC, Dieppe PA, *et al*. Osteoarthritis: New insights. Part 1: The disease and its risk factors. *Ann Intern Med* 2000; 133: 635-646.
2. Guccione AA, Felson DT, Anderson JJ, *et al*. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994; 84: 351-358.
3. Jordan JM, Helmick CG, Renner JB, *et al*. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project. *J Rheumatol* 2009; 36: 809-815.
4. Lawrence RC, Felson DT, Helmick CG, *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58: 26-35.
5. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum* 2006; 54: 226-229.
6. Morrey BF. A historical perspective of hip arthroplasty and reconstructive surgery. In: Cashman J, Goyal N, Parvizi J, editors. The Hip: Preservation, Replacement and Revision. *Brooklandville, MD: Data Trace Publishing Company* 2015; pp. 1.1-1.19.
7. Charnley J. Total hip replacement by low-friction arthroplasty. *Clin Orthop Relat Res* 1970; 72: 7-21.
8. Maradit Kremers H, Larson DR, Crowson CS, *et al*. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am* 2015; 97: 1386-1397.
9. "Inpatient Surgery". FastStats. National Center for Health Statistics. Centers for Disease Control and\Prevention. [Last accessed on 2016 Jun 26]. Available from: http://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberprocedureage.pdf .
10. Kurtz S, Mowat F, Ong K, *et al*. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am* 2005; 87: 1487-1497.
11. Singh JA. Epidemiology of knee and hip arthroplasty: A systematic review. *Open Orthop J* 2011; 5: 80-85.
12. Nevitt MC, Xu L, Zhang Y, *et al*. Very low prevalence of hip osteoarthritis among Chinese elderly in Beijing, China, compared with whites in the United States: the Beijing Osteoarthritis Study. *Arthritis Rheum* 2002; 46(7): 1773-1779.
13. Quintana JM, Arostegui I, Escobar A, *et al*. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. *Arch Intern Med* 2008; 168(14): 1576-1584.
14. Kim C, Linsenmeyer KD, Vlad SC, *et al*. Prevalence of radiographic and symptomatic hip osteoarthritis in an urban United States community: the Framingham Osteoarthritis Study. *Arthritis Rheumatol* 2014; 66(11): 3013-3017.
15. Barbour KE, Lui LY, Nevitt MC, *et al*. Hip osteoarthritis and the risk of all-cause and disease-specific mortality in older women: a population-based cohort study. *Arthritis Rheumatol* 2015; 67(7): 1798-1805.
16. Jordan JM, Helmick CG, Renner JB, *et al*. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol* 2009; 36(4): 809-815.
17. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; 16: 494-502.
18. Kellgren J. *The Epidemiology of Chronic Rheumatism.* Vol. 2. Oxford: Blackwell Scientific; 1963. Atlas of standard radiographs in arthritis.
19. *Atlas of standard radiographs of arthritis.* Oxford, UK: Blackwell Scientific; 1963.
20. Masonis JL, Bourne RB. Surgical approach, abductor function, and total hip arthroplasty dislocation. *Clin Orthop Relat Res* 2002; 405: 46-53.
21. Woo RY, Morrey BF. Dislocations after total hip arthroplasty. *J Bone Joint Surg Am* 1982; 64: 1295-1306.
22. Ritter MA, Harty LD, Keating ME, *et al*. A clinical comparison of the anterolateral and posterolateral approaches to the hip. *Clin Orthop Relat Res* 2001; 385: 95-99.
23. Barrack RL. Neurovascular injury: avoiding catastrophe. *J Arthroplasty* 2004; 19(4 suppl 1): 104-107.
24. Bertin KC, Rottinger H. Anterolateral mini-incision hip replacement surgery: a modified Watson-Jones approach. *Clin Orthop Relat Res* 2004; 429: 248-255.

25. Dorr LD, Maheshwari AV, Long WT, *et al*. Early pain and function results comparing posterior minimally invasive to con ventional total hip arthroplasty: a prospective, randomized blinded study. *J Bone Joint Surg Am* 2007; 89: 1153-1160.
26. Laffosse JM, Chiron P, Molinier F, *et al*. Prospective and comparative study of the anterolateral mini-invasive approach versus minimally invasive posterior approach for primary total hip replacement. Early results. *Int Orthop* 2007; 31(5): 597-603.
27. O'Brien DA, Rorabeck CH. The mini-incision direct lat eral approach in primary total hip arthroplasty. *Clin Orthop Relat Res* 2005; 441: 99-103.
28. Malik A, Dorr LD. The science of minimally invasive total hip arthroplasty. *Clin Orthop Relat Res* 2007; 463: 74-84.
29. Pfluger G, Junk-Jantsch S, Scholl V. Minimally invasive total hip replacement via the anterolateral approach in the supine position. *Int Orthop* 2007; 31Suppl 1: S7-S11.
30. Ogonda L, Wilson R, Archbold P, *et al.* Aminimal-incision technique in total hip arthroplasty does not improve early post operative outcomes. A prospective, randomized, controlled trial. *J Bone Joint Surg Am* 2005; 87(4): 701-710.
31. Noble PC, Johnston JD, Alexander JA, *et al*. Making minimally invasive THR safe: conclusions from biomechanical simula tion and analysis. *Int Orthop* 2007; 31 Suppl 1: S25-S28.
32. Rittmeister M, Callitsis C. Factors influencing cup orienttation in 500 consecutive total hip replacements. *Clin Orthop Relat Res* 2006; 445: 192-196.
33. Wang G, Gu G, Li D, *et al*. Comparative study of anterolateral approach versus posterior approach for total hip replacement in the treatment of femoral neck fractures in elderly patients. *Chinese Journal of Traumatology* 2010; 13(4): 234-239.
34. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg Am* 1969; 51(4): 737-755.
35. Riddle DL, Stratford PW, Singh JA, Strand CV. Variation in outcome measures in hip and knee arthroplasty clinical trials: a proposed approach to achieving consensus. *J Rheumatol* 2009; 36(9): 2050-2056.
36. Soderman P, Malchau H. Is the Harris hip score system useful to study the outcome of total hip replacement? *Clin Orthop Relat Res* 2001; 384: 189-197.
37. Soderman P, Malchau H, Herberts P. Outcome of total hip replacement: a comparison of different measurement methods. *Clin Orthop Relat Res* 2001; 390: 163-172.
38. Kavanagh BF, Fitzgerald RH. Jr Clinical and roentgenographic assessment of total hip arthroplasty. A new hip score. *Clin Orthop Relat Res* 1985; 193: 133-140.
39. Wright JG, Young NL. A comparison of different indices of responsiveness. *J Clin Epidemiol* 1997; 50(3): 239-246.
40. Shields RK, Enloe LJ, Evans RE, *et al.* Reliability, validity, and responsiveness of functional tests in patients with total joint replacement. *Phys Ther* 1995; 75(3): 169-176.
41. Singh JA, Schleck C, Harmsen S, Lewallen D. Clinically important improvement thresholds for Harris Hip Score and its ability to predict revision risk after primary total hip arthroplasty. *BMC Musculoskelet Disord* 2016; 17: 256.
42. Soderman P, Malchau H. Is the Harris Hip Score system useful to study the outcome of total hip replacement? *Clin Orthop* 2001; (384): 189-197.
43. Shi HY, Mau LW, Chang JK, *et al*. Responsiveness of the Harris Hip Score and the SF-36: five years after total hip arthroplasty. Qual Life Res. 2009 Oct;18(8):1053-60. doi: 10.1007/s11136-009-9512-0. Epub 2009 Jul 16. PMID: 19609722
44. Terwee CB, Bot SD, De Boer MR, *et al*. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; 60(1): 34-42.

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ММР

Original article

TREATMENT OF DEGENERATIVE KNEE OSTEOARTHRITIS USING INJECTIONS OF HYALURONIC ACID

ЛЕКУВАЊЕ НА ДЕГЕНАРАТИВНИОТ ОСТЕОАРТРИТ НА КОЛЕНОТО СО ПРИМЕНА НА ХИЈАЛУРОНСКА КИСЕЛИНА

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Abstract

Introduction. Osteoarthritis of the knee is the most common chronic degenerative joint disease. Many patients with knee osteoarthritis seek treatment with non-surgical strategies as a choice of delaying or avoiding surgery. In addition to traditional non-surgical methods of treatment, such as weight loss and physical therapy, the use of intra-articular injections of viscous supplements and biological preparations is becoming more common.

Methods. Knee osteoarthritis (OA) is characterized by pain, numbness, swelling, and progressive functional limitation. Intra-articular corticosteroid and hyaluronic acid injections have been used for a long time to relieve the symptoms of OA of the knee. Viscosupplementation has been used as a therapeutic modality for the treatment of knee OA. The principle of viscosupplementation is based on the physiological properties of hyaluronic acid (HA) in the synovial joint which helps the tissue to lubricate, cushion, and reduce joint pain.

Results. The study included 88 patients of both sexes with osteoarthritis of the knee, treated with hyaluronic injections - monodose with over 75 mg high molecular weight hyaluronic acid.

The treated patients had grade 1 and 2 knee osteoarthritis according to the Kallgren-Lorence scale.

Conclusion. All measurements were used at the time of enrollment in the study before administration of any injection. They were measured again at the end of three months using the WOMAC index.

The reduction was significant in the WOMAC score for pain, numbness, functional limitations, and an overall score 3 months after initiation of therapy compared to admission values, 6 months after initiation of therapy compared to admission, and 6 months compared to 3 months of therapy with hyaluronic acid.

All patients had minimal results before the treatment.

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Key words: osteoarthritis, joint cartilage, hyaluronic acid

Апстракт

Вовед.Остеоартитот на коленото е најчестото хронично дегенеративно заболување на зглобот. Голем дел од пациентите со остеоартрит на коленото бараат нехируршки третман, со цел да го избегнат хируршкиот третман. Покрај традиционалните нехируршки методи на третман, како на пример губиток на телесна тежина и физикална терапија, употребата на интраартикуларни инјекции од вискозни суплементи и биолошки препарати станува се почеста.

Методи.Остеоартитот на коленото се карактеризира со болка, вкочанетост и прогресивно функционално ограничување. Интраартикуларните инјекции на кортикостероиди и хијалуронска киселина се користеле долго време за ослободување на симптомите од остеоартит на коленото. Вискосуплементацијата се користела како тераписки модалитет за третман на остеоартит на коленото. Принципот на вискосуплементацијата е базиран на физиолошките карактеристики на хијалуронската киселина во синовијалниот зглоб, кои помагаат ткивото да се подмачка, омекне и да се редуцира болката во зглобот.

Резултати. Студијата вклучува 88 пациенти од двата пола со остеоартит на коленото, третирани со инјекции на хијалуронска киселина - монодоза (единечна доза), со повеќе од 75 mg високомолекуларна хијалуронска киселина.

Третираните пациенти имале остеоартит градус 1 и 2 според Kallgren-Lorence скалата.

Заклучок. Сите мерења беа користени во времето на запишуваењто во студијата, пред администрацијата на било која инјекција. Тие повторно беа мерени после 3 месеци, со користење на WOMAC index.

Редукцијата беше сингнификантна во WOMAC бодовникот за болка, вкочанетост, функционално ограничување и целокупниот резултат 3 месеци после започнувањето на терапијата во споредба со почетните вредности, 6 месеци после започнување на терапија во споредба со 3 месеци од терапијата со хијалуронска киселина.
Сите пациенти имале минимални резултати пред третманот.

Клучни зборови: остеоартрит, зглобна рскавица, хијалуронска киселина.

Introduction

Osteoarthritis is a chronic progressive and degenerative disease that affects the cartilage and its surrounding tissue. It is one of the most common chronic diseases in the world and imposes a significant economic burden on patients and society. Osteoarthritis of the hips and knees, in particular, tends to cause the greatest burden on the population, as the deterioration of these large weight-bearing joints seriously affects the ability to perform daily activities. There is currently no definitive cure for osteoarthritis, and most treatments aim to relieve pain and delay functional decline [1]
There is cartilage damage combined with a significant reduction in viscoelastic properties of synovial fluid and molecular weight and concentration of natural hyaluronic acid in the synovial fluid reduces [2]. This loss of viscoelasticity reduces the lubrication between the joint surfaces and erodes the articular surfaces and is a mechanism of origin of pain in osteoarthritis [3]
The patient presents with pain, swelling, numbness, deformity, reduced range of motion, and disability, which significantly affect the quality of life. Treatment is aimed at reducing symptoms like reducing pain as well as inflammation process and normal joint movement and slowing disease progression [4]. That includes holistic therapeutic modalities including non-pharmacological measures such as patient education, physical therapy with exercises to maintain the range of movement and strength, lifestyle modifications such as diet and weight loss. The purpose of this study was to evaluate the efficacy of HA intra-articular injections in the management of osteoarthritic knee pain [5]
Kellgren and Lawrence system for classification of osteoarthritis.

Classification

Numerous variations of the Kellgren and Lawrence classification system have been used in clinical studies [7]. Below is the original description [6-8]:

- Grade 0 (none): definite absence of x-ray changes of osteoarthritis;
- Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping;
- Grade 2 (minimal): definite osteophytes and possible joint space narrowing;
- Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends;
- Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

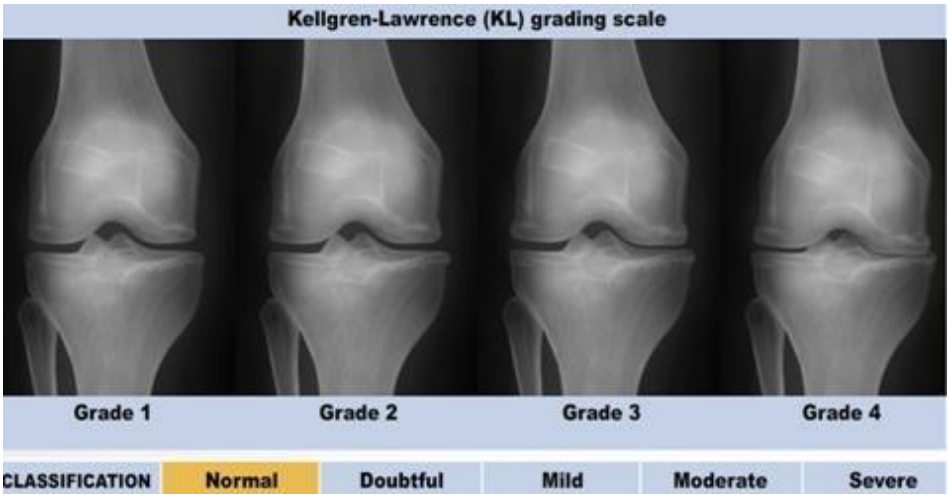

Fig. 1. Kellgren and Lawrence classification system, radiographic characteristics of different stages in knee osteoarthritis

Characteristics of Hyaluronic Acid

Hyaluronic acid is found naturally in many tissues and fluids, but more abundantly in the articular cartilage and synovial fluid. The content of hyaluronic acid varies in different joints and types. Hyaluronic acid is a non-sulfate, naturally occurring non-protein glycosaminoglycan with various physical and chemical proper-

ties, produced by synoviocytes, fibroblasts, and chondrocytes. Hyaluronic acid plays an important role in the biomechanics of normal synovial fluid, where it is partly responsible for the lubrication and viscoelasticity of synovial fluid. Hyaluronic acid concentration and its molecular weight (MW) decrease as osteoarthritis progress with age. For this reason, hyaluronic acid has been used for more than four decades in the treatment of osteoarthritis in dogs, horses, and humans. Hyaluronic acid produces anti-arthritic effects through several mechanisms involving receptors, enzymes, and other metabolic pathways. This study provides an explanation based on the mechanisms for the use of hyaluronic acid in some conditions of the disease with particular reference to osteoarthritis [9].

Materials and methods

A total of 88 subjects were enrolled in this prospective randomized study in line with various criteria. These included both genders (44 men and 44 women), age (45-70 years) and Grade of disease by Kellgren-Lawrence (K-L) severity grade I and II OA of the knee.
A total of 88 patients were treated with hyaluronic injections - monodose (IAHA) with over 75 mg of high molecular weight hyaluronic acid. The treated patients had grade 1 and 2 knee osteoarthritis according to the Kallgren-Lorence scale. All patients diagnosed with OA of the knee by orthopedic surgeon using X-rays were rated as stages I and II according to Kellgren and Lawrence Scale [10]. The injection was given on the spot near the superolateral side of the patella in the suprapatellar sac under aseptic conditions. All measurements were made at the time of enrollment in the study before and after any injection, and repeated again at the end of 3 months using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). This is a self-administered test to compare pain and functional improvement before and after using HA injection [11].

Results

Eighty-eight patients enrolled in our study suffered from osteoarthritis, which was treated with hyaluronic acid intra-articular injections. Pain and numbness, and physical function of patients with knee OA were assessed before and after treatment using the WOMAC index. Subjective scoring with the WOMAC after 6 months showed a gradual decrease suggesting pain relief, stiffness, and physical improvement.
All patients were treated with hyaluronic injections - monodose with over 75 mg high molecular weight hyaluronic acid.
The treated patients had grade 1 and 2 knee osteoarthritis according to the Kallgren-Lawrence scale.

Table 1. Gender distribution of patients to whom hyaluronic acid was applied

Gender	Subgroup (with milder symptoms)	
	n	Hyaluronic acid n (%)
men		44 (50)
women		44 (50)

The hyaluronic acid subgroup with milder symptoms
In the subgroup of patients with milder symptoms treated with hyaluronic injections, the WOMAC score for pain, numbness, functional limitations, and overall score had significantly different values at the three-time points (F=35.8 p<0.0001, Friedman ANOVA=15.25 p<0.000=44.1 p<0.0001, F=48.5 p<0.0001). Post-hoc comparison in pairs confirmed all comparisons as statistically significant.
The decrease was significant in the WOMAC score for pain, numbness, functional limitations, and an overall score, 3 months after initiation of therapy compared to admission values, 6 months after initiation of therapy compared to admission, and 6 months compared to 3 months of therapy with hyaluronic acid.

Table 2. Results obtained after application of hyaluronic acid at all analyzed time points

WOMAC	Hyaluronic acid - with milder symptoms			
	Pain (mean ± SD)	Numbness (mean ± SD)	Functional constraints (mean ± SD)	Total Score (mean ± SD)
Admission	11.89 ± 3.7	2.93 ± 2.2	39.77 ± 12.1	54.59 ± 17.34
3rd month	10.43 ± 3.2	2.43 ± 1.7	33.89 ± 11.2	46.75 ± 15.1
6th month	9.32 ± 2.3	2.07 ± 1.4	30.29 ± 7.5	41.68 ± 10.3
Decrease in %	21.6%	29.3%	23.8%	23.6%
p value	F=35.8 p<0.0001sig post hoc admission *vs* 3rd p<0.0001sig admission *vs* 6th p<0.0001sig 3rd vs 6th p<0.0001sig	Friedman ANOVA=15.25 p=0.00049sig admission vs 3rd p=0.046sig admission vs 6th p=0.0005sig 3rd *vs* 6th p=0.0077sig	F=44.1 p<0.0001sig post hoc admission *vs* 3rd p<0.0001sig admission *vs* 6th p<0.0001sig 3rd *vs* 6th p<0.0001sig	F=48.52 p<0.0001sig post hoc admission *vs* 3rd p<0.0001sig admission *vs* 3rd p<0.0001sig 3rd *vs* 6th p<0.0001sig

F (ANOVA repeated-measures), adjustment for multiple comparisons: Bonferroni Friedman ANOVA, post hoc (Mann-Whitney test)

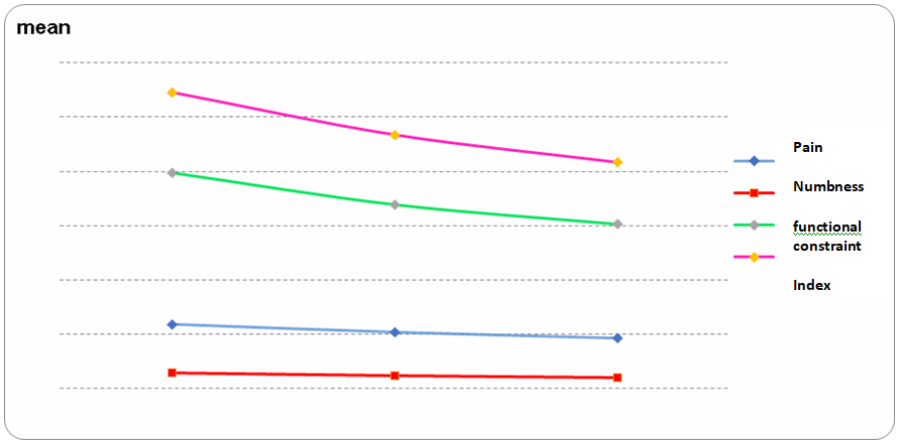

Fig. 2. Shows the percentage reductions in the WOMAC score for pain, numbness, functional limitations, and overall score after 6 months of therapy

Table 2 shows the percentage reductions in the WOMAC score for pain, numbness, functional limitations, and overall score after 6 months of therapy.

In the subgroup of patients with milder symptoms treated with hyaluronic acid, the VAS scale had significantly different values at the three-time points ($p < 0.0001$).

Post hoc analysis confirmed a significantly lower VAS score 3 and 6 months after the start of treatment ($p = 0.00013$, $p<0.0001$, respectively after 3 and 6 months), but also after 6 months compared to 3 months ($p= 0.00004$).

Table 3. Results from the VAS scale after application of hyaluronic acid at all analyzed time points

Variable VAS scale	**Hyaluronic acid - with milder symptoms VAS scale (mean ± SD)**
Admission	6.98 ± 2.4
3rd month	6.16 ± 2.7
6th month	5.25 ± 2.4
	24.8%
p value	Friedman ANOVA=53.63 p<0.0001 sig
	Admission vs 3rd p=0.00013sig
	Admission vs 6th p<0.0001 sig
	3rd vs 6th p=0.00004sig

post hoc (Mann- Whitney test)

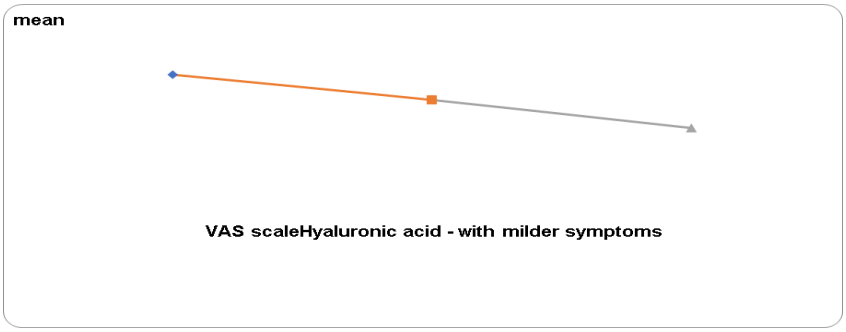

Fig. 3. Decrease of pain in patients at all analyzed time points after application of hyaluronic acid

Discussion

The primary goal of treatment in osteoarthritis of the knee is to reduce pain as well as to improve joint mobility and function. The secondary goal is to reduce disease progression. According to WOMAC, the results obtained in our study showed improvement in all the listed parameters post-intervention after 6 months. When the joints are lubricated, the bones are less likely to grind against each other and cause a reduction in persistent pain. Hyaluronic acid supplements are used in people who have problems with osteoarthritis. The main functions of injected hyaluronic acid derive from its antinociceptive properties, ability to improve the viscoelastic properties of synovial fluid, and indirect lubrication of the joint through stimulated endogenous hyaluronic acid synthesis. Other potential anecdotal benefits of hyaluronic acid injections include chondroprotection and potential function as a disease-modifying agent for OA. Improvement was more significant in the group with Hyaluronic Acid at the end of 6 months providing a good sign for comparison of clinical efficacy before and after intervention over six months.

We analyzed 17 meta-analyses investigating the efficacy of intra-articular (IA) application of hyaluronic acid, from which 13 reported treatment benefits [12 -24], 2

showed intermediate effect [25,26], and 2 of them presented negative effect [27,28]; 17 meta-analyses registered a positive effect of the usage of hyaluronic acid *versus* placebo, with an effect size (ES). In addition, 3 meta-analyses compared the efficacy of intra-articular application of hyaluronic acid *versus* other treatments, and all of them suggested that hyaluronic acid was as effective as NSAIDs for pain relief [29] and that they provided better benefits than IA corticosteroids, from 8 week onwards [30,31].

Bannuru *et al*. conducted a study in which they examined the therapeutic trajectory of the hyaluronic acid, finding that IAHA showed its first effects after 4 weeks, and reached its peak at 8 weeks and the residual effects were detectable up to 24 weeks [18].

Still, the question remains why IAHA is disregarded in some papers [32] and on the other hand, strongly recommended by rheumatologists and other professionals. It may be due to lack of working group, recommendation formulation and evidence of inclusion and assessment [33]. The effect of hyaluronic acid on the symptoms may also be important when patients require rehabilitation therapy, as a decrease in pain, which allow the patients an easier approach to physical therapy and exercises.

Our findings are in agreement with recent studies conducted in this field. A multidisciplinary group represented by Canadian experts reviewed the available evidences from 8 analyses, and they came to a conclusion that hyaluronic acid therapy was well-tolerated and effective option for patients with mild to moderate knee osteoarthritis, especially when pharmacologic therapy failed [34]. The European task force recommends the hyaluronic acid as an effective and well tolerated treatment for mild to moderate knee osteoarthritis, and they came to a conclusion that it should not be limited only in cases when pharmacologic therapy fails [35]. The ESCEO task force supports this conclusion [36]. The variability of the effect of hyaluronic acid among different patient phenotypes is not well understood; further investigation of patient characteristics with a better response to hyaluronic acid treatment is needed.

Conclusion

According to our results, the intra-articular hyaluronic acid injection was very effective in relieving pain and improving knee function at three months. There is good evidence for the effectiveness of hyaluronic acid injection in reducing pain and increasing knee function. This supports the potential use of intra-articular hyaluronic acid as an effective long-term therapeutic option for patients with knee OA and we recommend the use of hyaluronic acid injections in patients with mild to moderate OA of the knee in order to get best results.

Conflict of interest statement. None declared.

References

1. Castrogiovanni, P.; Trovato, F.M.; Loreto, C.; Nsir, H.; Szychlinska, M.A.; Musumeci, G. Nutraceutical supplements in the management and prevention of osteoarthritis. *Int. J. Mol. Sci.* **2016**, *17*, 2042.
2. Grecomoro, G.; Martorana, U.; Di Marco, C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: A controlled clinical trial versus placebo. *Pharmatherapeutica* **1987**, *5*, 137–141.
3. Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, Bailleul F, Pavelka K. Single, intra-articular treatment with 6 ml hylan GF 20 in patients with symptomatic primary osteoarthritis of the knee: a randomized, multi-centre, double-blind, placebo-controlled trial. Ann Rheumat Dis. 2010;69(01):113-9.
4. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-articular, single-shot hylan GF-20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: a double-blind, randomized controlled trial. J Bone Joint Surg Am. 2016;98:885-92.
5. Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. The Journal of the American Academy of Orthopaedic Surgeons. 2000.
6. Kellgren J & Lawrence J. Radiological Assessment of Osteo-Arthrosis. Ann Rheum Dis 1957; 16(4): 494-502.
7. Schiphof D, Boers M, Bierma-Zeinstra S. Differences in Descriptions of Kellgren and Lawrence Grades of Knee Osteoarthritis. *Ann Rheum Dis* 2008; 67(7): 1034-1036.
8. Kohn M, Sassoon A, Fernando N. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. *Clinical Orthopaedics & Related Research* 2016; 474(8): 1886-1893.
9. Freitag J, Bates D, Boyd R, *et al*. Mesenchymal stem cell therapy in the treatment of osteoarthritis: Reparative pathways, safety and efficacy - A review. BMC Musculoskeletal Disorders. 2016.
10. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee: a meta-analysis of randomized controlled trials. JBJS. 2004;86(3):538-45.
11. Wen DY. Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Physician. 2000;62(3):565.
12. Bannuru Raveendhara R, Christopher H Schmid, David M Kent, *et al*. "Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis." *Annals of internal medicine* 2015; 162(1): 46-54.
13. Trojian TH, Concoff AL, Joy SM, *et al*. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. *British journal of sports medicine*, 2016; 50(2): 84-92.
14. Wang CT, Lin J, Chang CJ, *et al*. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *JBJS* 2004; 86(3): 538-545.
15. Modawal A, Ferrer M, Choi H K, Castle J A. Hyaluronic acid injections relieve knee pain. Journal of Family Practice 2005; 54(9): 758-767.
16. Wu CW, Morrell MR, Heinze E, Concoff AL, Wollaston SJ, Arnold EL, et al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. Semin Arthritis Rheumatism. 2005;35(3):197-201.

17. Strand V, Conaghan PG, Lohmander LS, *et al.* An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee. *Osteoarthritis and cartilage* 2006; 14(9): 859-866.
18. Bannuru RR, Natov NS, Dasi UR, *et al*. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. *Osteoarthritis and cartilage* 2011; 19(6): 611-619.
19. Rutjes AW, Jüni P, da Costa BR, *et al*. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Annals of internal medicine* 2012; *157*(3): 180-191.
20. Miller LE and Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders* 2013; 6: CMAMD-S12743.
21. Campbell KA, Erickson BJ, Saltzman BM, *et al*. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2015; 31(10): 2036-2045.
22. Richette P, Chevalier X, Ea HK, *et al*. Hyaluronan for knee osteoarthritis: an updated meta-analysis of trials with low risk of bias. *RMD open*, 2015; 1(1): e000071.
23. Strand V, McIntyre LF, Beach WR, *et al*. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. *Journal of pain research* 2015; 8: 217.
24. Johansen M, Bahrt H, Altman RD, *et al*. Exploring reasons for the observed inconsistent trial reports on intra-articular injections with hyaluronic acid in the treatment of osteoarthritis: Meta-regression analyses of randomized trials. In *Seminars in arthritis and rheumatism, WB Saunders* 2016; 46(1): 34-48.
25. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *Jama* 2003; 290(23): 3115-3121.
26. Colen S, Van Den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis. *BioDrugs* 2012; *26*(4): 257-268.
27. Arrich J, Piribauer F, Mad P, Schmid D, *et al*. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *Cmaj* 2005; 172(8): 1039-1043.
28. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. *JBJS* 2015; 97(24): 2047-2060.
29. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. In *Seminars in arthritis and rheumatism, WB Saunders* 2014; 43(5): 593-599.
30. Bannuru RR, Natov NS, Obadan IE, *et al*. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Care & Research* 2009; 61(12): 1704-1711.
31. He WW, Kuang MJ, Zhao J, *et al*. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: a meta-analysis. *International Journal of Surgery* 2017; 39: 95-103.
32. Hunter DJ. Viscosupplementation for osteoarthritis of the knee. *New England Journal of Medicine* 2015; 372(11): 1040-1047.
33. Altman RD, Schemitsch E, Bedi A. October. Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid. In *Seminars in arthritis and rheumatism, WB Saunders* 2015; 45(2): 132-139.
34. Bhandari M, Bannuru RR, Babins EM, *et al*. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. *Therapeutic advances in musculoskeletal disease* 2017; 9(9): 231-246.
35. Henrotin Y, Raman R, Richette P, *et al*. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. In *Seminars in arthritis and rheumatism, WB Saunders* 2015; 45(2): 140-149).
36. Cooper C, Rannou F, Richette P, *et al*. Use of intra-articular hyaluronic acid in the management of knee osteoarthritis in clinical practice. *Arthritis care & research* 2017; 69(9): 1287-1296.

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ММР

Original article

OSTEOPOROSIS DURING A PANDEMIC

ОСТЕОПОРОЗАТА ВО ВРЕМЕ НА ПАНДЕМИЈА

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Abstract

Introduction. Osteoporosis is defined as a systemic skeletal disease characterized by low bone mineral mass and microarchitectural disorders. It is a disease in which the number of bone marrow and their connection decreases. At the same time, the cortical bone density decreases, making the bones porous, fragile, and easily brittle.
Aim. Presentation of recommendations for the treatment of osteoporosis in conditions of the Covid-19 pandemic, the risk of infection, vaccination and treatment at the same time.
Methods. A review of the guidelines of the world's leading bone health and osteoporosis associations presented in the available literature was made. Recommendations and guidelines for osteoporosis launched by the following associations were used: National Osteoporosis Foundation (USA), Royal Osteoporosis Association of Great Britain, Osteoporosis Canada, American Bone and Mineral Research Association (ASBMR), American Association of Clinical Endocrinology (AACE), European Association for Calcified Tissue (ECTS), International Osteoporosis Foundation (IOF), and National Osteoporosis Foundation (NOF).
Results. A compilation of the above guidelines and recommendations was made, and it has been a guideline for the treatment of osteoporosis during the covid-19 pandemic. Osteoporosis does not increase the risk of covid-19 infection and does not affect the complications of the disease. There is no evidence that treatment for osteoporosis increases the risk of infection and the severity of the infection. Vaccines are safe and effective and do not require a change in osteoporosis therapy. There are no contraindications for vaccination of patients with osteoporosis, if they do not have another disease; the general contraindications that apply to all apply to them.
Conclusion. Patients with osteoporosis should not discontinue current therapy during the covid-19 pandemic. In conditions of overload of the health system, it is allowed to delay the next dose of anti-osteoporotic drug, which is different in length depending on the drug used. Vaccination is recommended independently of osteoporosis therapy.

Keywords: osteoporosis, covid-19 pandemic, therapy, vaccination

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Апстракт

Вовед. Остеопорозата се дефинира како системско скелетно заболување кое се карактеризира со ниска коскена минерална маса и микроаритектурни нарушувања. Таа претставува болест кај која се намалува бројот на коскените гредички и нивната поврзаност. Истовремено доаѓа до намалување на кортикалната коскена густина, со што коските стануваат порозни, фрагилни и лесно кршливи.
Цел. Презентација на препораките за третманот на остеопороза во услови на пандемија на Ковид-19, ризикот од инфекција, вакцинација и лекување во исто време.
Методи. Направен е преглед на упатствата на водечките светски здруженија за коскено здравје и остеопороза од достапната литература. Како материјали се користени препораки и водичи за остеопороза на следните здруженија: Национална фондација за остеопороза (USA), Кралско здружение за остеопороза на Велика Британија, Остеопороза Канада, Американското здружение за истражување на коските и минералите (ASBMR), Американското здружение за клиничка ендокринологија (AACE), Европското здружение за калцифицирано ткиво (ECTS), Меѓународната фондација за остеопороза (IOF), и Националната фондација за остеопороза (NOF).
Резултати. Направена е компилација на горе наведените упатства и препораки која претставува упатство за лекување на остеопорозата во време на пандемија со ковид-19. Остеопорозата не го зголемува ризикот од инфекција со ковид-19 и не влијае на компликациите на болеста. Нема докази дека терапијата за остеопороза го зголемува ризикот од инфекција и сериозноста на инфекцијата. Вакцините се безбедни и ефективни и не бараат промена во терапијата за остеопороза. Нема контраиндикации

за вакцинација на пациенти со остеопороза, доколку немат и друго заболување за нив важат општите контраиндикации кои се однесуваат за сите.
Заклучок. Пациентите со остеопороза не треба да ја прекинуваат тековната терапија во време пандемијата со ковид-19. Во услови на преоптеретеност на здравствениот систем дозволено е одложување на следната доза на антиостеопоротичен лек кое е различно по должина во зависност од лекот кој се користи. Вакцинацијата се препорачува независно од терапијата за остеопороза.

Клучни зборови: остеопороза, ковид-19 пандемија, терапија, вакцинација

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mineral mass and microarchitectural disorders. It is a disease in which the number of bone marrow and their connection decreases. At the same time, the mineral cortical bone density decreases, making the bones porous, fragile and easily brittle [1,2].
The covid-19 pandemic has raised many questions about the treatment of osteoporosis, the risk of infection with the SARS-CoV 2 virus, the benefits of anti-covid-19 vaccination, and the combination of osteoporosis treatment and vaccination. The recommendations of the major world organizations working in the field of bone health are for the continuity of treatment of osteoporosis, adherence to the intervals and order of treatment, as well as the intake of vitamin D and calcium and maintenance of the musculoskeletal system.
Osteoporosis is a global epidemic and, together with the Covid-19 pandemic, poses a huge burden on health systems, countries economic resources and human relations. In the beginning of the epidemic, we were faced with ignorance of this infection, lack of experience and clear recommendations for treatment, as well as a diverse clinical picture of covid-19, which led to many contradictory and incorrect interpretations and recommendations.

Aim

The aim of the paper was to present our recommenddations on how to treat osteoporosis during the covid-19 pandemic as well as to indicate the need for vaccination.

Material and methods

In preparing this paper, a review of the latest guidelines and recommendations for the treatment of osteoporosis and the use of the anticonvalent vaccine during a covid-19 pandemic, available in the literature, was made. These are recommendations from the most eminent European and world associations dealing with bone health (see references). The summarized information is in line with the guidelines arising from the Ministry of Health of RN Macedonia and the Committee for Immunization at the Ministry and were accepted at a regular expert meeting of the Macedonian Rheumatology Association - MAAR as a Guide to the association.

Results

Vaccines are safe and effective and do not require a change in osteoporosis therapy. There are no contraindications for vaccination of patients with osteoporosis, except the general ones that apply to all people [3,5,7].
It is very important not to stop treatment of osteoporosis unjustifiably and for a long period. Depending on the mechanism of action of the drug and possible side effects, the recommendations are as follows [3-5]:
Treatment with bisphosphonates - alendronate, risdronate and ibandronate may be delayed for several weeks by oral administration and for several months by intravenous administration. There is no data on the interaction between the vaccine and the drugs. In patients treated with ibandronate or zoledronate administered intravenously, it is advisable to have a one-week interval between the vaccine and the drug**.** During treatment with denusumab, the interval between applications should not exceed 7 months, ie. the next application should not be more than one month late. This is logical, because after the 6-month interval, the loss of bone mass is significantly accelerated. If the vaccine is administered around the time of application, it is advisable to have an interval of 4-7 days between them. Denosumab should be given subcutaneously on the arm where no vaccine has been given. Although denosumab is a monoclonal antibody, it does not suppress the immune response, so its use does not affect the risk of complications from coronavirus infection. The interval from 4 to 7 days between the administration of the drug and vaccine is determined because both the drug and the vaccine can have very similar side effects, such as "fly-like syndrome". In the case of covid-19 disease, when patients are unable to go to the health facility where teriparatid and denosumab are administered, they should be allowed to temporarily discontinue therapy and be transferred to an oral anti-resorption agent. Mandatory, they should be switched to an anti-resorption agent immediately in order to avoid accelerated bone loss after discontinuation of teriparatide and denosumab [4]. During the covid-19 pandemic, the US Food and Drug Administration (FDA) temporarily approved and self-administered denosumab to patients at home [4]. It is necessary to take vitamin D and calcium regularly in the required doses [4,5]. Target values of 25-OH vitamin D should be ≥50 nmol /l. This is important for both musculoskeletal health and immune response. The American Society for Bone and Minerals Research (ASBMR), the American Asso-

ciation of Clinical Endocrinology (AACE), the Endocrinological Society, the European Society for Tissue Calcifications (ECTS), the International Osteoporosis Foundation (IOF), and the National Osteoporosis Foundation (NOO) recommend adults over 19 years of age to take a minimum of 800 IU of vitamin D daily with food or supplements [5,7-9,10]. Laboratory tests prior to injection therapy are not mandatory for all patients. If they take calcium and vitamin D regularly, and have had normal laboratory tests on two previous occasions and do not have kidney disease, patients can receive their regular therapy without new laboratory tests [3].

Dental care is needed constantly. If possible, in the event of a pandemic, patients should have their teeth monitored regularly. Such care reduces the risk of a very rare but well-known complication of the treatment of osteoporosis - osteonecrosis of the jaw. The reported incidence of this condition is 0.7 per 100,000 patients [6].

Patients should be advised to take care of the musculoskeletal system, its stability and balance, which will prevent falls and reduce the risk of fractures and visits to overcrowded hospitals [5]. It is advisable to do daily exercises that are from a standing or sitting position, and will help in the way of posture. Such are the movement of the toes and heels, getting up and sitting in a chair with and without the help of the hands according to the individual condition of each patient. Attention should be paid to the need for movement in the rooms where they live as well as practicing light exercises - standing on one leg, transferring weight from one foot to the other alternately, circular movements of the ankles and shoulders, straightening the back. Of course, if possible, outdoor walks would be more rewarding and enjoyable.

Conclusion

The pandemic has a significant negative impact on the health care of the chronically ill, including patients with osteoporosis. Remote treatment, fear of visiting a doctor, delayed determination - measurement of bone density and laboratory parameters or X-ray diagnosis, discontinuation of treatment - are just some of the factors that negatively affect the adequate treatment of osteoporosis. Osteoporosis, which is one of the leading causes of death in old age and has a significant increase in incidence worldwide, has not yet found its rightful place in general medical practice. A very large percentage of undiagnosed and untreated patients remain. With the spread of the Covid-19 pandemic, this mismatch between those diagnosed and those in real need of treatment has increased significantly. And not only that - those patients who have a certain treatment, do not follow the dosing regimen and drug intervals due to fear and ignorance. Osteoporosis does not increase the risk of covid-19 infection and does not affect the complications of the disease. There is no evidence that therapy for osteoporosis increases the infection risk and severity of infection [3-5]. Therefore, treatment of osteoporosis should be continued during a pandemic without significant deviations. Vaccines are safe and effective and do not require a change in osteoporosis therapy. There are no contraindications for vaccination of patients with osteoporosis, except the general ones that apply to all people [3,5,7].

We are in a difficult period that can last a long time. It is up to us to reduce its negative effects, to adapt and to move forward. This can be done by vaccination, continuous treatment of osteoporosis and other chronic diseases, adhering to proven medical recommendations.

Conflict of interest statement. None declared.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993; 94(6): 646-650.
2. Seeman E, and Delmas PD. Bone quality-the material and structural basis of bone strength and fragility. *N Engl J Med* 2006; 354(21): 2250-2261.
3. National Osteoporosis Foundation- https://www.osteoporosis.foundation/.
4. Royal Osteoporosis Society Coronavirus and osteoporosis, 2020.
5. Osteoporosis Canada Osteoporosis drug treatments & medication during COVID-19, 2020.
6. Blanchaert Remy H, *et al*. Bisphosphonate-Related Osteonecrosis of the Jaw.
7. Guidance on COVID-19 Vaccination and Osteoporosis Management from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinology (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), the International Osteoporosis Foundation (IOF), and the National Osteoporosis Foundation (NOF).
8. Institute of Medicine. 2011. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press. https://doi.org/10.17226/13050.
9. American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinology (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), International Osteoporosis Foundation (IOF), National Osteoporosis Foundation (NOF) Joint Guidance on vitamin D in the era of COVID-19, 2020.
10. www.osteoporosis.foundation/sites/iofbonehealth/files/2021-03/IOF-Factsheet-Vitamin-D.

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ММР

Original article

EVALUATION OF THE EFFECTS OF ANTI-VEGF TREATMENT ON SUBRETINAL FLUID IN THE WET FORM OF MACULAR DEGENERATION

ЕВАЛУАЦИЈА НА ЕФЕКТИТЕ НА АНТИ-ВЕГФ ТРЕТМАНОТ ВРЗ СУБРЕТИНАЛНАТА ТЕЧНОСТ КАЈ ВЛАЖНАТА ФОРМА НА МАКУЛАРНА ДЕГЕНЕРАЦИЈА

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Abstract

Introduction. AMD is a progressive disease that can lead to changes and obstruction of the central vision. The neurodegenerative process starts at the level of the Burch membrane/choriocapillaris and a complex of photoreceptors/and retinal pigment epithelium (RPE). Age-related macular degeneration (ARMD) in the United States and industrialized countries is a major cause of blindness in individuals aged 55 years and older. Degenerative changes affect the macula lutea (yellow dot) in the center of the retina.

The World Health Organization (WHO) ranks AMD among the leading ophthalmic causes of blindness globally, and the third most common cause of legal blindness in 8.7% of the population in industrialized countries. In 2020, the number of patients with ARMD increased from 3 to 6 million, while by 2050, an increase of 17.8 million cases of senile macular degeneration is projected.

Wet-exudative AMD covers 10-15% of patients with ARMD and is at high risk of severe impairment and/or loss of visual function.

Neovascular ARMD is characterized by the appearance of a choroidal neovascular membrane (CNVM) and a secondary finding of pigment epithelium detachment (RPE rip), i.e., its tractional dehiscence or macular disciform scar.

Common features of all exudative, wet forms of AMD are:

1. Leakage of fluid and serum components as a result of impaired blood-ocular barrier,
2. Intraretinal and subretinal fluid (IRF, SRF),
3. Lipid or (solid) exudates,
4. Subretinal hyperreflective material (SHRM).

Aims.

1. Fluid-filled subretinal space (SRF) segmentation using the posterior ocular coherence tomography (OCT) method.
2. Monitoring of volume changes (SRF) on ultimate best corrected visual acuity and morphological changes of retinal layers.
3. Monitoring of SRF response to anti-VEGF treatment regimen.

Methods. This is a retrospective-prospective, pilot study conducted on an initial small group of patients who are part of a clinical study. Several variables that correlate with retinal morphological, anatomical parameters of the retina and visual function will be evaluated. This study included 30 patients (30 eyes), 11 males and 19 females. All patients were diagnosed, treated and monitored exclusively at the University Clinic for Eye Diseases in Skopje in the Department for optical coherence tomography of the posterior ocular segment of the DRI Triton device, Swept Source OCT. The OCT method used in the diagnosis of n-AMD is a superior and non-invasive imaging technique. It provides segmentation of the retinal layers and quantitative comparative analysis of morphological anatomical biomarkers.

Each patient gave an informed consent for his/her participation in the study.

Results. The expectation from the analysis of individual morphological parameters is to obtain certain data on the impact of the anti-VEGF treatment and the response of the subretinal fluid, (monitoring its withdrawal, reduction, increase and recurrence) at different time intervals after starting treatment.

Through comparative analysis of the individual parameters with the final best corrected visual function we obtained data that are the same or similar to the data presented in major world clinical studies, and are prognostic parameter in anti-VEGF personalization treatment and outcome at the final visual acuity (functional parameter) in the patients at our Clinic.

Keywords: subretinal fluid, intraretinal fluid, age-related macular degeneration, pigment epithelium detachment

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Апстракт

Вовед. AMD е постепено и прогресивно заболување кое доведува до промени и нарушувања на централниот вид. Неуродегенеративниот процес отпочнува на ниво на комплексот Брухова мембрана/хориокапиларис и комплекс на фоторецептори/и клетки на ретинален пигментен епител, *retinal pigment epithelium* (RPE).

Светската здравствена организација (The World Health Organization, WHO), AMD ја вбојува во водечките офталмолошки причини за слепило на глобално ниво, односно 3та најчеста причина за развој на легално слепило кај 8,7 % од популацијата во индустриски развиентите земји. Vo 2020та година бројката на пациенти со наод на ARMD порасна од 3 на 6 милиони заболени додека пак до 2050та година се предвидува пораст од 17,8 милиони случаи со наод на сенилна макуларна дегенерација.

Влажна, неоваскуларна *(Wet-Exudative AMD)* опфаќа 10-15% од пациентите со ARMD и има голем ризик за тешко нарушување и/или загуба на видната функција.

Неоваскулана ARMD се одликува со појава на хороидална новоформирана васкуларна мрежа *(choroidal neovascular membrane, CNVM)* и секундарен наод на одлепување на пигментен епител, расцеп на пигментен епител *(RPE rip)* т.е негова тракциона дехисценца или на дисциформна лузна.

Заеднички карактеристики кај сите ексудативни, влажни форми на AMD се:

1. Пропуштање на течност и серумски компоненти како резултат на нарушена хемато-окуларна бариера.
2. Интраретинална и субретинална течност *(intraretinal and subretinal fluid, IRF,SRF)*
3. Липидни или (цврсти) ексудати.
4. Субретинален хиперефлектирачки материјал, *(subretinal hyperreflective material, SHRM.*

Цели на студијата.

1. Сегментирање на субретиналниот простор исполнет со течност (SRF) со помош на методата на оптичка кохерентна томографија на задниот очен сегмент (OCT).
2. Пратење на промените на волументот на (SRF) врз крајната најдобро корегирана видна острина и морфолошките промени на слоевите на ретината.
3. Пратење на одговорот на SRF на режимот на треман со anti-VEGF медикаментозна терапија.

Методи. Станува збор за ретроспективно-проспективна, пилот-студија спроведена на почетна мала група испитаници кои се дел од клиничка студија. Ќе бидат евалуирани неколку варијалбли кои се во корелација со ретиналните морфолошки, анатомски параметри на ретината и видната функија. Во студијата ќе бидат вклучени 30 пациенти (30 очи), 11 машки и 19 женски. Сите пациенти беа дијагностицирани, третирани и следени исклучиво на Универзитетската клиника за очни болести во Скопје во кабинетот за оптичка кохерентна томографија на задниот очен сегмент на апаратот DRI Triton, Swept Sourse OCT. OCT методотата што се користи во дијагнозата на n-AMD претсвува супериорна и неинвазивна техника на снимање. Овозможува сегментација на ретиналните слоеви и квантитативна конпаративна анализа на морфолошките анатомски биомаркери. Секој доби информирана согласност во која детално е објаснето неговото учество во студијата.

Резултати. Очекувањата од анализата на поединечни морфолошки параметри се да дојдеме до одредени податоци за влијанието на анти-VEGF тертмантот и одговорот на субретиналната течност на истиот (следење на нејзино повлекување, намалување, зголемување и рекурентноста) во различен временски интервал по одпочнување со лекувањето.

Преку споредбена анализа на засебните параметри со крајната најдобро корегирана видна функција добивме податоци кои се исти или слични со податоците изнесени во поголемите светски клинички студии, при што истите се водечки и прогностички параметар во персонализирање на anti-VEGF третманот и очекуваниот исход на крајната видната острина (функционалниот параментар)од истиот.

Клучни зборови: субретинална течност, интраретинална течност, течност под ретиналниот пигменетн епител, видна функција, anti-VEGF третман, неоваскуларна макуларна дегенерација

Introduction

Age-related macular degeneration (ARMD) in the United States and industrialized countries is a major cause of blindness in individuals aged 55 years and older. It is estimated that macular senile degeneration in USA residents is 10 million. Degenerative changes affect the macula lutea (yellow dot) in the center of the retina.

The World Health Organization (WHO) ranks AMD among the leading ophthalmic causes of blindness globally [1], and the third most common cause of legal blindness in 8.7% of the population in industrialized countries [2]. In 2020, the number of patients with ARMD increased from 3 to 6 million, while by 2050, it is expected an increase of 17.8 million cases of senile macular degeneration is projected [3,4].

According to the International Classification of Diseases (ICD), there are two basic clinical forms of AMD:

- Dry, non-vascular form (Sicca AMD) which accounts for 85-90% of ARMD cases and
- Wet-exudative AMD, which accounts for 10 to 15% of patients with ARMD that presents a high risk of severe impairment and/or loss of visual function.

AMD is a gradual and progressive disease that leads to changes and disorders of the central vision. The neuro-

degenerative process begins at the level of the Bruch membrane/choriocapillary complex and the retinal pigment epithelium (RPE)/photoreceptor cell complex. The process is characterized by the development of pathologic choroidal neovascularization (CNV) that breaks through Bruch's membrane into the sub-pigment epithelium space and/or the subretinal space, leading to exudation and retinal fluid accumulation that can be found inside the neurosensory retina (IRF), beneath the neurosensory retina (NSR), but above the RPE (SRF) or underneath the RPE, separating Bruch's membrane and the RPE (pigment epithelium detachment-PED) [5].

Macular fluids and their differentiation between distinct fluid compartments are essential biomarkers of exudative activity in n-AMD. For example, subretinal fluid (SRF) has been discussed as a protective factor against macular atrophy in eyes with neovascular age-related macular degeneration (n-AMD) [6].

Incidence and growth of macular atrophy are strongly dependent on CNV activity and result in anti-VEGF therapy [7]. CNV activity and the need for retreatment are mostly defined by the presence of macular fluid, i.e., intraretinal fluid (IRF), subretinal fluid (SRF), and, less prominently, sub-pigment epithelium fluid [8]. While many studies have shown a robust association of IRF with worsening visual acuity and increasing rates of macular atrophy [9], subretinal fluid presence has paradoxically been shown to correlate with better visual acuity as compared to a completely dry macula, especially if located subfoveally.

After the invention (Huang *et al*., 1991) and the introduction in the field of ophthalmology (Fercher *et al*., 1993), optical coherence tomography became the leading diagnostic method and novelty in determining the exudative and degenerative stages in neovascular forms of macular senile degeneration [10].

Up-to-date, traditional and leading ARMD diagnostic (two-dimensional) methods using contrast medium (fluorescein (FA) and indocyanine green angiography (ICGA)) have been upgraded with the 3D non-invasive optical coherence tomography (OCT), posterior eye segment imaging.

Regarding the treatment of wet forms, the introduction of intraocular administration of anti-vascular endothelial growth factor (anti-vascular, anti-VEGF) drugs has led to a revolution in the treatment of this disease.

Clinical studies have shown the benefit of anti-VEGF compared to photodynamic laser therapy or course monitoring for the disease [1], but despite this fact, data from real clinical practice have shown a worrying decline in visual function over the years of follow-up and treatment of patients [2]. The creation of fibrous tissue and atrophy are two important factors in contributing to the gradual but progressive decline of visual function [3]. Hence, the growing interest in the diagnostic value of biological parameters, i.e., the so-called biomarkers of retinal layers which, according to the National Institutes of Health, are defined as a quantitative parameter and indicator of the normal biological, pathogenetic or pharmacological response to treatment [4].

Aims

OCT assessed segmentation of fluid in the sub-retinal compartment.

1. To analyze the relationship between SRF, best corrected visual acuity and retinal anatomic features.
2. To evaluate effects of anti-VEGF treatment on SRF after 3 initial doses.

Material and methods

This retrospective-prospective, observational case-control study is a pilot project to evaluate several variables, as few of doctorial research examples that are in correlation with the functional and morphologic outcomes. Thirty patients (30 eyes) were enrolled, 11 males and 19 females. All patients were diagnosed, treated and monitored in the University Clinic for Eye Diseases in Skopje, using the DRI OCT Triton, Swept Sourse Optical Coherence Tomography imaging method. The method used in diagnosis of n-AMD is the most useful non-invasive tool in long-term management of patients with n-AMD, allowing quantitative measurements of retinal thickness and quantitative observation of retinal fluid on OCT. This small study group was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments of comparable ethical standards. It was approved by the Institutional ethical board.

Exclusion criteria: patients with diabetes, glaucoma, high myopic patients, patients with vascular occlusions, cataract patients, patients with irregularity, corneal haze or active inflammation on the anterior eye segment.

Main inclusion criterion was the presence of retinal fluid in one or more retinal compartments *(subretinal fluid SRF, intraretinal IRF or under the retinal pigment epithelium PED fluid)*, as well as presence of choroidal neovascularization seen on OCT angiography *(non-invasive imaging technique based on OCT, developed to visualize vascular networks in the human retina and choroid).*

All patients underwent full eye examination that included best corrected visual acuity (BCVA), intraocular pressure measured with air puff tonometry, anterior segment slit lamp examination and funduscopic exam of the retina with 90D eye lens in mydriasis. Using the OCT and OCT-A, the presence and the localization of the fluid in different retinal compartments was diagnosed in every patient, the central macular thickness (CMT) was measured as well as the type of CNV lesion. Best corrected visual acuity, presence of IRF, SRF, PED, CNV and CMT were assessed prior to treatment on day 1 and the 3rd month of treatment.

We analyzed the correlation between the functional 30 patients treated with one of the anti-VEGF agents. Twenty patients were treated prospectively with *aflibercept* for 3 months and 10 were treated with *bevacizumab*. Both groups had 3 consecutive monthly doses of each anti-VEGF agent, respectively.

Results and Discussion

Thirty eyes of 30 patients were assessed in the beginning of the clinical study. Nineteen of them were female and the other 11 were male. The age ranged from 64 to 86 (mean: 72) years. There were 14 right (47%) and 16 left (53%) eyes with findings of n-ARMD.

Table 1 shows the BCVA on the first visit in our hospital and the quantitative OCT measure of the central macular thickness before the anti-VEGF treatment and after the 3 initial monthly doses of the anti-VEGF agent. The mean BCVA in the beginning was 0.326667, mean CMT was 317.5333 μm. On the 3rd month after 3 doses, the mean BCVA was 4.49 and CMT 3 was 277.5 μm. By comparing BCVA and BCVA3, an improvement of 2 lines was seen, according to Snellen eye chart (chart used to measure visual acuity by determining the level of visual detail that a person can discriminate). Mean CMT decreased from 317.5 to 277.5 μm (-40 μm).

Exudative AMD (CLEAR-IT 2), Phase II, randomized 1-year study showed the importance of 3 monthly consecutive injections (regardless of dose, 0.5 mg, 2 mg or 4 mg) [11].

In all patients, there was an improvement in the average best-corrected visual acuity at 12 weeks and reduced retinal thickness. In our study, decreased CMT showed a strong connection with better visual outcome. Only one patient CMT showed no correlation with BCVA3 and in one patient CMT was increased and it correlated with reduced BCVA3.

It remains controversial whether there is any correlation between foveal thickness (FRT) and VA outcome. It is well accepted that FRT is an early, sensitive parameter for reduced baseline BCVA. However, it is not always in correlation with the visual outcome, but according to our study it is an early sensitive predictor of decreased VA [12].

It is also controversial whether there is any correlation between foveal retinal thickness (FRT) and VA. At baseline, all 30 patients had at least one feature of fluid on OCT, which included subretinal fluid (26 eyes), intraretinal fluid (19 eyes) and fluid under the retinal pigment epithelium (21 eyes).

At the beginning of the study, 21 of all 30 patients had sub-PED fluid at baseline. After application of 3 monthly doses, the fluid resolved in 7 eyes. SRF at the beginning as the only parameter was present in 26, and after the loading doses resolved in 7 patients. Intraretinal fluid (IRF) was present in 19 patients and resolved in only two of them.

Out of a total of 30 patients analyzed in this study, 10 eyes received Bevacizumab and 20 Aflibercept for three consecutive months.

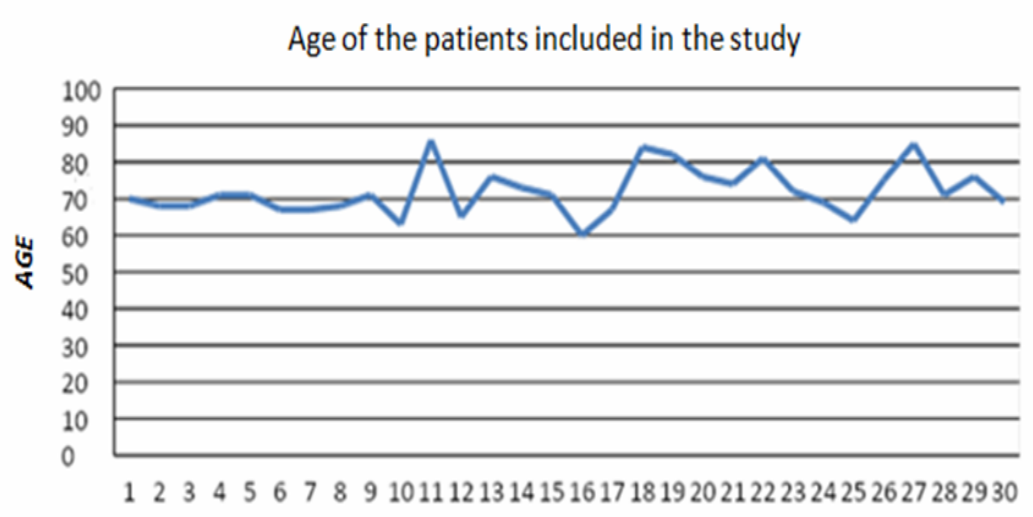

Fig. 1. Age of patients included in the study

Table 1. Changes in baseline BCVA (Best Corrected Visual Acuity) and CMT (Central Macular Thickness) from beginning of treatment and on the 12th week of treatment

Number of patients	Age	BCVA	BCVA 3	CMT	CMT 3
1	70	0.4	0.5	301	254
2	68	0.5	0.7	306	266
3	68	0.3	0.6	310	295
4	71	0.1	0.1	267	220
5	71	0.2	0.4	353	300
6	67	0.5	0.5	321	315
7	67	0.9	0.7	278	301
8	68	0.1	0.3	342	292
9	71	0.3	0.4	286	200
10	63	0.4	0.7	294	224
11	86	0.1	0.3	320	293
12	65	0.3	0.5	290	271
13	76	0.5	0.7	279	249
14	73	0.4	0.6	288	234
15	71	0.4	0.5	344	146
16	60	0.5	0.7	265	255
17	67	0.4	0.6	278	227
18	84	0.3	0.5	330	299
19	82	0.2	0.5	345	302
20	76	0.6	0.7	264	230
21	74	0.2	0.4	372	342
22	81	0.1	0.5	370	283
23	72	0.4	0.5	321	289
24	69	0.1	0.2	382	371
25	64	0.2	0.2	340	347
26	75	0.2	0.5	343	298
27	85	0.2	0.4	348	331
28	71	0.5	0.7	295	243
29	76	0.4	0.3	324	353
30	69	0.1	0.5	370	295
Mean value	72	0.326667	0.49	317.5333	277.5

The mean value of BCVA of patients treated with Bevacizumab before initiating treatment was 0.25 (interval from 0.1 to 0.5), after three consecutive doses, the mean BCVA3value was 0.41 (interval from 0.1 to 0.7), which was for almost 2 rows of the average improvement on Snellen chart.

The mean value of BCVA in patients treated with Aflibercept before treatment was 0.36 (interval from 0.1 to 0.9), after three consecutive doses, the mean BCVA3 value was 0.53 (interval from 0.1 to 0.7), which was approximately 2 rows of improvement according to Snellen eye chart.

Following anti-VEGF therapy, in the 2 treatment groups, the proportion of eyes with any type of fluid at the beginning (IRF, SRF, or sub-RPE fluid) decreased after 3 monthly injections with the specific agent. As shown Figure 1, this correlated with reduction on CMT and increasing VA. There was no significant difference between the anti-VEGF agent and the BCVA3.

Table 2. Drug-associated morphologic parameter outcomes

Before treatment	Number of patients	After 3 loading doses	Number of patients
PED before treatment with Aflibercept	14	Withdrawal of PED after three doses of Aflibercept	6
PED before treatment with Bevacizumab	7	Withdrawal of PED after three doses of Bevacizumab	1
Total number of patients with PED before treatment	21	Total number of patients with PED withdrawal after treatment	7
SRF before treatment with Aflibercept	18	Withdrawal of SRF after three doses of Aflibercept	5
SRF before treatment with Bevacizumab	8	Withdrawal of SRF after three doses of Bevacizumab	2
Total number of patients with SRF before treatment	26	Total number of patients with SRF withdrawal after treatment	7
IRF before treatment with Aflibercept	11	Withdrawal of IRF after three doses of Aflibercept	2
IRF before treatment with Bevacizumab	8	Withdrawal of IRF after three doses of Bevacizumab	0
Total number of patients with IRF before treatment	19	Total number of patients with SRF withdrawal after treatment	2

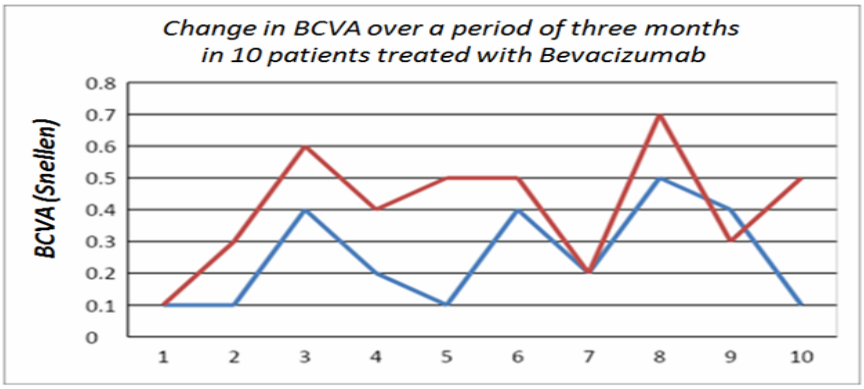

Fig. 2. Vision acuity response in 10 patients with Bevacizumab after 3 months of treatment

Table illustrates that 21 out of 30 patients had a finding of subretinal fluid (sub-RPE) after an interval of three consecutive monthly doses of anti VEGF drug and there was liquid absorption in 7 out of 21 eyes. The subretinal fluid (sub-retinal fluid SRF) was present in 26 eyes and after an interval of three consecutive monthly doses absorption occurred in 7/26 eyes. Intraretinal fluid (IRF) was present in 19 patients, absorption occurred in 2 out of 19 patients. IRF remained present in most of the eyes on the 3rd month of treatment [13].

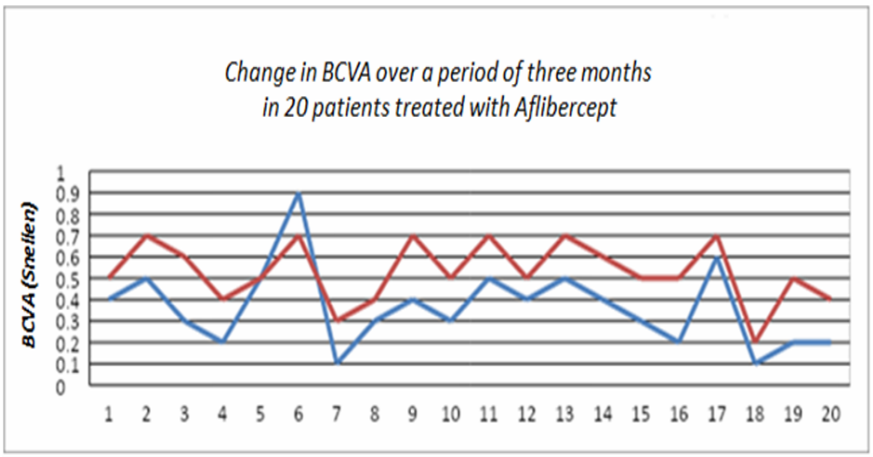

Fig. 3. Vision acuity response in 20 patients with Aflibercept after 3 months of treatment

During the 3-month period, 10 eyes out of the 30 analyzed patients were treated with Bevacizumab (anti VEGF agent) and 20 eyes with Aflilibercept (anti VEGF).
The CATT study provides data on better visual function in patients with persistent SRF than in those with complete macular fluid resorption [14]. CATT, EXSITE and VIEW trials of n-AMD (neovascular age-related macular degeneration) in post-hoc analysis of intraretinal fluid (IRF) as the only biomarker/ or in a combination with the other biomarkers (SRF, sub-retinal pigment epithelial fluid) was a negative prognostic predictor [13-15]. The EXCITE study shows the stability of the visual function in patients with persistent residual fluid despite the frequency of applications of the anti-VEGF treatment. Also, the BCVA gains from infrequent treat- - ment gave similarity to those in frequent treatment in eyes with SRF at baseline in a post-hoc analysis of the EXCITE trial [15].

Conclusion

In recent years, retinal morphologic characteristics have attracted increased interest in evaluation of the biological parameters, i.e., the so-called biomarkers of retinal layers which, according to the National Institutes of Health, are defined as a quantitative parameter and indicator of the normal biological, pathogenetic or pharmacological response to treatment [16].
After initiation of treatment in our small group of patients, full SRF resorption and dry macula was associated with BCVA 3 improvement. Latest evidence suggests that presence of SRF is not associated with a decline of VA. Studies have shown that SRF, which is refractory to monthly treatment, still results with good visual function [17].

Conflict of interest statement. None declared.

References

1. Friedman DS, Katz J, Bressler NM, *et al.* Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. *Ophthalmology* 1999; 106(6): 1049-55.
2. Friedman DS, O'Colmain BJ, Muñoz B, *et al*. Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004; 122(4): 564-572.
3. WHO [webpage on the Internet]. Prevention of Blindness and Visual Impairment. Priority Eye Diseases; 2012.
4. Białek-Szymańska A, Misiuk-Hojło M, Witkowska K. Ocena czpstości wystepowania czynników ryzyka zwyrodnienia plamki zwiazanego z wiekiem [Risk factors evaluation in age- related macular degeneration]. *Klin Oczna, Polish* 2007; 109(4-6): 127-130.
5. Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog Retin Eye Res* 2016; 50: 1-24.
6. Siedlecki J, Fischer C, Schworm B, *et al*. Impact of Sub-Retinal Fluid on the Long-Term Incidence of Macular Atrophy in Neovascular Age-related Macular Degeneration under Treat & Extend Anti-Vascular Endothelial Growth Factor Inhibitors. *Sci Rep* 2020; 10(1): 8036.
7. Mehta H, Tufail A, Daien V, *et al*. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. *Prog Retin Eye Res* 2018; 65: 127-146.
8. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying GS, Jaffe GJ, Daniel E, Grunwald JE, Toth CA, Ferris FL 3rd, Fine SL. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology* 2016; 123(8): 1751-1761.
9. Bailey C, Scott LJ, Rogers CA, *et al*. Intralesional Macular Atrophy in Anti-Vascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration in the IVAN Trial. Ophthalmology. 2019; 126(1): 75-86.
10. Fercher AF, Hitzenberger CK, Drexler W, *et al*. In vivo optical coherence tomography. *Am J Ophthalmol* 1993; 116(1): 113-114.
11. Heier JS, Boyer D, Nguyen QD, *et al*. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. *Ophthalmology* 2011; 118(6): 1098-106.
12. Keane PA, Patel PJ, Liakopoulos S, *et al*. Evaluation of age-related macular degeneration with optical coherence tomography. *Surv Ophthalmol* 2012; 57(5): 389-414.
13. Jaffe GJ, Ying GS, Toth CA, *et al*. Macular Morphology and Visual Acuity in Year Five of the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology* 2019; 126(2): 252-260.
14. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012; 119(7): 1388-1398.
15. Schmidt-Erfurth U, Eldem B, Guymer R, *et al*. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology* 2011; 118(5): 831-839.
16. FDA-NIH Biomarker Working Group. BEST (biomarkers, endpoints, and other tools) resource. [cited 2019 Aug 22].
17. Jang L, Gianniou C, Ambresin A, Mantel I. Refractory subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome. *Graefes Arch Clin Exp Ophthalmol* 2015; 253(8): 1211-1216.

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ММР

Original article

EVALUATION OF POSTOPERATIVE RESULTS IN PATIENTS WITH RHINOSEPTOPLASTY

ЕВАЛУАЦИЈА НА ПОСТОПЕРАТИВНИТЕ РЕЗУЛТАТИ КАЈ ПАЦИЕНТИ СО РИНОСЕПТОПЛАСТИКА

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Apstract

Aim. The objectives of the surgical technique septo-rhinoplasty are to remodel and redesign the nose, to remove the excessive bone and cartilaginous structures, and/or to correct the nasal insufficiencies in order to obtain a harmonious proportion of the nose in regards to the other facial structures. Furthermore, rhinoseptoplasty is one of the most frequently used aesthetic-surgical procedures. The cartilaginous part of the nasal septum is an integral part of the isthmus region and has a significant role in the air circulation and turbulence. Due to this central role of the nasal septum, it is of crucial importance to undertake an adequate surgical technique since it is the key for a successful treatment both in the esthetic and in the functional rhinosurgery. Confirmed by clinically relevant data, the aim of this study was selection of patients for rhinoseptoplasty

Methods. A statistical analysis of 300 patients was made. Patients experienced deformities of the nasal pyramid: rhinokyphosis, rhinoscoliosis, rhinolordosis ("saddle nose"), and "functional tension nose" separate from or along with the deviations of the nasal septum (*deviatio septi nasi*). The examined patients were added on the list for surgical rhinoseptoplasty procedures performed at the Sante Plus Hospital in Skopje, during the period of April 2021 till April 2022. After the surgical intervention, a survey was conducted in order to find out how patients were satisfied after the performed correction (functional and aesthetic). Patients could choose from 5 options/scores: 1 - very satisfied, 2 - satisfied, 3 - undecided, 4 - dissatisfied and 5 - extremely dissatisfied. According to the type of surgical technique applied while performing the surgical intervention, patients were divided into two groups: - group 1: in which septoplasty was performed; the group was consisted of patients with Dg. *deviatio septi nasi*, - group 2: in which rhinoseptoplasty was performed; the group was consisted of patients who besides nasal septum deviation, also had some deformity of the nasal pyramid, such as: rhinokyphosis, rhinoscoliosis, rhinolordosis ("saddle nose"), and "functional tension nose".

Results. The results obtained have demonstrated that during the check-ups at 7, 14 days and 2, 6 months postoperatively, patients experienced a mild nasal obstruction that had not posed a problem in their everyday life and sleep. Dissatisfaction presented as a predominant symptom in patients with deformities of the nasal pyramid and its constancy in the postsurgical period showed that it was also caused by certain subjective reasons, most commonly of psychogenic nature such as anxiety, restlessness and great expectations of the intervention. The occurrence of epistaxis was detected along the nasal septal deviations in the front and front-back sections, but it was of no significance.

Discussion. We note that the most satisfactory patients are those in whom the nasal septal deviation is present with an obvious aesthetic problem. We have shown that performing septoplasty is not only for centralization of the septum. The space between the septum and the nasal concha is very important for proper nasal respiration. Septal correction is a fundamental component in both, functional and aesthetic aspects of rhino surgery. Therefore, we have shown that surgical procedure rhinoseptoplasty is not a rigid procedure. Which type of intervention is to be done depends on the pathology of the septum, and the shape of the nose which is different from one to another patient.

Conclusion. The results showed a significant correlation between the anatomical (objective) and the psychological (subjective) causes that determined the frequency and the intensity of the occurrence of nasal symptoms and satisfaction of the aesthetic result.

Keywords: rhinoseptoplasty, deviation of the nasal septum, deformities of the nasal pyramid, surgical techniques, psychological causes

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Апстракт

Цел. Оперативната техника ринсептопластика има за цел да го ремоделира и редизајнира носот, да ги отстрани екцесивните коскени или ’рскавични структури, и/или со неа да се корегираат носните инсуфициенции, со цел носот да претставува хармонична единица во однос на останатите лицеви структури. Таа воедно претставува една од најфреквентните естетско - хируршки процедури. Картилагинозниот дел на назалниот септум претставува интегрален дел во регионот на истмусот и има значајна улога во струењето и турбуленцијата на воздухот. Поради оваа централна улога на носната преграда, многу е важна адекватноста на преземената оперативна техника како клуч за успешен третман, како во функционалната така и во естетската хирургија. Поддржана од клинички важни информации, целта на оваа студија е правилна селекција на пациентите за риносептопластика.
Методи. Во оваа студија статистички беа анализирани вкупно 300 пациенти со деформитети на носната пирамида: rhinokyphosis, rhinoscoliosis, rhinolordosis (седлест нос), „долг нос” (анг: functional tension nose) одделно или во склоп со деформитетина носната преграда (deviatio septi nasi). Испитуваните пациенти беа ставени на оперативна листа во периодот од април 2021 год. до април 2022 год. По извршената оперативна интервенција, испитаниците беа анкетирани колку се задоволни од извршената корекција (функционално и естетски), при што им беа понудени 5 скорови: 1-многу задоволни, 2-задоволни, 3-неодредени, 4-незадоволни и 5- екстремно незадоволни. Според *видот на оперативната техника*, при изведба на оперативната интервенција, пациентитебеа поделени во две групигрупа 1: каде се изведе само септопластика; тоа беа пациенти со Dg: Deviatio septi nas- група 2: каде се изведе риносептопластика: тоа беа пациенти кои освен девијација на носнатапреграда имаа и деформитет на носната пирамида од типот на: rhinokyphosis, rhinoscoliosis,rhinolordosis (седлест нос) „долг нос” (анг: functional tension nose).
Резултати. Резултатите од истражувањето покажаа дека на контролите по 7, 14 дена и 2, 6 месеци мал е бројот на испитаници кои назалната опструкција ја чувствуваа како слаба и која не им ги попречува секојдневните активности и спиењето. Укажувањето на незадоволство како доминантен симптом кај пациентите со деформитети на носната пирамида и нејзината константност и во постоперативниот период укажа дека таа кај пациентите се појавува и од одредени субјективни причини кои се најчесто од психогена природа: анксиозност, немир, преголеми очекувања од интервенцијата. Појавата на епистакса беше детектирана кај назални септални девијации во предните и предно-задните партии, но без сигнификантност.
Дискусија. Забележавме дека најзадоволни пациенти се оние кои имале девијација на септумот и очигледен естетски проблем. Ние покажавме дека изведувањето на септопластика не значи само централизација на септумот. Просторот помеѓу септумот и носната конха е многу важен за адекватна назална респирација. Септопластиката е фундаментална за функцијата и за естетикиот изглед на носот. Со тоа ние покажавме дека риносептопластика не е ригидна хирушка процедура. Кој тип на хирушка техника ке биде спроведен зависи од патологијата на септумот и од формата на носот која е различниа од пациент до пациент.
Заклучок. Резултатите сигнификантно ја прикажуваа корелацијата помеѓу анатомските (објективни) и психолошките (субјективни) причини кои ја одредуваа тежината и присутноста на назалните симптоми и задоволството од естетскиот резултат.

Клучни зборови: риносептопластика, девијацијата на носната преграда, деформитет на носната пирамида, оперативни техники, психолошки причини

Introduction

The surgical technique of rhinoseptoplasty consists of two surgical parts: septoplasty (Greek: septum – partition + plassein – modeling) is an operative intervention to correct structural deformities and anatomical variations of the nasal septum. It is one of the most frequent surgical procedures. “When septum goes, the nose follows”, is an old but true saying.
Rhinoplasty (Greek: rhinos – nose + plassein – modeling) represents a surgical procedure for correction of structural deformities of the nose. It includes nose remodeling and redesign, with removal of excessive bone or cartilage structures, and/or correction of nasal insufficiency so that the nose is a harmonious unit in relation with other facial structures. When we see a face, the nose is the first thing we notice.

Central role of the nasal septum

The primary role of the nasal septum is to connect the structures in the nasal cavity with the other parts of the nasal exterior. The septum serves as a contact with the lateral cartilage, and is a necessary connection between the anterior parts of the nose and the facial skeleton, the premaxilla, the nasal spine and the perpendicular plate of the ethmoidal bone. At the same time, the cartilaginous part of the nasal septum is an integral part of the region of the isthmus and has a significant role in the flow and turbulence of the air. The septum supports the function of the alar and other cartilages,

forming a unit, called the septolateral cartilage [1,2]. The nose participates in humidifying the air. It is the primary organ that filters the inhaled particles, and at the same time it is in the first line of defense as part of the immune system, which is provided by the inspired air that comes in contact with the mucosa and the secretory IgA [17-19]. The inspired air in the nasal cavity comes into contact with the olfactory nerve, through which the sense of smell is provided, and also it is in close connection to the sense of taste [9-11].

Anatomy of the nose and nasal septum

The shape of the nose is determined by its infrastructure, both bone and cartilaginous parts. The bone base of the outer part of the nose consists of: nasal extension of the frontal bone (*processus nasalis ossis frontalis*), nasal bones (*ossa nasalia*) and the frontal extension of the upper jaw (*processus frontalis maxillae*). The cartilaginous base of the outer nose consists of: triangular cartilage, right and left (*cartilago nasi lateralis dexter et sinister*), major alar or lobular cartilage, right and left (*cartilago allae nasi major*), minor alar cartilage right and left (*cartilage allae nasi minor*) and the quadrilateral piece of the hyaline cartilage, or the septal nose cartilage [1,2].

Nasal walls

Upper wall (roof) - the mucosa that covers the following bone structures: *ossa nasalia* (Figure 1), *lamina cribrosa* of the ethmoidal bone and the anterior mandibular side of the *corpus ossis sphenoidalis*.
Lower wall (floor) - the upper side of the palate bone (*ossa palatina*).
Lateral wall - it consists of several bones including: maxilla (Figure 1), lacrimal bone, the labyrinth of the ethmoidal bone, the vertical plate of the palatine bone, the pterygoid processus of the sphenoidal bone and the lower nasal concha.

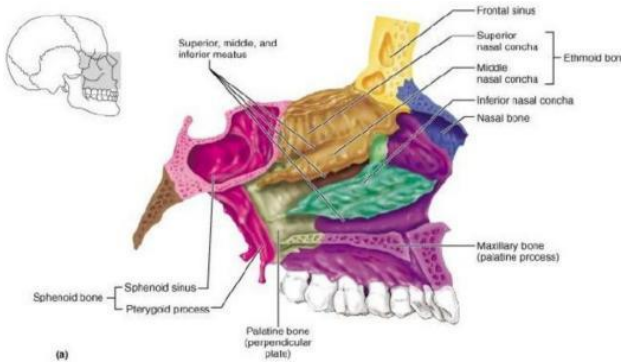

Fig. 1. Anatomy of the nasal walls

Medial wall - it is the nasal septum, containing three parts: membranous part, septal nasal cartilage and a bone part including perpendicular plate and vomer [16].

Classification of septal deformities

Septal deformities can be located in the skeletal area or cartilaginous area, but mostly they are in both areas. Cartilaginous deformities have the biggest impact on air flow abnormalities of the upper respiratory tract. Deformities of the nasal septum can be a consequence of both external or internal factors.
Internal factors: trauma with dislocation or fracture of the septal elements; theory of birth trauma. External factors: abnormally big or dislocated *spina premaxillaris*, vomer fracture or deformations of the perpendicular lamina; previous fracture of the nasal bones; and cartilaginous deformities [1-3].
The surgical management of nasal deformities has anatomical subdivisions: dorsum of nose (*dorsum nasi*), lateral parts, hemilobules, triangular cartilages, alar cartilages and the columella. These subdivisions are the subject of corrections and reconstructions. From an aesthetic point of view, the nose, starting from the nasion (middle point of nasofrontal connection) all the way through the columella makes the middle third of the face.
Nasofrontal angle - between the frontal bone and the nasion, usually is 120˚; it is sharper in men than in women.
Nasofacial angle – the angle between the nose and the rest of the facial structures, usually between 30˚ and 40˚.
Nasolabial angle - the angle between the columella and the philtrum; it is 90˚-95˚ in men and 100˚-105˚ in women.
Facial proportions in relation to the nasal tip (distance between nasal tip and face) is determined by the method of Goode [17], where the projection of the nasal tip is supposed to be 50-60% of the distance between nasion and nasal tip, so the ideal projection of the nasal tip should be 0.55:1 to 0.61:1 [13-15].

Surgical protocol

In this paper, our aim was to determine and establish the surgical procedures when performing rhinoseptoplasty. In doing so, we were guided to a certain direction by aesthetic and functional rhinosurgery. This surgery is performed under general anesthesia, and at the same time a local anesthetic is injected in the nasal area (Lidocaine 2%, Adrenaline 1% in saline 0.9% solution, in a quantity of 5-10 ml) in order to achieve less bleeding during surgery, and painless postoperative period, over several hours.
Open rhinoseptoplasty is a surgical procedure, which is approached with a transcolumellar and infracartilaginous incision, after which the cartilaginous and bone elements of the nose are prepared and displayed, with elevation of the skin. Firstly, modeling of the bones and cartilage parts of the nasal roof, with the help of files (manual and electric), with medial osteotomy [8] and excision is made. Septoplasty [7] is performed. A classic lateral internal osteotomy is performed, to close

the roof of the nasal pyramid. Modeling of the nasal ridge is achieved by cephalic resection of the lateral cartilages and by placement of a cartilaginous columella graft.
In nasal septal surgery, septoplasty (closed surgical procedure), we basically followed the seven steps of nasal septum surgery (Huizing and Groot) in all patients [11,12]: a -hemistransfixion incision is made into the septum. From here, we can an approach every bone and cartilage parts. The border between the mucosa and the skin (2 mm below it) is sufficient for good orientation. Complete mobilization of all deformed and dislocated parts of the septum is necessary for good postoperative, functional and aesthetic results. In all cases, resection of the extensor spines (cartilaginous parts) and crests (bone parts) of the nasal septum is performed and in some cases vertical lamellar resection of the septum is performed, when indicated, but never extensive resections. All parts of the cartilage and bone of the septum should be exposed in the midline between both nasal walls. Fixation of the nasal pyramid is completed with external fixator and silicone tampons. Tampons are placed in both nasal openings, and removed after seven days. External fixator, tile, is changed on the seventh day, and worn for another seven days.
In terms of the type of surgical technique, patients were divided in two groups: the first groups of patients were those who underwent only septoplasty, and the second group were those with rhinoseptoplasty. The first group of patients had a diagnosis of nasal septum deviation, while the second group included patients who, in addition to deviation of the nasal septum, also hade a deformity of the nasal pyramid.

Aims of the study

The frequency and intensity of nasal symptoms in rhinoseptoplasty patients were evaluated before and after the intervention. The satisfaction of the aesthetic result with the open rhinoseptoplasty as a surgical technique was evaluated. An adequate psychological model of personality was determined when selecting the patients for intervention. The most common complications within the first 24 to 48 hours postoperatively were evaluated. Supported by clinically relevant information, this study aimed to be a protocol in the selection of patients for rhinoseptoplasty.

Test material

The study included 300 patients with nasal pyramid deformities: rhinokyphosis, rhinoscoliosis, rhinolordosis, saddle nose, elongated nose as a unique deformity or in combination with nasal septum deviation. Patients were listed for rhinoseptoplasty at the Sante Plus Group hospital in Skopje, during a one-year period (April 2021 to April 2022).
Inclusion criteria were: patients older than 16 years, patients with deviation of the nasal septum, evidence of sinusitis, headaches due to deviation of the nasal septum.
Patients not included in the study: patients under the age of 16 years and above the age of 60 years, patients with coagulopathies, patients with chronic diseases (autoimmune, rheumatic, renal etc.), addicts, patients with septal perforation, previously operated patients, candidates for secondary rhinoseptoplasty.
According to the degree of nasal obstruction, patients were divided into three groups: group IA - subjects with severe nasal obstruction, group IB - subjects with moderate nasal obstruction and group II - subjects with mild nasal obstruction. The first postoperative evaluation was performed on the seventh and the fourteenth day. Later, patients were examined after two and six months.
According to the type of surgical technique, when performing the surgical intervention, patients were divided into two groups: group I - where only septoplasty was performed; these were patients with a diagnosis deviation of the nasal septum (closed surgical technique); group II- where rhinoseptoplasty was performed, these were patients who, in addition to nasal septum deviation, also had deformity of the nasal pyramid, such as rhinoscoliosis, rhinokyphosis, rhinolordosis, saddle nose, functional elongated nose, nasal tip defect (open surgical technique). All patients had their subjective symptoms noted, before and after surgery.
After the surgical intervention, a survey was conducted about patients' satisfaction with functional and aesthetic intervention, where they were offered five scores/options: 1 - very satisfied, 2 - satisfied, 3 – indefinite, 4 - dissatisfied and 5 - extremely dissatisfied. Over a period of 6 months, patients were monitored to see if they had still persistent subjective symptoms after surgery, and whether they continued to use any drugs to reduce nasal obstruction. Photographs of patients before and after surgery, in accordance with our ethical principles, were published in our paper, only with their written consent.
Psychological analysis was performed only in candidates for rhinoseptoplasty, who voluntarily agreed to complete the selection questionnaire of patients – candidates for intervention and their psychological preferences. However, there were no objective criteria. All the criteria were subjective and completely different for each patient and surgeon.

Test methods

The protocol analyzed the following data: basic clinical data - sex, age, routine tests (blood pressure, ECG, blood count, allergy examinations), physical examination, radiographic examinations (native x-ray or computed tomography of the facial bones).

Examination of nasal symptoms: nasal obstruction, rhinorrhea, headache, hyposmia, snoring, nasal speech and others. Nasal symptoms were recorded and grouped in the scale of subjective nasal symptoms, separately for each symptom: 0 - no symptoms, 1 - mild degree, with symptoms that do not interfere, 2 - moderate degree (partial disturbance of daily activity / sleep), 3 - severe degree (severe disturbance of daily activities / sleep).
Intraoperative monitoring of structural deformities: in all patients for rhinoseptoplasty, structural deformities of the nasal symptoms and their correction during the surgical intervention were followed intraoperatively. Intraoperative findings of the nasal septum were documented for each patient (in recorded and previously determined schemes).
Selection of the patient for rhinoseptoplasty and his/her psychological preferences: "self body image". What is the objective disorder in breathing or deformity of the nose? (fill in by the doctor), patient gender, national and religious affiliation, cultural habits, his/her attitude towards changes in certain body parts.

Brief Symptom Inventory (BSI) test

Herein we present the results obtained by analyzing the questions from Brief Symptom
Inventory (BSI) questionnaire, which is a standard psychological questionnaire which includes the following psychological symptoms in: somatisation, obsessive-compulsive reactions, interpersonal sensitivity, depression, anxiety, phobia, paranoid ideas, and patients without symptoms.
In the first postoperative 24-48 years, patients were hospitalized and complications such as bleeding, temperature and fiver were monitored.

Statistical analysis of data

For statistical data processing, we created a statistical database in the Statistics for Windows 7.0 program. The following statistical methodologies were used:

1. To determine the values and analyze the parameters of quantitative character, minimum and maximum values, we used the method of central tendency and method of variability.
2. To determine the significance of the obtained differences in the parameters with groups and subgroups of patients - candidates for rhinoseptoplasty, depending on the distribution of adequate data tests for independent primers we used: t-test for independent samples, Breakdown one-way ANOVA in data with symmetry Mann Whitney U test, Kolmogorov-Smirnov two-sample and Kruskal-Wallis test for data with asymmetry in distribution.
3. To determine the significance of differences in parameters before interventions, after intervention and at 2, 6 months intervals, depending on the distribution of data tests for dependent samples, we used: t- test for dependent samples and data with Wilcoxon distribution symmetry matched-pairs test at asymmetry distributed data or small examples.
4. To determine the relationship on two analyzed parameters we used Pearson's correlation coefficient (r) to quantitative and Spearman coefficient of rank correlation (R) with attribute variable; multiple correlation methods were used for determining correlation of dependent and several independent variables.

Results

Based on the clinical findings, patients were divided into three groups:
Group I - patients with severe stage of nasal obstruction (severe stage of nasal resistance), 39.3% of candidates for rhinoseptoplasty.
Group II - patients with middle stage of nasal obstruction (middle stage of nasal resistance), 39.3%.
Group III - 21.4% of patients, who had low nasal passages obstruction (low nasal resistance).
In the group of patients with severe nasal obstruction, predominant were patients with unilateral airway resistance (72.7%). The remaining patients (18.2%) had a total nasal resistance.
Deviation of the septum with severe deformity of the nasal pyramid was registered as an indication in the largest number and percentage of patients in the group with the highest degree of nasal obstruction (36.4%).
After the surgical intervention, patients were asked for their satisfaction with the performed aesthetic and functional correction, where they were offered 5 scores/options:
1- very satisfied (65% of patients)
2- satisfied (15% of patients)
3 - unspecified (5% of patients)
4 - dissatisfied (10% of patients)
5 - extremely dissatisfied (5% patients)

The postoperative analysis of 300 patients showed that 85% of them were satisfied with the postoperative results. About 15% of patients in this study were not satisfied. In the group of patients with objective nasal obstruction and aesthetic problems, there was a high degree of satisfaction with the surgical intervention; 45.45% said they were very satisfied, and 30.9% that they were satisfied.
In the group of patients with septum nasal deviation and severe deformity of nasal pyramid, 40% were very satisfied, while there were no patients from this group who were dissatisfied or extremely dissatisfied. Dissatisfaction from the intervention was stated by1 5% of patients due to deviation of the septum or deformity of the nasal pyramid.

The questionnaire for psychological testing - questionnaire for "body image" was completed by 300 respondents, candidates for rhinoseptoplasty, of which 55.55% were women, and the remaining lower percentage, 44.45%, were male respondents.
The ethnic structure of the respondents was: 39.8% were of Macedonian, 40.75% of Albanian, and 5.55% of Turkish nationality and of others nationalities.

Discussion

Septoplasty as functional or in combination with rhinoseptoplasty (aesthetic-functional) is one of the most common procedures performed in the departments of Plastic Reconstructive and Aesthetic Surgery as well as Otorhinolaryngology. We note that the most satisfactory patients are those in whom the nasal septal deviation is present with an obvious aesthetic problem. Also, there is an indication for rhinoseptoplasty in patients with low nasal passages obstruction and small aesthetic correction.
The postoperative analysis of 300 patients showed that 85% of them were satisfied with the postoperative results (aesthetic and functional). About 15% of patients in this study were not satisfied. Our results were very similar to the results presented by Dommerby *et al*. [4] It was performed only in patients who had undergone surgery with severe nasal resistance (obstruction). Bohlin and Dahlqvist [7] showed that up to 85% of patients were satisfied with postoperative results after 10 years. We have shown that performing septoplasty is not only for centralization of the septum. The space between the septum and the nasal concha is very important for proper nasal respiration [5,18]. Septal correction is a fundamental component in both, functional and aesthetic aspects of rhino surgery. Therefore, we have shown that surgical procedure rhinoseptoplasty is not a rigid procedure. Which type of intervention is to be done depends on the pathology of the septum, and the shape of the nose which is different from one to another patient.
In this study, in 36.4% of patients septoplasty alone was performed, and in the remaining 63.6% rhinoseptoplasty. We had a low incidence of postoperative dry nasal mucosa and postoperative complications (16%). In some other studies it is around 20%.

Conclusion

The exact decision had to be made on the surgical intervention of the nasal septum and the aesthetic correction of the nasal pyramid as well as on the exact surgical method.
In this study, about 15% of patients were not satisfied with the postoperative result and were followed for 6 months. We followed these patients and prescribed medications such as nasal corticosteroids to avoid revision, and secondary rhinoseptoplasty.
Surgeons, especially aesthetic surgeons, should know that rhinoseptoplasty is a difficult surgical procedure. Therefore, one has to apply a surgical technique that will yield the best results, aesthetic and functional, and to work comfortably with it. It has to be pointed out that the surgeon should know all surgical techniques. Also, he/she should not be satisfied with the first results, or one week after the surgical intervention. The real results are seen after two months postoperatively. With each rhinoseptoplasty, the most important moment is achieved, and that is the functional-aesthetic balance [6-8].
We wanted to test the psychological profile of the person, the patient, whether he/she would recognize the possible change that would occur, which would change not only the physical appearance, but would also have impact on his/her mental life. Thus, we created a profile of people who would consider them "good" and "bad" candidates when choosing rhinoseptoplasty.
It would be very useful for the surgeon in making the right decision about the surgical intervention, as well about distinguishing the postoperative subjective expectations of the patient and the objective expectations of the surgeon from the performed surgical procedure. But the criterion is subjective and completely different for each patient and surgeon. Through the Brief Symptom Inventory (BSI) standard test, we found that rhinoseptoplasty surgery positively affected the patient to find himself in social and emotional life. This is in line with a study conducted in 1991 by Goin MK and Ress TD [21] on 200 patients seeking septorhinoplasty at the New York Medical Center, Department of Plastic and Reconstructive Surgery, and the American Association of Plastic and Reconstructive Surgeons. Cash and Horton noted that generally patients who were depressed did not show it openly to either the surgeon or the nurse. They found it common for patients to hide emotional concerns; they were much freer to discuss physical problems with doctors and nurses. Sometimes, emotional concern is hidden behind the veil of complaints about surgical results and changes in patient's appearance. Often, blaming the doctor for the "bad" postoperative result around his/her nose hides deep dysmorphophobic disorders. The study, published in the August number of Issue of Plastic and Reconstructive Surgery [20], showed a surprisingly large increase in body pattern disorder (BDD) in patients - rhinoseptoplasty candidates. This would mean that one of three patients show a disorder of her/his own body pattern (BDD). Previous studies have shown that only 10% of patients show the same disorders. We have shown that through the examination made with the Questionnaire for selection of patients - candidates for rhinoseptoplasty and their psychological abilities as well as through the Brief Symptom Inventory test

(BSI) we helped patients to make a correct, realistic and reasonable decision which aesthetic intervention was to be performed.

At the same time, it would be of great benefit to the surgeon in making the correct decision about the surgical course of the intervention, as well as in distinguishing the objective expectations of the surgeon from the performed surgical procedure and the patient's expectations [20,21]. If experience, expertise and the choice of adequate equipment are very important for the surgical course, communication and selection of patients for rhinoseptoplasty are very important for the results.

Conflict of interest statement. None declared.

References

1. Wengraf Cl, Gleeson MJ, Siodlak MZ. The stuffy nose: a comparative study of two common methods of treatment. *Clin Otolaryngol* 1996; 111: 61-68.
2. Vainio-Mattilla J. Correlation of nasal symptoms and signs in random sampling study. Thesis, University of Turky. *Acta Otolaryngol Suppl* (Stockh) 2007; 318: 1.
3. Cole P, Chaban R, Naito K. The obstructive nasal septum. *Arch Otolaryngol Haed Neck Surg* 2000; 114: 410-412.
4. Dommerby H, Rasmussen O, Rosborg J. Long Term results of septoplastic operations. *ORL J Otorhinolaryngolo Relat Spec* 2002;47: 151-157.
5. Jessen M. Malm I. The importance of nasal airway resistance and nasal symptoms in the selection of patients for septoplasty. *Rhinology* 2004;) 47: 157-164.
6. Mertz J, McCaffrey T, Kern E. Objective evaluation of anterior septal surgical reconstruction. *Otolaryngol Haed Neck Surg* 2006; 92: 308-311.
7. Bohlin L, Dahlqvist A. Nasal airway resistance and complications following functional septoplasty: A ten-year follow-up study. *Rhinology* 1994; 32: 195-197.
8. Haarmann S, Budihardja AS, Wolff KD, Wangerin K. Changes in acoustic airway profiles and nasal airway resistance after Le Fort I osteotomy and functional rhinosurgery: a prospective study. *Int J Oral Maxillofac Surg* 2009; 38(4): 321-325.
9. Flemons W, Ward, Chair, American Association of Sleep Medicine Task Force (AASMTF). Sleep Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. *Sleep* 1999; 22(5): 667-689.
10. Ayappa I, Norman RG, Krieger AC, *et al*. NonInvasive Detection of Respiratory Effort-Related Arousals (RERAs) by a Nasal Cannula/Pressure Transducer System. *Sleep* 2000; 23: 763-771.
11. Clark SA, Wilson CR, Satoh M, *et al*. Assessment of Inspiratory Flow Limitation Invasively and Non-Invasively During Sleep. *Am J Respir Crit Care Med* 1998; 158: 713-722.
12. Epstein MD, Chicoine SA, Hanumara RC. Detection of Upper Airway Resistance Syndrome using a Nasal Cannula/ Pressure Transducer. *Chest* 2000; 117: 1073-1077.
13. Guyatt AR, Parker SP, and McBride MJ. Measurement of Human Nasal Ventilation Using an Oxygen Cannula as a Pitot Tube. *Am Rev Respir Dis* 1982; 126: 434.
14. Hernandez L, Ballester E, Farre R, *et al*. Performance of Nasal Prongs in Sleep Studies. *Chest* 2001; 119: 442-450.
15. Montserrat JM, Farre R, Ballester E, *et al*. Evaluation of Nasal Prongs for Estimating Nasal Flow. *Am J Respir Crit Care Med* 1997; 155: 211-215.
16. Geurkink N. Nasal anatomy, physiology, and function. *J Allergy Clin Immunol* 1983; 72: 123-128.
17. Proctor DF. Nasal physiology and defence of the lungs. *Am Rev Respir Dis* 1977; 115: 97-129.
18. Ferris B, Mead J, Opie L. Partitioning of respiratory flow resistance in man. *J Appl Physiol* 1964; 19: 653-658.
19. Eccles R. A role for the nasal cycle in respiratory defence. *Eur Respir J* 1996; 9: 371-376.
20. Sarwer DB. High prevalence of body dysmorphic disorder symptoms in patients seeking rhinoplasty. *Plast Reconstr Surg* 2011; 128(2): 518-519.
21. Goin MK, Rees TD. A prospective study of patient's psychological reactions to rhinoplasty. *Ann Plast Surg* 1991; 27: 210-215.

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Case report

EFFECTIVENESS OF TREATMENT WITH RADIAL EXTRACORPOREAL SHOCK WAVE THERAPY IN PATIENT WITH KNEE OSTEOARTHRITIS

ЕФИКАСНОСТА ОД ТРЕТМАНОТ СО РАДИЈАЛНА ЕКСТРАКОРПОРАЛНА ТЕРАПИЈА КАЈ ПАЦИЕНТ СО ОСТЕОАРТРИТИС НА КОЛЕНО

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Abstract

Introduction. Knee osteoarthritis is a common musculoskeletal disorder characterized by gradual thinning of the cartilage and increased friction of the bone structures leading to pain, numbness, as well as heavier and impaired movement. It is usually treated with different modalities of physical therapy where radial extracorporeal shockwave therapy comes as a new effective conservative method.

Case report. This case report presents a 61-year-old female patient, a housewife, who was complaining on pain in the last 2 months; she had limited movements and demonstrated crepitations during active movement of the right knee. The patient received 5 treatments of radial extracorporeal shock therapy continuously, one treatment per week, applied at 2-bar pressure, 10 Hz frequency, with 2000 shocks. Parallel to the treatment, the patient underwent kinesiotherapy in duration of 30 minutes per session, 5 days a week for a total of 2 weeks. The patient's progress was monitored on the Numeric scale of pain, the WOMAC Index of functional ability, as well as by knee joint circumference and mobility measurements. The clinical findings were evaluated before the treatment with radial extracorporeal shockwave therapy started, then immediately after its completion, and finally 3 months afterwards. The patient achieved a subjective and objective improvement of the local finding: her pain decreased and her range of motion and functional ability both improved.

Conclusion. Radial extracorporeal shock wave therapy is an effective, safe and non-invasive physical treatment in patients suffering from knee osteoarthritis.

Keywords: knee osteoarthritis, radial extracorporeal shock wave therapy

Апстракт

Вовед. Остеоартритисот на коленото претставува често мускулно-скелетно нарушување што се карактеризира со постепено истенчување на 'рскавицата и зголемено триење на коскените структури што води до болка, вкочанетост и отежнато и нарушено движење. Вообичаено се третира со различни модалитети на физикален третман, каде радијалната екстракорпоралната терапија со ударни бранови се јавува како нова ефективна конзервативна метода.

Приказ на случај. Во овој приказ на случај презентираме пациентка на 61 годишна возраст, домаќинка, која се жали на болка во период од 2 месеци, ограничени движења и присуство на крепитации при активно движење на десното колено. Кај пациентката се примени радијална екстракорпорална терапија со ударни бранови континуирано, 5 третмани, 1 неделно, со притисок од 2 бари, фреквенција 10 херци, бр. на удари 2000. Истовремено за времетраење на третманот пациентката применуваше и кинезитерапија во времетраење од 30 минути, 5 дена во неделата, вкупно 2 недели. Кај пациентката се евалуираше Нумеричката скала за болка, WOMAC индексот за одредување на функционална способност и беа направени мерења на обемот и подвижноста на коленовиот зглоб. Клиничките наоди беа евалуирани пред започнување со третманот со радијална екстракорпорална терапија со ударни бранови, веднаш по завршувањето и после 3 месеци од применетиот третман. Кај пациентката се постигна субјективно и објективно подобрување на локалниот наод, намалување на болката, подобрување на обемот на движење како и подобрување на функционалната способност.

Заклучок. Радијалната екстракорпорална терапија со ударни бранови претставува ефикасен, безбеден

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и неинвазивен физикален третман кај пациенти со остеоартритис на колено.

Клучни зборови: остеоартритис на колено, екстракорпорална терапија со ударни бранови

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder characterized by gradual loss of articular cartilage. This leads to a gradual thinning of the cartilage which results in bones rubbing together, creating stiffness, pain, and impaired movement [1]. It is a major cause of disability of the elderly population around the globe, especially in developing countries. The prevalence is increasing and will continue to do so, with the increase in population, its aging and the epidemic increase of weight gain. This type of musculoskeletal disorder places a heavy burden on individuals, communities, health and social care systems [1].
Osteoarthritis has been found to be the fifth highest cause of years lost to disability in the whole population in high-income countries, and the ninth highest cause in low- and middle-income countries. Worldwide estimates are that 9.6% of men and 18.0% of women over the age of 60 have symptomatic osteoarthritis. Radiographic evidence of knee osteoarthritis is present in approximately 30% of men and women over the age of 65.2 [2]. Approximately 80% of those with osteoarthritis will have limitations in movement, and 25% cannot perform their major activities of daily life [3].
Osteoarthritis has a multifactorial etiology consisting of both systemic and local risk factors. Systemic risk factors include: age - the most important factor in the development of osteoarthritis [4]; gender - where women have a higher degree of pain and disability than men; genetic factors - it has been proven that between 39% and 65% of osteoarthritis in the general population is due to genetic factors [4]. Local risk factors include: injury or trauma to the joint where articular cartilage joint loses its flexibility, destroys cells, and reduces the load on the subchondral bone; obesity; occupational or workplace risks involving recurrent injuries, and physical injuries [5]; physical activity/sports activities also play an important role in the development of knee osteoarthritis [4]. Professional athletes who participate in sports with high physical impact have an increased risk of knee osteoarthritis [5]. Knee osteoarthritis is most often manifested by pain which is the earliest and dominant symptom. Other symptoms include: stiffness in the knee, especially in the morning or after prolonged sitting; swelling; a feeling of warmth in the joint; decreased mobility in the knee joint, and crepitations when the knee moves [4]. The diagnosis of knee osteoarthritis is made on the basis of clinical examination, and is confirmed by a conventional radiography, which is the simplest and the most cost-effective method [6]. The Kellgren and Lawrence Scale is considered as a gold standard for diagnosing knee osteoarthritis and consists of four degrees of radiological diagnosis of knee osteoarthritis [7].
Treatment of knee osteoarthritis can be conservative and surgical. Conservative treatment consists of non-pharmacological and pharmacological treatment. Non-pharmacological treatment primarily consists of educating patients, self-managing the condition, applying kinesitherapy, and weight loss. This treatment also includes the application of physical modalities as well as the application of orthoses.
Radial extracorporeal shock wave therapy (RECTUB) is a treatment with a high-intensity acoustic radiation that is used for therapeutic purposes. The extracorporeal shock wave is an acoustic wave characterized by high positive pressures of more than 1000 bar (100 MPa), which can be developed within an extremely short rise time (10^{-9} seconds) and followed by a low pressure phase of tensile stress equivalent to 100 bar (10 MPa). As the pulse duration of the shock wave is extremely short (3 to 5μs) and is generated at low frequencies, it is minimally absorbed by the tissues and therefore no thermal effect is generated [8].

Case report

We herein present a 61-year-old woman, a housewife, who was complaining on pain for the last 2 months; had limited movements and noticed the presence of crepitations during active movement of the right knee. The patient had not performed any physical activity in the last 3 months, nor she received any physical treatment for 6 months before starting the RECTUB therapy. She took an analgesic once a week for pain relief. The patient is overweight with BMI - 28.4 and suffers from hypertension and diabetes treated with oral antidiabetic therapy. During the examination, the patient preserved tone and reduced tropism of the musculature, primarily on the thigh musculature. The right knee was with periarticular thickening and pain on palpation medially. The patient performed active movements in the hip and ankle in the normal range, while the active knee movements were accompanied with pain and limited flexion. Knee movements were accompanied by crepitations, especially when performing maximum flexion. The patient walked freely without any assistance. The following clinical scales and measurements were used: Numeric scale of pain, WOMAC osteoarthritis index, and measurements of the circumference of the knee joint with centimeter tape and the knee mobility with goniometer. The evaluation was done before the start of the physical therapy; after its completion, and 3 months afterwards.
Both inclusion and exclusion criteria were taken into consideration to decide on the treatment. Criteria pla-

cing the patient in the inclusion group were her age (between 40 to 65 years), and a physical examination done confirming the presence of at least one of the following clinical criteria: knee pain, morning stiffness not longer than 30 minutes and presence of crepitations during active movement of the knee, whereas knee osteoarthritis radiographically diagnosed according to the Kelgren and Lawrence scale. The exclusion criteria would have been the patient's age (if under 40 and over 65), existence of pregnancy, presence of acute and chronic diseases: neurological, infectious, malignant diseases, ulcers of the skin of the knee joint, secondary arthritis, information on any surgical treatment in the examined knee, data on the application of physical therapy for less than 3 months from the treatment with RECTUB and data on intraarticular injections with corticosteroids and hyaluronic acid for less than 6 months before RECTUB treatment.

The therapy was applied by a physiatrist: a total of five treatments performed once per week, 2000 strokes in the area of painful points of the right knee with pressure of 2 Bar, frequency of 10 Hz and duration of the application for 5 min. The patient underwent kinesitherapy treatment consisting of isotonic and isometric exercises to strengthen the thigh muscles, as well as active exercises to increase the range of motion of the knee joint for 10 consecutive days with weekend breaks.

Evaluation of the treatment efficacy: The patient achieved a subjective and objective improvement of the condition after the end of the treatment and 3 months following its completion. The intensity of the pain went from strong to mild and remained the same even 3 months after the completion of the physical treatment. The circumference of the knee joint decreased and mobility increased, indicating that the patient continued to exercise regularly after receiving RECTUB therapy. The WOMAC index showed that the patient immediately and 3 months after the end of the physical treatment experienced less pain and stiffness of the knee joint and had a greater functionality in performing her daily activities.

Discussion

The results of this case report demonstrate the benefits of using RECTUB as a safe, non-invasive, conservative treatment for knee osteoarthritis. It turned out that the therapeutic effect of its application was maintained for 3 months after its application, primarily with a better clinical result than before the start of the treatment. The systematic review and meta-analysis of Lou *et al.* for the application of extracorporeal shock wave therapy in osteoarthritis and comparison of its use in correlation with other conventional treatments showed that the application of shock wave therapy resulted in a significant reduction in pain and improvement in functional capacity compared to placebo, intraarticular administration of corticosteroids or hyaluronic acid, analgesics, and ultrasound therapy. Randomized controlled trials were identified comparing the effect of ECTUB with other types of osteoarthritis treatment. The Numeric scale of pain and WOMAC index for pain relief and functional fitness were examined. The application of shock wave therapy in the treatment of osteoarthritis was recommended as a non-invasive method, safe, secure and effective in the treatment of various forms of osteoarthritis [9]. A study by Ji-Hyun Lee *et al*., which presented the effects of shock wave therapy in combination with conventional physical therapy and the effects of conventional physical therapy alone on pain and functional capacity in patients with degenerative osteoarthritis of the knee, found that there was a greater improvement in the measured parameters in the first group. This does not exclude the possibility of considering the combined application of conventional physical therapy with the application of shock wave therapy in the treatment of knee osteoarthritis [10]. In the first meta-analysis of the application and efficacy of shock wave therapy in osteoarthritis of the knee published by Tengqui *et al*., out of a total of 127 studies, seven comprised a total of 366 patients, of whom 169 were included in the shock wave group, 140 were in the placebo group and 57 patients belonged to the physical therapy group. The Visual Analogue Scale (VAS), range of motion (ROM), Lequesne index (LI) and WOMAC index were examined. The final results in terms of pain, range of motion, LI and WOMAC index were with a statistically significant difference of the ECTUB group compared to the other two groups. This meta-analysis suggests that shock wave therapy in patients with knee osteoarthritis may achieve a better therapeutic effect than conventional physical therapy [11].

Conclusions

RECTUB therapy in combination with kinesitherapy showed improvement in the volume and mobility of the knee joint of our patient. A better and longer lasting analgesic effect was achieved which took place even after 3 months of the treatment termination. Improvement and increase of the functional ability of the patient were accomplished. RECTUB treatment is a safe, secure, and non-invasive treatment in patients with knee osteoarthritis.

Conflict of interest statement. None declared.

Reference

1. Rachel Wittenauer, Lily Smith, and Kamal Aden. *Osteoarthritis* January 28th 2013.
2. Teitel AD, Zieve D. MedlinePlud Medical Encycolpedia. National Institutes of Health. "Osteoarthritis." Last updated: Sept 26, 2011.

3. World Health Organization. “Chronic Rheumatic Conditions”. Chronic diseases and health promotion. 2012. http://www.who.int/chp/topics/rheumatic/en/.
4. Johanne Martel-Pelletier. Pathophysiology of osteoarthritis. Osteoarthritis Cartilage 2004; 12 Suppl A: S31-S33.
5. Messier SP, Leagult C, Mihalko S, *et al*. The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. *BMC Muscul Dis* 2009; 10: 93 49.
6. David Zelman. Osteoarthritis of the Knee (Degenerative Arthritis of the Knee), June 20, 2019.
7. Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. *Ann Phys Rehabil Med* 2016; 59(3): 161-169.
8. Gladys LY Cheing, Hua Chang. Extracorporeal Shock Wave Therapy. J Orthop Sports Phys Ther 2003; 33(6): 337-343.
9. Lu Chen, Ling Ye, Hui Liu, *et al.* Extracorporeal Shock Wave Therapy for the Treatment of Osteoarthritis: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2020; 1907821.
10. Ji-Hyun Lee, Sangyong Lee, SeokJoo Choi, *et al*. The effects of extracorporeal shock wave therapy on the pain and function of patients with degenerative knee arthritis. *J Phys Ther Sci* 2017; 29(3): 536-538.
11. Tengqi Li, Jinhui Ma, Tingting Zhao, *et al*. Application and efficacy of extracorporeal shockwave treatment for knee osteoarthritis: A systematic review and meta-analysis. *Exp Ther Med* 2019; 18(4): 2843-2850.

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Тимес Нењ Роман големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

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Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) listata na Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

3. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

4. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):
а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.
б) заеднички автор
GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.
в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).
г) ***поглавје во книга или монографија***
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Уплата за испечатен труд во списанието ММП изнесува 3.000, 00 денари и се уплаќаат на жиро сметката на: Македонско лекарско друштво
300000000211884 - Комерцијална банка
со цел на дознака : уплата за стучен труд

Адресата на Редакцијата
Даме Груев бр. 3

Градски ѕид блок II,
1000 Скопје,
Тел.: ++ 389 02 3162 577
Електронска адреса (Е-маил): info@mld.mk

Авторите што сакаат да објавуваат трудови во списанието треба да ја имаат уплатено членаринатa за тековната година во висина од 1440 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД - 3162 557.