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CONTENT

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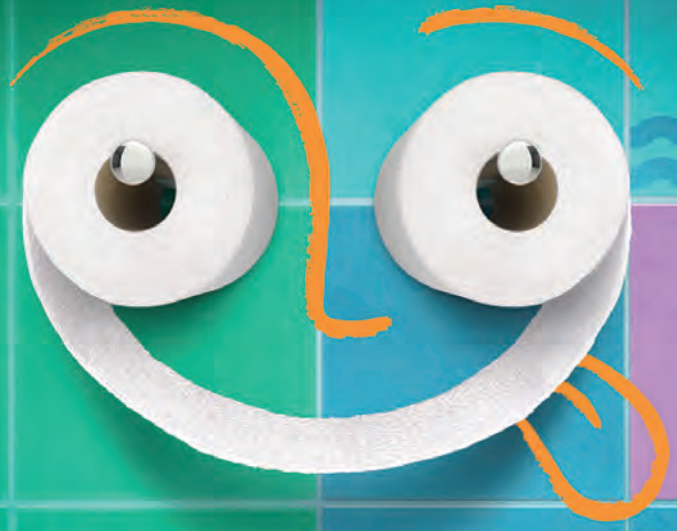

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Pacienţii cărora li se administrează concomitent, pe cale orală, medicamente care pot creşte riscul de apariţie al ulcerului sau hemoragiei gastrointestinale, cum sunt corticosteroizii, anticoagulantele (varfarina), inhibitori selectivi ai recaptării serotoninei sau medicamente antiplachetare cum este aspirina trebuie atent monitorizaţi. Tratamentul trebuie întrerupt dacă apare sângerare gastro-intestinală sau ulceraţie la pacienţii care administrează Nimesil. AINS trebuie administrate cu prudenţă la pacienţii cu afecţiuni gastrointestinale în antecedente (colită ulcerativă sau boală Crohn), deoarece li se pot exacerba aceste afecţiuni. La pacienţii cu antecedente de hipertensiune arterială şi/sau insuficienţă cardiacă congestivă uşoară până la moderată, sunt necesare monitorizare şi recomandări adecvate, deoarece raportările au arătat că tratamentul cu AINS se poate asocia cu reţenţie de lichide şi edeme. Deoarece nimesulida poate interfera cu funcţia plachetară, trebuie utilizată cu precauţie la pacienţii cu diateze hemoragice. Totuşi, Nimesil nu este un înlocuitor al acidului acetilsalicilic în profilaxia unor afecţiuni cardiovasculare. Administrarea de Nimesil, trebuie întreruptă la prima apariţie a erupţiilor cutanate, leziunilor mucoaselor, sau orice alt semn de hipersensibilitate. Întreruperea tratamentului cu Nimesil trebuie luată în considerare la femeile care au tulburări de fertilitate sau care sunt în cursul unei investigaţii pentru infertilitate. Nimesil granule pentru suspensie orală conţine zaharoză. Pacienţii cu afecţiuni ereditare rare de intoleranţă la fructoză, malabsorbţie la glucoză-galactoză sau insuficienţă a zaharazeiizomaltazei nu trebuie să utilizeze acest medicament. **Reacţii adverse** Reacţiile adverse cele mai frecvente sunt de natură gastrointestinală. Lista de reacţii adverse se bazează pe studii clinice controlate* (aproximativ 7800 pacienţi) şi pe date de farmacovigilenţă. Tulburări hematologice şi limfatice: Rare - anemie*, eozinofilie*; Foarte rare - trombocitopenie, pancitopenie, purpură. Tulburări ale sistemului imunitar: Rare - hipersensibilitate*, anafilaxie. Tulburări metabolice şi de nutriţie: Rare – hiperkaliemie*, Tulburări psihice: Rare – anxietate*, nervozitate*, coşmar*. Tulburări ale sistemului nervos: Mai puţin frecvente - vertij*, Foarte rare - cefalee, somnolenţă, encefalopatie(Sindrom Reye). Tulburări oculare: Rare - vedere încetoşată*, Foarte rare - tulburări vizuale. Tulburări acustice şi vestibulare: Foarte rare - vertij. Tulburări cardiace: Rare - tahicardie*. Tulburări vasculare: Mai puţin frecvente - hipertensiune arterială*, Rare-hemoragii*, oscilaţii ale tensiunii arteriale*, bufeuri*. Tulburări respiratorii, toracice şi mediastinale: Mai puţin frecvente - dispnee*, Foarte rare - astm, bronhospasm. Tulburări gastrointestinale: Frecvente - diaree*, greaţă*, vărsături*, Mai puţin frecvente- constipaţie*, flatulenţă*, sângerări gastrointestinale, ulcer duodenal şi perforaţie, ulcer gastric şi perforaţie, Foarte rare - gastrită*, durere abdominală, dispepsie, stomatită, melenă. Tulburări hepato-biliare: Frecvente - creşterea valorilor enzimelor hepatice, Foarte rare - hepatită, hepatită fulminantă (inclusiv cazuri letale), icter, colestază. Afecţiuni cutanate şi ale ţesutului subcutanat: Mai puţin frecvente - prurit*, erupţie cutanată tranzitorie*, transpiraţie abundentă*, Rare - eritem*, dermatită, Foarte rare - urticarie, edem angioneurotic, edem al feţei, eritem polimorf, sindrom Stevens- Johnson, necroliză epidermică toxică. Tulburări renale şi ale căilor urinare: Rare - disurie*, hematurie*, Foarte rare - retenţie urinară*, insuficienţă renală, oligurie, nefrită interstiţială. Tulburări generale şi la nivelul locului de administrare: Mai puţin frecvente - edeme*, Rare - Stare generală de rău*, astenie*, Foarte rare - hipotermie. Investigaţii diagnostice: Frecvente - creşterea enzimelor hepatice. * Frecvenţa bazată pe studii clinice DEŢINĂTORUL CERTIFICATULUI DE ÎNREGISTRARE_Laboratori Guidotti S.p.A Via Livornesse, 897 Pisa La Vettola, Italia CERTIFICATUL DE ÎNREGISTRARE Nr. 26648. **DATA REVIZUIRII TEXTULUI** Decembrie 2020.

Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie şi/sau să elibereze medicamente. Nimesil® este un produs cu prescripţie medicală. Citiţi cu atenţie RCP-ul pentru lista completă a reacţiilor adverse, contraindicaţii, atenţionări şi precauţii speciale pentru utilizare.. Certificatul de înregistrare Nimesil® nr. 26648 din 14.12.2020. Codul materialului: MD_NIM_05_2022_V01_print. Material elaborat: 29.11.2022.

1) RCP Nimesil® din decembrie 2020; 2) Kress HG, Baltov A, Basiński A, Berghea F, Castellsague J, Codreanu C, et al. Curr Med Res Opin. 2016;32(1):23-36. 3) Rainsford KD; Members of the Consensus Report Group on Nimesulide. Curr Med Res Opin. 2006 Jun;22(6):1161-70.

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RESEARCH ARTICLE

Immune and mathematical procedures in early diagnosis of psoriatic and seronegative rheumatoid arthritis

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What is not yet known on the issue addressed in the submitted manuscript

It is of particular interest to determine the early diagnosis of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) based on clinical data, immunological and mathematical research methods.

The research hypothesis

The difficulties in the early diagnosis of PsA and RA especially when RA is seronegative drive clinicians to search for different methods to establish the diagnosis – these may include clinical, immunological, and mathematical methods.

The novelty added by manuscript to the already published scientific literature

Immune disorders in the early stages of RA and PsA are nonspecific and are characterized by an increase in CD16+ and CD29+ in RA, which is significantly higher than in PsA, that is why mathematical model of RA and PsA has been developed and may serve as an additional way in diagnosing seronegative RA and early PsA.

Abstract

Objectives. Improvement of early diagnosis of psoriatic arthritis based on clinical data, immunological and mathematical research methods.

Material and methods. The study was carried out between 2019 and 2022 at the Rheumatology and Nephrology Discipline, in the arthrology and rheumatology departments of the *Timofei Moșneaga* Republican Clinical Hospital. To accomplish the tasks set out in the study, 110 patients were examined, including 55 patients with psoriatic arthritis (group I) and 55 patients with rheumatoid arthritis (group II).

Results. The range with the highest probability of psoriatic arthritis for the instrumental index is between 0.54 and 1.86. Of the 55 patients with psoriatic arthritis in 95% of patients clinical, laboratory, immunological and instrumental indices were within the range of the highest probability of the disease, which indicates a fairly high reliability of the mathematical model.

Conclusions. Immune disorders in the early stages of rheumatoid arthritis and psoriatic arthritis are nonspecific and are characterized by an increase in CD16+ (26.2±1.5) and CD29+ (24.8±2.1) in rheumatoid arthritis, which is significantly higher than in psoriatic arthritis CD16+ (22.0±1.3) and CD29+ (17.4±3.2) ($p < 0.05$). A mathematical model of rheumatoid arthritis and psoriatic arthritis has been developed, which serves as an additional way of diagnosing rheumatoid arthritis and early psoriatic arthritis.

Keywords: rheumatoid, psoriatic arthritis, mathematical, immune diagnosis.

Introduction

Psoriatic arthritis (PsA), as well as rheumatoid arthritis (RA) refer to diseases of great medical and social importance, due to the significant prevalence and progressive character of the disease, leading to early disability in individuals [1-3]. Lately, revisions have appeared dedicated to the description of new clinical forms of PsA and RA [4-6]. This creates difficulties in diagnosing the early stages of the diseases. At the same time, many joint lesions at the initial stage do not have sufficiently characteristic clinical and radiological signs that can be used as diagnostic criteria. In some cases, the recognition of joint conditions is extremely difficult in atypical natural history of diseases, especially with mono- or oligoarthritis [2, 4].

At the same time, it became known that the early years of the evolution of PsA and RA are crucial in the development and progression of the pathological process [1, 4, 7, 8]. It has

been established that the early stage of PsA and RA differs significantly from the later stages of the disease from a morphological point of view [3, 5, 9]. Therefore, remissions of the diseases are much more frequently observed in the initial period of PsA and RA [5, 6, 10]. This is fundamental for the initiation of appropriate pathogenetic treatment, when it is possible to suppress the active immuno-inflammatory process faster and more firmly and therefore prevent irreversible destruction of the joints [2, 5, 7].

However, such an approach to therapy is possible only under the conditions of early diagnosis of PsA and RA. Nevertheless, the problem of early diagnosis, especially PsA, remains an unresolved problem and of the most urgent in modern rheumatology.

PsA and RA are considered diseases where the pathogenesis are of great importance to immunological disorders [1, 3, 11, 12]. However, quantitative data and qualitative characteristics of individual indicators of the immune system and their significance in the development of PsA and RA are contradictory [2, 8, 9]. Therefore, the question of the importance of immunological disorders in the diagnosis of these pathologies remains relevant.

Thus, the polymorphism of clinical forms of PsA and RA, the lack of reliable early diagnostic criteria and methods create difficulties in recognizing the early stages of PsA and RA.

The purpose of the study was to improve the early diagnosis of psoriatic arthritis based on clinical data, immunological and mathematical research methods.

Material and methods

The study was carried out between 2019 and 2022 at the Rheumatology and Nephrology Discipline, in the arthrology and rheumatology departments of the *Timofei Moşneaga* Republican Clinical Hospital - Favorable opinion of the Research Ethics Committee at minutes No.21 from 21.12.2019. To accomplish the objectives, 110 patients were examined, including 55 patients with PsA (group I) and 55 patients with RA (group II). The diagnosis of RA was established according to the EULAR criteria (2010), PsA was established using the CASPAR classification criteria [1-3].

The age of patients at enrollment in the study ranged from 18 to 64 years (average 42.69±1.09 years), of them women – 82 patients (74.5%) and men – 28 patients (25.5%). The duration of the disease at the time of observation was the following – less than one-year (on average 5.91±0.38 months) – 85 (77.3%) patients, from 1.1 years to 3 years (on average 26.33±2.84 months) – 3 patients (2.7%) and with a course of the disease over 3 years (on average 157.5±18.43 months) – 22 patients (20%). Statistical analysis of the results was carried out through Statistics Software Package 9.0.

Results

Arthralgias were the most common symptom that persistently precedes joint syndrome in PsA and RA, however, joint pain was significantly more common in the group of patients with RA than in the group with PsA ($p < 0.05$). At the same time, in the group of patients with RA, the pain was more often localized in the joints of the upper extremities and most often in the shoulder (38.2%). In the group of patients with PsA, the joints of the lower extremities were the most common affected, while the knee joints were in first place in terms of frequency of occurrence (25.5%). Pain in the lumbo-sacral region was found only in the 2nd group of patients, being one of the causes of inflammatory low back pain (in 9.5% of patients). Talalgia was isolated as a separate element and was significantly more common ($p <0.05$) in the group of patients with PsA (25.5%) than in patients with RA (5.5%).

The onset of RA in most of the cases in our study had a classical course, in patients with RA joint damage was predominated arthritis – 76.4%, which was more often detected in women (61.8%). The disease began with lesions of the joints of the hands – radiocarpal joints (41.8%), proximal interphalangeal (47.3%) and metacarpophalangeal (58.2%); the lesions were symmetrical. The joints of the knee (34.5%) and ankles (25.5%) were often involved in the process, and the injury was asymmetrical in 24.2% of patients. However, in 23.6% of RA patients, the disease started atypically with mono-oligoarthritis, and these cases showed the greatest difficulties in establishing the diagnosis, but this form was not stable and turned into polyarthritis during the first year of the disease.

In the first year of the disease in the group of patients with RA, the indicators of the number of inflamed joints (10.4±0.8), the Ritchie articular index (11.05±0.69) and the Lee functional test (11.8±0.82) were significantly higher ($p <0.05$) than in the group of patients with PsA (2.88±0.36, 6.71±0.82, and 7.16±0.86 correspondingly). Especially they differ by the number of inflamed joints. In any case, over time and as PsA progress, these indicators become similar to the characteristics of RA.

Statistically significant differences in the groups of patients with early RA and PsA were detected by hemoglobin (113.6±1.8 g/l, 120.6±2.5 g/l), ESR (34.9±2.1 mm/h, 22.0±2.4 mm/h) RF (2.46±0.07 and 1.56±0.09) and CIC (88.6±5.2 and 68.3±6.1). In the group of patients with PsA with a duration of the disease of more than 3 years, the indicators of ESR, RF and CIC increase and correspond to the group of patients with RA.

The statistical analysis of the immunological parameters revealed significant differences ($p <0.05$) in the IgG content (20.09±0.09 and 14.35±1.2) in patients with early RA versus patients with early PsA, which correlate with the increase in RF content and the frequency of its detection in patients with RA. In the group of patients with early RA, the content of CD16+ cells at IgG Fc fragment were significantly higher, which correlates with an increased IgG content in this group compared to the group of patients with early PsA. This increase is natural, because in the group of patients with early RA, RF is detected more frequently. However, in the group of patients with PsA with a duration of the disease of more than 3 years, this difference disappears, which is because in these patients the frequency of RF detection increases over time.

The level of CD29+ (Th2) cells in early RA was also significantly higher than in early PsA ($p <0.05$), which can be

explained by the higher activity and systemic autoimmune reactions, with more implications of humoral immunity. The rate of CD38+, CD45+ and CD11+ in patients with RA and PsA was higher than normal, although their absolute values were normal, which is possible due to the increased level of leukocytes and lymphocytes (Table 1).

Table 1. Quantitative indicators of T lymphocyte subpopulations involved in autoimmune reactions in patients with PsA and RA at different stages of the disease.

Normal indexes and values	Duration of the disease			
	<1 year (I)		≥3 years (II)	
	RA (n = 55)	PsA (n = 30)	PsA (n = 25)	
CD38+	23±6	31.3±1.0	29.8±2.1	39.6±2.7
	Absolute values (300-600)	544.1±34.3	444.0±43.7	545.3±60.2
CD45+	25±5	31.3±1.8	34.4±2.9	34.4±3.9
	Absolute values (500 - 700)	483.0±45.4	504.3±63.2	487.2±79.8
CD29+	24±6	24.8±2.1	17.4±3.2*	25.7±5.6
	Absolute values (400-600)	391.8±39.6	239.6±52.1	336.6±67.1
CD16+	12±6	26.2±1.5	22.0±1.3*	29.5±1.8
	Absolute values (200-300)	447.2±37.7	358,1±42.0	416.4±36.2
CD11+	21±6	30.2±1.7	29.9±1.9	33.9±3.4
	Absolute values (300-600)	475.0±38.7	404.3±41.2	515.5±77.8

***Note:** * - p <0,05; group ≥3 years consist of: 1.1 to 3 years – 3 and over 3 years 22 patients. CD – clonal determinant; PsA - psoriatic arthritis; RA - rheumatoid arthritis.*

To form a mathematical model of PsA and RA the results of the study were accumulated in 2 groups of patients with PsA and RA. Clinical, laboratory, immunological and instrumental studies were evaluated on the three-point scale depending on the severity of symptoms. Indexes of immunoglobulins and lymphocyte populations on a two-point scale were evaluated. Next, the diagnostic value of each characteristic was evaluated, and the highest informative value was achieved (Table 2).

Table 2. Mathematical expectations and X^2 deviation of indexes in the group of patients with RA.

Indexes	M	I	Indicators	M	I
Clinical indexes			**Immunological indexes**		
Decrease in body mass	0.78	1.13	RF (latex test)	1.92	1.04
Arthralgia	2.26	0.56	ICC	1.60	0.91
Morning stiffness	1.68	0.73	IgA	0.39	0.78
Articular index, points	1.54	0.64	IgM	1.43	0.90
NSJ	2.34	0.59	IgG	1.14	0.95
Lee test, points	1.56	0.70	CD3+	1.14	0.40
Laboratory indexes			CD19+	1.13	0.67
ESR (mm\hour)	2.02	0.93	CD4+	1.29	0.49
α_2-globulins	0.90	0.61	CD8+	1.31	0.46
γ- globulins	1.24	0.88	CD4+/CD8+	0.88	0.77
CRP	0.90	1.15	CD16+	1.76	0.42

***Note:** M – median; I – informative value of index; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein.*

The most informative of the clinical indexes in early RA were – joint pain, the nature of joint damage and the number of inflamed joints. All laboratory indicators were of low informative value due to low average indices and significant data dispersion. Among the immunological data, the indicators RF, CIC, CD4+, CD8+ were the most informative. Then the laboratory (φL), clinical (φC) and immunological (φI) indexes were calculated according to the following formulas:

$\varphi C = a1S1 + a2S2 + a3S3 + \ldots + a11S11;$

$\varphi L = b1C1 + b2C2 + \ldots + b6C6;$

$\varphi I = c1D1 + c2D2 + \ldots + c12D12;$

where a, b, c is the informative coefficient of indicators, S – clinical indicators, C – laboratory indicators, D – Immunological indicators.

As a result, the clinical index corresponded to the range from 1.26 to 2.60; laboratory – from 0.11 to 2.24; immunological – from 0.85 to 1.68. Provided that the patient is clinical, laboratory and immunologically framed in the above intervals, then it can be stated with a high degree of probability that he has RA. In our group of 55 patients with RA in 89% of patients by clinical, laboratory and immunological indices calculated according to the proposed formulas, in the elaborated model they were within the range with the highest probability of the disease, which demonstrates a fairly high reliability of the model. The three previously introduced indices were complemented by another instrumental one, which was determined as a weighted average of 60 instrumental indicators, each of which was detected in 30 patients out of 55. The introduction of the instrumental index is a development of the previously developed RA mo-

del. The instrumental index was calculated by the formula: $\varphi In = 0{,}02\sum_{p=1}^{60} DS(Ap)$, where Ap – Instrumental indicator with the number p, SD (Ap) – the standard deviation of the indicator, if SD = 0, then the indicator is insignificant and was not taken into account.

The range with the highest probability of RA for the instrumental index is between 0.82 and 2.21, which corresponds to the mathematical expectation of 1.52, increased and decreased by 0.69. Distribution histograms were constructed for all four indices. The PsA model was developed according to the regressive methodology. The formulas for clinical, laboratory and immunological indices were determined by the method of the lowest X^2 based on the evaluation of the severity of the disease by the doctor on a scale of three points similar to RA. The mathematical model can be expressed by the formulas: $\varphi C = \sum_{1=1}^{12} a1S1$, $\varphi L = \sum_{1=1}^{6} b1C1$, $\varphi In = \sum_{1=1}^{12} c1D1$, where a1, b1, c1 unknown coefficients, to be determined, S1 – clinical indicators, C1 – laboratory indicators, D1 – immunological indicators.

The coefficients a1, b1, c1 were found from the best state (in the sense of standard deviation) the coincidence of the subjective assessment of the severity of the disease φC, determined by the doctor with a combination of indicators from the above formulas. For example, the coefficients a, were in the state $\sum_{k=1} a1\,(-\sum_{k=1}^{12} a1S1(k))$. In the result, the following formulas were obtained:

φC = 0.367S1- 0.130S2 + 0.073S3 + 0.121S4 + 0.038S5 + 0.155S6 + 0.014S7 + 0.122S8 + 0.327S9 + 0.266S10 – 0.026S11 – 0.151S12

φL = 0.409C1 + 0.211C2 + 0.162C3 + 0.142C4 – 0.012C5 + 0.246C6

φI = 0.498D1 + 0.405D2 + 0.106D3 + 0.183D4 + 0.293D5 – 0.166D6 – 0.096D7 – 0.013D8 + 0.148D9 + 0.043D10 – 0.106D11 + 0.099D12

The values of the indecency determined by these formulas in most cases coincided with the subjective evaluation of the doctor. The range of values for the clinical index corresponded from 0.58 to 1.84, for the laboratory – 0.63 - 1.93, immunological – 0.63 - 1.66, which corresponds to the increased and low mathematical expectation of SD.

The instrumental index for PsA was determined by the same method as for RA, as a weighted average: $\varphi In = 0{,}015\sum_{p=1}^{60} DS(Ap)$.

Discussions

In our study, the most common symptoms in the prenosological period, that is, the previous stage chronologically the development of persistent joint syndrome in both groups, were arthralgia (RA – 69.1%, PsA – 38.2%), an increase in body temperature (RA – 36.4%, PsA – 29.1%), a decrease in body weight (RA – 25.5%, PsA – 5.5%). Weight loss was significantly more common in patients with RA ($p < 0.05$), which may indirectly indicate a more systemic nature of the inflammatory process in RA [7-9].

However, the picture of immunopathological indicators between RA and early PsA shows more similarities than differences. In all groups, there was a decrease in the level of CD3+ cells (RA – 58.3±1.3% and 57.3%±1.9% PsA). CD8+ levels in patients with RA and PsA were determined at the upper limit of the norm (23.9±1.7% and 26.4±1.9%). The rate of CD19+ cells (RA 21.6±1.5%, 20.8±1.2% PsA) and CD4+ (50.9±1.8% RA, 48.3±2.2% PsA) in both diseases were increased compared to the norm. In any case, the absolute values of CD19+ (355.0±32.8 RA, 311.4±26.4 PsA) and CD4+ (833.5±53.7 RA, 695.2±64.7 PsA) are close to normal. With an increase in the duration of PsA, inflammatory and immunological indicators in absolute and percentage values approach those in RA.

Based on the results obtained from clinical, laboratory and instrumental studies using multidimensional methods of statistical analysis, we have developed mathematical models of PsA and RA.

The range with the highest probability of PsA for the instrumental index is between 0.54 and 1.86. Of the 55 patients with PsA in 95% of patients, clinical, laboratory, immunological and instrumental indices were within the range of the highest probability of the disease, which indicates a fairly high reliability of the model [4, 9, 11]. In order to test the effectiveness of the mathematical models created for PsA and RA, we converted the results of studies on patients with RA (clinics, laboratory, immunological and instrumental) into a mathematical model of PsA and vice versa, then the results of patients with PsA into a mathematical model of RA. Results are presented in Table 3.

Table 3. Correlation of index values in batches of patients with PsA and RA, converted into a mathematical model of RA and PsA, respectively.

Group of patients		φL	φC	φI	φL, φC, φI	φIn
Convert RA to PsA	%	62	64	16	8	95
	Absolute values	31	32	8	4	28
Convert PsA to RA	%	60	12	58	5	77
	Absolute values	33		32		23

Note: *laboratory (φL), clinical (φC) and immunological (φI) indexes. PsA – psoriatic arthritis; RA – rheumatoid arthritis.*

As can be seen from Table 3, there were fewer coincidences in laboratory and immunological indices (12% and 16%, respectively). Several values coincided with the clinical index of 62% and 60%. The instrumental index rate was the highest 95% and 77%. However, the associated index is a combination of clinical, laboratory and immunological indices, which demonstrated the lowest error result of 8% and 5%. This indicates a fairly marked reliability of PsA and RA models.

Thus, according to the mathematical model, persistent arthralgia for more than 4 months can be a manifestation from

the early stage of chronic arthritis, especially RA and PsA, which require clinical and laboratory examination and monitoring of patients with persistent arthralgia syndrome, and in case of detection of low back pain syndrome, the early manifestation of psoriatic sacroiliitis should be assumed, which is determined in 9.5% of patients with skin psoriasis. Significant disorders of the immune status of patients were observed from the early stages of RA and PsA. These data indicate a large contribution of immunopathological disorders already at the beginning of RA and PsA, which confirms the appropriateness of timely prescribing the medication DMARD [2, 3, 7, 11]. The mathematical model of early RA and PsA is easy to handle and can be used in a wide medical practice, as an auxiliary method that allows optimizing the diagnosis of these diseases.

Conclusions

1. Arthralgias were the most common early symptoms of RA and PsA, which occurred even in the prenosological period of the disease in 69.1% and 38.2% of patients, respectively. The arthralgia stage of PsA was significantly longer than in RA, amounting to 4.62±0.03 months in RA and 10.91±2.21 months in PsA ($p < 0.05$).
2. The number of inflamed joints in the first year in early RA (10.4±0.8), Ritchie articular index (11.05±0.69) and functional Lee test (11.8±0.82) were significantly higher ($p < 0.05$) than in the group of patients with PsA (2.88±0.36, 6.71±0.82, 7.16±0.86, respectively). Over time, as PsA progress, these indicators become close in value and the clinical picture acquiring RA characteristics.
3. Immune disorders in the early stages of RA and PsA are nonspecific and are characterized by an increase in CD16+ (26.2±1.5) and CD29+ (24.8±2.1) in RA, which is significantly higher than in PsA CD16+ (22.0±1.3) and CD29+ (17.4±3.2) ($p < 0.05$).
4. A mathematical model of RA and PsA has been developed, which serves as an additional way of diagnosing RA and early PsA.

Abbreviations

CD – Cluster of Differentation; CIC – Circulating Immune Complexes; CRP – C-reactive protein; DMARD – Disease-Modifying Antirheumatic Drugs; ESR – Erythrocyte Sedimentation Rate; NSJ – Number of Swollen Joints; PsA - Psoriatic Arthritis; RA – Rheumatoid Arthritis; RF – Rheumatoid Factor.

Declaration of conflict of interest

Nothing to declare

Authors' contribution

Study conception and design: ER, LG. Data acquisition: ER, LC, LD, AN, LGo. Analysis and interpretation of data: ER, LC, AN. Drafting of the manuscript: ER, LGo. Significant manuscript review with significant intellectual involvement: ER, LD, AN. All authors approved the „ready for print" version of the manuscript**.**

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RESEARCH ARTICLE

Impact of comorbidities on the clinical and ultrasound features of psoriatic arthritis

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What is not yet known on the issue addressed in the submitted manuscript

It is not known the relationship between comorbidities and clinical evolution and ultrasound characteristics of psoriatic arthritis, which can help to optimize the tactics of patient management and to appreciate the connection between main syndromes and specific clinical expression.

The research hypothesis

When comparing comorbidities in groups of young and middle-aged patients, it was shown that it was higher in the group of middle-aged patients, but the chronological appearance of comorbidities did not differ, which indicates an increase with age in the number of comorbid diseases pathogenetically associated with the evolution of psoriatic arthritis.

The novelty added by manuscript to the already published scientific literature

During clinical and ultrasound examination of the joints and entheses, it was found that, synovitis was detected significantly more often when using ultrasound, which indicates subclinical synovitis. The frequency of enthesitis in the large joints of the upper and lower extremities according to ultrasound data was 13.3%, which is significantly higher than in the case of a clinical examination (7.7%, p<0.001), and this indicates asymptomatic enthesitis.

Summary

Objectives. The objective was to evaluate the relationship of comorbid pathology with the clinical and ultrasound characteristics of the evolution of psoriatic arthritis in order to optimize the management.

Material and methods. In order to achieve the purpose and objectives of the study, a group of 92 patients with psoriatic arthritis was selected, established in accordance with the CASPAR diagnostic criteria (2006). The patients were treated in the rheumatology and arthrology departments of the *Timofei Moșneaga* Republican Clinical Hospital and of the *Saint Trinity* Municipal Clinical Hospital in Chisinau during 2017-2020. A type 1 cohort study is planned (prospective study with retrospective components).

Results. Expression at the time of examination of the history data was observed in 54 (58,7%), clinical enthesitis was observed in 47 (51.1%) patients. During the clinical examination of patients, it was found that the frequency of TJC/14 was 11.3% (145/1288), SJC/14 – 4.5% (58/1288), which was 40% (58/145) among all painful joints. During clinical examination, it was found that the TJC of the upper limbs (74/736, 10.1%) and lower (71/552, 12.9%) do not differ significantly ($\chi^2 = 2.489$, $p = 0.115$). At the same time, the SJC of the lower limbs (43/552, 7.8%) was significantly higher than the upper one (15/736, 2.04%) ($\chi^2 = 24.267$, $p < 0.001$). According to ultrasound data, the number of joints examined was 228/1288 (17.7%), number of inflamed entheses – 90/1288 (6.9%), which was 39.5% among the detected synovitis (90/228). The number of enthesitis were 661/4968 (13.3%), of which 19.4% (128/661) of the entheses were vascularized.

Conclusions. According to ultrasound data, the frequency of detection of enthesitis and synovitis was significantly higher than during the clinical examination ($p < 0.01$). For its part, the psoriatic arthritis activity index (DAPSA) did not correlate with inflammatory changes detected during extensive ultrasound of large joints and entheses according to the "gray scale" and the use of Power-Doppler ($p > 0.05$). On the other hand, vascularization in the entheses is an index of activity independent of age and activity of psoriatic arthritis and psoriasis ($p > 0.05$), and it is a sign of active inflammation which correlates with laboratory markers of inflammation (hs-CRP, $p < 0.05$; ESR, $p < 0.01$).

Keywords: psoriatic arthritis, comorbidities, joint ultrasonography.

Introduction

Psoriatic arthritis (PsA) is a chronic musculoskeletal and cutaneous inflammatory disease that affects about 20-30%

of patients with psoriasis [1, 2]. In addition to musculoskeletal and cutaneous manifestations, patients with PsA have a higher prevalence of comorbidities compared to the general population. More than half of patients with PsA have at least one comorbidity, with up to 40% of patients having more than three comorbidities [2-4]. PsA has a particularly strong association with metabolic diseases and, as a result, with cardiovascular diseases (CVD) [5-6]. There is a higher prevalence of metabolic diseases such as high blood pressure, dyslipidemia, diabetes and obesity compared to patients with psoriasis and without PsA [2, 6-8] or with the general population [2, 5, 9]. PsA is associated with a 55% increased risk of developing CVD, such as ischemic heart disease, cerebrovascular disease, and congestive heart failure [3, 4, 7]. Both, the higher inflammatory burden and the increased incidence and prevalence of traditional CVD risk factors, such as high blood pressure, glucose intolerance, dyslipidemia and obesity in psoriatic disease, seem to play an important role in the development of CVD in PsA [1, 2, 6]. CVD is a major source of morbidity and a leading cause of mortality in PsA [5, 8, 9]. Therefore, addressing these comorbidities can improve quality of life and functional status and reduce healthcare costs as well as mortality in PsA. In this research, we will explore the complex relationship of PsA with metabolic diseases and CVD.

Metabolic syndrome (MetS) is defined by the presence of central obesity, hypertension, insulin resistance, and dyslipidemia [3, 6, 9, 10]. Approximately 24-58% of patients with PsA have MetS, which is higher than that of the general population [4, 7, 9, 11]. In some cohorts that use MetS' NHLBI/AHA validated definition, MetS's prevalence in PsA is up to 59% [6, 9, 11-12]. The chances of having MetS in PsA compared to the general population were 2.68 (CI 95% 1.60 - 4.50) in an outpatient clinic-based study in China [3, 4, 7, 13]. The prevalence of MetS and its components is also usually higher in PsA compared to psoriasis alone: hypertension (37% vs. 20%), hyperlipidemia (21% vs. 15%), diabetes (12% vs. 7%) and obesity (30 vs. 27%) [5, 9, 12]. In addition, there is a higher proportion of patients with MetS PsA compared to rheumatoid arthritis (RA) and other spondyloarthritis (SpA) [3, 7, 8]. MetS prevalence was higher in PsA compared to RA or ankylosing spondylitis (AS) (OR 2.44, CI 95% 1.48–4.01) in an outpatient study of the clinic arthritis. The chances were higher for all components of MetS, including central obesity, decreased blood glucose levels during fasting, hypertriglyceridemia and decreased HDL-C levels [6, 9, 14].

Patients with PsA who are also obese and/or have MetS have been observed to have higher disease activity and weaker treatment results. There may be several reasons for this difference. First, one study found that obese patients tend to have a longer time for diagnosis compared to patients with normal BMI (5.7 vs. 2.8 years). This may be due to the difficulty to examine joints in these patients. Then, obese patients may have worse disease activity reported by patients due to obesity-related functional deficits, and obesity is associated with increased CRP [1-4]. Data from Danish and Icelandic biological registries with 1943 PsA patients also showed higher initial activity of the disease (DAS28, CRP, and visual analog-pain scale) in obese compared to non-obese patients [3, 8, 9].

The purpose of the study was to evaluate the relationship of comorbid pathology with the clinical and ultrasound characteristics of the evolution of psoriatic arthritis in order to optimize the management.

Material and methods

In order to achieve the purpose and objectives of the study, a group of 92 patients with psoriatic arthritis was selected. The diagnosis of PsA was established in accordance with the CASPAR classification criteria (2006). Patients were treated in the rheumatology and arthrology departments of the *Timofei Moșneaga* Republican Clinical Hospital and in the *Saint Trinity* Municipal Clinical Hospital in Chisinau during 2017-2020. A type 1 cohort study is planned (prospective study with retrospective components).

The average age of patients with PsA was 42.9 ± 9.6 years, the average duration of psoriasis was 11 (7; 25.8) years, the average duration of PsA was 7 (2; 11.8) years. Among patients included in the study were 42 men (45.7%) and 50 women (54.3%). Patients' characteristics are given in table 1.

Table 1. Characteristics of patients with PsA.

Index	Values
Men, n (%)	42 (45.7%)
Women, n (%)	50 (54.3%)
Age, years, M ± SD, min-max	42.9 ± 9.6, 22-60
Duration of PsA, years, Me (25; 75)	7 (2; 11.8)
DAPSA, Me (25; 75)	15.2 (10.2; 21.4)
Skin psoriasis (Ps), n (%)	91 (98.9%)
Ps duration, years, Me (25; 75)	11 (7; 25.8)
PASI, Me (25; 75)	3.8 (1.2; 9.6)
TJC/14, Me (25; 75)	1 (0; 3)
SJC/14, Me (25; 75)	0 (0; 2)
hs-CRP, mg/l, Me (25; 75)	5.1 (2.2; 16.1)
ESR, mm/h, Me (25; 75)	20 (11; 30)

Note: *Ps – psoriasis; PASI - Psoriasis Area Severity Index, TJC - tender joints count; SJC – swollen joints count; M – median; SD – standard deviation; DAPSA - Disease Activity in PSoriatic Arthritis.*

A positive family history of psoriasis was detected in 31 (33.7%) patients. At the time of inclusion in the study, 19 (20.6%) patients had disabilities, of which 15 (16.3%) had disabilities due to PsA, and 4 (4.3%) of the patients had a general disease.

Treatment of patients with PsA was carried out in accordance with the recommendations of the National Clinical Protocol „Psoriatic Arthritis in adults" at the time of the study.

Distribution of patients by PsA activity in calculating the DAPSA (Disease Activity in PSoriatic Arthritis) index: most had moderate activity (14-28) of 33 (42%), high (> 28) in

13 (16%) patients, decreased (4 - 14) – 30 (38%), remission (< 4) was observed in 3 (4%) patients.

The distribution of patients according to the activity of cutaneous psoriasis in the calculation of the PASI index was as follows: remission - 7 (8%), mild - 57 (68%), average - 9 (11%) severe - to 11 (13%) patients.

According to the clinical and instrumental methods of the study, the distribution of patients by the involvement of peripheral joints and spine was as follows: polyarthritis was in 63 (68.5%) patients, oligoarthritis – in 19 (20.7%), monoarthritis – 10 (10.9%), included axial manifestations sacroiliitis – in 30 (32.6%) patients and spondylitis – in 23 patients (25%), a combination of sacroiliitis and spondylitis – in 13 patients (14.1%). Patients with isolated axial lesions were absent.

The areas evaluated in the clinical examination (visual evaluation and determination of pain on palpation) and ultrasonographic areas included similar areas:

- Joints (14 in each patient) – acromioclavicular, shoulder, elbow, radiocarpal, hip, knee, talocrural;
- Entheses (54 per patient):
- The lower pole of the calcaneus: plantar aponeurosis entheses (thickness of the planting aponeurosis ≥4.4 mm; erosion of the lower pole of the calcaneus; enthesophyte of the lower pole of the calcaneus);
- Upper pole of the calcaneus: entheses of the Achilles tendon (thickness of the Achilles tendon ≥5.29 mm; retrocalcaneal bursitis; erosion of the posterior pole of the calcaneus; enthesophyte of the posterior pole of the calcaneus);
- Tibial tuberosity: distal patellar ligament entheses (thickness of the patellar ligament ≥4 mm; infrapatellar bursitis; erosion of tibial tuberosity; enthesophyte of tibial tuberosity);
- Lower pole of the patella: entheses of the proximal patellar ligament; the thickness of the patellar ligament ≥4 mm; erosion of the lower pole of the patella; enthesophyte of the lower pole of the patella);
- Upper pole of the patella: entheses of the quadriceps tendon (thickness of the quadriceps tendon ≥6.1 mm; suprapatellar bursitis; erosion of the upper pole of the patella; enthesophyte of the upper pole of the patella);
- Tuberosity of the olecranon: triceps tendon entheses (thickness of the triceps tendon ≥4 mm; olecranon bursitis; olecranon erosion; olecranon enthesophyte; olecranon enthesophyte)

Ultrasound modifications of enthesitis were evaluated according to the ultrasound definition of entheses proposed by OMERACT, using a „gray scale" and Power-Doppler to evaluate vascularization (table 2) [5-8].

Table 2. Definition of ultrasound signs of inflammatory and structural changes in entheses (Consensus of experts).

Inflammatory signs (agreement 100%)	**Structural features (agreement) 100%)**
Localization of the Doppler signal in the entheses	Calcification/enthesophyte in the entheses
Hypoechoic entheses	Erosion at the place of attachment
Thickening of the entheses	

Note: *Final definition of enthesitis - Hypoechoic and/or thickened tendon at the site of insertion on the bone (on the bone at 2 mm), with Doppler signal for active entheses and the presence of erosions and enthesophytes/calcified as a sign of structural damage.*

Ultrasound included counting the following signs:

- in the „gray scale" mode: the number of joints with ultrasound signs of synovitis (the number of synovitis), the number of joints with osteophytes;
- in Power-Doppler mode: the number of joints with ultrasound signs of active synovitis (number of vascularized synovitis);
- number of affected entheses: decrease in echogenicity and thickening of the entheses, number of entheses with the presence of vascularization, number of entheses with structural changes: the presence of erosions, enthesophytes, calcifications.

Taking into account the identified changes, the following ultrasound indices were calculated: GUESS (Glasgow Ultrasound Enthesitis Scoring System), BUSES (Belgrade Ultrasound Enthesitis Score), MASSI (Madrid Sonography Enthesitis Index) and SEI (Sonographic Enthesitis Index).

Results

The patients included in the study were clinically examined and an ultrasound of large joints and entheses were performed (the total number of joints examined was 1288, entheses – 4968).

Expression at the time of examination of the history data was observed in 54 (58,7%), clinical enthesitis was observed in 47 (51.1%) patients. During the clinical examination of patients, it was found that the frequency of TJC/14 was 11.3% (145/1288), SJC/14 – 4.5% (58/1288), which was 40% (58/145) among all painful joints.

During clinical examination, it was found that the TJC of the upper limbs (74/736, 10.1%) and lower (71/552, 12.9%) do not differ significantly ($\chi 2 = 2.489$, $p = 0.115$). At the same time, the SJC of the lower limbs (43/552, 7.8%) was significantly higher than the upper one (15/736, 2.04%) ($\chi 2 = 24.267$, $p < 0.001$).

It should be noted that pain and swelling of the hip joints could not be determined by physical examination; therefore, they were not taken into account in this analysis. TJC/14 and SJC/14 in terms of localization were as follows: acromioclavicular joints - 5 and 0, shoulder - 29 and 2, elbow - 13 and 1, hand joints - 29 and 15, knees - 38 and 25, talocrural - 33 and 18 respectively.

When assessing the involvement of entheses in the projection of large joints, it was found that the number of painful entheses of the upper extremities (71/1472, 4.8%) was significantly lower than the lower ones (310/3496, 8.9%)

($\chi2 = 23,923$, $p < 0.001$). The localization of painful entheses on palpation was as follows: at the place of attachment of the supraspinous muscle - 7, the subosteal muscle - 1, the subscapular muscle - 1, the triceps muscle - 2, at the lateral epicondyle - 35, at the medial epicondyle - 25, at the anterior spines of the iliac bones (upper and lower) - 37, at the posterior spines of the iliac bones - 11, at the sciatic tubercle - 1, in the large trochanter - 5, the medial collateral ligament: proximal section - 16, distal - 25, the lateral collateral ligament: proximal section - 26, distal section - 23, quadriceps muscle - 7, semimembranosus muscle - 8, anterior muscle - 5, posterior muscle - 6, Achilles tendon - 38, plantar fascia - 9.

According to ultrasound data, the number of joints examined was 228/1288 (17.7%), the number of inflamed entheses – 90/1288 (6.9%), which was 39.5% among the detected synovitis (90/228). The number of entheses was 661/4968 (13.3%), of which 19.4% (128/661) of the entheses were vascularized. The number of confirmed was 876/4968 (17.6%). The frequency of enthesitis and synovitis detected in the gray scale mode according to ultrasonographic data is shown in table 3.

Table 3. Frequency of enthesitis and synovitis detected in the "grayscale" mode according to ultrasonographic data.

Upper limbs	Frequency	Lower limbs	Frequency
Joints:			
Acromio-clavicular	46/736 (6.3%)	Coxofemural	28/552 (5.1%)
Humeral	7/736 (0.95%)	Knee	42/552 (7.6%)
Ulnar	18/736 (2.4%)	Talocrural	32/552 (5.8%)
Radiocarpal	47/736 (6.4%)		
Total	118/736 (16%)	**Total**	112/552 (20.3%)*
		Enthesitis:	
Short head of the biceps muscle of the shoulder	10/1472 (0.7%)	Great trochanter: - gluteus minor - gluteus medium	28/3496 (0.8%) 45/3496 (1.3%)
Subscapular muscle	20/1472 (1.4%)	Sciatic tubercle	28/3496 (0.8%)
Nastular muscle	13/1472 (0.9%)	Collateral ligament medial - proximal - distal	53/3496 (1.5%) 20/3496 (0.6%)
Subosteal muscles	2/1472 (0.1%)	Lateral collateral ligament: - proximal - distal	33/3496 (0.9%) 19/3496 (0.5%)
Triceps muscle of the shoulder	11/1472 (0.7%)	Own patellar ligament - proximal - distal	6/3496 (0.2%) 21/3496 (0.6%)
Medial epicondyle	30/1472 (2%)	*"Pes anserinus mirror"*	70/3496 (2%)
Lateral epicondyle	54/1472 (3.7%)	Femoral biceps	9/3496 (0.3%)
		Semi-membranous muscles	36/3496 (1%)
		Quadriceps femoral	23/3496 (0.7%)
		Anterior tibial muscle	19/3496 (0.5%)
		Posterior tibial muscle	18/3496 (0.5%)
		Achilles	27/3496 (0.8%)
		Plantar fascia	43/3496 (1.2%)
Total	144/1472 (9.8%)	**Total**	517/3496 (14.8%)**

Note: **p < 0.05, **p < 0.01.*

When evaluating the differences in the frequency of synovitis of the lower (112/552, 20.3%) and superior (118/736, 16%) limbs, it was found that the synovitis of the lower extremities was significantly more frequent ($\chi2 = 3.897$, $p < 0.05$).

When evaluating the differences in the frequency of enthesitis, it was found that enthesitis of the lower extremities (517/3496, 14.8%) occurred significantly more often than the upper one (144/1472, 9.8%, $\chi2 = 22.502$, $p < 0.001$).

The changes detected in the „gray scale" mode can be a sign not only of an active process, but also of chronic inflammation, therefore the presence of vascularization of synovitis and enthesitis, detected with the help of Power-Doppler, is more likely to indicate the activity of the process. Comparing the frequency of vascularization of large joints of the upper and lower extremities is not possible, since piloting the Doppler signal during inflammation of the hip and talocrural joints is difficult due to the anatomical features of these joints.

In the study it was found that the frequency of enthesitis detected during the clinical examination was 7.7% (the number of painful entheses, 381/4968) compared to 13.3% according to the ultrasound data (the number of entheses, 661/4968), which was significantly lower ($p < 0.001$).

When comparing ultrasound data in the groups of patients with isolated peripheral arthritis (n = 52) and in

combination with axial lesions (n = 40), no differences were found in groups (number of synovitis (by ultrasound examination), number of enthesitis, number of entheses with structural disorders, number of vascular Doppler-positive entheses, GUESS, BUSES, SEI, MASSI, p > 0.05). DAPSA scores were significantly higher in the group of patients with a combination of peripheral arthritis with spinal injuries (p < 0.01). The groups were different in terms of duration of PsA (p = 0.013), severity of psoriatic onychodystrophy (NAPSI, p < 0.01), TJC/14 (p = 0.037) and CRP-hs (p = 0.031) and were higher in the group of patients with peripheral arthritis and axial involvement.

Discussions

It is known that spondyloarthritis mainly affects the joints and entheses of the lower extremities, therefore, in most cases; the entheses of the lower extremities were included in various clinical indices of enthesitis. In this study, during an extensive clinical examination and ultrasound of the joints and entheses of the upper and lower extremities, depending on the „gray scale", it was shown that the frequency of synovitis of the lower limbs (20.3%) was significantly higher than the upper one (16%) (p < 0.05), and the entheses of the lower extremities (14.8%) were observed significantly more often than the upper part (9.8%), (p < 0.001), which corresponds to the literature data [6, 10, 13]. The identified differences can be explained by the higher frequency of trauma of the enthesis of the lower extremities, which, according to the theory of biomechanical stress, is one of the triggers for the development of enthesitis [2, 8, 11, 14]. However, this has not been demonstrated for vascularized entheses, the frequency of which does not differ according to location (p > 0.05).

Despite the low incidence of obesity (25%), it should be noted a higher frequency of overweight patients (33.3%), as well as an increase in the ratio of chest circumference to body circumference (57.1%), which should also be taken into account. With the increase in thoracic circumference, body circumference and BMI of the patient, the number of comorbid conditions increased significantly (p < 0.01). Several directions of research are needed to examine the link between PsA and obesity to further determine whether obesity is a consequence of PsA. Other potential mechanisms linking obesity in PsA and cardiovascular risk (dyslipidemia, high blood pressure, insulin resistance, and smoking) have not yet been identified. The effect of obesity on the activity of PsA and the response to DMARD therapy and TNFα inhibitors [6, 11-13] has been demonstrated, in addition, weight loss has contributed to a decrease in the severity of joint and entheses inflammation, as well as in the activity of skin psoriasis [4, 6, 9].

When comparing comorbidities in groups of young and middle-aged patients, it was shown that comorbidity was higher in the group of middle-aged patients (p < 0.05), and chronological comorbidities (p > 0.05) in groups does not differ, which indicates an increase with age mainly in the number of comorbid diseases pathogenetically associated with the course of PsA. The presence of axial lesions in patients with peripheral arthritis did not increase the number of comorbid diseases in patients with PsA (p > 0.05).

In this case, patients with peripheral arthritis and spinal cord injury had a longer duration of PsA (p = 0.013), severity of psoriatic onychodystrophy (NAPSI, p < 0.01), PsA activity (DAPSA), TJC/14 (p < 0.05) and higher levels of hs-CRP (p < 0.05) compared to patients with isolated peripheral arthritis. Interestingly, ultrasonographic parameters of joint and entheses lesions do not differ.

During the clinical examination carried out and the ultrasound of the joints and entheses, it was found that synovitis (17.7%) was detected significantly more often than with the help of a clinical examination (TJC/14 and SJC/14, 4.7% and 11.3%, p < 0.01), which indicates subclinical synovitis. The frequency of entheses in the large joints of the upper and lower extremities according to ultrasound data was 13.3%, which is significantly higher than in the case of a clinical examination (7.7%, p < 0.001), and this also indicates asymptomatic entheses, a finding consistent with the literature [4-7, 9-12].

The higher frequency of detection of pathological changes according to ultrasound data compared to a clinical examination is a serious reason for an extensive evaluation of the ultrasound signs of inflammation and joint entheses - its nature and localization - and the determination of their role in patient management.

Conclusions

According to ultrasound data, the frequency of detection of enthesitis and synovitis were significantly higher than during the clinical examination (p < 0.01). In turn, the activity index PsA (DAPSA) did not correlate with the inflammatory changes detected during the extensive ultrasound of large joints and entheses according to the „gray scale" and with the use of Power-Doppler (p > 0.05).

Vascularization in the entheses is an index of activity independent of age and activity of PsA and psoriasis (p > 0.05) a sign of active inflammation with correlation with laboratory markers of inflammation (hs-CRP p < 0.05, ESR p < 0.01). At the same time, the SMI technique demonstrated comparable results with Power-Doppler in identifying the frequency of vascularized synovitis of large joints (52.6% vs 44.4%, p > 0.05); when assessing entheses vascularization, the frequency of SMI+ vascularized entheses were significantly higher than Power-Doppler+ (33.3% vs. 17.1%, p < 0.001).

Abbreviations

AS – Ankylosing Spondylitis; BMI – body mass index; BUSES – Belgrade Ultrasound Enthesitis Score; CASPAR – The ClASsification for Psoriatic Arthritis; CI – Confidence Interval; CVD – cardiovascular diseases; DAPSA – Disease Activity in PSoriaticArthritis; DAS-28 – Disease Activity Score; DMARD – Disease-modifying antirheumatic drugs; ESR – erythrocyte sedimentation rate; GUESS – Glasgow Ultrasound Enthesitis Scoring System; hs-CRP – high sensitivity C-reactive protein; M – median; MASSI – Madrid Sonography Enthesitis Index; MetS – metabolic syndrome; NAPSI –

Nail Psoriasis Severity Index; NHLBI/AHA – National Heart; Lung; and Blood Institute / American Heart Association; OR – Odds Ratio; PASI – Psoriasis Area Severity Index; Ps – psoriasis; PsA – psoriatic arthritis; RA – rheumatoid arthritis; SD – standard deviation; SEI – Sonographic Enthesitis Index; SJC – swollen joints count; SpA – Spondyloarthritis; TJC – tender joints count; TNFα – Tumor Necrosis Factor-α.

Declaration of conflict of interest

Nothing to declare

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RESEARCH ARTICLE

Personalized approach to cytoprotective treatment in ischemic heart disease

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What is not yet known on the issue addressed in the submitted manuscript

Cardiocytoprotection is a big problem in cardiology today and remain unclear using of these drugs to increase the effectiveness of complex treatment of ischemic heart disease (IHD) resulted in the introduction into clinical practice of metabolic pharmacotherapy.

The research hypothesis

The direction of personalized medicine is developing extensively and the main objective of researchers is the genetic factor, despite the fact that it defines only 50% of the ability to individual reaction to drug and 10-20% the chance of developing a multifactorial disease. The methodology of personalized medicine is reduced to the definition of biomarkers, the conduct of pharmacogenetic and pharmacologic studies.

The novelty added by manuscript to the already published scientific literature

To develop the individualized treatment approaches doctors should be taken into account not miss the genetic factor, but also a number of other phenotypic characteristics of each individual patient. In this paper, an attempt was made to expand the understanding about personalized medicine by developing a separate direction - personalized metabolic pharmacotherapy.

Summary

Objectives. To assess the efficacy and harmlessness of the cytoprotective treatment with meldonium of ischemic heart disease by developing personalized approaches.

Materials and methods. Our study included 160 patients with IHD (117 men and 43 women) aged 37 to 81 years. Of them, 142 patients had angina pectoris of stable effort from different functional classes, and 21 – unstable angina pectoris. The average age of patients was 59.26±0.74 years. All patients were divided into 2 groups: 1 group (n=80) only with background treatment and 2 group included (n=80) with background treatment and meldonium. The observation period was 12 months (one year).

Results. Significant differences were found in the pathogenesis of the underlying pathology and in the effectiveness of meldonium treatment in men and women. In this way, for men on the background of exertion angina is characteristic of more frequent occurrence of myocardial infarction, and for women – heart failure and diabetes mellitus, but meldonium remain the same effectiveness for both groups. Men smoke 16 times more, and women suffer from abdominal obesity 2 times more, which could be the cause of the more atherogenic lipid profile in them. According to the survey, the hereditary predisposition to cardiovascular diseases is higher in women, although most likely women are simply better informed about the pathologies of relatives and they were more disciplined in treatment with meldonium.

Discussions. The effectiveness of treatment in women is significantly better according to the indicators of subjective and objective improvement compared to men, which is confirmed by many existing studies. Sex factor determines the presence of a number of pathogenetic peculiarities of the course of ischemic heart disease, and therefore can be considered as one of the criteria for personalizing pharmacotherapy, however, for the individual choice of metabolic corrector, this factor is not significant. The age factor determines some pathogenetic peculiarities of the course of ischemic heart disease and the effectiveness of pharmacotherapy, however, it is not decisive for the choice of metabolic corrector.

Conclusions. The standard criteria for the personalization of pharmacotherapy in cardiology - sex, age, environmental risk factors, the presence of an underlying disease and concomitant pathology, pharmacogenetic and psychological profile - affect the pathogenesis of the development of coronary artery disease, to some extent determining the sensitivity of patients to meldonium, but they are not decisive for a personalized choice of metabolic corrector.

Keywords: cardiocytoprotector, cardiac metabolism, ischemic heart disease.

Introduction

An attempt to substantially increase the effectiveness of complex treatment of ischemic heart disease (IHD) resulted in the introduction into clinical practice of metabolic pharmacotherapy in order to ensure cardiocytoprotection [1, 2].

Despite the pathogenetic argumentation of the use of metabolic preparations in the complex treatment of ischemic heart disease [2-4], the interest in cardiocytoprotectors is more characteristic for drugs that have demonstrated their effect on the duration of life, with a proven mechanism of action, as demonstrated by the high frequency of prescribing metabolic drugs for the treatment of patients with angina pectoris [2, 3-6]. Lately, cardiologists have also begun to notice the effectiveness of this group of drugs; publications have appeared, indicating the effectiveness of medications of the metabolic group [4]. The solution to the mentioned problem, in our view, lies in the need to personalize the indication of metabolic correctors.

The direction of personalized medicine is developing extensively and the main objective of researchers is the genetic factor, despite the fact that it defines only 50% of the ability to individual reaction to drug and 10-20% the chance of developing a multifactorial disease [1, 5-8]. The methodology of personalized medicine is reduced to the definition of biomarkers, the conduct of pharmacogenetic and pharmacologic studies [3, 5-9]. In our opinion, for the development of individualized treatment approaches should be taken into account not miss the genetic factor, but also a number of other phenotypic characteristics of each individual patient. In this paper, an attempt was made to expand the understanding about personalized medicine by developing a separate direction - personalized metabolic pharmacotherapy.

The purpose of the study: to assess the efficacy and harmlessness of the cytoprotective treatment with meldonium of ischemic heart disease by developing personalized approaches.

Material and methods

Our study included 160 patients with IHD (117 men and 43 women) aged 37 to 81 years. Of them, 142 patients had angina pectoris of stable effort from different functional classes, and 21 – unstable angina pectoris. In most patients with angina pectoris was associated with hypertension (HTA) (143 [89.4%]), rhythm disturbances (39 [24.4%]), postinfarct cardiosclerosis (CSPI) (78 [48.8%]), chronic heart failure (CHF) (151 [94.4%]), some with diabetes mellitus (DM) type II (37 [23.1 %]). The average age of patients was 59.26±0.74 years. All patients were divided into 2 groups: 1 group (n=80) only with background treatment and 2 group included (n=80) with background treatment and meldonium. The observation period was one year (12 month). Each participant was introduced to the research program and signed an informed agreement (a favorable decision of Ethics Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy nr.17 from 10th April 2012).

The diagnosis of angina pectoris of stable effort was confirmed after conducting the clinical, instrumental and laboratory evaluation, according to the recommendations of the National Clinical Protocol, prepared by the working group of experts of the Institute of Cardiology; diagnosis of unstable angina pectoris – after carrying out the complex assessment.

Results

Initially, the batches were comparable according to the indices of physical capacity: the strength of the last step (SLS), determined in the dosed physical effort test (Table 1). Starting with the 3rd month, but also subsequently, the SLS index marked a continuous and eloquent improvement in both groups of patients, but with a difference with very high statistical significance (p<0.001) starting with the 6th month of medication: 689.00±43.64 m/min (35.54%) in group I vs. 871.21±53.54 (42.82%) in group II. At 9 months of treatment this parameter demonstrated an augmentation with 57.32% in group I vs 62.84% in group II (p<0.001), and at 12 months of medication the SLS index reached the peak of positive dynamics, constituting 845.02±53.05 m/min (66.23%) in group I and 1051.38±57.33 (72.29%) in group II (p<0.001) (Table 1).

Table 1. Evolution of the SLS index depending on the medication

	SLS, m/min				
	Initial	3 months	6 months	9 months	12 months
Group I (n=80)	508.33±35.66	599.33±34.56* 17.9%	689.00±43.64** 35.54%	799.71±48.59** 57.32%	845.02±53.05** 66.23%
Group II (n=80)	610.00±43.83	789.67±51.75** 29.45%	871.21±53.54** 42.82%	993.34±55.29** 62.84%	1051.38±57.33** 72.29%
	P-value between groups				
	p>0.05	p<0.05	p<0.001	p<0.001	p<0.001

***Note:** *- p<0.05 from initial; ** - p<0.001 from initial; SLS - strength of the last step. SLS - strength of the last step.*

Thus, the data obtained revealed a continuous positive evolution of the physical capacity to administer both treatments, the effect being directly proportional to the duration of the medication, but with a superior benefit to the meldonium combination equipment, being recorded statistical authenticity between the batches even from the 3rd month of treatment. In this context, the evolution of tolerance to physical exertion was similar to that of the de-

terminants of physical capacity. If initially the groups did not show statistically significant differences according to the share of patients with low tolerance (64.29% in group I and 62.22% group II) and average (35.71% vs. 37,78%, respectively, p<0.05), with the initiation of treatment, the number of patients with low tolerance was progressively reduced in favor of those with medium and high tolerance, highlighting a superior performance in the group treated with meldonium association. Therefore, after 3 months of medication, the number of patients with low tolerance in group II was statistically significantly reduced compared to group I (35.56% vs. 57.14%, p<0.001) and 3 patients (6.67%) with high tolerance were registered in the group under medication with meldonium association compared to 1 patient (1.79%) in the group treated with basic treatment, p<0,001. Continued treatment led to a decline in the number of patients with low tolerance in both groups (42.86% in group I vs. 17.78% in group II, p<0.001), the increase in the number of patients with medium and high tolerance, maintaining the authentic statistical gap between the groups in favor of treatment with meldonium association (10 patients with high tolerance in group II compared to 2 patients in group I, p<0.001). By the 9th month of treatment, the number of patients with both low and medium tolerances decreased, in favor of the category of patients classified at high tolerance. The same trend was maintained towards the end of the treatment period, with an authentic statistical advantage for meldonium combination medication: low tolerance showed 3 patients (6.67%) in group II vs. 10 patients (17.86%) in group I, p<0.001; average tolerance - 10 patients (22.22%) vs 19 patients (33.93%), p<0,001 and high – 32 patients (71.11%) vs 27 (48.21%), p<0.001, respectively.

Based on the values of Fisher's criterion F (F), we arranged the analyzed factors as the statistical value of their influence increases in the following order: sex (F=2.89, p=0.10), the patient's age (F=2.89, p=0.09), the concomitant presence of diabetes mellitus (F=4.84, p=0.06), the presence of the underlying disease (F=4.84, p<0.05), smoking (F=4.84, p<0.05), the number of affected coronary arteries (F=10.98, p<0.0001), metabolic pharmacotherapy (F=19.51, p<0,0001). The rest of the factors studied (genetic and psychological factor) did not have a significant effect on the integral indicator - the coefficient of effectiveness of treatment, however, when conducting comparative analysis on subgroups of patients, many factors had an essential role in achieving certain effects of complex pharmacotherapy and / or in determining the effectiveness of the use of certain metabolic preparations.

The following describes in detail the value of each factor as a criterion for personalizing the pharmacotherapy of patients with ischemic heart disease.

Sex. We conducted a comparative analysis of the studied parameters in men and women with ischemic heart disease. We received a number of significant differences (Table 2).

Significant differences were found in the pathogenesis of the underlying pathology and in the effectiveness of its treatment in men and women. In this way, for men on the background of exertion angina is characteristic of more frequent occurrence of myocardial infarction, and for women – heart failure and diabetes mellitus. Men smoke 16 times more, and women suffer from abdominal obesity 2 times more, which could be the cause of the more atherogenic lipid profile in them. According to the survey, the hereditary predisposition to cardiovascular diseases is higher in women, although most likely women are simply better informed about the pathologies of relatives. Men show signs of more severe organic changes in the target organs compared to women: subclinical signs of damage to the glomerular apparatus of the kidneys, enlargement of the heart cavities, lower values of the ejection fraction of the left ventricle, more severe disorders of local contractility with corresponding changes in the repolarization phase on the electrocardiogram, tendency to myocardial dystrophy, high degree of stenosis of some coronary arteries. In women there are corresponding changes in the blood as a result of the concomitant and frequent presence of type 2 diabetes mellitus (increase in the level of glycated hemoglobin), fewer organic changes in the heart and vessels, and lower concentrations of endothelial and inducible nitric oxide synthase, a higher level of anxiety of the person.

Table 2. Comparative analysis of the indicators of pathogenic peculiarities and effectiveness of the treatment of ischemic heart disease in men and women

Indicator	Men, n = 117	Women, n = 43	p
Height, m	1.73±0.01	1.60±0.01	0.001
The number of infarcts (MI) in the anamnesis	0.73±0.07	0.41±0.09	0.021
MI: duration in years	2.98±0.49	1.61±0.55	0.070
DM: duration in years	0.99±0.31	2.57±0.79	0.074
Smoking, the number of cigarettes per day	8.56±1.04	0.41±0.41	0.001
Glycated hemoglobin, %	5.66±0.13	7.10±0.63	0.058
LDL mmol / l	3.18±0.12	3.92±0.25	0.005
VLDL, mmol / l	0.58± 0.05	0.77±0.09	0.070
EchoCG: DTD LV, mm	28.01±0.38	26.31±0.65	0.024
EchoCG: VTD LV, ml	140.27±4.68	114.81±6.54	0.004
EchoCG: VTS LV, ml	66.84±3.94	50.33±5.95	0.031
EchoCG: FELV, %	54.53±1.26	60.48±2.19	0.018
eNOS in the erythrocytic lysis, ng / ml	1116.75±358.32	466.03±101.85	0.092
iNOS in the erythrocytic lysis, ng / ml	25.03±3.29	13.74±5.25	0.074

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. MI – myocardial infarct, DM - diabetes mellitus, LDL – low density cholesterol, VLDL – very low density cholesterol, EchoCG – echocardiography, DTD LV– telediastolic diameter of the left ventricle, VTD LV – telediastolic volume of the left ventricle, VTS LV– telesistolic volume of the left ventricle, FELV - ejection fraction of the left ventricle, eNOS - Endothelial nitric oxide synthase, iNOS - Inducible nitric oxide synthase.*

Age. In order to elucidate the importance of the age factor in personalizing the pharmacotherapy of patients with

ischemic heart disease, we performed a comparative analysis between two groups of patients: middle age (up to 60 years) and old age (60 years and older). I received a number of significant differences (Table 3).

Comparison of patients of different age groups showed the presence of pathogenetic peculiarities of ischemic heart disease in people of old age. Thus, elderly patients experience a number of involutional changes: reduction of height and body weight, a longer anamnesis of diabetes mellitus concomitantly with a higher degree of severity, they smoke less. In elderly patients atherosclerosis of the coronary vessels and aorta is significantly more pronounced, according to the data of coronary angiography the average degree of stenosis of almost all vascular basins of the heart is twice as high in the elderly, as well as the number of affected coronary arteries is higher constituting on average 4 vessels. In elderly patients, lower ATP values are observed in the blood both before and after treatment, which indicates the presence of involutional hypoergia.

Table 3. Comparative analysis of the indicators of pathogenic peculiarities and effectiveness of the treatment of ischemic heart disease in patients of middle and old age

Indicator	Middle-aged patients, n = 82	Patients of old age, n = 78	p
Average age, years	51.56±0.61	66.76±0.57	0.001
Height, m	1.71±0.01	1.68±0.01	0.032
Weight, kg	93.46±2.39	84.33±1.60	0.002
DM: duration in years	0,72±0.29	2.11±0.55	0.029
Smoking: the number of cigarettes per day	10.35±1.46	2.84±0.65	0.001
Index Quetelet, kg / m^2	31.87±0.76	29.81±0.51	0.026
EchoCG: AoV pressure gradient, mmHg	6.39±0.41	8.91±0.69	0.002
EchoCG: Regurgitation AoV	0.51±0.07	0.81±0.10	0.015
Coefficient of effectiveness of treatment, %	30.64±3.07	37.96±3.02	0.091
Serum ATP before treatment, mmol / l	227.39±4.34	207.20±3.52	0.001
Serum ATP after treatment, mmol / l	240.38±4.49	224.97±4.16	0.015
Erythrocytic ATP, mmol / l	681.62±2.44	693.64±3.72	0.008

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. DM – diabetes mellitus, EchoCG – echocardiography, AoV – aortic valve, ATP – adenozin triphosphate*

Smoking. In order to elucidate the importance of smoking in the personalized pharmacotherapy of ischemic heart disease, a comparative analysis of the two groups of patients – smokers and non-smokers – was performed. We detected a number of significant differences (Table 4). Smoke to a greater extent the younger ones, probably due to the priority effect of the age factor in this group of patients is less pronounced the severity of the underlying pathology, comorbidities (diabetes mellitus) and the lipid profile is more favorable.

Table 4. Comparative analysis of the indicators of pathogenetic peculiarities and effectiveness of the treatment of ischemic heart disease in smokers and non-smokers

Indicator	Smoking patients, n=60	Non-smoking patients, n=100	p
Average age, years	55.77±1.15	61.27±0.87	0.001
Height, m	1.73±0.01	1.67±0.01	0.001
DM: duration in years	0.60±0.31	1.95±0.48	0.019
BPs: mm Hg	133.09±2.84	141.11±2.31	0.032
BPd: mm Hg	96.67±4.01	83.07±2.41	0.007
Total cholesterol, mmol / l	5.01±0.17	5.70±0.16	0.007
LDL, mmol / l	3.05±0.16	3.56±0.15	0.030
EchoCG: DTD LV, mm	55.51±1.27	51.94±0.96	0.025
EchoCG: VTD LV, ml	151.20±6.77	122.43±4.45	0.001
EchoCG: VTS LV, ml	72.94±5.82	55.91±3.89	0.012
EcoCG: FELV, %	53.41±1.85	57.78±1.36	0.054

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. BPs – blood pressure systolic, BPd – blood pressure diastolic, DM – diabetes mellitus, EchoCG – echocardiography, DTD LV– telediastolic diameter of the left ventricle, VTD LV– telediastolic volume of the left ventricle, VTS LV– telesistolic volume of the left ventricle, FELV - ejection fraction of the left ventricle.*

Smoking patients have a higher level of hemoglobin and chromatic index, which may indicate smoking as an additional factor of hypoxemia. The objective status of smoking patients is significantly more precarious according to echocardiography and electrocardiography: the cavities of the heart are more dilated, the ejection fraction is lower, the disorders of local contractility are more expressed, and the voltage on the ECG is reduced to the level of myocardial dystrophy. The effectiveness of the treatment of the smoking patients was significantly lower according to the indicators of subjective and objective improvement, the integral coefficient of treatment effectiveness.

Discussions

The individual reaction of the body to the administration of the drug depends on several factors: genotype, sex, age, severity of the underlying disease, the presence of comorbidities, especially liver and kidney pathologies, harmful habits (smoking, alcohol consumption), eating style, concomitant administration of other medicinal preparations, etc. [4, 10]. In this chapter it is described whether it is possible to take into account these factors as criteria for personalizing metabolic pharmacotherapy in the treatment of patients with exertion angina pectoris, and their value in choosing the drug.

The effectiveness of treatment in women is significantly better according to the indicators of subjective and objective improvement compared to men, which is confirmed by many existing studies [2, 7]. A tendency to a different reaction of the mitochondria to meldonium administration was determined: in men in the form of inhibition, in women - in the form of activation ($p<0.05$).

Sex factor determines the presence of a number of pathogenetic peculiarities of the course of ischemic heart disease, and therefore can be considered as one of the cri-

teria for personalizing pharmacotherapy, however, for the individual choice of metabolic corrector, this factor is not significant [4, 7, 8].

The age factor determines some pathogenic peculiarities of the course of ischemic heart disease and the effectiveness of pharmacotherapy, however, it is not decisive for the choice of metabolic corrector [1-3, 9].

Thus, our study of patients with stable effort angina pectoris, a significant 4-fold increase in the effectiveness of complex pharmacotherapy in ischemic heart disease was detected when adding mildronate compared to the basic treatment because of the more pronounced antianginal effect, improved physical performance, potentiation of the positive, and hypotensive inotropic effects of basic pharmacotherapy [6, 9, 10]. According to experimental data in patients with myocardial ischemia, mildronate activates glycolysis, oxidative phosphorylation, and oxidative decarboxylation, stabilizes the cardiomyocyte membrane, significantly reduces the degree of hypoxia, thereby restoring the initial level of ATP and achieving adequate energy supply of the myocardium [1-3]. Meldonium quite harmoniously manages the metabolism of cardiomyocytes in conditions of experimental myocardial ischemia given the initial energy status, the degree of tissue hypoxia and the age of the patients.

The data obtained revealed a continuous positive evolution of the physical capacity to administer both treatments, the effect being directly proportional to the duration of the medication, but with a superior benefit to the meldonium association, being recorded statistical authenticity between groups even from the 3rd month of treatment. In this context, the evolution of tolerance to physical effort was similar to that of the determinants of physical capacity, confirmed by the data of the specialized literature [2, 4]. If initially the groups did not show statistically significant differences after the share of patients with low tolerance (64.29% in group I and 62.22% group II) and average (35.71% vs. 37.78%, respectively, $p<0.05$), with the initiation of treatment, the number of patients with low tolerance in favor of those with medium and high tolerance was progressively reduced, highlighting a superior performance in the group treated with meldonium association. Thus, after 3 months of medication, the number of patients with low tolerance in group II was statistically significantly reduced compared to group I (35.56% vs. 57.14%, $p<0.001$) and 3 patients (6.67%) with high tolerance were registered in the group under medication with meldonium association compared to 1 patient (1.79%) in the group treated with basic treatment, $p<0.001$. Continued treatment led to a decline in the number of patients with low tolerance in both groups (42.86% in group I vs. 17.78% in group II, $p<0.001$), the increase in the number of patients with medium and high tolerance, maintaining the authentic statistical gap between the groups in favor of treatment with meldonium association (10 patients with high tolerance in group II compared to 2 patients in group I, $p<0.001$). By the 9th month of treatment, the number of patients with both low and medium tolerances decreased, in favor of the category of patients classified at high tolerance. The same trend was maintained towards the end of the treatment period, with an authentic statistical advantage for the meldonium combination medication: low tolerance presented 3 patients (6.67%) in the II group vs. 10 patients (17.86%) in the first group, $p<0.001$; average tolerance - 10 patients (22.22%) vs 19 patients (33.93%), $p<0.001$ and high – 32 patients (71.11%) vs 27 (48.21%), $p<0.001$, respectively.

Thus, the long-term treatment with basic treatment and meldonium combination beneficially influenced all the parameters determined in the dosed physical effort test, but the use of meldonium combination improved more effectively compared to the basic treatment the indicators of physical capacity and exercise tolerance.

Conclusions

1. The inclusion of metabolic drugs in the complex treatment of patients with stable angina increases the clinical effectiveness of basic pharmacotherapy by 4 times when prescribing meldonium (59.16% compared to basic therapy 15.95%, $p <0.001$), mainly due to increased antianginal actions.
2. The standard criteria for the personalization of pharmacotherapy in cardiology - sex, age, environmental risk factors, the presence of an underlying disease and concomitant pathology, pharmacogenetic and psychological profile - affect the pathogenesis of the development of coronary artery disease, to some extent determining the sensitivity of patients to meldonium, but they are not decisive for a personalized choice of metabolic corrector.
3. A general concept of personalization of metabolic pharmacotherapy of meldonium has been developed, according to which it is able to present a cytoprotective effect depending on the initial state of the functional adaptation system and the phase of the general adaptation syndrome of a patient with coronary artery disease.

Abbreviations: IHD - ischemic heart disease; HTA - hypertension; CSPI - postinfarct cardiosclerosis; CHF - chronic heart failure; SLS - the strength of the last step; DM - diabetes mellitus; ATP/ADP - adenosine triphosphate and diphosphate; NO - nitric oxide; EchoCG – echocardiography; DTD LV– telediastolic diameter of the left ventricle; VTD LV– the telediastolic volume of the left ventricol; VTS LV– telesistolic volume of the left ventricle; FELV - ejection fraction of the left ventricle; AoV – aortic valve.

Declaration of conflict of interest

Nothing to declare

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RESEARCH ARTICLE

Clinical patterns and complete blood count parameters in young patients with primary myelofibrosis in the prefibrotic stage

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What is not yet known about the issue addressed in the submitted manuscript

The features of the prefibrotic stage of primary myelofibrosis in the young people and further evolution of the neoplasm.

The research hypothesis

The clinical and paraclinical features are the same for both stages of primary myelofibrosis in young patients.

The novelty added by the manuscript to the already published scientific literature

Determination of the characteristics of the prefibrotic stage of primary myelofibrosis will allow for further accurate detection of pathology in other patients in order to ensure better therapeutic management of these patients.

Abstract

Introduction. Primary myelofibrosis is a rare myeloproliferative neoplasm that affects 0.2-1.5 people per 100,000. As a rule, the diagnosis is confirmed after 60 years, but recently, hematologists around the world have encountered the problem of primary myelofibrosis in young people. The classic manifestations of myelofibrosis are characterized by splenomegaly, cytopenia, and bone marrow fibrosis, but in patients younger than 40 years, the diagnosis is most often made in the prefibrotic stage of the neoplasm. The aim of the paper is to identify and evaluate the clinical and hematological features of primary myelofibrosis in young patients in the prefibrotic stage.

Material and methods. A retrospective study was performed on clinical cases of primary myelofibrosis, registered at the Oncological Institute of the Republic of Moldova. The diagnosis was confirmed according to 2016 WHO criteria based on histological and molecular studies. We enrolled young patients under the age of 40 who had been diagnosed with prefibrosis in our study and analyzed them for clinical manifestations and complete blood count parameters. To optimize the analysis, all patients were divided into two groups according to their age: 18–29 and 30–40 years old.

Results. Changes in the complete blood count, manifested by thrombocytosis and leukocytosis, are the main laboratory patterns of primary myelofibrosis in young patients in the prefibrotic stage. The most relevant clinical features are splenomegaly and hepatomegaly, but no correlation between these manifestations has been found.

Conclusions. The classical clinical and hematological characteristics of primary myelofibrosis do not specify low- and intermediate-risk patients' management in the prefibrotic stage, as compared with the other chronic myeloproliferative BCR-ABL-negative neoplasms. The proliferation type of primary myelofibrosis is characteristic for young patients with pre-fibrotic stage. According to our results, the main manifestations in the prefibrotic stage are detected in a complete blood count and comprise anemia, leucopenia, leukocytosis, and thrombocytosis.

Key words: primary myelofibrosis, young patients, splenomegaly, thrombocytosis, bone marrow fibrosis.

Introduction

Myeloproliferative neoplasms are hemopathies with primary damage to the stem cell. In the case of polycythemia vera, there is a proliferation of all myeloid lineages in the bone marrow. The proliferation of only the megakaryocytic line is characteristic of essential thrombocythemia. The most interesting histological picture represents primary myelofi-

brosis with the proliferation of myeloid lines, the deformation of megakaryocytes with the formation of clusters with a terrible image, and collagenous fibrosis of various degrees [1]. The second important moment is the formation of foci of extramedullary hematopoiesis, with the most frequent involvement of the spleen and liver. Less commonly, the lungs, kidneys, central nervous system, and even peripheral lymph nodes are affected. The etiology is not known, which is why the inclusion of the word "idiopathic" in the name of this pathology is logical. It is assumed that causative factors may be chemicals, radiation, etc. Most cases are diagnosed in people over the age of 60 who are in the overtly fibrotic stage. For a long time, it was thought that primary myelofibrosis was a disease of the elderly. In recent years, there has been an increase in the number of articles published about primary myelofibrosis in young people, which is most diagnosed in the prefibrotic phase. The studies, observations, and analyses of these patients are few, which is why this neoplasm is of major interest to hematologists.

The aim of the manuscript was to identify and evaluate the clinical and hematological features of primary myelofibrosis in young patients in the prefibrotic stage.

Material and methods

The clinical aspects and the changes in the complete blood count of the disease were studied in 42 patients with NHL and primary myelofibrosis, aged between 18 and 40 years. The diagnosis was confirmed histologically and molecularly according to WHO criteria. The research was approved by the Research Ethics Committee of Nicolae Testemitanu State University of Medicine and Pharmacy (Protocol No. 1 of February 25, 2021).

The standard descriptive statistics kit was used for data analysis through Microsoft Excel and IBM SPSS Statistics 26.0. The use of the standard descriptive statistics kit facilitated the calculation of mean, median, and p value.

Results

Out of the 42 patients participating in the study, 9 (21.4%) were men and 33 (78.6%) were women. We divided the patients into two groups based on their ages: 18-29 and 30-40. There were 11 (26.2%) patients in the first group and 32 (73.8%) in the second.

The major interest represents the changes in the complete blood count. Starting with hemoglobin levels (Table 1), hemolytic anemia was found in both groups at 7.1%. In most cases (48.4%), the level of hemoglobin was perfectly normal. In 4 (36.4%) cases in the first group, there was anemia, and in 8 (25.8%) in the second group, according to WHO criteria for primary myelofibrosis. The elevated hemoglobin level in 6 (19.3%) patients aged 30 to 40 years, on the other hand, was quite surprising.

Table 1. Distribution of patients according to hemoglobin levels.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Hemolytic anemia	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Normal range of hemoglobin	Number of patients	5	15	20
	%	45.6%	48.4%	47.6%
Low value of hemoglobin	Number of patients	4	8	12
	%	36.4%	25.8%	28.6%
Elevated level of hemoglobin (>160 g/l for men, >140 g/l for women)	Number of patients	1	6	7
	%	9.1%	19.3%	16.7%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The second parameter analyzed is leucocyte count (Table 2). Leucopenia was detected in 1 (9.1%) case in the first group and in 3 (9.7%) cases in the second group. The most interesting difference between these two groups is the normal range of white blood cells in patients younger than 30 years: 6 (54.5%) in the first group and 10 (32.3%) in the second group. Leukocytosis in the second age group was revealed in 18 (58.0%) cases and proved to be more common than in the first age group (36.4%, $p < 0.05$).

Table 2. Distribution of patients according to leukocyte count.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Leukopenia (< $4x10^9$/l)	Number of patients	1	3	4
	%	9.1%	9.7%	9.5%
Normal range (4-$9x10^9$/l)	Number of patients	6	10	16
	%	54.5%	32.3%	38.1%
Leukocytosis (>$11x10^9$/l)	Number of patients	4	18	22
	%	36.4%	58.0%	52.4%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The most important and interesting parameter of peripheral blood is platelets (Table 3). Patients with myeloproliferative neoplasms are more often diagnosed with thrombotic complications, especially those with primary myelofibrosis. Most patients are diagnosed with primary myelofibrosis due to elevated levels of platelets. 30 patients (71.4%) had thrombocytosis. Thrombocytopenia was found in 1 (9.1%) case from the first group and in 2 (6.5%) cases from the second group. Platelets were within the normal range in 36.4% of patients younger than 30 years old and 16.1% of patients older than 30 years old ($p < 0.05$).

Table 3. Distribution of patients according to thrombocyte count.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Low level of platelets (<150x10^9/l)	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Normal range of platelets (150-400x10^9/l)	Number of patients	4	5	9
	%	36.4%	16.1%	21.4%
High level of platelets (>400x10^9/l)	Number of patients	6	24	30
	%	54.5%	77.4%	71.4%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The spleen is the primary organ involved in extramedullary hematopoiesis, and splenomegaly is always observed in the overt fibrotic stage. According to this analysis, 4 (36.4%) and 9 (29.0%) of patients, respectively, in the prefibrotic stage have severe splenomegaly (Table 4). But in 2 (18.2 %) of the first group and in 3 (9.7 %) of the second, the normal size of the spleen was found ($p < 0.05$).

Table 4. Distribution of patients according to the spleen sizes.

	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Normal size	Number of patients	2	3	5
	%	18.2%	9.7%	11.9%
Moderate splenomegaly	Number of patients	4	17	21
	%	36.4%	54.9%	50.0%
Severe splenomegaly	Number of patients	4	9	13
	%	36.4%	29.0%	31.0%
Splenectomy	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The last parameter that was analyzed was the size of the liver (Table 5). In most cases, in 8 (72.7%) patients from the first group and in 14 (45.1%) from the second, the size of the liver was in the normal range. But for the patients in the second group, moderate hepatomegaly occurred in 11 (35.5%) cases and severe hepatomegaly in 6 (19.4%) cases.

Table 5. Distribution of patients according to the liver sizes

	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Normal size	Number of patients	8	14	22
	%	72.7%	45.1%	52.4%
Moderate hepatomegaly	Number of patients	1	11	12
	%	9.1%	35.5%	28.6%
Severe hepatomegaly	Number of patients	2	6	8
	%	18.2%	19.4%	19.0%
Total	Number of patients	11	31	42
	%	100%	100%	100%

Discussion

The incidence of primary myelofibrosis is low. In the USA, primary myelofibrosis is detected in 0.5–1.5 cases per 100,000 [2], in Great Britain – 0.75, but in the Republic of Moldova, according to Ion Corcimaru's data from 2007, it is 0.2 per 100,000 [3]. Analyzing literature data, due to the diagnosis, a tendency towards an increase in the incidence and prevalence of 40–50% in the initial stage of primary myelofibrosis is observed. The pathology is seen in children only very rarely, being congenital and occurring in conjunction with other malformations. The peak incidence of primary myelofibrosis is between 50 and 70 years of age.

The clinical manifestations of primary myelofibrosis are variable and unusual. The diagnosis can be established early on by performing some prophylactic control analyses until long-term manifestations appear over time.

The weakness is a clinical manifestation that is detected most often in patients with primary myelofibrosis, even in those without anemia, which must attract maximum attention from internists. The second key pathogenic moment in fatigue is the development of anemia with the onset of the anemic syndrome. Most patients complain of constitutional symptoms, such as general weakness, weight loss, profuse night sweats, and fever, which interfere with their daily activities. These complaints can be explained by the already-mentioned imbalance in cytokine homeostasis [4]. These manifestations are associated not only with a negative impact on the patients' quality of life but also with an unfavorable prognosis [5].

Extramedullary hematopoiesis affects the spleen most often and rarely the liver, manifesting clinically through discomfort and pain under the costal arch caused by the increase in size. Splenomegaly is the result not only of myeloid hematopoiesis but also of the sequestration of myeloid cells. In some cases, there are pronounced pains in the left flank, along with fever and the clinical picture of acute abdomen caused by a splenic infarction. Hepatomegaly occurs in 40-70%. The involvement of the liver in the tumor process results in its dysfunction, manifesting itself through coagulopathy and thrombosis of the portal, splenic, and mesenteric veins [6, 7].

Often, anemia [8, 9, 10] and thrombocytopenia are the first paraclinical manifestations of myelofibrosis. Decreased hemoglobin and low platelet count are prognostic scores [10-14] and leukopenia often portends a poor prognosis [15, 16, 17]. Another special feature of primary myelofibrosis is the clinical-paraclinical variety. It can be manifested by cytopenia (cytopenic phenotype) and by bone marrow hypercellularity and pancytosis (proliferative phenotype) [18, 19]. However, the cytopenic phenotype is characterized by a reserved prognosis.

An interesting paper was published in 2022 on the prognostic impact of cytopenia in primary myelofibrosis. Two groups of patients in the prefibrotic and overt fibrotic phases were evaluated. In both cohorts, cytopenia resulted in progressive and unfavorable evolution. The most important indices were thrombocytopenia and anemia. The published results further extend the characterization of cytopenic features in PMF with a new understanding of the differences between the prefibrotic and overt fibrotic stages [20]. Primary myelofibrosis is characterized by anemia, which is detected in 50% of cases. Anemia is caused by both ineffective erythropoiesis in the bone marrow due to bone and extramedullary fibrosis and erythrocyte sequestration in the spleen.

It was mentioned above that thrombocytopenia is an unfavorable prognostic factor in primary myelofibrosis, and thrombocytosis is part of the proliferative phenotype.

The most common manifestations of primary myelofibrosis were described in the introduction of this article, but they are more characteristic of the overt fibrotic stage. Therefore, the hematologist knows how to manage these complications or minimize the intensification of constitutional symptoms. Young patients with primary myelofibrosis or other myeloproliferative neoplasms are understudied, resulting in unresolved treatment management. The changes in the complete blood count (thrombocytosis and leukocytosis) that are characteristic of the proliferative type are described in this study. Leukocytosis is one of the minor criteria for confirmation of myelofibrosis, but an elevated level of platelets is less common. It is very important for effective management because all patients with primary myelofibrosis are predisposed to thrombotic complications. Timely preventive measures can provide a better quality of life. Organomegaly was detected in most cases, which corresponds to the clinical features, but in the prefibrotic stage, it is smaller. So, the elevated level of platelets and leucocytes can be explained by hyperproliferation in the bone marrow and extramedullary hematopoiesis. Nevertheless, no correlations were found between the cellularity of peripheral blood and the sizes of the spleen or liver.

Conclusions

1. The classical clinical and hematological characteristics of primary myelofibrosis do not specify low- and intermediate-risk patients' management in the prefibrotic stage, as compared with the other chronic myeloproliferative BCR-ABL-negative neoplasms.
2. The proliferation type of primary myelofibrosis is characteristic for young patients in the prefibrotic stage.
3. According to our results, the main manifestations in the prefibrotic stage are detected in a complete blood count and comprise anemia, leukopenia, leukocytosis, and thrombocytosis.

Authors' contribution

NSB studied the bibliographic reference sources, summarized, and systematized the data of published research, studies, and clinical recommendations, collected the data, and structured and drafted the article. The manuscript was conceptualized by VM, MR, LJ, LM, AD, CD, and EC, who also summarized and systematized data from published research and studies and revised the draft of the article. All authors read and approved the final version of the article.

Declaration of conflicting interests

The author declares no conflict of financial or non-financial interests concerning the data and information presented in the manuscript.

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RESEARCH ARTICLE

Predisposing factors for surgical complications in chronic prostatitis and fibrosis of the prostate

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What is not yet known on the issue addressed in the submitted manuscript

The principles of selecting and determining factors of entomology therapy effectiveness for the treatment of NBCP in association with prostate fibrosis.

The research hypothesis

To determine the possibilities and efficacy of entomology therapy for the treatment of bladder outlet obstruction that develops because of prostate fibrosis.

The novelty added by manuscript to the already published scientific literature

Entomology treatment has proven to be a fast, harmless, and promising novelty method of treatment used to correct bladder outlet obstruction, with good clinical results focused on the size of the prostate and significantly decreasing the fibrosis area in the prostate.

Summary

Introduction. Prostatitis is an inflammatory process of the prostate, which continues to be considered one of the most common urological diseases in men under 45. Predisposing factors such as trophic, microcirculatory, and congestive disorders contribute to the onset and development of the inflammatory process in the prostate, as do risk factors such as the urethral catheter, urethrocystoscopy, endoscopic surgery for infection, and deterioration of the integrity of the urethral epithelium. The purpose of this study was to determine the impact of chronic inflammation and fibrosis of the prostate on urodynamics and local prostatic microcirculation and to evaluate the efficacy of conservative treatment.

Material and methods. The study included 58 patients (with pronounced clinical symptoms such as dysuria, stranguria, nocturnal frequent micturition 2-4 times per night, and residual urine greater than 50 mL) who received Adenosprosine® 250 mg treatment.

Results. A comparative study of the obtained data was performed on the pre- and post- treatment investigations with Adenoprosine® 250 mg suppositories, thus determining the correlation between urodynamic and microcirculation disorders depending on the degree of inflammation and prostate fibrosis.

Conclusion. According to the study results, we can outline that the level of microcirculation and urodynamic impairment indicates the level of prostate fibrosis. This process is reversible in chronic prostatitis with antifibrotic and anti-inflammatory therapy supplemented with Adenoprosine® 250 mg.

Keywords: prostatic fibrosis, chronic prostatitis, prostate, Adenoprosine® 250 mg.

Introduction

Prostatitis is an inflammatory process of the prostate of unknown etiology, for which methods of diagnosis and treatment have not been sufficiently highlighted [1, 2, 3]. However, prostatitis is still considered one of the most common urological diseases in men under the age of 45 and the third most common urological diagnosis in men over the age of 45, following benign prostatic hyperplasia (BPH) and prostate cancer, and accounting for 14–18% of outpatient visits [2, 4]. According to various literature data, the incidence of prostatitis ranges from 25–35% to 60–80%. The frequency of the disease increases with age, 35% of men under the age of 40 suffer from prostatitis, 45% of men over 40 years old, and 55% of men over 50 years old, etc. [5, 6]. The

early mean age of the patients, the decrease in reproductive function, the persistent disease evolution and treatment approaches, as well as the frequent recurrences, are reasons to consider this pathology both a medical and social problem [7]. The most common pathogens of bacterial prostatitis are the microorganisms of the family Enterobacteriaceae, namely, *E. faecalis, P. aeruginosa,* and *P. mirabilis* [1, 7]. However, over the last decade, there has been a marked tendency to involve both atypical microorganisms (*chlamydia, mycoplasma, and ureaplasma*) as well as staphylococci [8, 9]. The role of anaerobes, gonococci, and *trichomonas* in the development of prostatitis has not been sufficiently studied. The anterior and posterior urethra, as well as other parts of the urinary tract, might be sources of infection. Predisposing factors contribute to the development of inflammatory changes (trophic, microcirculatory, and congestive disorders) within the prostate, whereas the risk factors lead to infection of the prostate gland and damaged bladder epithelial integrity (urethral catheterization, use of urethral plugs, urethral instillation, and urethrocystoscopy). Chronic prostatitis is characterized by less severe clinical symptoms that last for more than 3 months, including perineum pain and discomfort, inguinal pain, difficulty urinating, frequent urination, reduced potency, and poor life quality. However, acute prostatitis differs in its clinical symptoms from the chronic one, being much more pronounced and compelling the patient to visit the urologist immediately.

The pathogenesis of chronic prostatitis has not been definitively highlighted; however, prostate inflammation has been determined to a greater extent due to the pathomorphological studies of surgical or biopsy samples retrieved from benign prostatic hyperplasia or cancer. There is a link between the degree of inflammation and the severity of LUTS (lower urinary tract symptoms) [6]. It has been assumed that the main reason is reduced tissue elasticity due to excessive fibrosis, which is the final stage of a chronic inflammatory process [5, 6]. The development of inflammatory processes involves the physiological healing response due to excessive production of fibrosis and damage or degradation of collagen, unless the inflammation is treated within the acute phase [10, 11]. Collagen is a major component of a large group of extracellular matrix proteins and a subtype that is mostly involved in fiber formation [12, 13]. These, in turn, play an essential role in the formation of the „tissue skeleton", which provides tissue strength and extensibility, cell migration and adhesion, and tissue regeneration after damage [14, 16]. There are two balanced multidirectional processes of collagen synthesis and degradation, whereas the imbalance results in excessive fibrous (scar) tissue formation that might disrupt the proper function of the target organ [3, 4].

Fibrosis caused by chronic inflammatory disease of the prostate is one of the major complications or causes of subsequent urinary disorders [8, 10], which has been proven experimentally to contribute to its spread on the bladder neck [14]. A retrospective case study in men who underwent surgical intervention for benign prostatic hyperplasia and prostate cancer showed a significant correlation between the fibrosis degree and malignant prostate tumor development, whereas the tumor was more aggressive in inflammatory processes [10, 13]. It should be noted that prostate fibrosis not only affects the urination process but may also worsen surgical outcomes. The literature data have reported a potential regression of inflammatory consequences due to the enzymatic effect of drugs that might reduce collagen biodegradation and stromal fibrosis by decreasing the process of periglandular and perivascular fibrosis and increasing the vascularization in the prostate [7, 17, 18].

A series of studies has demonstrated the successful use of conservative treatment in acute bacterial prostatitis, leading to regression of inflammatory changes as well as insignificant denaturation of collagen [11, 17, 18]. The early treatment of inflammation in parenchyma of the prostate decrease the risk of early development of fibrosis, however, experimental studies have found that acute inflammation in prostate produce minimal fibrosis, while chronic inflammation, followed by the development of fibrotic changes, leads to a complete recovering of inflammatory process in parenchyma of the prostate [8, 16]. An individual treatment approach for patients with prostate fibrosis is possible due to the emergence and development of ultrasound diagnostic techniques that diagnose the disease, assess the prostatic blood flow, monitor its dynamics, identify the prognosis of blood flow disorders within the impaired prostatic vessels via Doppler ultrasound, and predict possible postoperative complications [3, 7, 18]. A value of quantitative indicators of prostate regional blood flow allows identifying qualitative indicators that may determine the nature of the impaired organ's regional blood flow, such as pulse rate and venous flow velocity, which reveal the venous tone status as well as the presence of pelvic venous disease, including that of the prostate gland [4, 11, 17].

Material and methods

The clinical trial was carried out at Nicolae Testemitanu SUMPh's Department of urology, dialysis, and renal transplantation. The research project and protocol were approved by the Ethics Committee of Nicolae Testemitanu SUMPh. (Minutes No. 6, 11/12/2019). All subjects who participated in the clinical trial signed the informed consent form for participation in the trial.

The purpose of this study was to determine the degree of impact of chronic inflammation and prostate fibrosis on urodynamics and local prostate microcirculation, as well as to identify possibilities for their correction and improvement via drug therapy.

The mandatory diagnostic investigations include laboratory tests that should be carried out in primary health care (complete blood count and urinalysis; the three-glass test (an increase in the number of WBCs in the third portion of urine is characteristic for chronic prostatitis); and a microbiological urine test), as well as instrumental methods, including transrectal ultrasound of the prostate and digital rectal examination. Additional diagnostic assessment in-

cludes serological methods, PCR diagnostic testing (for detection of mycoplasma and chlamydia), uroflowmetry, and prostate biopsy (if necessary).

Blood flow assessment was carried out via transrectal ultrasound dopplerography with General Electric LOGiQP9 equipment, using a sensor at a frequency of 4–10 MHz, which determined the following indicators: maximum systolic blood flow rate, minimum diastolic blood flow rate, resistance and pulsation indices, vein lumen size of the periprostatic venous plexus, and venous blood flow.

Both before and after treatment, a direct relationship to the severity degree of blood flow disorder in the prostate vessels was assessed. Thus, patients with prostate and bladder neck fibrosis exhibited blood flow disorders in the prostatic tissues, which created favorable conditions for complications during different periods of treatment. A retrospective, comparative study was carried out to confirm the correlation between chronic inflammation and prostate fibrosis on urodynamics and microcirculation in the prostate. The study included 58 patients with pronounced clinical symptoms (dysuria, stranguria, 2-4 times nocturnal pollakiuria, post-void residual volume, on average 50 mL), which are characteristic of prostate fibrosis, resulting from chronic prostatitis.

A transrectal ultrasound was initially performed to determine the prostate structure and volume and the presence of prostate fibrosis with or without signs of acute or chronic inflammation. At the same time, patients with benign prostatic hyperplasia or suspected prostate cancer were barred from participating in the study. All patients underwent uroflowmetry, including the assessment of maximum flow rate (Qmax), average flow rate (Qmed), and speed of urine flow over time. According to the study findings, the patients were divided into two groups. Group I included 26 patients with inflammation and severe fibrosis of prostate tissue, and group II included 32 patients with inflammation and less severe fibrosis, which were graded from 0 (no changes) to 3 points (pronounced changes) based on ultrasound and clinical data.

Subsequently, all patients were given a course of treatment with Adenoprosine® 250 mg (as suppositories) for three weeks. The complaints decreased in 21 patients at the end of treatment, and they ceased. These patients – 6 (23.1%) from the group with severe inflammation and fibrosis and 15 (46.9%) from the group with inflammation and initial fibrosis – were recommended for dynamic outpatient care visits to the urologist. Despite an improvement in the condition of the other 37 patients, characterized by reduced complaints and better clinical and paraclinical parameters, it was recommended that they continue administering conservative Adenoprosine® suppositories for 30 days more, followed by subsequent follow-up investigations. Three patients from the study (2 from group I and 1 from group II, respectively) underwent endoscopic bipolar transurethral incision of the bladder neck and prostate (TURP) under spinal anesthesia, followed by the retrieval of biopsy material for pathomorphological examination.

Results and discussions

A comparative study of the obtained data was performed on the pre- and post-treatment investigations with Adenoprosine® 250 mg suppositories, thus determining the correlation between urodynamic and microcirculation disorders depending on the degree of inflammation and prostate fibrosis.

The fibrosis degree in patients from group I (with severe prostate fibrosis) decreased insignificantly by 0.1 points compared to 0.4 points in the group with milder fibrosis. The degree of inflammation was significantly lower in both groups, namely, 0.8 and 1.0 points, respectively, which proves the effectiveness of anti-inflammatory treatment with Adenoprosine® 250 mg suppositories. These very results were confirmed by the pathomorphological assessment (in three patients), characterized by a more reduced fibrous tissue area in patients from group II and a lack of acute inflammatory areas in the histological samples from both groups. All 37 patients from both groups exhibited an improvement in the maximum and average flow rates at the end of treatment and an insignificant decrease in prostate volume, resulting from a reduced inflammatory process in the prostate following treatment with Adenoprosine®.

According to ultrasound findings, all 37 patients undergoing an additional treatment approach showed some structural changes of the prostate, including inhomogeneous echogenic tissue and increased and decreased foci of echo density. Patients from group I had only a 0.1-point decrease in the degree of fibrosis, whereas the degree of inflammation decreased by 0.8 points. The second group showed more significant alterations in fibrosis and inflammation degree, viz. 0.4 and 1.0 points, respectively. Qmax increased by 1.5 mL/s and Qmed by only 0.5 mL/s in patients from the first group with severe prostate fibrosis. The second group (patients with minimal prostate fibrosis) had significantly better uroflowmetry values, viz. 3.9–4.0 and 4 mL/s, respectively. Microcirculatory disorders were also more pronounced in patients from group I compared to those with moderate fibrotic changes from group II. The indices of microcirculatory disorders were three times higher in group I compared to group II. Prior to treatment, 17 (46.0%) patients out of the 37 patients exhibited vein dilation of the periprostatic venous plexus up to 3.5±0.6 mm and a blood flow rate of up to 6.2±1.3 cm/s. The post-treatment indices showed a reduced vein dilation of the periprostatic venous plexus up to 2.5±0.2 mm in 9 (24.3%) patients and a better blood flow rate up to 9.1±0.3 cm/s. Table 1 shows a comparison of data analysis in patients before and after treatment.

Ultrasound investigations with the transrectal sensor recorded an irrelevant decrease in the mean volume of the prostate due to reduced prostate edema and a decreased inflammatory process. The pathomorphological study of a biopsy sample obtained via endoscopy in 3 patients confirmed stromal fibrosis with elements of paravascular fibrosis, which was more severe in two patients from group I.

Table 1. The investigation findings in both groups of patients, depending on the degree of fibrosis and inflammation before and after therapy with Adenoprosine® 250 mg, suppositories (37 patients).

Groups Qmax mL/s		Indices					
		Qmed mL/s	Degree of fibrosis	Degree of inflammation	Fibrosis stage (ultrasound-based)	Prostate volume, cm^3	
Group I (20 patients)	Before therapy	10.8±2.5	6.3±0.4	2.5±0.2	2.6±0.25	Advanced > 70%	36±0.2
	After therapy	12.3±2.3*	6.8±0.1***	2.4±0.1**	1.8±2.3**	> 60%	35.5±0.03*
Group II (17 patients)	Before therapy	15.6±1.2	9.4±1.5	0.6±0.01	2.2±0.15	Moderate 50-70%	37.6±0.52
	After therapy	19.5±1.5**	13.4±1.5*	0.2±0.15*	0.2±0.13*	> 30%	36.4±0.01**

Note: *statistically significant values after treatment compared to initial ones: * - p <0.05; ** - p <0.01; *** - p <0.001; Qmax – maximum flow rate; Qmed – medium flow rate.*

Therefore, it has been found that chronic inflammation associated with fibrosis might exacerbate the local microcirculation and the urodynamics. Chronic prostatitis, complicated by advanced fibrosis tissue, causes significant, irreversible damage to the prostate parenchyma and local blood flow. However, moderate impairment of the prostate parenchyma is likely to partially restore and improve the urodynamics and microcirculation. Thus, the conservative treatment with Adenoprosine® 250 mg suppositories used to prevent fibrosis formation and regression has a good pathogenetic rationale.

Conclusion

In conclusion, the study results proved that the impaired microcirculation and urodynamics indirectly indicate the stage of prostate fibrosis. In chronic prostatitis, this process is reversible if anti-fibrotic and anti-inflammatory drugs are administered, supplemented with Adenoprosine® 250 mg suppositories.

Declaration of conflicting interests

The author declares the absence of any conflict of interest in the elaboration of this article.

Authors' contribution

Both authors contributed equally to the development of the manuscript and approved its final version.

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RESEARCH ARTICLE

Contemporary surgical options in large benign prostatic hyperplasia treatment

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What is not yet known about the issue addressed in the submitted manuscript

The surgical treatment of large benign prostate hyperplasia is a topic of great interest. The use of contemporary technologies in prostate surgery extends opportunities for minimally invasive treatment.

The research hypothesis

Transurethral prostate enucleation becomes the new "gold standard" for surgical treatment of large benign prostate hyperplasia.

The novelty added by the manuscript to the already published scientific literature

The implementation of laser and bipolar energy in the surgical treatment of large benign prostatic hyperplasia allows for improved functional postoperative results and reduces the recovery time and perioperative complication rate.

Abstract

Introduction. Specialists are currently interested in the method of choice for surgical treatment in patients with enlarged benign prostate hyperplasia (> 80 cm^3). The introduction of laser and bipolar technologies for benign prostate hyperplasia surgery has allowed effective treatment regardless of the size of the prostate gland.

Material and methods. During 2020-2021, 65 patients underwent surgical treatment for large benign prostate hyperplasia. Depending on the type of surgical treatment performed, 3 study groups were identified: 22 patients underwent transurethral Thulium: YAG laser prostate vapoenucleation; 21 patients underwent transurethral bipolar prostate enucleation; and 21 patients underwent a simple prostatectomy. All patients were examined before and after surgery (at 3 and 6 months) using the International Prostate Symptom Score, Quality of Life Score, prostate-specific antigen assessment, transrectal prostate ultrasound examination, and uroflowmetry to assess residual urine volume. Postoperative complications were recorded in accordance with the 2004 Clavien-Dindo classification.

Results. There was a significant difference in the mean operative time ranging from 72±19 min (ThuVEP group) vs. 56±10 min (SP group) and 70±15 min (TUEB group), as well as a decrease in hemoglobin levels, viz. 1.2±0.4 g/dl vs. 2.6±1.1 g/dl vs. 1.6±0.5 g/dl (ThuVEP vs. SP vs. TUEB). The catheterization lasted for 2±1 days (ThuVEP) vs. 10±1 days (SP) vs. 3±1 days (TUEB). A significant improvement in Qmax was registered in the ThuVEP group (122.9%) and in the TUEB group (111.7%). However, patients after a simple prostatectomy showed an increase in Qmax of only 94%. The PVR values were reported to be the same. ThuVEP is an effective surgical technique for large BPH patients. The reduced trauma and lower complication rate of ThuVEP, as well as its effectiveness, have confirmed the need for widespread implementation of minimally invasive laser interventions.

Keywords: laser, bipolar enucleation, prostate.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common urinary tract pathologies that causes LUTS (lower urinary tract symptoms) [1]. The incidence of BPH increases with age and exceeds 90% by the age of 90 [2]. LUTS progression significantly affects the quality of life in elderly patients with BPH [3]. According to the recommendations of the American Urological Association and the European Society of Urology, only surgery is a radical treatment

for BPH. Transurethral resection of the prostate (TUR-P), which is currently the „gold standard", is well known in patients with small- (< 30 cm3) and medium-sized (< 80 cm3) total prostate volume [4, 5, 6]. The recommendations for patients with a large prostate volume (> 80 cm3) are less accurate and vary. Thus, according to the recommendations of the European Association of Urology, simple prostatectomy (SP), TUR-P, transurethral bipolar enucleation of the prostate, and transurethral laser enucleation of the prostate can be used in patients with a large prostate volume [4, 6]. Recommended surgical techniques totally vary depending on the procedure, surgical trauma, and postoperative recovery. It is noteworthy that at present, SP is the benchmark for assessing postoperative outcomes and is the oldest surgical method used [7, 8]. Over several decades, numerous attempts have been made to replace open surgical treatment in patients with large benign prostatic hyperplasia. For this purpose, the use of TUR-P is difficult and risky due to its long operative time and significant complication rate, making it the choice of only some specialists in transurethral resection. Since the 1990s, bipolar surgery has been introduced into the treatment of large BPH (6, 9). Bipolar transurethral enucleation of the prostate has paved the way for endourological treatment of large BPH. However, SP is still widely used, particularly in developing countries. The latest innovation in transurethral BPH surgery is the use of laser energy [6, 7, 10]. The use of laser generators provides a safe and efficient surgical technique. According to the conducted studies, the functional results are comparable to those of SP, whereas the surgical safety is higher than in bipolar surgery. The obtained results are encouraging in terms of laser surgery durability [11, 12].

Material and methods

During 2020-2021, 65 patients with BPH underwent surgical treatment for large BPH. Depending on the surgical approach used, 3 study groups were identified: 22 patients underwent transurethral Thulium:YAG laser vapoenucleation of the prostate (ThuVEP), 21 patients underwent bipolar transurethral vapoenucleation of the prostate (TUEP), and 21 patients underwent transvesical adenomectomy. All patients were assessed preoperatively and postoperatively (at 3 and 6 months) using the International Prostate Symptoms Scale (IPSS), Quality of Life (QoL), physical examination and digital rectal examination, serum prostate-specific antigen (PSA) assessment, uroflowmetry (Qmean and Qmax), transrectal ultrasound with prostate volume, and postvoiding residual urine volume (PVR) measurements. Postoperative complications were recorded according to the 2004 Clavien-Dindo classification. Inclusion criteria: total prostate volume ≥ 80 cm^3, age ≤ 80 years, post-void residual (PVR) ≥ 70 mL, Qmax ≤ 10 mL/s. ThuVEP was performed during the lithotomy positioning of the body. Exclusion criteria: prostate cancer at histological examination. ThuVEP was performed in all cases using a Karl Storz 26Fr continuous saline irrigating resectoscope. Tissue vapo-enucleation was performed using a Thulium:YAG laser (Revolix Duo, LisaLaser, Germany) set to 80W. The laser energy was delivered via a RigiFib 550mc optical fiber with terminal emission.

After performing a vapoenucleation plan along the pathway of the prostatic pseudocapsule, the prostatic nodules were detached concomitant with continuous hemostasis. Vapoenucleated nodules were removed from the bladder lumen by resection of devascularized pedunculated tissue. At the end of the surgery, all patients were fitted with a biluminal Foley type 20Fr autostatic urethrovesical catheter for postoperative bladder drainage. The removed tissues were sent for histological examination. In the case of severe hematuria in the early postoperative period, a continuous irrigation system was installed.

Bipolar transurethral vapoenucleation of the prostate was performed under spinal anesthesia, with the patient in the lithotomy position. The Olympus 26Fr continuous-flow resectoscope with saline irrigation (Sol. NaCl 0.9%) was used in all cases. The Olympus generator was used as the bipolar power source (200 W for vaporization and 120 W for coagulation). A three-lobar technique was used for vapoenucleation, and separate retrograde detachment of the hyperplastic nodules from the prostatic capsule was performed. Vapoenucleated tissue was subsequently fragmented by resection. Postoperative bladder drainage was provided by the installation of a Foley 20Fr biluminal autostatic probe for a period of at least 24 hours. Continuous bladder lavage was performed only in cases of significant postoperative hematuria. Histological examination of the vapoenucleated tissue was performed in all cases.

SP was performed under spinal anesthesia using the Fuller-Freyer procedure, which involves bimanual enucleation of adenomatous nodes. All patients underwent biluminal autostatic Foley catheterization and cystostomy. A continuous lavage system was installed for 24 hours to prevent the formation of blood clots in the bladder lumen. Histological examination of the BPH was performed in all cases.

After the removal of the urethrovesical catheter, all patients were followed up in the urology department within 24 hours.

Excel tables were used to process the data. Data is presented in absolute and relative terms, as well as mean and standard deviation. Descriptive statistics.

Results

All patients underwent similar examinations during the follow-up. During their visits, all parameters presented in the study were evaluated. At the end of the follow-up, all data were analyzed using the Student's t-test. The study groups were homogeneous (Table 1). Operative indices were also recorded and analyzed (Table 2). The operation lasted longer in the ThuVEP and TUEB groups, mostly due to complete enucleation and subsequent fragmentation of hyperplastic prostate tissue. At the same time, a more significant hemoglobin drop was found in the SP group. Bladder catheterization in patients who underwent SP lasted much longer (+400%) due to surgical trauma to the bladder and the impossibility of performing definite he-

mostasis. The hospital stay length was determined by the duration of postoperative catheterization, thus being comparably longer in patients who underwent SP (+250%). The period of macrohematuria in patients after TUEB lasted on average one day longer compared to the ThuVEP group, thus resulting in a longer catheterization and hospitalization.

Table 1. Preoperative assessment (65 patients).

	ThuVEP	TUEB	SP
No. patients	21	22	21
Age, years	64±4	63±3	65±3
Q_{max}, mL/s	8.3±1.4	8.5±2	8.3±1.5
Q_{mean}, mL/s	7.7±1.2	7.8±1.4	7.5±1.3
IPSS	27±2	28±2	27±1
QoL	5±1	5±1	5±1
Prostate volume, mL	89±7	88±5	90±6
PVR, mL	91±11	85±10	87±11
PSA, ng/mL	2.6±1.1	2.3±1.2	2.5±1.3

Note: *ThuVEP – transurethral Thulium:YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation; Q_{max} – maximum urinary flow rate; Q_{mean} – average urinary flow rate; IPSS – International Prostate Symptom Score; QoL – quality of life index; PVR – postvoiding residual urine volume; PSA – prostate specific antigen.*

Table 2. Surgical data (65 patients)

	ThuVEP	TUEB	SP
Operating time, min	72±19	70±15	56±10
Hemoglobin drop, g/l	1.2±0.4	1.6±0.5	2.6±1.1
Catheterization duration, days	2±13	3±1	10±1
Hospital stay length, days	5±1	6±1	12±2

Note: *ThuVEP – transurethral Thulium:YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation.*

At 6 months of follow-up, no significant differences were detected between the 3 groups regarding IPSS and QoL. At the same time, 3 months after the operation, patients who underwent ThuVEP noted a more significant improvement in IPSS and QoL values. Thus, at the 6-month check-up, the values were almost the same. A faster recovery to baseline indices can be easily explained by the less traumatic techniques of ThuVEP and TUEB (Table 3).

Table 3. Postoperative dynamics of symptoms (65 patients).

	Preoperative	Postoperative	
		3 months	6 months
IPSS			
ThuVEP	27±2	12±2	6±1
TUEB	28±2	13±2	6±1
SP	27±1	15±2	10±1
QoL			
ThuVEP	5±1	3±1	1±1
TUEB	5±1	3±1	1±1
SP	5±1	3±1	2±1

Note: *ThuVEP – transurethral Thulium:YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation; IPSS – International Prostate Symptom Score; QoL – quality of life index.*

Considering the technical features of the surgical approaches (ThuVEP, TUEB and SP), namely the complete enucleation of hyperplastic prostate tissues, the prostate ultrasound in the postoperative period showed a significant decrease in prostate volume in all three groups. At the same time, PVR changes reported during the follow-up period differed among the study groups. PVR in the ThuVEP group had a significantly faster positive trend and a considerable improvement at 6 months after surgery (-76.4%) compared to other groups. The changes recorded in the TUEB group were almost the same as in the ThuVEP group, and only the reduction in PVR was slightly lower (73.8% vs. 76.4%) (Table 4). The slower improvement in the SP group may be explained by more significant traumatic injuries, which required a longer recovery time.

Table 4. Dynamics of ultrasound parameters (65 patients).

	Preoperative	Postoperative, 3 months	Postoperative, 6 months
ThuVEP			
Prostate volume, mL	89±7	22±3 -75.2%	21±3 - 76.4%
PVR,mL	91±11	21±7 -76.9%	14±5 -84.6%
TUEB			
Prostate volume, mL	88±5	23±4 -73.8%	23±2 -73.8%
PVR, mL	85±10	22±5 -74.1%	17±5 -80%
SP			
Prostate volume, mL	90±6	24±5 -73.3%	23±4 -74.4%
PVR, mL	87±11	30±5 -65.5%	20±5 -77%

Note: *ThuVEP – transurethral Thulium YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation; PVR – postvoiding residual urine volume.*

Similar urodynamic changes were reported in both the TUEB and ThuVEP groups postoperatively, due to the use of the same enucleation procedure and the relatively rapid recovery time of the postoperative prostate. Thus, Qmax increased by 122.9% in the ThuVEP group and by 111.7% in the TUEB group. However, Qmax at 6 months after open adenomectomy showed an improvement of only 94% (Table 5).

Table 5. Changes in urodynamic values (65 patients).

	Q_{max} preoperative, mL/s	Q_{max} postoperative, mL/s	
		3 months	6 months
ThuVEP	8.3±1.4	17.2±1 +107%	18.5±1 +122.9%
TUEB	8.5±2	17±1 +100%	18±1 +111.7%
SP	8.3±1.5	14.1±1 +69.8%	16.1±1 +94%

Note: *ThuVEP – transurethral Thulium:YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation; Q_{max} – maximum urinary flow rate.*

The incidence of postoperative complications varied significantly in the study groups (Table 6), mainly due to the extremely different surgical techniques, different surgical injuries, and long-term catheterization in patients who underwent open surgery. In groups with transurethral vapoenucleation, the frequency of reported complications did not differ significantly. Sexually active patients reported postoperative retrograde ejaculation: 17 of 21 patients (80.9%) in the ThuVEP group and 19 of 21 patients (90.4%) in the SP group. The incidence of retrograde ejaculation after TUEB was 81.8%. It was found that retrograde ejaculation was stable and irreversible in all the patients under study. During the follow-up period, several complications of varying severity were diagnosed; however, they did not pose a threat to the lives of the patients. There were no cases of massive bleeding in the ThuVEP and TUEB groups. At the same time, one patient from the SP group required a blood transfusion. Postoperatively, 2 patients (9.5%) in the ThuVEP group and 3 patients (13.6%) in the SP group had complaints of transient urinary incontinence, which spontaneously resolved within 3 months of follow-up. Patients reported stress urinary incontinence in 13.6% of cases after TUEB. Urinary tract infections were registered preoperatively in one patient (4.76%) from the ThuVEP group, in one patient (4.54%) from the TUEB group, and in two patients (9.52%) from the SP group. The antibacterial treatment proved to be appropriate in all cases, in accordance with the urine culture. One episode of acute urinary retention was reported in both the TUEB and AE groups. This complication was resolved by re-catheterization within 48 hours and the administration of non-steroidal anti-inflammatory drugs. At 6 months, there was one case of urethral stricture in the TUEB group and one case of bladder neck sclerosis in the SP group. These complications were treated surgically with a cold-blade stricture incision and a bipolar bladder neck incision. At the same time, after ThuVEP, no sclerotic complications were reported during the follow-up period. The high incidence of infectious-inflammatory complications after SP is probably due to long-term urinary catheterization during the postoperative period. Cases of TUR syndrome were not recorded in the present study. The lowest overall rate of complications was reported in the ThuVEP group (14.27%) due to less traumatic injuries and the physical and surgical properties of the Thulium:YAG laser, whereas the overall incidence of complications in the TUEB group was insignificantly higher (18.1%) due to a minimally invasive approach. Open surgical treatment showed a very high complication rate of 42.85%. Such a high complication rate may be due to extensive surgical trauma and long-term postoperative catheterization.

Table 6. Postoperative complications, 2004 Clavien-Dindo classification (65 patients).

	ThuVEP, No. patients (%)	TUEB, No. patients (%)	SP, No. patients (%)	Severity of complications
Transient urinary incontinence	2 (9.51%)	2 (9.09%)	3 (14.28%)	Grade I
Re-catheterization	-	1 (4.54%)	1 (4.76%)	
Blood transfusion	-	-	1 (4.76%)	Grade II
Urinary infections	1 (4.76%)	1 (4.54%)	2 (9.51%)	Grade III
Urethral stricture	-	-	1 (4.76%)	
Bladder neck sclerosis	-	-	1 (4.76%)	Grade IIIb
TURP syndrome	-	-	-	Grade IV
Total	3 (14.27%)	4 (18.1%)	9 (42.85%)	

Note: *ThuVEP – transurethral Thulium:YAG laser prostate vapoenucleation; SP – simple prostatectomy; TUEB – transurethral bipolar enucleation; TURP syndrome – Transurethral resection of the prostate* syndrome.

Discussions

The postoperative assessment of patients showed a significant progressive improvement in the patients' overall condition according to the IPSS scale and QoL in all groups. A positive tendency for Qmax and urine flow rate was also recorded. The ultrasound exam showed a significant decrease in the total prostate volume and post-void residual urine volume. At the same time, the assessed methods showed different results. The patients undergoing ThuVEP and TUEB exhibited a significantly faster postoperative recovery and improvement in baseline indices. This is due to massive surgical injuries in SP, resulting in a prolonged recovery time of the prostate gland during the postoperative period. The impossibility of performing a high-quality primary hemostasis in SP may lead to longer hematuria and catheterization, which entails greater risks of bleeding as well as a prolonged hospitalization. Patients diagnosed with infravesical obstruction caused by large BPH (>80 cm^3) and severe lower urinary tract symptoms have a higher rate of therapeutic failure, which commonly requires surgical treatment. In these cases, qualified specialists will recommend first-line surgical methods such as endoscopic enucleation with bipolar energy, endoscopic enucleation with laser energy, and SP [13]. Despite the development of new technologies, SP remains the standard treatment for large BPH due to the limited availability of new technologies within healthcare facilities, as well as the frequent need for concomitant surgical treatments such as cystolithotomy and diverticulectomy. However, SP is known to be invasive and shows a higher morbidity rate, followed by higher bleeding and transfusion rates ranging from 7 to 14% [14, 15, 16], bladder neck sclerosis up to 6% [16, 17], and repeated surgeries up to 3.6% [18]. The introduction of bipolar surgery has allowed for the radical treatment of bulky BPH by significantly reducing surgical injuries and hospital stay. Thus, a decrease in blood loss (1.7 vs. 3.1 g/dL), postoperative hematuria (2.9% vs. 12.9%), and postoperative hospital stay (2.1 vs. 6.9 days) is being reported compared to SP [19]. At the same time, the functional results obtained after TUEB are similar to those obtained after open surgery, as confirmed by other studies as well.

Using ThuVEP seems to make even more sense. Thus, the conducted study proved maximum efficacy, comparable to SP, as well as better surgical safety. ThuVEP has been shown

to be a size-independent, safe, and effective treatment for large BPH [20]. Bach et al. evaluated the safety and efficacy of ThuVEP in patients with a total prostate volume of 108.6 mL (80-200 mL). At 12 months postoperatively, an 86% (67-99%) reduction in prostate volume and an 88% (58-100%) reduction in PSA levels were recorded [10]. Functional outcomes were comparable to those of open adenomectomy in most studies [21]. Given the significantly faster postoperative recovery, ThuVEP can be considered the treatment of choice for the management of large BPH [20-24].

Conclusions

The advantages of ThuVEP compared to TUEB and especially to SP are obvious. Thus, the maximum improvement in PVR was obtained in the ThuVEP group and amounted to 84.6%. The Qmax values in this group of patients also showed an excellent +122% increase. Considering the similar postoperative urodynamic results obtained after all types of surgical interventions, which were assessed within the present research (ThuVEP, TUEB, and SP), as well as a significantly lower complication rate (14.27%) found in the ThuVEP group, we consider it rational to use Thulium:YAG laser energy in the treatment of large BPH.

Declaration of conflicting interests

Nothing to declare.

Authors' contribution

All authors contributed equally to the elaboration of the manuscript. The final version has been read and approved by all authors.

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RESEARCH ARTICLE

Impact of drainage technique on surgical treatment of ureteropelvic junction obstruction in adults

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What is not yet known about the issue addressed in the submitted manuscript

Urinary drainage is one of the most important parts of ureteropelvic junction obstruction reconstruction. There is currently no consensus regarding the optimal method of drainage of the upper urinary tract in pyeloplasties in adults. There are few publications on this subject, most of them concerning some aspects of drainage methods but not comparing two different techniques.

The research hypothesis

Research on the impact of urinary drainage methods on outcomes of surgical treatment of ureteropelvic junction obstruction in adults.

The novelty added by the manuscript to the already published scientific literature

Ureteral double-J stents are associated with a shorter operating time, fewer postoperative pain medications, a shorter postoperative hospital stay, and a lower number of postoperative complications compared with external urinary drainage methods.

Abstract

Introduction. Urinary drainage is a key part of ureteropelvic junction obstruction treatment. Both external and internal drainage methods have been widely used for many years, but there is now relevant research comparing these methods and their impact on surgical outcomes in adults. The aim of the current research was to assess the efficacy and safety of two different types of urinary drainage on adult pyeloplasty.

Material and methods. We conducted a retrospective and prospective clinical controlled study in the Department of Urology at the Republican Clinical Hospital from Chisinau. We reviewed 118 consecutive adult pyeloplasties for ureteropelvic junction obstruction. In 62 (52.54%) patients, we used double-J ureteral stent insertion (DJ); in another 56 (47.46%) patients, we used different types of external drainage (ED): uretero-pyelo-nephrostomy, nephrostomy, or a combination of both. Operative time, hospital stay, use of analgesics, overall complications, type of complications, and success rates were compared between the two groups.

Results. The mean operative time in the DJ group was 93.52±18.10 min. vs. 95.77±20.48 min. in the ED group (p = 0.001). The average postoperative hospital stay in the DJ group was 8.45±2.02 days vs. 14.71±3.45 days in the ED group (p=0.000). The DJ group used 7.77±3.48 analgesics on average, while the ED group used 9.86±4.64 (p = 0.006). Overall complication rate was 9.68% in the DJ group and 32.14% in the ED group (p = 0.002). The most frequent complication for all patients was acute pyelonephritis (12.71%): 4.84% in the DJ group vs. 21.43% in the ED group (p = 0.007). The success rate was 96.77% in the DJ group and 92.86% in the ED group.

Conclusions. Both urinary drainage methods appear equivalent concerning overall success rates, but double-J ureteral stents are associated with a shorter operating time, fewer postoperative pain medications, a shorter postoperative hospital stay, and a lower number of postoperative complications compared with external urinary drainage methods.

Key words: ureteropelvic junction obstruction, pyeloplasty, urinary drainage, ureteral stent, nephrostomy, uretero-pyelo-nephrostomy.

Introduction

Ureteropelvic junction obstruction (UPJO) is a well-known clinical entity that represents an obstruction to the urine evacuation from the renal pelvis into the ureter, which, if not properly diagnosed and treated, can lead to

the complete loss of function of the affected kidney [1]. It may be caused by intrinsic or extrinsic factors, which may be congenital or acquired. UPJO is most caused by congenital causes that result in primary obstruction of the ureteropelvic junction, but it can also be caused by extrinsic compression by an aberrant vessel or by high ureter insertion [2]. Secondary UPJO can be caused by previous surgeries, recurrent stone passages, or inflammatory diseases [3].

Since its first description, Hynes-Anderson dismembered pyeloplasty has become the standard of surgical treatment for patients with UPJO [4]. The technique includes complete removal of the UPJ and performing with absorbable wires a new, wide anastomosis. A key element of the operations is urinary drainage, which aims to decompress the renal pelvis, maintain the caliber of the ureter, and maintain the anastomotic alignment [5].

There are several methods of urinary drainage described. The external drainage (ED) method involves decompressing the renal collecting system using various catheters externalized through the renal parenchyma, the most used being nephrostomy, uretero-pyelo-nephrostomy, or a combination of both [6]. Internal urinary drainage is accomplished by inserting a double-J (DJ) ureteral stent from the renal pelvis into the urinary bladder [7]. Both DJ and ED have been widely used for many years and have proven their effectiveness during pyeloplasty; however, each method is associated with its advantages and disadvantages [4].

The ED procedure allows for the assessment of the repair in pyeloplasty and, if necessary, allows a pyelography to be performed. They can be simply removed without the need for sedation [8]. However, they have several potential unfavorable conditions, such as increased risk of renal parenchyma damage, bleeding, flank pain, urinary tract infections, and reduced quality of life [4]. In addition, the presence of an external drain increases the risk of urinary infection.

The use of the DJ offers advantages, especially for the postoperative period; it is associated with better cosmetic results and a shorter hospital stay [9]. The disadvantage of this method is the risk of dysuria, suprapubic pain, and terminal hematuria [10, 11].

Most of the publications related to the topic of urinary drainage methods address particular aspects of DJ or ED. There is a lack of data concerning intraoperative or postoperative particularities, postoperative complications, types of complications, and the overall success rate of pyeloplasties in adults comparing two different techniques. A better understanding of all these particularities would allow us to identify the risk factors associated with each method of urinary drainage and, in the end, would help us better plan our surgery and obtain better surgical results.

The aim of the current research was to assess the efficacy and safety of two different types of urinary drainage on adult pyeloplasty.

Material and methods

The retrospective and prospective clinical controlled study was conducted at the Urology Clinic of the "Timofei Mosneaga" Republican Clinical Hospital and the Department of Urology and Surgical Nephrology of the Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova. The research protocol was positively approved by the Research Ethics Committee of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova (Protocol No. 29/54 of 06.05.2014).

We reviewed 118 consecutive adult pyeloplasties for ureteropelvic junction obstruction. The information was gathered from medical records (Form 003/e) with the ICD-10 code N13.0 between 2008 and 2016. The retrospective part included the period between 2008 and 2014; the prospective part included the period between 2012 and 2016. All cases were evaluated clinically and by ultrasound at 6 and 12 months after the surgery.

In all cases, the diagnosis of UPJO was confirmed based on renal ultrasound, intravenous urography, or contrast-enhanced computed tomography. For the standardization and reporting of the pre- and postoperative ultrasound data, we used the Nguyen [12] urinary tract dilatations classification from 2014, as shown in Table 1.

Table 1. Classification of upper urinary tract dilatations.

Grade	Imaging aspect
Grade I	Renal pelvis dilatation
Grade II	Central and peripheral caliceses dilated
Grade III	Parenchyme thin

All patients underwent Hynes-Anderson dismembered pyeloplasty. Depending on the urinary drainage method, all subjects were divided into two groups:

Group I (the DJ group) consisted of 62 (52.54%) patients, in whom we used Double-J ureteral stent insertion.

Group II (the ED group): 56 (47.46%) patients in whom we used different types of external drainage (ED), namely nephrostomy (3.57%, n = 2), uretero-pyelo-nephrostomy (46.42%, n = 26), or a combination of both (48.21%, n = 27).

The following aspects were evaluated: epidemiological data; intraoperative particularities, highlighting operation time and intraoperative complications; postoperative particularities, including the assessment of postoperative hospital stay duration, analgesic consumption, the number and type of postoperative complications, the need for reintervention and hospitalization within the next 12 months, and the overall success rate. Surgical success was defined as the absence of flank pain and the absence of progression of hydronephrosis after 12 months.

PSPP 1.6.2 and MS Excel 2016 were used for statistical data processing, and standard statistical analysis methods were applied. Different statistics were used for group comparisons depending on the type of data. For the frequencies and percentage values, the Pearson $\chi 2$ statistic and the degrees of freedom (gl) applicable to the analyzed table were

calculated, and based on these values, the p value was deduced. In cases where the minimum conditions of the χ2 test were not met (fewer than 5 observations in one of the cells of the tested table), to confirm the conclusions, the Fisher Exact test was also applied, which does not have such limitations and directly calculates the p value. For the analysis of the quantitative (measured) data, the mean, the standard deviation, the median, and the minimum and maximum values were observed, and the ANOVA (analysis of variance) procedure was applied with the calculation of the F statistic and the deduction of the applicable p-value. The statistical significance threshold was set at the widely accepted level of $p < 0.05$, but this level was interpreted with caution if p-values were slightly higher.

Results

A general characterization of the study lots is shown in Table 2.

The average age of the patients enrolled in the research was 36.88±14.24 years, with a median of 34 years and values between 18 and 74 years, without a statistically significant difference between the groups, determining the homogeneity of the groups. The mean age in the DJ group was 37.97±14.12 years, ranging from 19 to 74 years; the median was 37 years; in the ED group, the mean age was 35.68±14.39 years, ranging from 18 to 64 years, with a median of 30 years and oscillations between 18 and 64 years. Distribution by age groups also did not identify differences between the researched groups. The distribution by gender identified a slight male predominance of 69.64% (39) in the ED group, compared to 38.71% (24) in the DJ group (x2 = 11.3, gl = 1, p = 0.001). The distribution according to place of residence did not identify statistically significant differences between the researched groups, with residence in an urban environment in the DJ group being 45.16% (28) vs. 41.07% (23) in the ED group, and from rural areas in the DJ group being 54.84% (34) vs. 58.93% (33) in the ED group.

The analysis of the etiology of UPJO identified that in both groups the most frequent cause of UPJO was its congenital obstruction – 59.32% (70), followed by the presence of aberrant vessels – 31.36% (37), without statistically significant differences between the groups, which once again confirmed the homogeneity of the study groups. The results are presented in Table 2.

Most frequently, patients complained of dull pain located in the lumbar region. In the DJ group, this sign was present in 60 (96.67%) patients, and in the ED group, in 55 (98.21%) patients. The left-right location of the disease is presented in Table 2.

All subjects had advanced urinary tract dilatations (as determined by renal ultrasound), with degree II in 45.76% (54) of cases and degree III in 54.24% (64) of cases. Distribution by groups identified that in the DJ group, 29 (46.77%) patients had grade II hydronephrosis and 33 (53.23%) patients had grade III. In the ED group, grade II hydronephrosis was diagnosed in 25 (44.64%) patients and grade III in 31 (55.36%). The results are shown in Table 2.

Table 2. Comparative analysis of registered parameters according to study groups.

Parameters	DJ group (n = 62)	ED group (n = 56)	p
Age, years	37.97±14.12 (19-74)	35.68±14.39 (18-64)	p > 0.05
Grouping by age:			
18-30 years, n (%)	23 (37.10)	29 (51.79)	p > 0.05
31-40 years, n (%)	12 (19.35)	6 (10.71)	p > 0.05
41-59 years, n (%)	22 (35.48)	17 (30.36)	p > 0.05
≥ 60 years, n (%)	5 (8.06)	4 (7.14)	p > 0.05
Grouping by gender:			
Men, n (%)	24 (37.81)	39 (69.64)	p = 0.001
Women, n (%)	38 (61.29)	17 (30.36)	p > 0.05
Residency:			
Urban, n (%)	28 (45.16)	23 (41.07)	p > 0.05
Rural, n (%)	34 (54.84)	33 (58.93)	p > 0.05
Etiology of UPJO:			
UPJ stenosis, n (%)	38 (61.29)	32 (57.14)	p > 0.05
aberrant vessel, n (%)	19 (30.65)	18 (32.14)	p > 0.05
uretero-pelvic implantation defect, n (%)	1 (1.61)	5 (8.93)	p > 0.05
stenosing periurethritis, n (%)	1 (1.61)	0 (0.00)	p > 0.05
cicatricial uretero-pelvic retraction, n (%)	3 (4.84)	0 (0.00)	p > 0.05
combination (uretero-pelvic implantation defect + aberrant vessel)	0 (0.00)	1 (1.79)	p > 0.05
Clinical picture:			
Back pain, n (%)	60 (96.67)	55 (98.21)	p > 0.05
• right, n (%)	21 (33.87)	27 (48.21)	p > 0.05
• left, n (%)	38 (61.29)	26 (46.43)	p > 0.05
• bilaterally, n (%)	3 (4.84)	3 (5.36)	p > 0.05
Degree of hydronephrosis:			
II, n (%)	29 (46.77)	25 (44.64)	p > 0.05
III, n (%)	33 (53.23)	31 (55.36)	p > 0.05

Note: *statistical test applied: Pearson χ2; p – statistical significance; DJ – Double-J; ED – External Drainage; UPJO – ureteropelvic junction obstruction; UPJ – ureteropelvic junction.*

In 63.56% (75) of the cases, we performed only a pyeloplasty; in another 36.44% (43) of the cases, due to the association of other urological conditions, we also performed some other surgical procedures like stone extraction, nephropexy, and resection of renal cysts or aberrant vessels. In the DJ group, only pyeloplasties were performed in 56.45% (35) of the cases, compared to 71.43% (40) cases in the ED group, and the ratio of more complex interventions was 43.55% (27) to 28.57% (16) cases, with no statistically significant differences between the studied groups, which once again demonstrates their homogeneity.

The mean operative time for all operations was 95.77±20.48 minutes, with 93.52±18.10 minutes in the DJ group and 98.21±22.69 minutes in the ED group. (F = 5.361, p = 0.002; Kruskal-Wallis H = 16.078, gl = 3, p = 0.001). The results are presented in Table 3.

Table 3. Particularities of surgical interventions.

Parameters	DJ group (n = 62)	ED group (n = 56)	p
Pyeloplasty, n (%)	35 (56.45)	40 (71.43)	p > 0.05
Pyeloplasty + other operations, n (%)	27 (43.55)	16 (28.57)	p > 0.05
Mean operative time (min.):			
mean	93.52±18.10	98.21±22.69	p = 0.001
median	90	100	
IIQ	85-105	85-120	
Min-Max	60-140	60-150	

Note: *statistical test applied: Pearson χ2; p – statistical significance; DJ – Double-J; ED – External Drainage.*

The mean postoperative hospital stay for all patients was 11.37±4.26 days, the median being 11 days, with ranges between 4 and 30 days. In the DJ group, it was 8.45±2.02 days on average, with a median of 8 days and values between 4 and 18 days; in the ED group, it was 14.71±3.45 days, the median being 14 days with ranges between 9 and 30 days, this difference being statistically significantly higher (F = 147.851, p = 0.000; Kruskal-Wallis H = 79.388, gl = 1, p = 0.000). The results are presented in Table 4.

Table 4. Duration of postoperative hospitalization (in days).

Parameters	DJ group (n = 62)	ED group (n = 56)	p
Mean	8.45±2.02	14.71±3.45	p = 0.000
Median	8	14	
IIQ	7-9	13-16	

Note: *statistical test applied: Pearson χ2; p – statistical significance; DJ – Double-J; ED – External Drainage.*

The analysis of the consumption of non-opioid analgesic medication identified that in the DJ group, the need for drugs was lower than in the ED group (7.77±3.48 vs. 9.86±4.64 administrations) (F = 7.911, p = 0.006). The evaluation of the number of opioid drugs did not identify statistically significant differences between the investigated groups, constituting 2.50±1.24 administrations in the DJ group, and 2.76±1.63 administrations in the ED group. The data are presented in Table 5.

Table 5. Postoperative pain medications (number)

Parameters	DJ group (n = 62)	ED group (n = 56)	p
Opioid analgesics			
mean	2.50±1.24	2.76±1.63	2.62±4.18
median	2	3	2
IIQ	2-3	2-3	2-3
Min-Max	0-6	0-10	0-10
Non-opioid analgesics			
mean	7.77±3.48	9.86±4.64	8.77±4.18
median	7	9	8
IIQ	5-10	7-12	6-10
Min-Max	2-20	3-29	2-29

Note: *statistical test applied: Pearson χ2; p – statistical significan**ce**; DJ – Double-J; ED – External Drainage.*

The only intraoperative complication (0.85%, n = 1) was significant bleeding that required hemostatic transfusion; it occurred during the extraction of the stone from the renal pelvis, and the patient was from the DJ group.

From the day of surgery until discharge, complications were recorded in 22 (18.64%) patients, of whom 6 (9.68%) were in the DJ group and 16 (28.57%) in the ED group (x2 = 6.925, gl = 1, p = 0.009). From the time of discharge until the end of the follow-up period (12 months), complications were recorded in 3 (2.54%) patients, all of them from the ED group (5.36%, n = 3). Overall, from the day of surgery until the end of the follow-up period, different types of complications were recorded in 20.34% (24) of the cases, of which 9.68% (6) were in the DJ group and 32.14% (18) were in the ED group (x2 = 6.165, gl = 1, p = 0.002). Thus, for patients in the DJ group, the chance of developing postoperative complications was 4.4 times lower compared to those in the ED group (OR = 4.42; CI: 1.61–12.16). The results are presented in Table 6.

Table 6. Complications of the reconstructive interventions.

Parameters	DJ group (n = 62)	ED group (n = 56)	p
Intraoperative complications, n (%)	1 (0.85)	0 (0.00)	p > 0.05
Overall postoperative complications, n (%)	6 (9.68)	18 (32.14)	p = 0.002
Early postoperative complications, n (%)	6 (9.68)	16 (28.57)	p = 0.009
Late postoperative complications, n (%)	0 (0.00)	3 (5.36)	p = 0.065
Reinterventions, n (%)	1 (1.61)	5 (8.93)	p > 0.05

Note: *statistical test applied: Pearson χ2; p – statistical significance; DJ – Double-J; ED – External Drainage.*

Due to several obstructive complications occurring in the postoperative period, in 5.08% (6) of cases, it was necessary to perform different endoscopic interventions (stent replacement, stent insertion, and ureteral catheter insertion), of which 8.93% (5) occurred in the ED group and 1.61% (1) in the DJ group.

The most frequent postoperative complication was acute pyelonephritis of the operated kidney (12.71%, n = 15); this was recorded in 4.84% (3 cases) in the DJ group and in 21.43% (12 cases) in the ED group (x^2 = 7.298, gl = 1, p = 0.007). Postoperative bleeding that required transfusion of blood components was recorded in 3 (2.54%) patients, all of them from group II (MDE) (5.36%, n = 3). Prolonged urinary leakage occurred in 2 (1.69%) patients, all from the ED group (3.57%, n = 2). Renal colic occurred in 2 (1.69%) patients, one in each group (1.61% in DJ and 1.79% in ED). In the DJ group, we also had one case of postoperative wound infection (0.85%), one case of 4-day polyuria (0.85%), and one case of thrombophlebitis (0.85%).

In our study, the overall success rate was 94.92% (112 cases). In 5.08% (6) cases, patients presented flank pain and ultrasound progression of hydronephrosis, so they were considered treatment failures. The DJ group had a success rate of 96.77% (60 cases), while the ED group had a

success rate of 92.86% (52). Treatment failure was recorded in 3.23% of the (2) DJ cases and in 7.14% of the (4) ED cases. The results are shown in Figure 1.

Discussions

In this study, we compared the impact of two different methods of urinary drainage on the outcomes of surgical treatment of ureteropelvic junction obstruction in adults. There is consensus that dismembered pyeloplasty is the treatment of choice and standard of care for patients with UPJO. On the other hand, the same cannot be said regarding the method of urinary drainage [7]. The number and quality of studies comparing different methods of urinary drainage in adults are low. Our study seeks to identify the benefits and drawbacks of internal and external urinary drainage methods, as well as their impact on treatment outcomes.

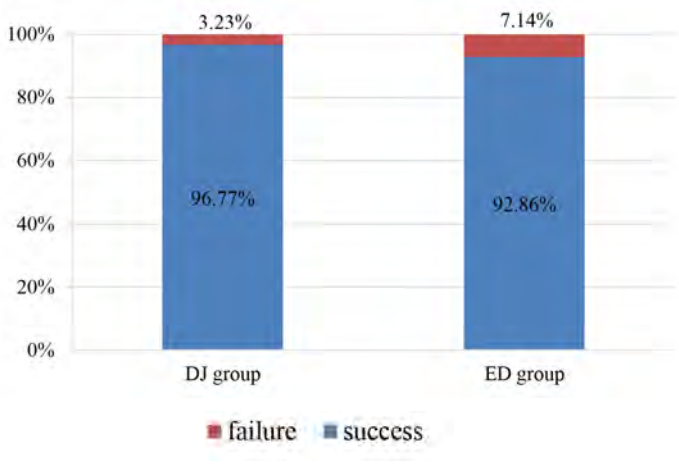

Fig. 1. Success rate.

Note: *DJ – Double-J; ED – External Drainage; success – absence of flank pain and hydronephrosis progression on renal ultrasound examination at 12 months from intervention; failure – presence of flank pain and/or ultrasound progression of hydronephrosis at 12 months from intervention.*

Braga et al. [7] consider that the potential benefits of using a ureteral stent are decreased postoperative urine leakage, alignment of the anastomosis to avoid ureteral kinking, and early discharge from the hospital. On the other hand, the advantages of external methods are the absence of bladder spasms and their easy removal. According to Joshi et al. [13], external methods offer an advantage when it is necessary to evaluate the urinary tract, but they are associated with increased risks of renal parenchyma damage, bleeding, urinary tract infections, back pain, and decreased quality of life. In a network meta-analysis performed by Liu et al. [4], it was found that according to the ranking results, the DJ stenting procedure had the highest operative success rate, renal function improvement, and the shortest hospital stay, while the external stenting method had the lowest rate of overall complications and redo pyeloplasty.

According to our findings, ED is associated with a longer operation time than DJ. It was also demonstrated that ED is associated with a higher requirement for postoperative pain medications; this could be explained by the fact that external drainage is more traumatic, requiring perforation of the renal parenchyma and flank muscles.

The length of hospital stay is an important indicator of morbidity and the economic evaluation of different treatment methods. In our trial, the postoperative length of stay was significantly longer in the ED group than in the DJ group.

Our results have shown that intraoperative complications are not influenced by the urinary drainage method, but a strong association was found between urinary drainage and the number and type of postoperative complications. Early complications were observed more frequently in the ED group than in the DJ group. Late complications were present only in the ED group. The overall complication rate during the past 12 months has shown that the chance of developing postoperative complications in the case of DJ is 4.4 times lower compared to ED.

The most frequent postoperative complication was acute pyelonephritis; it was associated with ED, which could be explained by the renal trauma caused by the trans-parenchymal exteriorization of the drainage tubes and the possibility of their infection.

The overall operative success rate in our study was slightly higher in the DJ group, but without a statistically significant difference, so we can say that both methods are associated with high outcomes and are equal in operative success.

Conclusions

Both urinary drainage methods appear equivalent concerning overall success rates, but double-J ureteral stents are associated with a shorter operating time, fewer postoperative pain medications, a shorter postoperative hospital stay, and a lower number of postoperative complications compared with external urinary drainage methods.

Declaration of conflict of interests

Nothing to declare.

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RESEARCH ARTICLE

Perinatal outcomes of multiple cesarean sections

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What is not yet known about the issue addressed in the submitted manuscript

Multiple cesarean sections (CSs), especially elective CSs without medical indications, are associated with short- and long-term risks for the child. Cesarean delivery (CD) is also associated with an increased incidence of perinatal complications, such as stillbirth, small-for-gestational-age neonates, and preterm birth.

The research hypothesis

To assess the fetal and perinatal outcomes of multiple CSs in pregnant women aged 18 to 40 years, as well as their incidence according to the number of cesarean sections performed.

The novelty added by the manuscript to the already published scientific literature

The study allowed for the clarification of the incidence and structure of perinatal outcomes according to the number of cesarean sections performed. The mode and timing of delivery have a greater impact on adverse neonatal outcomes than the number of previous CSs.

Abstract

Introduction. The literature suggests that the mode and timing of delivery have a greater impact on adverse neonatal outcomes than the number of previous cesarean sections.

Materials and methods. A retrospective observational case-control study was carried out. The study included 352 pregnant women with a singleton pregnancy and at least one previous cesarean section: 177 pregnant women with two or more previous cesarean sections (experimental group) and 175 with a primary cesarean section (control group). Excel tables were used to organize the data. For comparing categorical variables in groups, the χ^2 test was used. A $p < 0.05$ was considered statistically significant.

Results. Termination of the pregnancy by cesarean section at 39 + 0 – 39 + 6 weeks of gestation (56.5% and 27.4%, respectively; $p < 0.001$) was statistically significantly more frequent in the experimental group. Analysis of deliveries revealed that emergency cesarean sections in pregnancy (18.9% and 9.0%, respectively; $p < 0.01$) and emergency cesarean sections during labor (60.6% and 30.5%, respectively; $p < 0.001$) were performed statistically significantly more frequently in the control group. Planned cesarean sections during pregnancy (60.5% and 20.6%, respectively; $p < 0.001$) were performed statistically significantly more frequently in the experimental group. The rate of full-term neonates was statistically significantly higher in women from the experimental group (96.6% and 83.4%, respectively; $p < 0.001$), and the rate of post-term neonates was statistically significantly higher in women from the control group (12.0%; $p < 0.001$). The Apgar score values 1 minute after birth equal to 8–10 points (130 – 84.4% and 10 – 47.6%, respectively; $p < 0.001$) were statistically significantly more frequent in pregnant women without acute fetal distress during labor, and the Apgar score values 1 minute after birth equal to 1–7 points (11 – 52.4% and 24 – 15.6%, respectively; $p < 0.001$) were statistically significantly more frequent in pregnant women with acute fetal distress during labor. Similar results were found in the Apgar score at 5 minutes after birth.

Conclusions. In our research, it was demonstrated that the mode and timing of delivery have a greater impact on adverse neonatal outcomes than the number of previous cesarean sections.

Keywords: cesarean section, multiple cesarean sections, elective cesarean section, perinatal outcomes, perinatal complications.

Introduction

CS is one of the most common abdominal surgeries performed on women in most countries. The CS rate has increased dramatically in recent decades worldwide, particularly in middle- and high-income countries, despite a lack of evidence supporting substantial maternal and perinatal benefits [1-6]. The CS rates varies significantly by geographic region, ranging from less than 10% to more than 50% at the national level, according to the World Health Organization global survey [1, 2, 7].

Multiple CSs, especially elective CSs without medical indications, are associated with short- and long-term risks for both mother and child. There are significant maternal complications, such as visceral injuries, uterine rupture, abnormal placentation, hysterectomy, hemorrhages and blood transfusions, severe adhesions, etc. Cesarean delivery (CD) is also associated with an increased incidence of perinatal complications, such as stillbirth, small-for-gestational-age neonates, and preterm birth. Children born by repeated cesarean sections are prone, in the short term, to breathing difficulties (transient tachypnea of the newborn, respiratory distress syndrome) and the need to be admitted to the neonatal intensive care unit (NICU). There are significant long-term risks associated with immune disorders, obesity, and asthma [2, 3, 5, 7, 8, 9].

The purpose of the study is to assess the fetal and perinatal outcomes of multiple CSs in pregnant women aged 18 to 40 years, as well as their incidence according to the number of cesarean sections performed.

Material and methods

The work was carried out at the Department of Obstetrics and Gynecology, Obstetrics and Gynecology Discipline of the *Nicolae Testemitanu* State University of Medicine and Pharmacy and the Municipal Perinatological Center of the *Gheorghe Paladi* Municipal Clinical Hospital. The study protocol was approved by the Research Ethics Committee of the *Nicolae Testemitanu* State University of Medicine and Pharmacy (minutes No. 2 of 09.06.2021).

To achieve the objective, a retrospective observational case-control study was carried out. The study included 352 pregnant women with a singleton pregnancy and at least one previous CS: 177 pregnant women with two or more previous CSs (experimental group, EG), and 175 with a primary CS (control group, CG). The women were selected in a systematic manner based on an examination of medical records from the Archives of the *Gheorghe Paladi* Municipal Clinical Hospital, and for greater research accuracy, a series of inclusion and exclusion criteria were followed, making the study more well defined and centered on a specific representative group.

The inclusion criteria for the study were: (1) multiparous pregnant women with at least one CS in their history and an unlimited number of vaginal births; (2) pregnant women aged 18-40 years; (3) women with segmental-transverse hysterotomies; (4) longitudinal position of the fetus; (5) singleton pregnancy; (6) pregnancy without fetal anomalies; (7) pregnancy with a gestational age greater than 35 weeks; (8) patients without serious extragenital diseases (autoimmune diseases, diabetes, cardiovascular diseases, deficiency of coagulation factors); (9) patients who were subject to all investigations according to the study protocol.

The exclusion criteria from the study were: (1) patients with previous gynecological surgery, other than CS, with penetration into the uterine cavity (myomectomy); (2) fetal macrosomia, malformations, or antepartum fetal death; (3) pregnant women over 40 years of age; (4) pregnancy with a gestational age less than 35 weeks; (5) anterior „T" or „J"-shaped hysterotomy; (6) transverse fetal position; (7) multiple pregnancies; (8) patients with severe extragenital diseases (autoimmune diseases, diabetes, cardiovascular diseases, deficiency of coagulation factors); (9) patients with uterine rupture, bleeding tendency, and infections; (10) patients with incomplete data who did not undergo all the investigations according to the study protocol.

The primary data were collected and extracted from the medical documentation (medical records), which included: socio-demographic data (age, occupation, parity, and number of pregnancies); anthropometric parameters; risk factors; medical and obstetrical-gynecological anamnesis; the results of clinical, instrumental, and laboratory investigations; the evolution of previous pregnancies and the current pregnancy; and the newborn`s status (sex, gestational age, weight, and height at birth; the Apgar scores at 1 minute and 5 minutes after birth; and birth injuries in the newborn). The indications for CS were exclusively medical. The collected data were analyzed and compared across study groups (the experimental group and the control group).

The primary study materials were entered into an electronic database and processed on a personal computer using the functions and modules of the programs „Statistical Package for the Social Science" (SPSS) version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and Microsoft Excel 2019 through descriptive and inferential statistical procedures. To compare discrete variables, methods such as Pearson's χ^2, Yates' χ^2 correction, or Fisher's exact test were used; to determine the statistical difference in mean values between groups, an independent samples t-test (for interval-scaled variables with a normal distribution of values) or non-parametric statistical tests (for ordinal-scaled or interval-scaled variables with a non-normal distribution of values) were used.

Differences that were statistically significant with a bilateral value of $p < 0.05$ were considered.

Results and discussions

The mean age of pregnant women in the EG was statistically significantly higher as compared to patients in the CG (30.56±0.3 years and 29.31±0.4 years, respectively; $p < 0.05$). In the CG, there were statistically significantly more women aged between 31 and 40 years (51.4% and 38.3%, respectively; $p < 0.05$), and in the CG, there were statistically significantly more women aged 18-20 years (3.4% and 0.6%, respectively; $p < 0.05$). The proportion of women

aged 21-30 years was similar in both study groups (48.0% and 58.3%, respectively; p > 0.05). Rehman *et al.*, in a recent study, confirmed that most women who underwent CS were aged 21-30 years (67.1%) [10].

In the study, primigravid women were statistically significantly more prevalent in the CG 85 cases (49.1%, p < 0.001), whereas secundigravid women (79 – 44.6% and 48 – 26.9%, respectively; p < 0.001) and multigravida women (98 – 55.4% and 42 – 24.0%, respectively; p < 0.001) were statistically significantly more prevalent in the EG (Figure 1).

According to parity, primiparous women accounted for 121 cases (69.1%, p < 0.001) significantly predominating in the CG, while secundiparous women accounted for 126 cases (71.5%) and 34 cases (19.4%), respectively, and multiparous women accounted for 51 cases (28.5%) and 20 cases (11.5%), respectively (p < 0.001), significantly predominating in the EG (Figure 2).

Similar results were obtained in other studies. Blotniene *et al.* [1] found that women with two or more CSs had statistically significantly higher mean ages at birth, gestations, and parities than women with a primary CS in a study of 655 pregnant women with at least one CS and singleton pregnancies [1].

Maternal morbidity increases exponentially with the number of CSs. The risk of injury in infants is low but not absent. A high rate of elective CDs has contributed to the increase of fetal complications: respiratory morbidity (respiratory distress syndrome, transient tachypnea of the newborn), admission to the NICU, and increased length of hospitalization, with a significant medical, social, and financial impact on families and medical institutions [7, 11-15]. The adverse risks of CD at 37-38 weeks of gestation significantly increase, with a magnitude of 9–40% [15].

An increased risk of severe general respiratory morbidity has been identified in infants born by elective CS. Furthermore, the risk increased concurrently with the gestational age decrease: at 37 weeks (odds ratio: OR 3.9; 95% confidence interval: CI 2.4-6.5); at 38 weeks (OR 3.0; 95% CI 2.1-4.3); and at 39 weeks (OR 1.9; 95% CI 1.2-3.0). The risk of severe respiratory morbidity was more likely at 37 (OR 5.0; 95% CI 1.6-16.0) and 38 weeks of gestation (OR 4.2; 95% CI 1.6-11.0). Even after excluding pregnancies complicated by diabetes, preeclampsia, intrauterine fetal growth retardation, or breech presentation, the results remained consistent [14].

The lack of stress hormones associated with labor could explain this association. During spontaneous labor, fetal lung fluid secretion decreases and absorption increases, and stimulation of surfactant release may be mediated by elevated fetal catecholamines in response to rupture of the membranes and delivery. Thus, if CS is performed before the onset of labor, the concentration of catecholamines in the serum does not increase [11, 13, 14]. Studies have found that full-term neonates born via elective CS have significantly lower catecholamine levels and changes in lung function than those born vaginally [14].

In the cohort study, the rate of antepartum respiratory distress prophylaxis was similar in both study groups, both

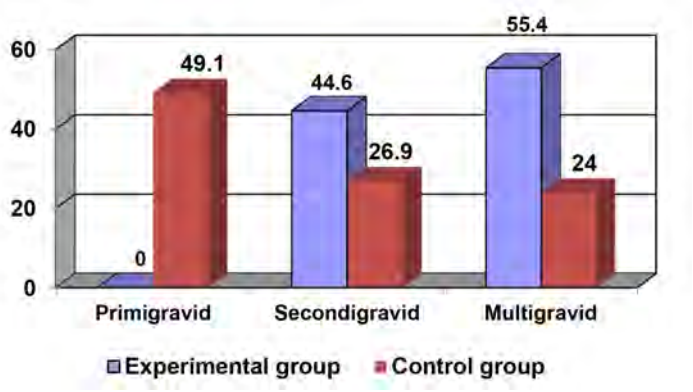

Fig. 1. Distribution of women in the study groups (%) according to gestation.

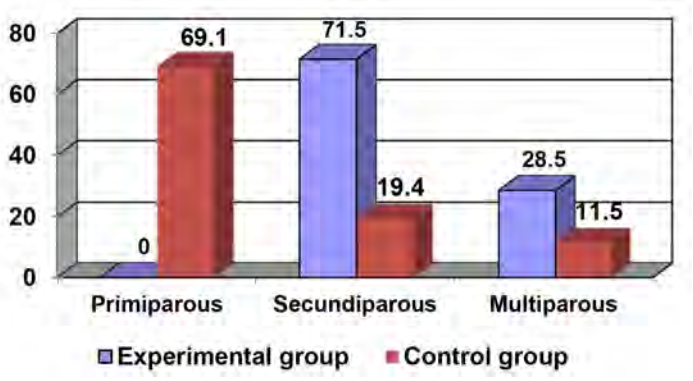

Fig. 2. Distribution of women in the study groups (%) according to parity.

overall (4.6% in the EG and 9.7% in the CG, respectively; p > 0.05) and by method: complete prophylaxis with 4 doses (3.4% in the EG and 4.0% in the CG, respectively; p > 0.05), incomplete prophylaxis with 3 doses (0% in the EG and 1.7% in the CG, respectively), incomplete 2-dose prophylaxis (0.6% in the EG and 1.1% in the CG, respectively; p > 0.05) and incomplete 1-dose prophylaxis (0.6% in the EG and 2.9% in the CG, respectively; p > 0.05) (Figure 3). According to literature data, women with two or more pre-

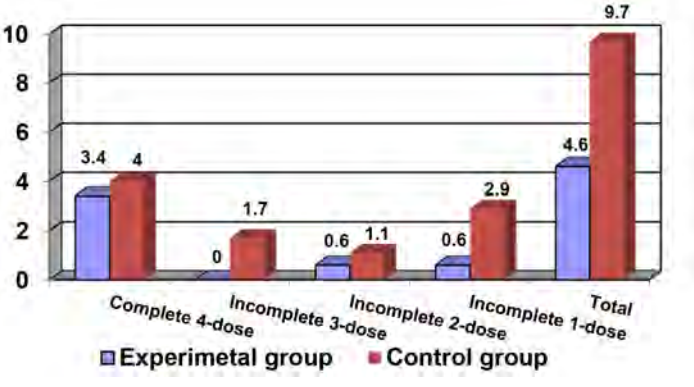

Fig. 3. Prophylaxis rates of antepartum respiratory distress (%) in pregnant women from the study groups.

vious CDs were scheduled for CS between 37 and 38 weeks of gestation. This tactic aims to reduce the risk of uterine rupture associated with spontaneous labor in women with post-cesarean scars [1, 16, 17]. In general, the gestational age of the fetus at birth is lower in pregnant women with multiple CSs. The higher the number of previous CDs, the higher the chances of a preterm birth during the next CS [1].

The newborns delivered by women with a previous CS were associated with a significantly increased risk of NICU admission (adjusted OR 1.31; 95% CI 1.23, 1.39; $p < 0.001$), neonatal loss (adjusted OR 1.19; 95% CI 1.12, 1.26; $p < 0.001$) and preterm birth (adjusted OR 1.07; 95% CI 1.01, 1.14; $p < 0.05$) [7].

A retrospective cohort study conducted on 672 singleton pregnant women without congenital anomalies (343 women delivered by planned repeat cesarean sections and 329 women delivered per *vias naturalis*) examined newborn data. Newborns delivered by repeat CS without labor had higher rates of NICU admission, primarily for hypoglycemia, compared to the group of newborns delivered vaginally (9.3% and 4.9%, respectively; $p = 0.025$), higher rates of oxygen supplementation for resuscitation in the delivery room (41.5% and 23.2%, respectively; $p < 0.01$) and in the NICU (5.8% and 2.4%, respectively; $p < 0.028$). Neonates born by elective repeat CS without labor demonstrated significantly higher rates of NICU admission [13].

In the study, the termination of the current pregnancy by CS in the general study group according to gestational age was as follows: 5.4% at 35 + 0 – 36 + 6 weeks of gestation, 7.4% at 3 7 + 0 – 37 + 6 weeks of gestation, 17.6% at 38 + 0 – 38 + 6 weeks of gestation, 42.0% at 39 + 0 – 39 + 6 weeks of gestation, 18.5% at 40 + 0 – 40 + 6 weeks of gestation, and 9.1% at ≥41 weeks of gestation.

This indicator was almost similar in both study groups: at 35 + 0 – 36 + 6 weeks of gestation (4.5% in the EG and 6.3% in the CG, respectively; $p > 0.05$), at 37 + 0 – 37 + 6 weeks of gestation (5.6% in the EG and 9.1% in the CG, respectively; $p > 0.05$) and at 39 + 0 – 39 + 6 weeks of gestation (21.5% in the EG and 13.7% in the CG, respectively; $p > 0.05$). In the EG, the termination rate of the current pregnancy by CS was statistically significantly higher at 39 + 0 – 39 + 6 weeks of gestation (56.5% and 27.4%, respectively; $p < 0.001$), and in the CG, it was statistically significantly higher at 40 + 0 – 40 + 6 weeks of gestation (25.7% and 11.3%, respectively; $p < 0.001$) and at 41 weeks of gestation or more (17.7% and 0.6%, respectively; $p < 0.001$) (figure 4).

Thus, in the CG, there is a tendency to increase CD at the gestational age of 37 + 0 – 37 + 6 weeks, and in the EG, there is a tendency to increase CD at 38 + 0 – 38 + 6 and 39 + 0 – 39 + 6 weeks of gestation. The medical indications for more severe CS in women with primary CS may explain these findings. Evaluation of medical indications for CS in pregnant women in the study revealed that uterine scarring (57.6% and 0%, respectively; $p < 0.001$), suspected uterine scar defect (16.9% and 0%, respectively; $p < 0.001$) and the onset of labor (23.2% and 2.3%, respectively; $p < 0.001$) were statistically significantly more common in the EG.

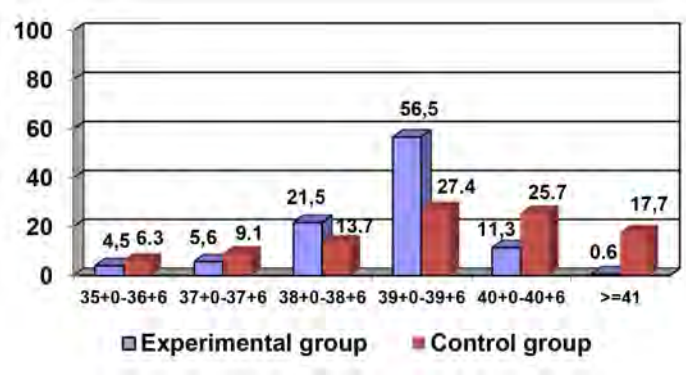

Fig. 4. The term for termination of the pregnancy by cesarean section (%) in pregnant women in the study groups.

The most common indications for CS in the CG were as follows: premature detachment of normally inserted placenta (5.1% and 0.6%, respectively; $p < 0.05$), pelvic presentation (25.1% and 5.6%, respectively; $p < 0.001$), post-term pregnancy (2.9% and 0%, respectively; $p < 0.05$), clinically narrow pelvis (7.4% and 0%, respectively; $p < 0.001$), primary dynamic uterine dystocia (12.0% and 1.7%, respectively; $p < 0.001$), secondary dynamic uterine dystocia (9.1% and 0%, respectively; $p < 0.001$), acute fetal distress during labor (12.0% and 0 .6%, respectively; $p < 0.001$), failure to induce labor with prostaglandins (10.3% and 0%, respectively; $p < 0.001$), extragenital diseases (7.4% and 1.7%, respectively; $p < 0.05$), complicated obstetric history (in vitro fertilization) (9.1% and 1.1%, respectively; $p < 0.01$), severe preeclampsia (4.6% and 0%, respectively; $p < 0.01$) and other indications (10.9% and 0.6%, respectively; $p < 0.001$) (table 1). In some cases, several medical indications for CS persisted in the same pregnant woman.

A previous CS is the most common indication for the next CS. A cross-sectional retrospective study performed on a group of 602 women with CD found that repeat CS (48.5%), followed by fetal distress (18.9%), oligohydramnios (6.6%), cephalopelvic disproportion (6.5%), failure of labor (5.6%) and malpresentation (3.8%) were the most common major indications for CS [10].

A previous CS is associated with a higher risk of preterm birth in subsequent pregnancies, which is due to an increased risk of subsequent preterm births through unplanned or emergency CS. The risk of preterm birth among women with an unplanned CS after a previous CS increased 5-fold (adjusted OR 5.53; 95% CI 5.25–5.83), compared to women with a planned CS or vaginal delivery [18].

A recent study conducted on a group of 100 women with a singleton pregnancy and a previous CS found that in 74% of cases repeat CS (elective or emergency) was performed at a fetal gestational age of 37 + 0 – 37 + 6 weeks; in 18% of cases, the gestational age of the fetus was 38 + 0 – 38 + 6 weeks. CS was not performed on pregnant women whose

fetus had a gestational age greater than 40 weeks. Scholars have noted that elective CS is most commonly performed 2 weeks before the expected date of birth [5]. CSs performed before 39 weeks of gestation may increase the newborn's risk of respiratory disorders and hypoglycemia [9].

Table 1. Medical indications for cesarean section in pregnant women in the study groups

Parameter	EG		CG		P
	abs.	%	abs.	%	
Uterine scarring (planned)	102	57.6	0	0	< 0.001
Suspected uterine scar defect	30	16.9	0	0	< 0.001
Premature detachment of the normally inserted placenta	1	0.6	9	5.1	< 0.05
Placenta previa	3	1.7	4	2.3	NS
Pelvic presentation	10	5.6	44	25.1	< 0.001
Abnormal fetal position	1	0.6	1	0.6	NS
Post-term pregnancy	0	0	5	2.9	< 0.05
Clinically narrow pelvis	0	0	13	7.4	< 0.001
Anatomically narrow pelvis	3	1.7	5	2.9	NS
Dynamic uterine dystocia (primary)	3	1.7	21	12.0	< 0.001
Dynamic uterine dystocia (secondary)	0	0	16	9.1	< 0.001
Acute fetal distress during labor	1	0.6	21	12.0	< 0.001
Intrauterine growth retardation of the fetus	3	1.7	8	4.6	NS
Premature rupture of the amniotic sac	25	14.1	29	16.6	NS
Failure to induce labor with prostaglandins	0	0	18	10.3	< 0.001
Transverse situs	1	0.6	0	0	NS
Extragenital disease	3	1.7	13	7.4	< 0.05
Complicated obstetric history (*in vitro* fertilization)	2	1.1	16	9.1	< 0.01
Isthmic-cervical insufficiency (cervical cerclage)	0	0	1	0.6	NS
Severe preeclampsia	0	0	8	4.6	< 0.01
Obstetric suction ventouse (cupping) failure	0	0	1	0.6	NS
Deflected presentation	1	0.6	3	1.7	NS
Onset of labor	41	23.2	4	2.3	< 0.001
Other	1	0.6	19	10.9	< 0.001

Note: *EG – experimental group, CG – control group, NS – statistically insignificant relationship, P – probability.*

There are many reasons to perform a CS. Most CSs are performed for maternal or fetal medical reasons; however, there has been an increase in the number of women requesting a CS without a medical indication [4, 11]. The literature shows that the main indications for CS (about 85% of cases) are previous CD (42.8%), failure to progress during labor, suspected fetal distress (15.5%), fetal malpresentation, and dystocia. In addition, the NICU admission rate is higher in emergency CS cases (fetal distress, neonatal sepsis) [1, 4, 11, 12].

Although emergency CSs are intended to reduce maternal and neonatal mortality and morbidity, CD can be associated with negative short-term and long-term consequences [11]. In the study, the analysis of deliveries revealed that emergency CS in pregnancy (33 - 18.9% and 16 - 9.0%, respectively; $p < 0.01$) and emergency CS during labor (106 - 60.6% and 54 - 30.5%, respectively; $p < 0.001$) were performed statistically significantly more frequently in the CG, while planned CS during pregnancy (107 – 60.5% and 36 – 20.6%, respectively; $p < 0.001$) was performed significantly more frequently in the EG (figure 5).

These results are similar to those of a recent study, in which 63.6% of cases were emergency CSs and only 36.4% of cases were planned CSs [10].

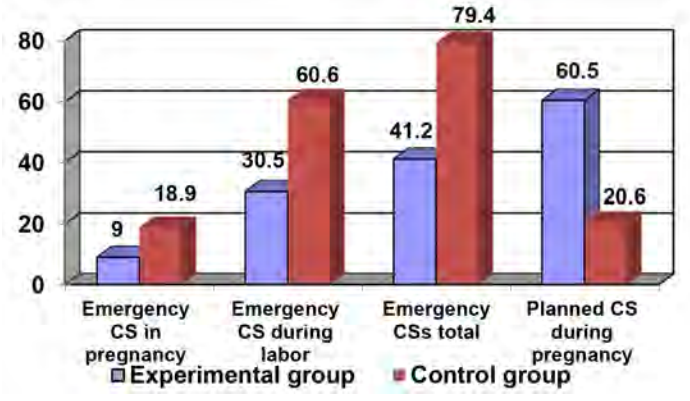

Fig. 5. Delivery types (%) in pregnant women from the study groups.

In the study, the rate of full-term neonates was statistically significantly higher in the EG (171 – 97.1% and 146 – 83.4%, respectively; $p < 0.001$), the rate of post-term neonates was statistically significantly higher in women from the CG (21 – 12.0%; $p < 0.001$), and the rate of premature newborns was similar in both study groups (6 – 2.9% in the EG and 8 – 4.6% in the CG, respectively; $p > 0.05$) (figure 6).

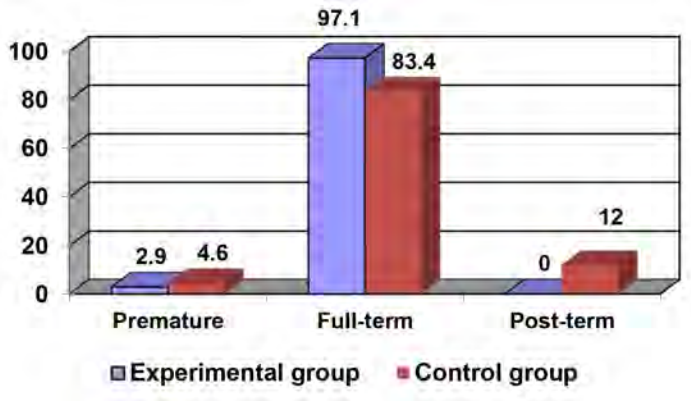

Fig. 6. The rate of premature, full-term and post-term newborns (%) in pregnant women in the study groups.

The newborns in both study groups did not differ in terms of sex, mass, and length. 90 (50.8%) newborns in the EG and 80 (45.7%) newborns in the CG ($p > 0.05$) were female; 87 (49.2%) newborns in the EG and 95 (54.3%) newborns in the CG ($p > 0.05$) were male.

The average mass of the newborns was 3435.37±29.8 g in the EG and 3431.6±38.1 g in the CG ($p > 0.05$), and the average length of the newborns was 52.19±0.1 cm and 52.25±0.2 cm, respectively ($p > 0.05$). Similar results have been reported in other studies. In women with a CS, the average mass of the newborn was 3467.40±752.51 g, and the average length of the newborn was 51.88±4.21 cm. In women with 2, 3, 4, and more CSs, these parameters were as follows: 3384.42±730.29 g and 51.09±4.18 cm, 3276.66±833.60 g and 50.20±5.86 cm, 3095.71±726.66 g and 50.00±3.92 cm ($p > 0.05$) [1].

The study groups were similar ($p > 0.05$) and according to different groups of mass and length of newborns: 1 (0.6%) newborn from the EG and 4 (2.3%) newborns from the CG had a body mass between 1000-1999 g, 22 (12.4%) newborns from the EG and 24 (13.7%) newborns from the CG had a body mass between 2000-2999 g, 154 (87.0%) newborns in the EG and 147 (84.0%) newborns in the CG had a body mass range of 3000-3999 g, 3 (1.7%) newborns in the EG and 6 (3.4%) newborns from the CG had a body length between 44-46 cm, 24 (13.6%) newborns from the EG and 30 (17.1%) newborns from the CG had a body length between 47-50 cm, 150 (84.7%) newborns from the EG and 139 (79.4%) newborns from the CG had a body length > 50 cm.

The mean values of the weight and length of the newborns were also similar according to the number of previous CSs: 3431.60±38.1 g in women with 1 CS, 3412.43±33.6 g in women with 2 CSs and 3522.16±63.8 g in women with 3-4 CSs ($p < 0.05$), 52.25±0.2 cm in women with 1 CS, 52.18±0.2 cm in women with 2 CSs and 52.22±0.4 cm in women with 3-4 CSs ($p < 0.05$).

The frequency of children with low body mass (≤2500 g) had an increasing tendency in the CG (10 – 5.7% and 4 – 2.3%, respectively; $p > 0.05$), but this difference did not reach any statistical certainty.

The Apgar score values at 1 minute after birth equal to 8-10 points (171 – 96.6% and 140 – 80.0%, respectively; $p < 0.001$) were statistically significantly more frequent in the EG, the Apgar score values at 1 minute after birth equal to 6-7 points (29 – 17.1% and 6 – 3.4%, respectively; $p < 0.001$) and 4-5 points (5 – 1.7% and 0 – 0%, respectively; $p < 0.05$) were statistically significantly more frequent in the CG; and the Apgar score values 1 minute after birth equal to 1-3 points (0 – 0% in the EG and 1 – 0.6% in the CG; $p>0.05$) were similar in both study groups (figure 7).

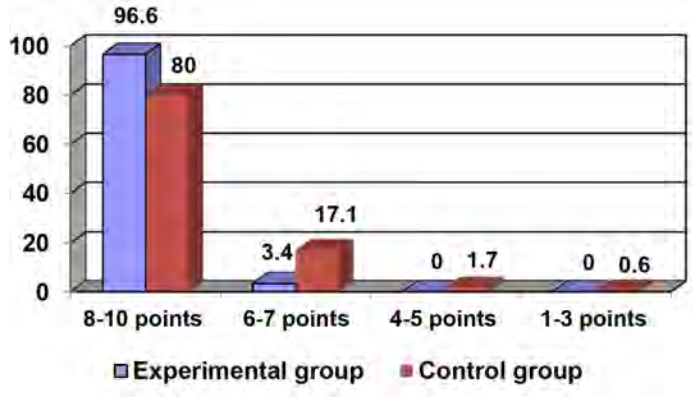

Fig. 7. The Apgar score values at 1 minute after birth (%) in newborns in the study groups.

The Apgar score values at 5 minutes after birth equal to 8-10 points (174 – 98.3% and 157 – 89.7%, respectively; $p < 0.001$) were statistically significantly more frequent in the EG; the Apgar score values at 5 minutes after birth equal to 6-7 points (17 – 9.7% and 3 – 1.7%, respectively; $p < 0.01$) were statistically significantly more frequent in the CG; and the Apgar score values at 5 minutes after birth equal to 4-5 points (0 – 0% in the EG and 1 – 0.6% in the CG; $p > 0.05$) were similar in both study groups (figure 8).

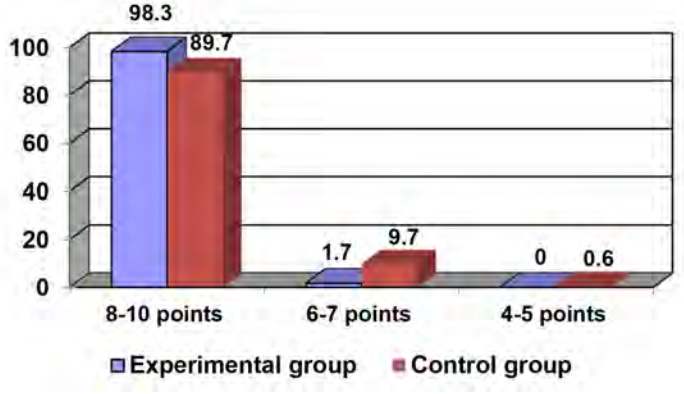

Fig. 8. The Apgar score values at 5 minutes after birth (%) in newborns in the study groups.

Analysis of the Apgar score at 1 minute and 5 minutes after birth according to the presence or absence of acute fetal distress during labor in pregnant women in the CG

found that the Apgar score values 1 minute after birth equal to 8-10 points (130 – 84.4% and 10 – 47.6%, respectively; $p < 0.001$) were statistically significantly more frequent in pregnant women without acute fetal distress during labor, and the Apgar score values 1 minute after birth equal to 1-7 points (11 – 52.4% and 24 – 15.6%, respectively; $p < 0.001$) were statistically significantly more frequent in pregnant women with acute fetal distress during labor.

Similar results were found in the Apgar score at 5 minutes after birth. The Apgar score values 5 minutes after birth equal to 8-10 points (142 – 92.2% and 15 – 71.4%, respectively; $p < 0.05$) were statistically significantly more frequent in pregnant women without acute fetal distress during labor, and the Apgar score values 5 minutes after birth equal to 1-7 points (6 – 28.6% and 12 – 7.8%, respectively; $p < 0.05$) were statistically significantly more frequent in pregnant women with acute fetal distress during labor.

Some studies did not identify significant increased risks of stillbirth, early neonatal death, perinatal death, low Apgar score, and low birth weight between women with and without prior CSs [7]. A recent study, carried out on a group of 655 pregnant women with at least one CS and with singleton pregnancies, found no significant differences in the mean values of the Apgar score at 1 minute and 5 minutes after birth according to the number of CSs: 9.01±1.07 points and 9.65±0.68 points in women with primary CS, 9.05±1.11 points and 9.60±0.84 points in women with 2 previous Cs, 8.60±2.03 points and 9.20±1.86 points in women with 3 previous CSs, 9.14±0.69 points and 9.43±0.53 points in women with 4 or more previous CSs [1].

A systematic literature review revealed a statistically significant difference in the Apgar score <5 points at 5 minutes after birth between the group of women with 1 CS and the groups of women with 2 CSs (9.39% and 2.11%, respectively; $p < 0.001$), 3 CSs (9.39% and 2.18%, respectively; $p < 0.001$), 4 and more CSs (9.39% and 4.49%, respectively; $p < 0.01$) [2].

The evaluation of some parameters according to the delivery type found that in pregnant women with emergency CSs, an increased number of newborns with low body mass (≤2500 g) was determined (10 – 4.8% and 4 – 2.8%, respectively; $p > 0.05$), an increased Apgar score rate equal to 1-7 points at 5 minutes after birth (16 – 7.7% and 5 – 3.5%, respectively; $p > 0.05$) and a statistically significant increase in the rate of the Apgar score equal to 1-7 points at 1 minute after birth (35 – 16.7% and 6 – 4.2%, respectively; $p < 0.001$).

The discharge rate of neonates in the study was higher in the EG (165 – 93.2% and 136 – 77.7%, respectively; $p < 0.001$), and the transfer rate to stage II was higher in the CG (39 – 22.3% and 12 – 6.8%, respectively; $p < 0.001$). The frequency of neonatal trauma (scalpel injury) was low and similar in both study groups: 0 (0%) in the EG and 3 (1.7%) in the CG ($p > 0.05$).

In general, the literature suggests that the mode and timing of delivery have a greater impact on adverse neonatal outcomes than the number of previous CSs [2].

Conclusions

(1) The termination of the pregnancy by CS at 39 + 0 – 39 + 6 weeks of gestation (56.5% and 27.4%, respectively; $p < 0.001$) was statistically significantly more frequent in the EG, and at 40 + 0 – 40 + 6 weeks of gestation (25.7% and 11.3%, respectively; $p < 0.001$) and at 41 weeks of gestation or more (17.7% and 0.6%, respectively; $p < 0.001$) was statistically significantly more common in the CG.

(2) Analysis of deliveries revealed that emergency CS in pregnancy (18.9% and 9.0%, respectively; $p < 0.01$) and emergency CS during labor (60.6% and 30.5%, respectively; $p < 0.001$) were significantly statistically more frequent in the CG, and planned CS in pregnancy (60.5% and 20.6%, respectively; $p < 0.001$) was statistically significantly more frequent in the EG.

(3) The rate of full-term neonates was statistically significantly higher in women from the EG (97.1% and 83.4%, respectively; $p < 0.001$), and the rate of post-term neonates was statistically significantly higher in women from the CG (12.0% and 0%, respectively; $p < 0.001$).

(4) Neonates in both study groups were similar in terms of sex, mass, and length. However, the Apgar score values equal to 8-10 points at 1 minute after birth (96.6% and 80.0%, respectively; $p < 0.001$) and at 5 minutes after birth (98.3% and 89.7%, respectively; $p < 0.001$) were statistically significantly more frequent in the EG; the Apgar score values equal to 6-7 points at 1 minute after birth (17.1% and 3.4%, respectively; $p < 0.001$) and at 5 minutes after birth (9.7% and 1.7%, respectively; $p < 0.01$) and the Apgar score values equal to 4-5 points at 1 minute after birth (1.7% and 0%, respectively; $p < 0.05$) were statistically significantly more frequent in the CG.

Abbreviations

CD – cesarean delivery; CDs – cesarean deliveries; CI – confidence interval; CS – cesarean section; CSs – cesarean sections; CG – control group; EG – experimental group; NICU – neonatal intensive care unit; OR – odds ratio; SPSS – Statistical Package for the Social Science.

Declaration of conflicting interests

The author declares the absence of any conflict of interest in the elaboration of this article.

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RESEARCH ARTICLE

Risk management – component part of the quality assurance system of pharmaceutical care

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What is not yet known on the issue addressed in the submitted manuscript

Despite the significant amount of research in the field of risk management, many important issues have yet to be resolved. Until now, in the Republic of Moldova, there is no consensus regarding the essence and content of risk from pharmaceutical activity, the criteria, and indicators for risk assessment are not justified, and there is no scientifically based classification of risk factors, especially the risk factors present in community pharmacies.

The research hypothesis

Demonstrating the usefulness of modern risk management strategies and assessing the impact of risk management to optimize pharmacy activities and increase their performance.

The novelty added by manuscript to the already published scientific literature

This research represents a scientific approach to the application of modern risk management methods in community pharmacy and may be of use to pharmaceutical specialists, community pharmacists, and especially pharmacist managers. Based on the results obtained from the experiment, by highlighting the pharmaceutical activities, during which risks of errors may occur, the causes that can lead to errors in the pharmacy were identified.

Abstract

Introduction. In the pharmaceutical field, the quality management is a priority and the risk management is a valuable component of an effective quality system. It involves anticipating hazards and controlling risk through a process of risk awareness, reduction, and review. The aim of this paper was to reveal the usefulness of modern risk management strategies and to assess the impact of risk management in the provision of quality services by community pharmacies.

Material and methods. The causes that can lead to medication errors in community pharmacies were identified by applying the CNAM Method combined with the Delphi Technique, later the risks were categorized by the Ishikawa diagram, analyzed and evaluated by applying the expert analysis method (MAE) in risk assessment, graphically represented by the Matrix risks and ranked, highlighting pharmacy activities during which medication errors may occur.

Results. The risk factor was calculated for 56 potential risks that can cause medication errors, of which 8 for the activity of ordering medicines, 8 potential risks for the activity of receiving products, 6 risks for the activity of storing products, 17 risks for the preparation of drugs and 17 risks for drug dispensing activity. Applying the MAE method in risk assessment, risk occurrence probability and outcome impact values were obtained for each risk. The potential risks of error were graphically represented using the Risk Matrix. Thus, the following activities with a major level of risk were highlighted, for which urgent measures to minimize the impact are required: illegible writing in prescriptions (15.5), fatigue of pharmaceutical staff (15.48), overwork/multitasking (14.99), prescriptions containing errors (14.26), insufficient staff knowledge (13.81), ordering inappropriate quantities of products in pharmacies (13.59), incomplete prescriptions (12.86) and similar packaging of medicines (12.63).

Conclusions. The results of this paper provide the basis for further research in order to develop a Risk Management Plan in community pharmacy. The causes that can lead to errors in the pharmacy have been identified, by highlighting pharmaceutical activities, during which risks of errors may occur. The work has practical use, and the research results can be applied by pharmacies, contributing to the improvement of their performance.

Key words: risk management, community pharmacy, risk assessment, medication errors, impact.

Introduction

As in any human activity, the pharmaceutical activity faces a lot of classic and emerging risks. Numerous organizations and companies in the pharmaceutical field, national and international, are concerned with the issue of risks, risk management being a valuable component of an effective quality system.

Modern risk identification methods have developed from techniques already tested and applied in risk management. For example, the Risk Score Method has its origins in balanced scorecard methods used to quantify the performance of organizations, while the process mapping methodology developed from the field of quality management and is based on techniques from the field of flow charting [1]. Any organization develops on the basis of a variety of processes. By representing these processes in the form of a diagram - their mapping - risk management tries to improve the organization's activity.

This method has its origins in quality management during the process reorganization in the 80's and 90's in the United States of America and Europe. The current's slogan was *„if it ain't broke, fix it*!". In this way, even if an organization operates efficiently and effectively, it can benefit from a detailed analysis of processes in order to improve them.

Since then, risk assessment and treatment methods and techniques have developed, covering almost all areas [2].

In 2009, good practice in the field of risk is included in the ISO 31000:2009 standard, which tries to standardize the terminology and concepts in the field of risk, placing a special emphasis on the organizational context, as well as on the description of a risk management process, a process that can be applied only integrated within organizational processes and practices. Subsequently, the risk assessment techniques available at the time are presented in ISO 31010:2010 [3, 4]. ISO 9001:2015 does not require a risk management process, whereas ISO 14001 does. If the management system is integrated, then at the level of this system there must be a risk management process that will apply to both quality and environment. The same requirement is imposed by ISO 45001:2018 [5].

The integration of risk management at the level of organizational processes and practices ensures the following advantages:

- increasing effectiveness and efficiency in achieving objectives;
- increasing confidence and taking appropriate responsibility for the effective application of risk and opportunity thinking;
- creating a safe working environment for pharmacists and patients;
- control of all processes within the organization.

The great advantage of the ISO 9001:2015 standard is represented by the description of all the stages of applying a risk management process, namely thinking based on risk and opportunity [6]. Omitting one or more stages in this process leads us to a formal approach that has nothing to do with the future, nor with a proactive management system that ensures the prevention of the materialization of risks and their negative effects, in other words, do we prevent it instead of evaluating managers by results, not by effort [7].

Despite a significant amount of research in the field of risk management, many important issues have yet to be resolved. Until now, in the Republic of Moldova, there is no consensus regarding the essence and content of risk from pharmaceutical activity, the criteria, and indicators for risk assessment are not justified, and there is no scientifically based classification of risk factors, especially the risk factors present in community pharmacies.

Another problem is to achieve a common approach to the application of the concept of risk management among different stakeholders, because each stakeholder perceives the possibility of the occurrence of other harmful aspects perceives differently the probability of occurrence of each harmful phenomenon and can attribute different impact to each such factor of risk. In the pharmaceutical field, despite the diversity of stakeholders, from patients and doctors to the state and industry, patient protection through quality risk management must be considered of utmost importance [8].

This research represents a scientific approach to the application of modern risk management methods in community pharmacy and may be of use to pharmaceutical specialists, community pharmacists, and especially pharmacist managers.

The purpose of the study was to research and demonstrate the usefulness of modern risk management strategies and to evaluate the impact of risk management in the provision of quality services by community pharmacies.

Material and methods

Risk management provides scientific and practical support for decision-making. It provides documented and reproducible methods for implementing the quality risk management process based on current knowledge of risk probability, impact, and exposure [9].

The purpose of risk management is not to avoid risks at all costs, reducing risks to zero, in most cases being impossible and rarely can be done at reasonable cost. Therefore, accepting a certain degree of risk is sometimes necessary within the organization. We are talking here about „risk appetite" which according to ISO 31000 (risk management standard) is „the amount and type of risk that an organization is prepared to pursue, retain or assume" [10].

Risk can be identified and assessed using risk management tools. Risk identification and assessment methods can be used in combination with statistical tools [11]. Combined use provides the flexibility that can facilitate the application of quality risk management principles [12]. By applying modern risk management methods, this research presents the risks that may arise during the exercise of pharmaceutical activity within the community pharmacy. The modern risk management methods applied in this research are the following: the CNAM (Conservatoire national des arts et métiers) method combined with the Delphi Technique, the Ishikawa Diagram, the analysis method of

MAE experts in risk assessment, the Risk Matrix and the risk ranking method.

The principle of the CNAM method consists in identifying all the risks that can influence the activity of employees [13, 14]. A group of 10 pharmacists was given a checklist, which was discussed in 3 rounds, applying the Delphi Technique. The checklist contains a series of risks and a question that must be answered with YES or NO: „Can the presented risks negatively influence the activity of the pharmacist and increase the incidence of medication errors?". If the treated problem indicates the existence of a new risk, regardless of whether it is considered important or not, real or assumed, it is entered in a special form „Identification of new risks" [15].

After all the check-lists were completed, the identification form was resumed, regroupings were made and it was completed with the risks that were not initially identified during the investigation. Thus, 56 potential risks that can cause medication errors in community pharmacies were identified.

To sort all identified risks into categories, the Ishikawa diagram was used, this being an important method used in quality management [16]. The Ishikawa diagram was applied in this research to graphically illustrate the causes that can generate errors in the preparation, ordering, receiving, storage, and dispensing of medicines.

To assess the level of probability and impact of each identified risk, the expert analysis method (MAE) in risk assessment was used [17]. The method was based on surveying several independent experts to assess the level of risk.

Assessing the probability of occurrence of risks involves determining or estimating a probability. A possible method of estimating the probability of the materialization of the risk is the calculation of the frequency of the materialization of some risks in the past, table 1.

The assessment of the impact on the objectives/activities in case of materialization of risks was carried out according to the Impact Assessment Scale, presented in table 2.

Afterwards follows the stage in which the risk exposure (risk factor), which is a combination of probability and impact, being a two-dimensional, matrix-type indicator [18], is set up. It can be represented in several forms, depending on the model adopted to estimate the probability and impact of materializing the risk. In this research we used the Risk Matrix, for a graphical visualization of the results. Based on the calculated risk factor, the risks can be ranked. The ranking of risks is used to establish priorities in order to plan preventive actions. The risk that obtained the highest value of the risk factor is entered first on the document used for ranking [19].

The risk matrix (figure 1), allows a qualitative assessment and facilitates the grouping of risks according to the impact on the OX axis and according to the probability of occurrence on the OY axis. The matrix graphically highlights minor risks, moderate risks and major risks [20].

The interaction between the level of probability and the impact associated with a risk generates the following priority categories.

- *major risks (Priority 1)* **–** require attention to address/implement urgent and appropriate prevention/control measures;
- *moderate risks (Priority 2)* **–** can be monitored or controlled, by increasing the effectiveness of existing measures or, as the case may be, establishing additional prevention / control measures;
- *minor risks (Priority 3)* **–** can be tolerated and will be considered inherent in the activities against which additional prevention/control measures should not be established, but only the application of the existing ones [21].

According to the results of the priority categories, risk response actions can be developed according to the following classification:

- *risk acceptance (tolerance)* – recommended for low exposure risks and does not require risk control measures to be taken;
- *risk monitoring* – acceptance of the risk, provided that it is kept under permanent supervision. The monitored parameter is the probability, because the monitoring strategy is applied in the case of risks with a significant impact, but with a low probability of occurrence. Monitoring implies a postponement of taking control measures, until the moment when the circumstances determine an increase in the probability of occurrence of the risks subject to this type of treatment;
- *risk avoidance (elimination)* – elimination of the activities that generate the risks;
- *risk transfer (outsourcing)* – entrusting risk management to a third party that has the necessary capacity to manage this risk;
- *treating (mitigating) risks* – implementing managerial internal control tools/measures to keep risks within acceptable (tolerable) limits [22, 23].

Results

By applying the CNAM Method combined with the Delphi Technique, a number of 56 potential risks, that can influence the occurrence of medication errors, were identified. Because of the multitude of causes that can lead to errors, the potential risks of errors were sorted by applying the 5-step Ishikawa Diagram, figure 2.

The next stage of risk analysis is the assessment of the degree of its influence on the pharmacist's activity in community pharmacies. The estimation of the probability of materialization and the impact was carried out by the expert analysis method (MAE) in risk assessment. The concrete criteria that served as a basis for the selection of experts were: place of work, position held, work experience, studies, scientific title, qualification category, approximate number of scientific articles held in the field of pharmaceutical system activity. In the pre-selection process, 21 specialists were trained, 14 of whom were the staff of the Faculty of Pharmacy of *Nicolae Testemitanu* State University of Medicine and Pharmacy, 2 experts were selected from the Medi-

cines and Medical Devices Agency, 3 from community pharmacies, and 2 experts from hospital pharmacies, figure 3.

The results of the risk assessment by experts as well as the amount of risk exposure (risk factor) at various stages of drug circulation are presented in tables 3-7. Risk factors with major values are marked in red, and those with moderate values - with yellow corresponding to the risk matrix.

The value of each risk factor determines the levels of intervention priorities for risk removal, described in Table 8.

Discussion

In total, the risk factor was calculated for a number of 56 potential risk factors that can cause medication errors, categorized in 5 stages, of which 8 for the activity of ordering medicines (grouped into 3 categories: order, personnel, suppliers), 8 potential risks for the product reception activity (grouped into 4 categories: qualitative reception, reception in terms of value, personnel, quantitative reception), 6 risks for the activity of storing products in the pharmacy (grouped into 3 categories: personnel, environment, equipment), 17 causes of errors for the drug preparation activity (grouped into 6 categories: personnel, methods, materials, measurements/calculations, environment, equipment) and 17 causes of errors for the activity of dispensing medicinal products (grouped into 5 categories: personnel, names of medicines, packaging of medicinal forms, medical prescriptions, counseling of patients).

Based on the calculated risk factor value, the risks were ordered into major level risks (Intervention Priority 1), moderate level risks (Intervention Priority 2) and minor level risks (Intervention Priority 3). Thus, for the stage of ordering the medicines, 7 moderate risks (priority 2) and 1 major risk (priority 1) were detected, for the stage of receiving the medicines there are 7 moderate risks (priority 2) and 1 major risk (priority 1), for the drug storage stage there are 6 moderate risks (priority 2), for the drug preparation stage 14 moderate risks (priority 1) and 3 major risks (priority 1) were calculated and the drug release stage contains 9 moderate risks (priority 2) and most major risks (priority 1) - 8. In total, in the 5 stages analyzed, no minor level risk (priority 3), 43 moderate level risks (priority 2) and 13 major level risks (priority 1) were detected.

All moderate and major risks will be included in the „Risk Assessment Sheet", indicating: Preventive actions used; Risk evaluation; Planned actions to reduce risk, in descending order, the first being the risks that obtained the highest value of the risk factor.

Following the research carried out, the following activities with a major level of risk (priority 1) were highlighted, for which urgent measures to minimize the impact are required: illegible writing in medical prescriptions (15.5), fatigue of pharmaceutical staff (15.48), overwork/multitasking (14.99), prescriptions containing errors (14.26), insufficient staff knowledge (13.81), ordering inappropriate quantities of products in pharmacies (13.59), incomplete prescriptions (12.86), similar drug packaging (12.63) and insufficient staff concentration (12.18).

Conclusions

Risk management, as a component of an effective quality system, is an activity that integrates the identification, analysis, assessment of risk and the development of their management strategies. By applying the CNAM Method and the Delphi Technique, 56 potential risks that can cause medication errors were identified, which were later categorized using the Ishikawa Diagram in 5 stages, of which 8 for the activity of ordering medicines (grouped into 3 categories: order, personnel, suppliers), 8 potential risks for the product reception activity (grouped into 4 categories: qualitative reception, reception in terms of value, personnel, quantitative reception), 6 risks for the activity of storing products in the pharmacy (grouped into 3 categories: personnel, environment, equipment), 17 causes of errors for the drug preparation activity (grouped into 6 categories: personnel, methods, materials, measurements/calculations, environment, equipment) and 17 causes of errors for the activity of dispensing medicinal products (grouped into 5 categories: personnel, names of medicines, packaging of medicinal forms, medical prescriptions, counseling of patients).

All the risks that can generate medication errors in community pharmacies were researched through the expert analysis method (MAE) in risk assessment and values of the probability of occurrence of risks and the impact of the result were obtained for each risk. The potential risks of error were graphically represented using the Risk Matrix and then ranked to be entered in the Risk Assessment Sheet. Thus, the following activities were highlighted with a major high level of risk (priority 1), for which urgent measures to minimize the impact are required: illegible writing in medical prescriptions (15.5), fatigue of pharmaceutical staff (15.48), overwork/multitasking (14.99), prescriptions containing errors (14.26), insufficient staff knowledge (13.81), ordering inappropriate quantities of products in pharmacies (13.59), incomplete prescriptions (12.86), similar drug packaging (12.63) and insufficient staff concentration (12.18).

The results of this work constitute the basis for future research with proposals to reduce the risks of errors in community pharmacy.

In this research, risk management methods were used to optimize pharmacy activities and increase their performance.

In order to ensure the continuity of the chain of ordering-receiving-storage-preparation-dispensing the medicines, and to minimize or prevent the risks that can generate medication errors, we propose to follow the steps:

(1) Make risk management a key element;
(2) Identify risks using a holistic approach;
(3) Set up the risk assessment tools;
(4) Ensure that risk management is an ongoing activity, not a one-off action;
(5) Carry out periodic checks on the actions taken;
(6) Maintain appropriate standards for procedures, duties, responsibilities, etc.

This study presents practical utility, the research results can be applied by pharmacies, and following the key steps mentioned above will contribute to improving performance and modernizing pharmaceutical management.

Declaration of conflict of interest

Authors declare thar there is no conflict of a financial or non-financial nature in connection with research.

Author's contribution

NCB conceived the study, study design, performed the experimental procedures, data collection, analysis and interpretation, drafting the manuscript. NCB, MB, participated in the study design, data collection and helped to draft the manuscript, approved the final version of the manuscript, ready for publication. NCB, SA, MB performed the data collection, helped to draft the manuscript, manuscript preparation. SA, MB participated in the design of the study, revised the manuscript critically, providing important intellectual input, approved the final version of the manuscript.

Table 1. Risk probability assessment scale.

PROBABILITY	1	Rare	It is very unlikely to happen over a long period of time (3 - 5 years); it has not happened so far.
	2	Not likely	It is unlikely to happen over a long period of time (3 - 5 years); it has happened very few times so far.
	3	Possible	It is likely to happen over a medium period of time (1-3 years); it has happened a few times in the last 3 years.
	4	Most likely	It is likely to occur over a short period of time (< 1 year); it has happened a few times in the last year.
	5	Almost sure	It is very likely to happen over a short period of time (< 1 year); it has happened many times in the last year.

Table 2. Risk Impact Assessment scale [17].

IMPACT	1	Insignificant	With very low impact on activities and the achievement of objectives and/or no financial impact.
	2	Minor	With low impact on activities and achievement of objectives and/or with very low financial impact.
	3	Moderate	With medium impact on activities and the achievement of objectives and/or with medium financial impact.
	4	Major	With major impact on the activities and achievement of objectives and/or with major financial impact.
	5	Critical	With a significant impact on activities and the achievement of objectives and/or with a significant financial impact.

Table 3. The results of the application of the expert analysis method (MAE) in risk assessment of the MEDICINE ORDERING STAGE

Activities potential risks/hazards	Risk assessment		
	Probability (1-5)	Impact (1-5)	The value of the risk factor
Supply/Order			
Non-ordering the necessary products	2,75	3,81	10,47
Incorrect performing of stock management	3,00	3,87	11,62
Erroneous order (wrong products, from another manufacturer, another supplier)	2,50	2,75	6,87
Ordering inappropiate quantities of products (too large or too small) in relation to the needs of the pharmacy	3,75	3,62	13,59
Personnel			
Ignorance of the existing stock by the pharmacist	2,50	3,18	7,96
Inattention to the packaging, the differences in concentrations of products etc.	2,50	3,75	9,37
Suppliers			
Non-compliance with contractual obligations by the supplier	2,62	3,25	8,51
Lack of promptness and the quality of the services provided by the deposit	2,00	3,00	6,00

Note: *Red – major level risk factors; Yellow - moderate level risk factors.*

Table 4. The results of the application of the expert analysis method (MAE) in risk assessment of the STAGE ON RECEPTION

Activities potential risks/hazards	Risk assessment		
	Probability (1-5)	Impact (1-5)	The value of the risk factor
Qualitative reception			
Failure to check the apparent defects (ex. broken packaging, damaged blisters etc.)	2,12	3,43	7,28
Not verifying the period of validity of the products	2,75	4,12	11,33
Reception in terms of value			
Failure to check prices and calculations in invoices	2,00	3,37	6,75
Miscalculation of retail prices	1,25	3,25	4,06
Personnel			
Staff inattention/fatigue	3,12	3,75	11,7
Not knowing all pharmaceutical forms	2,75	3,75	10,31
Person receiving the products is involved in several activities at the same time	3,62	3,87	14,00
Quantitative reception			
Omission of the verification procedure of the correspondence of the quantity received with that indicated in the invoice	2,50	3,62	9,06

Note: *Red – major level risk factors; Yellow - moderate level risk factors.*

Table 5. The results of the application of the expert analysis method (MAE) in risk assessment of the MEDICINE STORAGE STAGE

Activities potential risks/hazards	Risk assessment		
	Probability (1-5)	Impact (1-5)	The value of the risk factor
Personnel			
Non-compliance with storage conditions	3,00	3,62	10,87
Non-observance of the arrangement of the products	3,25	3,00	9,75
Environment			
Infringement of the appropriate storage conditions taking into account the environmental factors that can affect the preservation of drugs (temperature, humidity, light, atmospheric air etc.)	2,87	3,75	10,76
Inadequate or insufficiently equipped rooms (lack of cupboards, shelves, safes)	2,25	3,62	8,15
Equipment			
Failure of equipment for ensuring the necessary preservation conditions (e.g. pharmacy display refrigerators etc.)	2,00	3,18	6,36
Failure of appropriate instruments to measure factors that may affect storage and preservation (e.g. thermometers, hygrometers etc.)	2,12	2,62	5,55
Personnel			
Insufficient training/ documentation of personnel	3,25	4,25	13,81
Fatigue	3,87	4,00	15,48
Overwork/multitasking	3,62	3,81	13,80
Insufficient concentration (monotonous work)	2,62	3,37	8,82
Methods			
Inadequate preparation method/ technique	2,50	3,50	8,75
Materials			
Wrong pharmaceutical substances used	2,12	4,12	8,74
Inappropriate quality of substances (expired, inadequately stored, improperly packed etc.)	1,87	3,81	7,12
Erroneous concentrations of substances	2,12	4,12	8,74
Measurements, calculations			
Incorrect weighing	2,50	3,93	9,84
Wrong calculations	2,62	3,93	10,31
Environment			
Lack of cleanliness at the pharmacy workplace	1,62	2,62	4,25
Excessive noise	2,62	2,87	7,53
Interruptions during preparation	2,25	3,25	7,31
Improper arrangement of the space	2,00	3,00	6,00
Equipment			
Defective measuring instruments (balances)	2,12	4,06	8,61
Inaccuracy of measuring instruments	2,00	4,12	8,25
Insufficient equipment (cabinets, utensils, raw materials)	2,37	3,56	8,44

Note: *Red – major level risk factors; Yellow - moderate level risk factors.*

Table 6. The results of the application of the expert analysis method (MAE) in risk assessment of the DRUG PREPARATION STAGE

Activities potential risks/hazards	Risk assessment		
	Probability (1-5)	Impact (1-5)	The value of the risk factor
Personnel			
Insufficient training/ documentation of personnel	3,25	4,25	13,81
Fatigue	3,87	4,00	15,48
Overwork/multitasking	3,62	3,81	13,80
Insufficient concentration (monotonous work)	2,62	3,37	8,82
Methods			
Inadequate preparation method/ technique	2,50	3,50	8,75
Materials			
Wrong pharmaceutical substances used	2,12	4,12	8,74
Inappropriate quality of substances (expired, inadequately stored, improperly packed etc.)	1,87	3,81	7,12
Erroneous concentrations of substances	2,12	4,12	8,74
Measurements, calculations			
Incorrect weighing	2,50	3,93	9,84
Wrong calculations	2,62	3,93	10,31
Environment			
Lack of cleanliness at the pharmacy workplace	1,62	2,62	4,25
Excessive noise	2,62	2,87	7,53
Interruptions during preparation	2,25	3,25	7,31
Improper arrangement of the space	2,00	3,00	6,00
Equipment			
Defective measuring instruments (balances)	2,12	4,06	8,61
Inaccuracy of measuring instruments	2,00	4,12	8,25
Insufficient equipment (cabinets, utensils, raw materials)	2,37	3,56	8,44

Note: *Red – major level risk factors; Yellow - moderate level risk factors.*

Table 7. The results of the application of the expert analysis method (MAE) in risk assessment of the PRODUCTS DISPENSING STAGE

Activities potential risks/hazards	Risk assessment		
	Probability (1-5)	Impact (1-5)	The value of the risk factor
Personnel			
Insufficient training/ documentation of personnel	3,12	4,31	13,44
Fatigue	3,50	3,87	13,56
Overwork/multitasking	3,87	3,87	14,99
Insufficient concentration (monotonous work)	3,25	3,75	12,18
Names of medicines			
Similar trade names of drugs	2,87	3,50	10,04
The packaging of medicinal forms			
Similar packaging	3,37	3,75	12,63
Damaged packaging	2,50	3,50	8,75
Improper packaging that does not allow for proper storage of medicines	2,25	3,75	8,43
Medicines placed in wrong packaging	1,50	3,75	5,62
Medical prescriptions			
Unreadable writing	4,00	3,87	15,5
Incomplete prescriptions	3,43	3,75	12,86
Prescriptions containing correctable/uncorrectable errors	3,68	3,87	14,26
Expired prescriptions	3,25	3,50	11,37
Counterfeit prescriptions	2,62	4,50	11,79
Incorrect prescription form	2,75	3,12	8,59
Counseling patients			
Incorrect information and inaccurate advice	2,62	4,25	11,13
Incorrect advice on how to store medicines at home	2,62	3,87	10,15

Note: *Red – major level risk factors; Yellow - moderate level risk factors*

Table 8. The priority of the intervention against the risk depending on the value of the risk factor.

Level of risk	Intervention priority	Response to risk	
Major level of risk The value of the risk factor (13-25)	Intervention priority 1	*Avoiding, transferring or dealing with risks*	These risks are not tolerable. The head of the entity must focus on the urgent adoption and implementation of appropriate prevention and control measures.
Moderate level of risk The value of the risk factor (5-12)	Intervention priority 2	*Risk monitoring Dealing with risks*	The manager could manage the risks by streamlining and effectively applying existing measures or, as necessary, by adopting additional prevention and control measures.
Minor level of risk The value of the risk factor (1-4)	Intervention priority 3	*Risk acceptance (tolerance). Risk monitoring*	The risk can be tolerated. The manager must effectively apply existing prevention and control measures. New measures are needed if possible without significant additional resources or efforts.

Note: *Red – major level risk factors; Yellow - moderate level risk factors; Green - minor level risk factors*

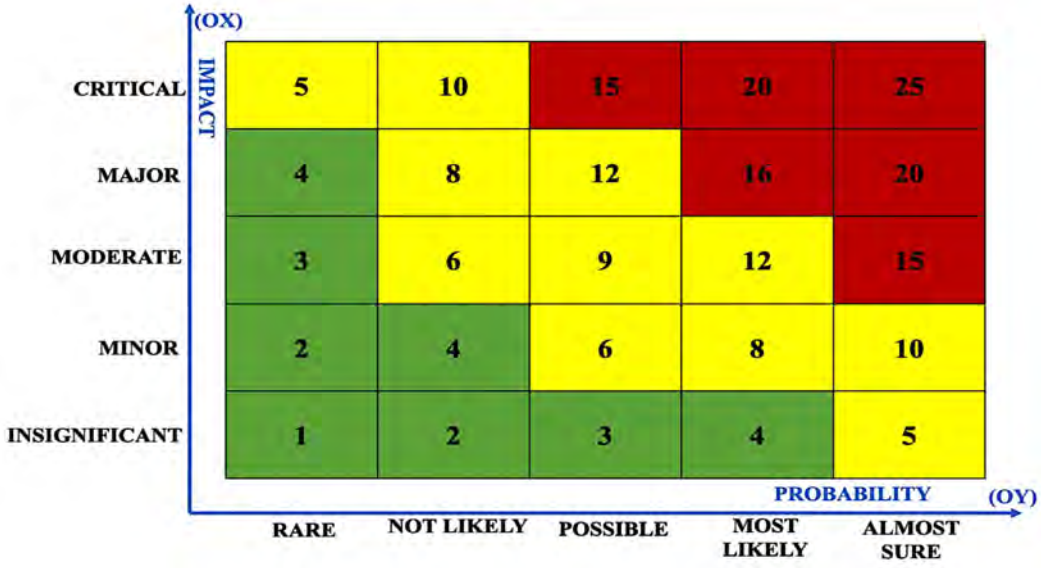

Fig. 1. Risk matrix.
The grouping of risks according to the impact on the OX axis and according to the probability of occurrence on the OY axis; Green - minor level risk factors; Yellow - moderate level risk factors; Red – major level risk factors.

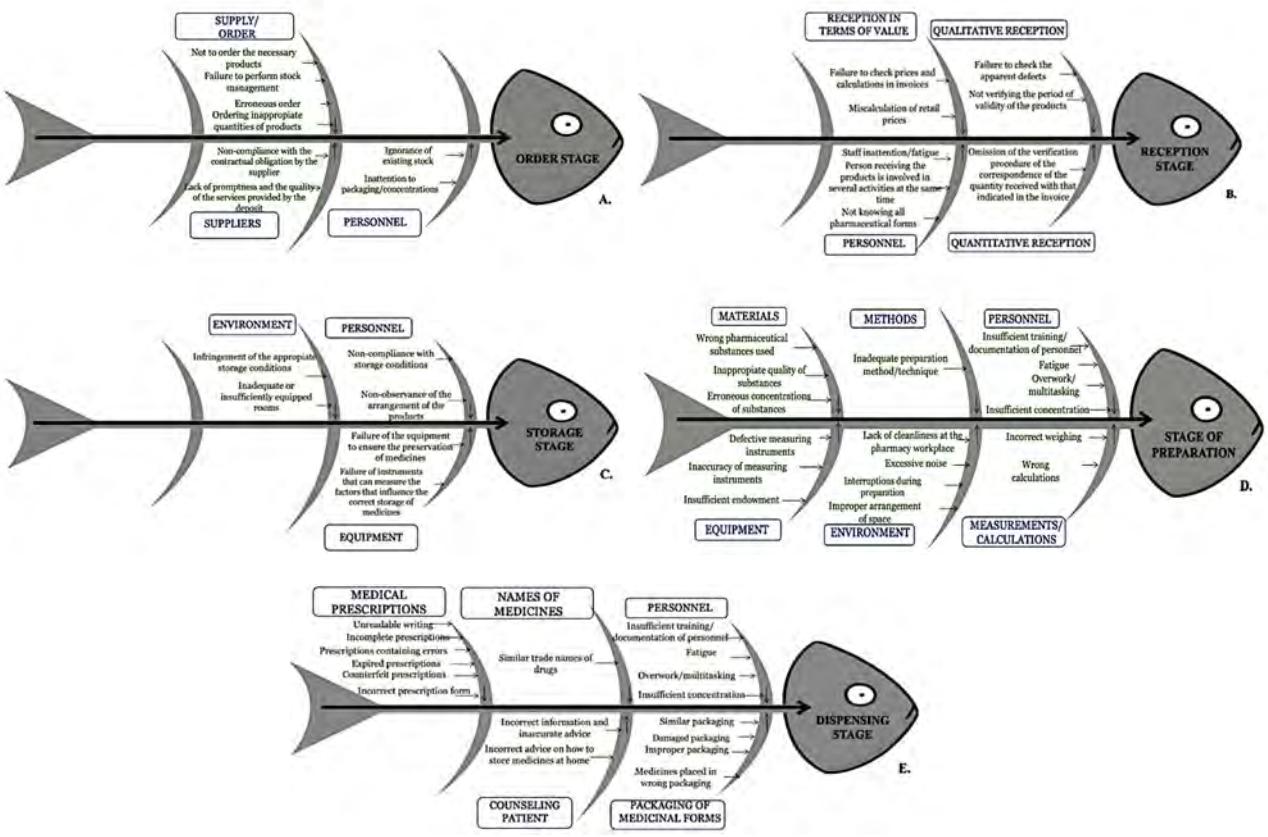

Fig. 2. The Ishikawa diagram

The diagram is illustrating the causes that can generate errors in the pharmaceutical activity: (A) the ordering stage; (B) reception stage; (C) storage stage; (D) preparation stage; (E) dispensing stage.

Fig. 3. The distribution by place of activity of the experts-respondents regarding the evaluation of the degree of influence of the pharmacist on his activity in community pharmacies

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RESEARCH ARTICLE

Epidemiological data and diagnosis pitfalls in aggressive extranodal non-Hodgkin's lymphomas: current issues

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What is not yet known on the issue addressed in the submitted manuscript

Despite the development of new methods of diagnosis and treatment with antineoplastic agents, the results of aggressive non-Hodgkin lymphomas treatment remain modest, with frequent relapses and primary refractory forms.

The research hypothesis

A study was carried out, which assumed the narrative synthesis of the literature to identify the current epidemiological characteristics and the difficulties in establishing the diagnosis of aggressive extranodal non-Hodgkin lymphomas.

The novelty added by manuscript to the already published scientific literature

Conducting a broad literary synthesis to demonstrate the importance of continuing research in the field of aggressive extranodal non-Hodgkin lymphomas, which remains a prevalent issue in modern haemato-oncology and public health.

Abstract

Introduction. Non-Hodgkin's lymphoma is a group of malignant tumors that develop from hematopoietic cells located outside the medullary. They are one of the most common forms of hemoblastosis. Non-Hodgkin lymphoma develops in people of all ages. Morbidity of non-Hodgkin lymphoma increases with age reaching its highest level in people over 50 years of age.

Material and methods. A study was carried out through a narrative review of the literature in the form of a synthesis article. The article summarized and systematized various primary studies, dedicated to the epidemiological and diagnostic aspects of aggressive extranodal NHL.

Results. Aggressive extranodal NHL remains a major problem, with a fairly large increase in incidence globally. This trend is observed in several countries of the world, thus morbidity increases by 3% annually for women and by 4% for men. Globally, aggressive non-Hodgkin's lymphoma continues to affect the working-age population. Although patients with primary extranodal NHL tend to report to a medical specialist at a lower stage than those with primary ganglion disease, the number of those addressing in advanced stages continues to be increased.

Conclusions. Although diagnosing NHL does not involve great impediments, primary care physicians often detect patients in the late stages of the disease either because of delayed referral to the doctor or because of incorrect diagnosis. Despite the development of new methods of diagnosis and treatment, aggressive extranodal NHL continues to be a current problem of clinical medicine and public health, requiring increased managerial and financial efforts.

Key words: aggressive non-Hodgkin's lymphomas, extranodal, morbidity, diagnosis

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant tumors of B-, T-and, less commonly, NK-cellular origin that may primarily affect any organ and tissue that contains lymphoid cells [1]. Currently, NLH is considered the most common group of malignant hemopathies, it ranks 7 as morbidity by malignant tumors and 6 as mortality by cancers [2]. Worldwide, there is a clear increase in the incidence of NHL by about 80% more than in the early 1970s [3]. Annually, 287.000 new cases of NLH are diagnosed worldwide [4]. The incidence of NHL varies significantly depending on the geographical region; these differences may be related to demographics, environmental

differences and other factors such as lifestyle and healthcare systems [5]. A higher incidence is found in males, especially in Israel (17.6 cases per 100k), in white Americans (14.5 per 100k), in Australia (15.3 per 100k), Canada (13.7 per 100k) and Portugal (13.3 per 100k) [6]. Similar geographical particularities were observed in females, with a higher incidence recorded in the population of Israel (13.0 per 100k), white Americans (10.4 per 100k), Canada (10.0 per 100k), Australia (12.3 per 100k) and lower in Central Africa (2.8 per 100k), South Africa (1.6 per 100k), Vietnam (3.5 per 100k), India (3.6 per 100k) [7]. The NHL morbidity index in the Republic of Moldova constitutes 4.1 per 100 000 people [8].

The aim of the study was to identify current epidemiological patterns and difficulties in establishing diagnosis in aggressive non-Hodgkin's extranodal lymphomas.

Material and methods

A study was carried out through a narrative review of the literature in the form of a synthesis article. The article summarized and systematized various primary studies, dedicated to the epidemiological and diagnostic aspects of aggressive extranodal non-Hodgkin lymphoma. The accumulation of information for this research was carried out by analyzing data from specialized international bibliographic sources and official statistics on the respective malignant myeloproliferative neoplasm. To achieve this, scientific medical publications were searched through Google Search, PubMed, Z-Library, NCIB, Medscape, Hinari database, using the following keywords: „non-Hodgkin lymphoma", „aggressive", „extranodal", „mortality", „survival", „incidence", „prevalence", „diagnosis". More than 50 reference bibliographic sources have been studied to conduct the qualitative research. In order to diversify the conclusions, the results of foreign studies were supplemented by research data published from the Republic of Moldova.

Results and Discussion

Aggressive extranodal NHL remains a major problem today, with a clear increase in incidence globally. The evolution and survival rate depend largely on the type and subtypes of lymphoma, the stage and severity of the disease, the age of the patient at the time of the diagnosis and comorbidities. Although patients with primary extranodal NHL tend to see a specialist at a lower stage than those with primary ganglion disease, the number of those who address in advanced stages continues to be high. At the moment, contemporary diagnostic methods allow accurate stabilization of the diagnosis and subsequent initiation of treatment according to the type of lymphoma.

NHL develops and disseminates at different rates, being divided according to histopathological and clinical-evolutionary features into indolent and aggressive [9]. Aggressive lymphomas are a heterogeneous group of malignant tumors that reflect a variety of clinical, biological, and pathological characteristics [16]. They refer to those rapidly growing subtypes (KI-67 proliferation index >40%) and would often be lethal within a few months without appropriate therapy [10]. According to data from the American Hematology Society in 2015, aggressive lymphoma accounted for about 60% of all cases of NHL in the United States [11].

There are different types and subtypes of aggressive NHL. In order to be able to apply effective treatment, it is essential to determine the type and subtype of lymphoma. Sometimes more than one type of lymphoma can be detected at the same patient [22]. Initially, it will be determined what is the initial cell from which the disease developed [19]. B-cell lymphoma is the most common - about 90% of people in Western countries are diagnosed with B-cell lymphoma. Lymphomas that have their onset from T cells make up about 10%, which are more common in Asian countries, while NK cell lymphoma affects less than 1% of people [23]. The most common subtype of aggressive NHL that develops from type B cells is diffuse large B-cell lymphoma (DLBCL) [25]. 30% of NLH in the United States is DLBCL type, which tends to develop extranodally in about 40% of cases [24]. Type B cells also have their starting point in mantle cell lymphoma, which affects 5 to 7 percent of people with lymphoma. It usually develops in people over the age of 60 and is much more common in males than females, commonly involving the bone marrow in the process [3]. Primary mediastinal lymphoma with large B-cells is an aggressive form of DLBCL. It often complicates with superior vein syndrome. This subtype of lymphoma is most commonly established in females between the ages of 30 and 40, and about 2.5% of people with NHL have this subtype [2].

From the subtypes that develop from T and NK cells, peripheral T cell lymphoma, not otherwise specified (PTCL, NOS) is most common. This is an aggressive form of lymphoma that is often in advanced stages when doctors detect it [26]. It mainly affects people over the age of 60 and accounts for about 6% of all lymphomas in the United States and Europe. Another subtype of aggressive lymphoma is anaplastic lymphoma, which accounts for about 2% of all lymphomas and about 10% of all childhood lymphomas [30].

The tumor originating from the extranodal tissue is called primary extranodal lymphoma (PENL), while the hematogenous spread of the disease from lymph nodes to extranodal tissue is secondary extranodal lymphoma [12]. The incidence of PENL is constantly increasing in recent years; there are many factors that „favor" this increase: HIV infection, the increasing use of immunosuppressive therapy, and indolent viral infection [27]. The primary extranodal sites of NHL constitutes 30-48%, with more frequent damage to the Waldeyer lymphatic ring (19-21%) followed by the gastrointestinal tract (17-19%) and spleen (4-6%) [13]. In other organs and tissues (soft tissues, skin, bones, pleura, lung tissue, central nervous system, orbit, mammary gland, ovary, uterus, prostate, and others) NLH develops rarely (from 0.8 to 3-4%) [14]. Worldwide, it has been observed that patients with primary extranodal NHL tend to present themselves at a lower stage than those with primary ganglion disease.

The only method to confirm the diagnosis of NHL remains excisional biopsy of the tissue with subsequent morphological, immunohistochemical, flow-cytometry, FISH for histological determination of the lymphoma subtype.

However, the most common causes of late diagnosis are late referrals to the specialist doctor, as well as misdiagnosis by other doctors, often treating the disease as an inflammatory/reactive process, and redirecting the patient to the hematologist after several attempts of treatment with anti-inflammatory drugs/antibiotics; this ultimately leads to an increase of patients detected in stages III-IV.

Worldwide, NHL caused 6.8 million DALYs (disability-adjusted life-years) in 2016 [21]. Despite the development of new antineoplastic agents, the outcome of aggressive NHL treatment remains poor, with frequent relapses and primary refractory forms [17]. The survival of patients differs depending on the stage at the time of diagnosis, the type, and subtype of lymphoma, severity of the disease, age of the patient at the time of the diagnosis and comorbidities [28]. According to a study conducted in the UK between 2004 and 2016, 60 out of 100 patients with DLBCL survive 5 years and longer after diagnosis. While 55 in 100 patients with Burkitt lymphoma survive about 5 years, and only 35 in 100 patients with T cell lymphoma survive up to 5 years after diagnosis [29].

The increase in morbidity and disability of the working-age population, the large number of cases diagnosed in the late stages of NHL and the poor results of the treatment of aggressive histopathological types remain a current problem of clinical medicine and public health, imposing increased policy changing and financial efforts [19, 20].

Conclusions

1. NHL is in the first place in the morbidity among malignant hemopathies, the incidence of which attests a continuous increase in the last years.
2. Worldwide, there is an increase of aggressive NLH morbidity indices for the working-age population as well as an increase in the degree of disability.
3. Although the diagnosing NHL does not have great obstacles, patients are often detected in the advanced stages of the disease either because of late referral to the specialist or because of misdiagnosis by primary care physicians.
4. Despite the development of new methods of diagnosis and treatment, aggressive extranodal NHL continues to be a current issue of clinical medicine and public health, requiring increased managerial and financial efforts.

Declaration of conflicting interests

Nothing to declare.

Authors' contributions

DU studied the bibliographic reference sources, summarized, and systematized the data of published research, studies, and clinical recommendations, structured and drafted the article. VM, MR, NSB, LM, VM conceptualized the manuscript, summarized and systematized the data of published research and studies and revised the draft of the article.

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CASE REPORT

Osteitis condensans ilii – difficulty in diagnosis and management. Clinical case study

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What is not yet known on the issue addressed in the submitted manuscript

Currently, *Osteitis condensans ilii* is often confused with sacroiliitis, which leads to misdiagnosing and the constitution of erroneous treatment tactics. Thus, in order to establish a true diagnosis, it is necessary to collect a detailed history and perform a comprehensive objective examination, which includes the character of the pain and its triggers, the lack of inflammatory lab markers and the radiological presence of the sclerosis areas at the level of the iliac bone, but not involving the sacroiliac joints.

The research hypothesis

This article aims to present the clinical manifestations of *Osteitis condensans ilii* in sacroiliac joints changes in women, as well as the problems that might interfere with the management of these patients.

The novelty added by manuscript to the already published scientific literature

This study proves the presence of different symptoms, particularly of the sacroiliac joints damage in women with unclear diagnosis of seronegative spondyloarthritis, which shows a diagnostic and therapeutic relevance.

Abstract

Introduction. *Osteitis condensans ilii* (OCI) is a condition characterized by benign sclerosis of the iliac bone in the portion adjacent to the sacroiliac joints, which is radiologically manifested by triangular opacities at the level of this portion. Among the clinical manifestations, localized low back or lumbosacral pain is often attested, which is found in the gestational or post-partum period. The pain may worsen during physical exertion or during menstruation and may be accompanied by myalgia.

Material and methods. The epidemiological, clinical and paraclinical data were used to highlight this study, followed by the conclusions of multidisciplinary specialists, retrieved from the inpatient medical records of 3 women with OCI, who were admitted for diagnosis and treatment.

Results. 3 cases of imaging-determined OCI will be presented, which were initially diagnosed with seronegative spondyloarthritis (SpA). Through them, we would determine the varieties between the OIC forms and their differential diagnosis with SpA. The results of the lab tests do not reveal specific changes, so the markers of inflammation (C-reactive protein, erythrocyte sedimentation rate) were normal. Also, unlike SpA, the marker HLA-B27 is in most cases negative.

Conclusions. According to the results of the presented clinical cases, OCI is often confused with sacroiliitis, which leads to misdiagnosing and erroneous treatment tactics. Thus, in order to establish a true diagnosis, it is necessary to collect a detailed history, perform a comprehensive objective examination, which includes the character of the pain and its triggers, the lack of inflammatory lab markers and the radiological presence of the sclerosis areas at the level of the iliac bone, not involving the sacroiliac joints.

Keywords: *osteitis condensans ilii*, spondylarthritis, differential diagnosis.

Introduction

Osteitis condensans ilii (OCI) is a condition characterized by benign sclerosis of the iliac bone in the portion adjacent to the sacroiliac joints, which is radiologically manifested by triangular opacities at this level. It is usually determined bilaterally, and in very rare cases unilaterally, the diagnosis being established exclusively radiologically [1]. The causes of the disease have not been completely elucidated, however, it is assumed that the influence of mechanical actions and instability (laxity of ligaments) of the sacroiliac joints, causes their overstrain, which is a chronic response to stress. Some

sources stipulate that the enlargement of the uterus in size during pregnancies could compress some branches of the iliac arteries, thus causing a transient local ischemia of the distal ileum. It is mainly found in multipara women, but cases have also been encountered in nulliparous women and men. Among the clinical manifestations, localized low back or lumbosacral pain is often attested, which is found in the gestational or post-partum period. The pain may worsen during physical exertion or during menstruation and may be accompanied by myalgia and morning redness. At the objective examination there is pain on palpation of the lumbar region and sacroiliac joints [2]. The data of the laboratory examination do not reveal specific changes, so the markers of inflammation (CRP, ESR) are normal. Also compared to spondylarthritis (SpA), HLA-B27 is negative in most cases [3]. It is important to know about the condition in order to be able to differentiate sacroiliitis from SpA, since both have similar clinical manifestations. Two cases of imaging-diagnosed OCI will be presented, which were initially diagnosed with seronegative spondyloarthritis. Through them, we would determine the varieties between the OIC forms and their differential diagnosis with SpA.

Materials and methods

This article reports three clinical cases of 3 women, who were admitted to *the Timofei Mosneaga* Republican Clinical Hospital in the Arthrology unit. The clinical and paraclinical data were retrieved from the inpatient medical records (lab tests included CRP, ESR, blood count, HLA-B27, 25-hydroxyvitamin D, rheumatoid factor, anti-nuclear antibodies). According to medical records, the patients were confirmed with *osteitis condensans ilii*. X-ray of sacroiliac joints and axial skeleton, abdomen ultrasound, neurologist consultation and gastroenterologist-hepatologist consultation, as well as at the specific infectious disease (for reactive arthritis) specialist were carried out.

Results

Clinical case No. 1.

A 48 year-old (multipara, 7 pregnancies, 6 births, 1 medical abortion) woman has addressed to the *Timofei Moșneaga* Republican Clinical Hospital. The patient is obese, obesity class I according to World Health Organization. The disease started with intense low back pain, immediately after the 5th birth, in 2007. The patient addressed to the neurosurgeon, who excluded radiculopathy and recommended the consultation of the rheumatologist, following treatment with NSAIDs, muscle relaxants, to relieve the symptoms. She administered the treatment, with beneficial effects, the general condition with positive course, so the patient postponed the visit to the rheumatologist. Over the years, migratory joint pain has associated, with a mechanical character. In 2015, patient went to the rheumatologist, was investigated, performed the radiography of the bones of the pelvis and the radiologist described the presence of bilateral sacroiliitis. In 2015, the diagnosis of undifferentiated seronegative arthritis was established, and it was recommended to initiate immunosuppressive treatment with methotrexate 10 mg. The patient administered the DMARD treatment for a short period of time, after which she abandoned it on her own. In 2019 she was hospitalized again to the *Timofei Moșneaga* Republican Clinical Hospital, due to the worsening of the low back pain and arthralgia, the diagnosis was reassessed, the diagnosis of psoriatic arthritis was assumed given the clinical picture, the radiological image of the pelvis, and the presence of hyperkeratosis in the elbows, plants and nail pitting. It was recommended to resume the DMARD treatment with methotrexate and to consult the dermatologist to specify the diagnosis. The patient neglected the recommendations of the rheumatologist, did not administer treatment, but was periodically hospitalized in the department of internal medicine at the place of living hospital, administered treatment with NSAIDs, muscle relaxants, vascular drugs, while her general condition was satisfactory. In 2021, the patient gave birth to her 6th child, after which the low back pain has worsened again, she had difficulties in performing daily activities and always required a break when walking. Thus, in June 2022, the patient was again hospitalized at the *Timofei Moșneaga* Republican Clinical Hospital. The laboratory tests excluded the presence of a generalized inflammatory process (table 1). Radiography of the lumbar region and bones of the pelvis was performed (Figure 1), where sclerosis of the subcortical joint surface of the iliac bone, which extends into the adjacent medullary space was outlined. The diagnosis of *osteitis condensans ilii* was established by clinical and instrumental results and excluding any kind of SpA, it was recommended treatment with NSAIDs, periodically, at the worsening of the dolor syndrome.

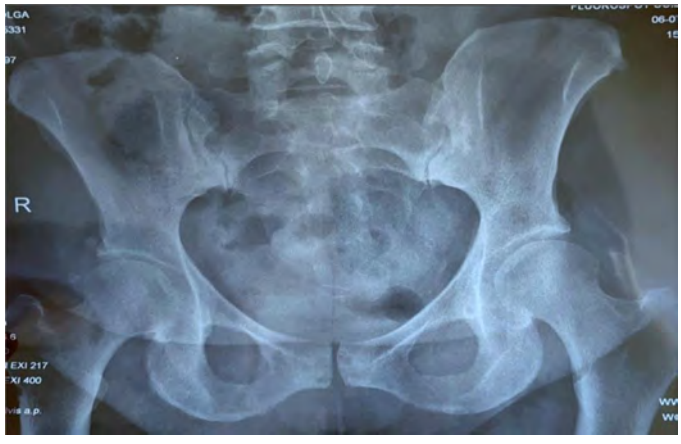

Fig. 1. X-ray of the pelvis – clinical case no. 1.
The joints surfaces, the articular fissures are congruent, regular coxofemoral joints. In the sacroiliac joints sclerosis of the articular surfaces, unevenly narrowed articular fissures (sacroiliitis grade 2-3). Osteoarthritis in the joint of pubic symphysis with subchondral cystic reconstruction. Entesopathies in the regions of iliac bones.

Table 1. Laboratory examination data of patient A., a 48-year-old woman

Lab indices	Values
Leukocytes	7.00 x 10^3/µL
ESR	19 mm/h
CRP	3.70 mg/L
Rheumatoid factor	7.80 IU/ml
Anti-nuclear antibodies	0.4 < 1.0 S/CO
25-hydroxyvitamin D	15.8 ng/ml
HLA-B27	Negative
Chlamydia trachomatis – DNA	Negative
Mycoplasma hominis – DNA	Negative
Mycoplasma genitalium – DNA	Negative
Ureaplasma urealyticum – DNA	Negative

Note: *ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, HLA – human leucocyte antigen, DNA – deoxyribonucleic acid.*

Clinical case No. 2.

Patient B., 46 years old, presents with low back pain, which appeared approximately during the 4th birth and became persistent at the onset of menopause. She mentions that they also worsened during the next 2 pregnancies. Patient is known to be multiparous, having 6 children, natural births, 2 of which were postterm births. Physiological menopause set in at the age of 40. She is overweight. According to the patient, she also had migratory peripheral polyarthralgia mainly at the level of the knees, talocrural and plantar joints, which made establishing the diagnosis more difficult. The lab tests were normal (table 2). Objective signs of spinal root damage have not been determined. No limitation has been observed in the hip joints. The X-ray of the pelvis was evaluated to determine the degree of sacroiliitis, but on the image we can definitely see the bilateral congruent, net articular surfaces, with sclerosis of the articular portion of the iliac bone in the form of a triangle, thus excluding the spondyloarthritis (Figure 2), establishing the OCI according to the image, the history of disease and the objective data.

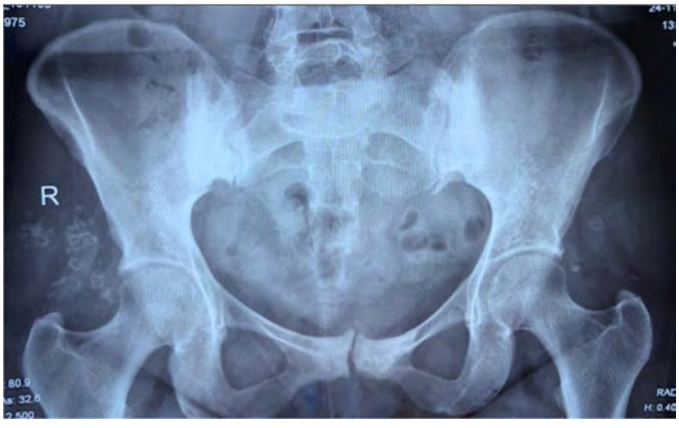

Fig. 2. X-ray of the pelvis – clinical case no. 2.
The congruent, net articular surfaces, with sclerosis of the articular portion of the iliac bone in the form of a triangle, bilaterally, thus excluding the spondyloarthritis.

Table 2. Laboratory examination data of patient B., a 46-year-old woman

Lab indices	Values
Leukocytes	6.82 x 10^3/uL
ESR	5 mm/h
CRP	0.09 mg/L
Rheumatoid factor	12.60 IU/ml
Anti-nuclear antibodies	0.3 < 1.0 S/CO
25-hydroxyvitamin D	17.1 ng/ml
HLA-B27	Negative
Chlamydia trachomatis – DNA	Negative
Mycoplasma hominis – DNA	Negative
Mycoplasma genitalium – DNA	Negative
Ureaplasma urealyticum – DNA	Negative

Note: *ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, HLA – human leucocyte antigen, DNA – deoxyribonucleic acid.*

Clinical case No. 3.

In contrast to these 2 classic cases, we report a patient C. who addressed the Republican polyclinic. The patient aged 43 years, had pain in the lumbosacral region. Physiological history: 3 pregnancies, 2 births, the last pregnancy was stagnant in evolution at 16 weeks. Menstruation is present, regular. From the history of the disease, it is known that the pain syndrome at the level of the lumbosacral region appeared after the third pregnancy in which it presented with a mild urinary infection. Given the fact that the patient is on record at the nephrologist with chronic pyelonephritis, in order to exclude low back pain due to kidney damage, she performed ambulatory US of internal organs and kidneys, excluding the renal diseases. The patient was consulted by the rheumatologist, who has performed physical examination with following signs: no costovertebral tenderness, normal mobility in the preserved hip joints, and lumbar region mobility insignificantly reduced. No other joints changes or swellings were attested. A set of lab tests was recom-

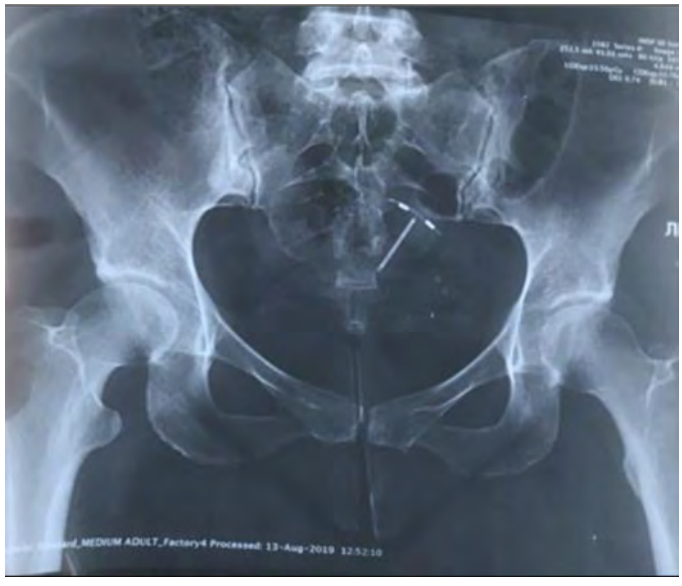

Fig. 3. X-ray of the pelvis – clinical case no. 3.
Sclerosis signs of the iliac bone in the shape of a triangle on the right, without affecting the sacroiliac joints.

mended, which included the investigation for the presence of urogenital infections, radiography of the lumbar region and pelvis. According to the laboratory results (table 3), the lack of urogenital infections was determined, at the radiography of the lumbar region – without signs of vertebral damage, at the radiography of the pelvis – sclerosis signs of the iliac bone in the shape of a triangle on the right, without affecting the sacroiliac joints, specifically by unilateral OIC (Figure 3).

Table 3. Laboratory examination data of patient C., a 43-year-old woman

Lab indices	Values
Leukocytes	7.12 x 10^3/uL
ESR	8 mm/h
CRP	1.30 mg/l
Rheumatoid factor	8.40 IU/ml
Anti-nuclear antibodies:	0.1 < 1.0 S/CO
25-hydroxyvitamin D	16.9 ng/ml
HLA-B27	Negative
Chlamydia trachomatis – DNA	Negative
Mycoplasma hominis – DNA	Negative
Mycoplasma genitalium – DNA	Negative
Ureaplasma urealyticum – DNA	Negative

Note: *ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, HLA – human leucocyte antigen, DNA – deoxyribonucleic acid.*

Discussions

In relation to the aforementioned clinical cases, the dependence of this condition on the female sex, on pluriparous and its mechanical action on the bones of the pelvis was highlighted. Taking into account the more frequent description of radiological changes manifested by periarticular sclerosis of bilateral iliac bones, however, there are also cases with imaging and unilateral manifestations, with the same clinical picture mentioned in case no. 3. Among the most common clinical manifestations were the lumbosacral pain, which is triggered mainly by the mechanical action of the fetus on the bones of the pelvis and the laxity of the periarticular ligaments.

The pain worsens with physical exertion and improves at rest, has a localized character, not involving other joints. Often it can be confused with axial spondyloarthritis, due to similar clinical manifestations, but the radiological manifestations are different for these conditions: in the axial spondyloarthritis, the presence of sacroiliitis is attested, characterized by changes in the sacroiliac joints (from the narrowing of the spaces, to ankylosis), in the OIC the sacroiliac joints are not involved, only the iliac bones are involved with their subchondral sclerosis. To differentiate OIC from an axial spondyloarthritis, clinical criteria proposed by the European Spondylarthropathy Study Group (ESSG) are used for the classification of spondylarthropathy. Clinical criteria include a history of inflammatory pain in the spine or synovitis in the lower limbs, along with any of the following: psoriasis, inflammatory bowel disease; alternative buttock pain and enthesopathy or a positive family history of spondylarthropathy. In addition to clinical and imaging manifestations, in laboratory manifestations of patients with OCI, the presence of inflammation or any marker specific to this condition is not attested.

In the management of these patients, treatment with NSAIDs, analgesics and physical therapy was initiated. The effect of which proved to be beneficial after about 2 weeks, with improvement of the local pain syndrome and the general condition of the patients. An equally important therapeutic measure is the weight loss down to normal BMI, also stretching exercises and strengthening of the pelvic muscles caused a decrease in the recurrences of the pain syndrome.

Conclusions

OCI is a condition, which can only be diagnosed radiologically in asymptomatic patients. It is more frequently identified in patients who have low back pain. According to the results of the presented clinical cases, it is often confused with sacroiliitis, which leads to misdiagnosing and the initiation of erroneous treatment methods. Thus, in order to establish a true diagnosis, it is necessary to collect the detailed history, perform a comprehensive physical examination, which includes information regarding the character of the pain and its triggers, the lack of inflammatory indices at the laboratory examination and the radiological presence of the sclerosis areas at the level of the iliac bone, not involving the sacroiliac joints. When the picture is complete, the final diagnosis and therapeutic tactics specific to the condition can be established.

Abbreviations

BMI – body mass index, CRP – C-reactive protein, DNA – deoxyribonucleic acid, ESR – erythrocyte sedimentation rate, HLA – human leucocyte antigen, NSAIDs – non-steroidal anti-inflammatory drugs, OCI – *Osteitis condensans ilii*, SpA – spondyloarthritis, USG – ultrasonography.

Declaration of conflicting interests

Nothing to declare.

Authors' contributions

The authors contributed equally to the search of scientific literature, the selection of bibliography, the reading, and analysis of biographical references, the writing of the manuscript and its peer review. All authors read and approved the final version of the article.

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CASE REPORT

Pathogenetic correlation of severe sepsis and multiple organ dysfunction syndrome provoked by multiple infections in perinatal period of women

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Short title: *Severe sepsis and MODS in perinatal period*

What is not yet known on the issue addressed in the submitted manuscript

At the moment, there are not exact pathogenetic mechanisms of uncontrolled systemic inflammatory response that is activated by multiple infections in perinatal period especially provoked by *Stenotrophomonas Moltrophilia*. But, if inflammation is not limited and becomes generalized, it can result in the constellation of signs and symptoms of a systemic inflammatory response syndrome (SIRS). The spread of the infection from the primary infected organ through the blood may result in systemic endothelial activation and precipitate sepsis, severe sepsis, and septic shock. Progression of sepsis to shock may lead to multiple organ dysfunction syndrome (MODS) and ultimately death.

The research hypothesis

Presentation of a life-threatening condition: septic shock with MODS resulting from multiple-antibiotic-resistant infections during pregnancy, perinatal period, child-birth.

The novelty added by manuscript to the already published scientific literature

It has been explained the pathogenetic correlation between severe sepsis and MODS provoked by multiple infections from the genital and urinary tracts in women within perinatal period. We report a case of refractive puerperal hematoma that developed progressively during two hours complicated with puerperal sepsis and multiple organ dysfunction syndrome (MODS) followed by an uncomplicated and nontraumatic vaginal delivery.

Abstract

Introduction. Despite significant advances in diagnosis, medical management and antimicrobial therapy, sepsis in the puerperium remains an important cause of maternal morbidity and mortality. The abnormalities associated with the clinical syndrome of sepsis result from a nonspecific innate inflammatory response. This is due to the fact that sepsis represents a systemic inflammatory response syndrome (SIRS) to infection or injury; therefore, it can rapidly progress to septic shock and death despite aggressive treatment. Severe sepsis with MODS has a mortality rate of 20–40%, rising to around 60% if septicemic shock develops. Symptoms of sepsis may be less distinctive than in the non-pregnant population and are not necessarily present in all cases; therefore, a high index of suspicion is necessary. The major pathogens causing sepsis in the puerperium are: group A streptococcus (*GAS),* also known as *Streptococcus pyogenes*, *Escherichia coli, Staphylococcus aureus, Streptococcus pneumonia*, methicillin-resistant *S. aureus* (MRSA), *Clostridium septicum*, *Morganella morganii* and antibiotic-resistant *Stenotrophomonas Moltrophilia*. Multiple risk factors for maternal sepsis have been identified: obesity, impaired glucose tolerance/diabetes, impaired immunity/immunosuppressant medication, anemia, vaginal discharge, history of pelvic infection, amniocentesis and other invasive procedures, cervical cerclage, prolonged spontaneous rupture of membranes, caesarean section, wound hematomas, retained products of conception, GAS infection, vaginal trauma.

Material and methods. Presentation of case report using the following key-words: „*infection*", *„systemic inflammatory response syndrome (SIRS)", „severe sepsis", „septic shock", „multiorgan dysfunction syndrome (MODS)".*

Results. We present a case of perinatal infections complicated with MODS.

Conclusions. The presence of pelvic hematomas triggers the sepsis caused by multiple infections in perinatal period and can significantly increase the morbidity related to bleeding, infection, surgery and blood product transfusion. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

Key words: perinatal infections, pelvic hematomas, systemic inflammatory response syndrome, septic shock, multiorgan dysfunction syndrome

Introduction

The presence of microorganisms causes inflammation that represents the response of damaged tissues to multiple infectious pathogens. Injured cells release preformed mediators (e.g., histamine) and synthesize proinflammatory substances, including eicosanoids (e.g., prostaglandins, thromboxane, and leukotrienes) and the cytokines (interleukin [IL]-1 and tumor necrosis factor [TNF]–α. These mediators are responsible for the initiation of a nonspecific inflammatory response. Microbial invasion is recognized by the immune system including endotoxins (lipopolysaccharide; LPS) and exotoxins from gram-negative bacteria as well as peptidoglycans (PGs), lipoteichoic acids (LTAs), enterotoxins, and super antigenic exotoxins from gram-positive bacteria [1]. The systemic activity of these proinflammatory mediators may result in an excessive, and often detrimental, response. SIRS is widespread endothelial activation, resulting in the increased production of vasoactive mediators and alteration of vascular homeostasis. Inflammatory cytokines (e.g., IL-1, TNF-α) are responsible for activation of the endothelium, and the activated cells produce inflammatory cytokines as well as increased amounts of NO (via inducible NO synthase), prostaglandins (via inducible cyclooxygenase-2), and endothelin-1 [2].

The initial effect of SIRS is pulmonary vasoconstriction leading to pulmonary hypertension [3] likely caused by thromboxane A_2 [4]. The initial hypertensive phase is followed by systemic hypotension caused by decreased arterial tone and results in decreased left ventricular preload, combined with venous vasodilation in the large-capacity vessels that decreases venous return.

The progression of these processes affecting the cardiovascular system ultimately results in shock. Shock occurs when cardiovascular function is severely impaired, such that hypotension cannot be corrected with intravenous fluid administration and requiring the use of inotropic and/or vasopressor agents [5]. Shock represents severe cardiovascular dysfunction associated with SIRS and is a primary component of MODS.

Materials and methods.

Analysis has been performed in woman in perinatal period, treated in emergency department of Clinical Municipal Hospital „Gheorghe Paladi" in Chisinau, Republic of Moldova, and obstetrics department from June 2021until august 2021. These effects are likely due to (PGI_2; prostacyclin) and iNOS knockout that can progress to the syndrome of hyperdynamic shock, with increases in heart rate and cardiac output developing as compensatory mechanisms to maintain tissue perfusion [6]. This compensatory response is impaired by the reduction in left ventricular preload, combined with the decreased cardiac contractility resulting from myocardial depressants (e.g., NO, TNF-α, IL-1), decreased myocardial responsiveness to β-adrenergic stimulation, and decreased compliance due to myocardial edema. Changes occurring in the microvasculature further contribute to the impairment of tissue perfusion. Progressive alteration of the microcirculation leading to failure may represent the common final pathway of SIRS-related injury contributing to or resulting in MODS.

Case report

Patient, 25 years-old, gravida 1, para 0, at 41-42 weeks of gestation, was admitted to the emergency department of Clinical Municipal Hospital „Gheorghe Paladi" in Chisinau, Republic of Moldova because of irregular, painful contractions during the last two weeks. Over eight hours of monitoring she was transferred to the obstetrics department with the onset of labor. From history: the desired pregnancy, visits to the family doctor were not regular. At 24 weeks she had an acute respiratory infection with a fever of 38°C, 4-5 days after the fever the smell and taste disappeared. She was treated unkindly at home. The COVID-19 test did not perform it. On the recommendation of the family doctor during pregnancy administered urinary antiseptics. Aggravated allergic history (cannot specify from which drugs). At a dilation of the cervix of 6 cm, considering the uterine contractions with pronounced pain syndrome and the exhaustion of the parturient in labor as well as at the request of the parturient epidural analgesia was performed. After 10 hours of labor, she delivered a male infant with a weight of 3800 gr., Apgar score 7/8 points. The umbilical cord wrapped once around the neck. The foul-smelling amniotic fluid was with meconium. No obstetrical maneuver was used to assist the delivery. A small median perineal and left vaginal rupture were sutured. Two hours later, she developed signs of shock. The patient complained of marked suprapubic pain, chills, and general weakness. The general condition of medium severity was assessed. The skin was pale, clean, fever 38.2°C, respiratory rate 16/min, pulse 96 b/min, BP 80/60 mmHg, and soft abdomen, sensitive to palpation in the suprapubic region.

The uterus was at the level of the umbilicus, well contracted, lochia in moderate amounts. The urination was free, painless. Given the immediate postpartum period complication with fever 38.2°C, leukocytosis $28.5x10^9$/L, immediately, intravenous access was established and it was indicated Cefazolin 2 g i/v (after performing the sensitivity test), Gentamicin 80 mg i/v, sol. Dexamethasone 8 mg i/v and Ringer solution 500 i/v with monitoring of vital signs. After 15 minutes, the patient's condition worsens: pain become stronger, pulse 130 b/min, BP 80/60 mmHg.

The patient was returned to the operating theater. Examination under general anesthesia revealed a large vaginal hematoma involving the entire right vaginal wall, displacing the uterus upwards and to the left. Uterine massage and manual control of the uterine cavity was performed during which 300 ml of clots were removed. Uterus under manual control was intact, well contracted. The vaginal hematoma (outside the intact vaginal mucosa) was opened and drained and 600 ml of clot blood was removed. The hematoma lodge and vagina was packed with gauze. The estimated overall blood loss was 1500 ml. The patient received transfusion with 2 units of packed red blood cells plus 8 units of fresh

frozen plasma, 3500 ml crystalloids and was given antibiotics. After the operation hemoglobin was 6.5 mmol/L and the clotting factors were stabilized. Lactate level was 2.2 mmol/l. Through the Foley catheter for 2 h 30 min from vaginal tamponade urine was absent. To exclude the possibility of the bleeding dissecting retroperitoneally or trauma of internal organs abdominal sonography was performed. The scan revealed a residual 5x6x2 cm sub peritoneal hematoma in the right side, but no sign of enlarging after compression. The kidney on the right slightly enlarged in size. Injuries to internal organs were not found. The patient was transferred to intensive care unit with oligo-anuria. Furosemide diuresis stimulation was tried without effect and after the decision of the medical council, with the arguments of Acute Renal Injury anuric phase more than 24 hours, severe metabolic acidosis in progression, it was decided to connect the patient to hemodiafiltration and continue broad-spectrum antibiotic therapy. After thirty-two hours delivery the cuff was removed without giving the patient anesthesia. No further bleeding was seen.

Despite intensive care, the patient's condition remained serious. Daily investigations were performed: abdominal USG, pelvic, pleural, echo-cord, monitoring of CBC, urine test, PCR, procalcitonin, lactate level, cultures (blood culture, uroculture, from nasopharynx and vagina) abdominal CT, chest CT. The patient is allergic to blood components, especially albumin. At the 8th day postpartum the ultrasonography of the abdominal cavity reveals: parenchymal organs without pathology, free fluid was absent in the abdominal cavity, pleural fluid on the right – 200-300 ml, on the left – 600-800 ml. The calyx/basin system was not dilated, emphasizing the pyramid design. Pathological fluid in the pericardium was absent. The uterus was normal (127.4 x 59.4 mm), and there was free fluid in the pouch of Douglas of 26.7 mm.

On the 15th postpartum day, the patient's condition was assessed as very serious, caused by Sepsis, acute renal injury, Respiratory Insufficiency gr. I-II on the basis of basal bilateral (septic) pneumonia. At the examination in the council, the following conduct was established: continuation of antibiotic therapy, repeated initiation of hemodiafiltration, correction of anemic syndrome with intravenous iron preparation, erythropoietin, initiation of cytosorb therapy, for contractile purposes to be administered tab. Misoprostol per rectum, gastroprotection, vitamin therapy, dynamic monitoring of PCR, procalcitonin, lactate, biochemical markers of liver function, hepatoprotectives, expectorants, bronchiolitis.

Due to the progression of the free fluid in the peritoneal cavity of more than 1000 ml, procalcitonin level 2.5 ng/mL, lactate level 4.5 mmol/l, on 18th day a diagnostic laparoscopy was performed during which 1500 ml of serocitrin peritoneal fluid were evacuated. Intraoperatively, pelvis-peritonitis was found to have a tendency to spread due to polyserositis as a result of the septic process. Uterus enlarged at 10-11 weeks, pale pink, normal appearance, bilateral ovaries 3x3 cm in diameter, with normal appearance, free fallopian tubes, and free fimbriae. On the right serous tube with hemorrhagic imbibition. On the right flank, in the projection of the round and infundibular-pelvic ligament: hemorrhagic imbibition of the parietal peritoneum because of the tamponade of the postnatal vaginal hematoma. Normal-looking liver, insignificantly enlarged, unstressed gallbladder with an omentum adhesive flange. Intestinal loops, omentum without peculiarities. The free fluid was aspirated from the flanks and the Douglas space. Peritoneal fluid was taken for bacteriological examination. Drained abdominal cavity with 3 tubes. Insignificant blood emission. Postoperative diagnosis: The 19th postpartum day. Pelvis- peritonitis. Sepsis.

Chest x-ray on the 20th postpartum day: Bilateral basal pneumonia with pleurisy. The thoracic surgeon performed the pleural cavity puncture, and then drained the pleural cavity on the right, removing 900 ml of serous fluid. The puncture procedure was complicated by right hemothorax. Belau drainage was applied to the right pleural cavity. On the 21st postpartum day, the patient's condition worsened repeatedly, with gastrointestinal bleeding, which was stopped and conservatively treated with hemostatics. Erosive esophagitis was found on fibro-gastro-duodenoscopy. On ultrasonography: biliary stasis. Insignificant changes in the pancreas. In the iliac fossae, free fluid in small amounts. Postpartum uterus. Clean uterine cavity. Bacteriological examinations collected from drains, urine, and vagina found the presence of *Stenotrophomonas Moltrophilia* with multidrug resistance.

At the 28th postpartum day, considering the serious condition of the patient with the appearance of clinical signs of purulent endometritis, peritonitis, progressive increase in leukocytosis (from 19.9 on 07.07.21 to 26.7 on 08.07.21), procalcitonin level 18 ng/mL, lactate level 7.2 mmol/l, the increased volume of free fluid in the abdomen found by ultrasonography, total hysterectomy without appendages was recommended, which was performed. Intraoperatively, 1.5 liters of ser-citrine content was aspirated when the abdominal cavity was opened. In the small pelvis, the uterus was enlarged at 10-11 weeks, flabby, pale gray, bilateral ovaries measuring 3x3 cm, with a normal appearance, free fallopian tubes, and free fimbriae. On the right flank in the projection of the round ligament towards the right iliac fossa, a conglomerate is palpably determined by the posterior sheet of the parietal peritoneum, medium hardness, immobile, of 5 cm. The Douglas space was free. A total hysterectomy with bilateral tubectomy was performed. The abdominal cavity was washed and drained. Douglas space drained with biluminal tube. At the level of the formation on the right flank, an incision was made on the parietal wall of about 5 cm, an organized hematoma of 5 cm was visualized, it was drained, the capsule was partially removed, the cavity processed with hydrogen peroxide solution, instead of the abscess applied 2 tubes of transcutaneous drain, parietal peritoneum in the incision region sutured with continuous vicril thread. Postoperative diagnosis: 28th puerperal day. Sepsis. Polyorganic insufficiency. Acute kidney damage. Respiratory failure. Heart failure. Liver failure. Puerperal metro endometritis. Organized parametrical hematoma.

On the 32nd postpartum day, positive dynamics were found on repeated radiography. Pneumonia on the right has been absorbed. Transparent left lung. Liquid was obtained from the anterior and posterior drains in minimal quantities, the posterior drain was extracted. On the 33rd day, the anterior pleural drain was extracted.

The patient's medical condition improved rapidly over the next few days. On the 34th day, the patient's condition was assessed as severe-moderate. Hemodynamically stable. Effective spontaneous breathing. Body temperature 36.7°C. Soft, painless abdomen. Laboratory tests were with improvement. She was transferred to the obstetrical department. On the 38th day in a satisfactory condition, she was discharged at home with recommendations. Drug treatment: erythrocyte concentrate 44 doses, fresh frozen plasma 6 doses, Albumin (200 ml) - 5 doses, Vancomycin 300 mg, Imipenem 1000 mg, Colestin 1 mln, Lincomycin 600 mg, Fluconazole 400 mg, Levofloxacin 500 mg, Amicacin 500 mg, Linezolid 1200 mg, Doxacycline 100 mg, Meropenem 500 mg, Ciprofloxacin 400 mg, Metrogil 500 mg , Ceftriaxon 2 gr, Clexan 0.2 ml, / hemostatic Etamzilat 500 mg, Furosemide, Mannitol, Pantoprazole, Heptral, Ademetionine, Hepamethionine, Linex, Panzimed, Venofer 100 mg, Erythropoietin 0.3 ml, Vit. B1, B12, B6, C, Folic acid 5 mg.

Discussion

Vaginal hematomas can develop rapidly and lead to significant pain and maternal hemodynamic compromise. Prompt recognition and management is required to prevent adverse outcomes. They are classified as vulvar, vaginal, vulvovaginal or retroperitoneal. The majority of puerperal hematomas are vulvovaginal and can involve even branches of the uterine artery and of the internal pudendal artery [7]. However, the hemorrhage can also be of venous origin since the veins of the perineum are valveless and have free anastomoses with large intrapelvic venous plexuses [8, 9]. Most hematomas will present within 24 hours of delivery. Perineal pain and pressure are common presenting symptoms along with a palpable tender mass [10].

Management of puerperal hematomas is controversial. Conservative management, surgical intervention and selective arterial embolization are the three main methods for managing puerperal hematomas. Conservative management consists of pressure packing, ice packs, analgesia and close surveillance [11]. Surgical intervention is indicated in cases of acute expansion, large hematomas or unsuccessful conservative management. It includes incision, evacuation of clots and ligation of the bleeding if identified, although in many cases, the lacerated vessel cannot be identified since the bleeding is venous in nature and from multiple sites. A layered closure should be performed to secure hemostasis. A vaginal pack or a balloon tamponade can be left in place for 12 to 24 hours. When mainstay methods of suture and packing fail or when arterial bleeding is identified, transcatheter arterial embolization becomes an interesting alternative [12]. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

In our patient the most common reason of severe sepsis is considered infection insult (association of multiple bacteria, viruses and fungi). Specific infections trigger a complex of pathophysiologic response such as inflammation and coagulation. Sepsis results when infections trigger a localized inflammatory process that than spreads with systemic symptoms of fever or hypothermia, tachycardia, tachypnea, leukocytosis or even leukopenia, altered mental state, and hyperglycemia in the absence of diabetes mellitus). These clinical symptoms are called systemic inflammatory response syndrome (SIRS).

SIRS such as syndrome comprises local and systemic manifestations. Local manifestations are characterized by vascular changes and leukocyte infiltration. Vascular reactions are changes in small blood vessels at the site of injury- vagina and perineum (persistent and paralytic arterial hyperemia and venous hyperemia, both of them associated with increased permeability of capillaries vessels walls with a resultant increase in capillary blood flow, causing heat and redness, which are two of cardinal signs of inflammation. This is accompanied by an increase in vascular permeability with outpouring of protein rich fluid (exudate) into the extravascular spaces. Accumulation of exudate in the tissue spaces, producing the swelling and impaired function of vagina and perineum. As fluid moves out of the vessels, stagnation of flow and clotting of blood occur. This aids in localizing the spread of infectious microorganisms.

Under optimal conditions, the inflammatory response remains confined to localized area. In our case (aggravated allergological history, compromised immune system), local inflammation results in prominent systemic manifestations as inflammatory mediators (IL-1, IL-6, TNF-α) are released into the circulation. The most prominent systemic manifestations of inflammation include the acute-phase response, leukocytosis and fever.

The acute phase response, which usually begins within hours or days of the onset of inflammation and/or infection, includes changes in the concentration of plasma proteins (e.g. acute phase proteins), skeletal muscle catabolism (muscles weakness), elevated erythrocytes sedimentation rate, and leukocytosis. These responses are generated by the release of cytokines, particularly IL-1, IL-6, TNF-α. These cytokines affect the thermoregulatory center in the hypothalamus to produce fever, the most obvious sign of the **acute phase response.** IL-1 and other cytokines induce an increase in the number and immaturity of circulating neutrophils by stimulating their production in the bone marrow. Other manifestations of acute phase response include anorexia, somnolence and malaise because of the actions of IL-1 and TNF -α on the central nervous system. The metabolic changes, including skeletal muscle catabolism, provide amino acids that can be used in the immune response and for tissue repair.

In severe bacterial infections (**sepsis),** the large quantities of microorganisms in the blood result in an uncontrolled inflammatory response with the production and release of enormous quantities of inflammatory cytokines

(most notably IL-1 and TNF-α and development of what is referred to as **SIRS.**

These cytokines cause generalized vasodilation, increased vascular permeability, intravascular fluid loss, myocardial depression, and circulatory shock.

Severe sepsis clinically is manifested by arterial hypotension, hypoxemia, oliguria, metabolic acidosis, edemas, thrombocytopenia, myocardial depression, and circulatory shock.

The pathogenesis of sepsis involves a complex process of cellular activation resulting in the release of proinflammatory mediators such as cytokines; recruitment of neutrophils and monocytes; involvement of neuroendocrine reflexes; and activation of compliment, coagulation, and fibrinolytic systems. Initiation of the response begins with activation of the innate immune systems by pattern-recognition receptors (e.g., Toll-like receptors [TLR]) that interact with specific molecules present on microorganism. Binding of TLRs to epitopes on microorganisms stimulates transcription and release of a number of proinflammatory and anti-inflammatory mediators. Two of these mediators, TNF-α and IL-1, are involved in leukocyte adhesion, local `inflammation, neutrophil activation, suppression of erythropoiesis, generation of fever, tachycardia, lactic acidosis, ventilation-perfusion abnormalities, and other signs of sepsis. Although activated neutrophils kill microorganisms, they also injure the endothelium by releasing mediators that increase vascular permeability. In addition, activated endothelial cells release nitric oxide, a potent vasodilator that acts as a key mediator of septic shock.

Another important aspect of sepsis is an alteration of the procoagulation- anticoagulation balance with an increase in procoagulation factors and a decrease in anticoagulation factors. Lipopolysaccharide on the surface of microorganism stimulates endothelial cells lining blood vessels to increase their production of tissue factor, thus activating coagulation. Fibrinogen is then converted to fibrin, leading to the formation of microvascular thrombi that further amplify tissue injury. In addition, sepsis lowers levels of protein C, protein S, antithrombin III, and antithrombin III, and tissue factor pathway inhibitor, substances that modulate and inhibit coagulation. Lipopolysaccharide and TNF-α also decrease the synthesis of thrombomodulin and endothelial protein C receptor, impairing activation of protein C, and they increase the synthesis of plasminogen activator inhibitor-1, impairing fibrinolysis.

Sepsis and septic shock typically manifest with hypotension and warm, flushed skin. Septic shock often presents with a decrease in systemic vascular resistance. There is hypovolemia due to arterial and venous dilation, plus leakage of plasma into interstitial spaces. Abrupt changes in cognition or behavior are due to reduced cerebral blood flow and may be early indications of septic shock. Regardless of the underlining cause, fever and leukocytosis are present. An elevated serum lactate or metabolic acidosis indicates anaerobic metabolism due to tissue hypoxia or cellular dysfunction and altered cellular metabolism. Tissue hypoxia produces continued production and activation of inflammatory mediators, resulting in further increases in vascular permeability, impaired vascular regulation, and altered hemostasis.

Septic shock usually may lead to **MODS (Multiple Organs Dysfunction Syndrome). MODS** represents the presence of altered organ function in an acutely ill patient that such homeostasis cannot be maintained without intervention.

MODS pathogenetically can be explained by the release of proinflammatory mediators (TNF- α, eicosanoids, proteases, platelet-activated factors, and oxidant generating enzymes). The imbalance between pro-and anti-inflammatory mediators with exceed levels of proinflammatory mediators or reduced levels of anti-inflammatory factors such as (soluble TNF receptor, IL-1 receptor antagonist and transforming growth factor).

Secretion of proinflammatory mediators increases the expression of adhesion molecules and increases the margination of blood cells such as platelets, that further reduces blood flow. At level of the liver plasma-derived mediators are synthesized as well as complement factors, acute-phase proteins and factor XII (Hageman factor activation). All of them increase the inflammatory cascade triggering **cardiac and pulmonary** injury accompanied by hepato-enteric syndrome.

Conclusions

The presence of pelvic hematomas in case of sepsis can increase significantly morbidity related to blood loss, infection, and surgery and blood product transfusion. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

Declarations of conflict of interests

Nothing to declare.

Authors' contribution

All authors have read and approved the final version of the manuscript

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CASE STUDY

Osteomyelitis of the jaws and facial bones caused by drug use (amphetamine, α-pyrrolidinovalerophenone)

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What is not known yet about the issue addressed in the submitted manuscript

A special form of toxic substance occurring against the background of the use of certain narcotic drugs has been identified.

The research hypothesis

A detailed study of the features of toxic osteomyelitis allows us to diagnose this disease in its early stages of development and make a proper treatment plan, while it differs from other forms of osteomyelitis of the jaw.

The novelty added by the manuscript to the already published scientific literature

The study of the peculiarities of the emergence, course, and treatment of toxic osteomyelitis against the background of drug use will make it possible to prevent and treat this form of osteomyelitis of the jaw.

Abstract

Introduction. An attempt was made to detect the pathogenetic factors involved in the occurrence of the disease by studying the clinical and laboratory data of 160 patients diagnosed with chronic osteomyelitis of the jaws treated in the clinic of oro-maxillo-facial surgery between 2005 and 2022. The patients studied were or are still drug users who use illicitly produced (amphetamine-type drugs) or other drugs (abbreviated α-PVP). We obtained positive results in the treatment of toxic osteomyelitis of the jaws following the implementation of a conservative and surgical treatment scheme.

Materials and methods. Detailed anamnesis of disease development, clinical examination, pictures, an orthopantomogram, general blood analysis and biochemical profile, urine analysis, blood markers, and AIDS analysis.

Results. The study of the composition of used substances is an important factor in the definition and development of the given disease's cause and mechanism. According to the patient's statement, this disease developed following the use of the amphetamine drug. This drug contained the main substance – ephedrine, and also red phosphorus and iodine, which accumulate and cause trophic changes. Almost all organisms' systems are affected by amphetamine intoxication. Given that only surgical treatment has a small effect on any of the patients in this group, we devised a conservative presurgical treatment plan. We prescribe medication for these patients: detoxification of the body from drugs that cause spasm of small blood vessels and accumulate in bone tissue, causing necrosis. Lavages of the mouth cavity are performed daily, and necrectomy is eventually performed.

Conclusions. Assistance to drug addicts with jaw necrosis is a demanding subject given that the majority of their population is unemployed and without insurance. According to unofficial data, there are only 5000 such patients in Chisinau.

Keywords: jaws, drug, necrosis, amphetamine, red phosphorus, α-PVP, osteomyelitis.

Introduction

Drug addiction is one of today's most serious social issues, and it has recently become a global pandemic. In the Republic of Moldova, this problem is very pronounced. This is due to many factors, the main one being easy accessibility. Consumption of cheap and low-quality drugs leads to necrosis of the jaws and, with prolonged use, to the destruction of all facial bones.

One of the important methods of diagnosing atypical osteomyelitis of the jaw bones is taking a thorough history. From the words of the patients, it was concluded that this disease appeared after the use of a substance called amphetamine. Besides the basic substance, which is ephedrine, this stuff contains other substances, such as red phosphorus and iodine, which lead to trophic changes when they accumulate in the tissues. Through its action, ephedrine leads to long-term vascular spasm that induces angiopathy [1].

A review of data from the modern literature as well as clinical cases of patients with jaw necrosis in recent years has shown that there are several narcotic drugs that lead to destruction of jaw bone tissue. Specialized treatment in the oromaxillofacial surgery department of patients with toxic osteomyelitis is difficult and tedious, with a number of impediments on the part of patients, who usually do not notice the seriousness of the problem. After the condition has improved, most of them continue to take drugs, abandoning their prescriptions, and end up with even more severe complications. Patients with toxic osteomyelitis of the jaw who do not attend regular check-ups cause a slew of medical and social issues [2].

The relevance of the problem lies in the detection of the causes of the development of this pathology, diagnostic methods and, most importantly, the development of effective treatment methods.

Osteomyelitis of the upper jaw is accompanied by such complications as abscesses or phlegmon of regional soft tissues, purulent sinusitis, frontitis, and ethmoiditis. Severe complications include meningitis and septicemia.

According to patients, another drug (abbreviated α-PVP, from English α-pyrrolidinovalerophenone) appeared in Moldova in 2021 – a synthetic cathinone psychostimulant that also causes necrosis of the facial bones [3].

Toxic osteomyelitis of the facial bones occurs not only in the Republic of Moldova but also in its neighboring countries – the Russian Federation and Ukraine. This pathology occurs because of the use of the drug amphetamine, which is cheap and accessible to synthesize under clandestine conditions. This drug contains ephedrine, red phosphorus, and iodine [4-7].

Material and Methods

Clinical cases of male and female patients aged 25–55 years with jaw necrosis associated with narcotic use (history, results of paraclinical research methods), and data from modern literature were studied.

The study has been conducted in the oro-maxillo-facial surgery department of the Institute of Emergency Medicine since 2005. All patients were drug users (ephedrine, red phosphorus, iodine compounds, and other chemicals, and, more recently, synthetic psychostimulants of the α-PVP cathinone class).

The following parameters were studied: social integration, whether they continue to use drugs, functional disorders (mastication, swallowing, phonation, breathing), aesthetic disorders (asymmetry, scars, aesthetic appearance), morphological disorders (lack of bone continuity, lack of teeth, oro-sinus communication, bone exposure).

The examination methods at the control visits were classical clinical examination of the patient; radiological examination (OPG, CBCT); laboratory examinations (general and biochemical blood analysis, urine analysis). Additionally, patients were documented through photography. All patients in the study signed informed consents for the examination and performance of medical procedures as well as the use of personal data for scientific and didactic purposes and the monitoring of disease progression over time.

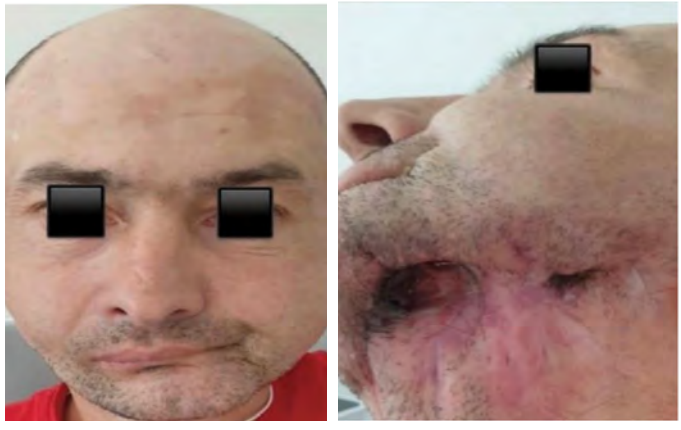
Results

Based on the data studied, it was revealed that there are several types of narcotics that lead to jaw necrosis. It was previously noted that these changes are caused by an amphetamine drug (containing ephedrine, iodine, and red phosphorus). Another drug (abbreviated α-PVP, from English α-pyrrolidinovalerophenone), a synthetic psychostimulant of the cathinone class, appeared in Moldova in 2021, according to patient reports. The central nervous system is stimulated after taking α-PVP due to increased dopamine and norepinephrine production and release in the brain. The common thing in these preparations is the red phosphorus content; only in the latter preparation does bone destruction occur much faster.

Clinical case

T. A., a 42-year-old man, has been using amphetamines for over 15 years. In this case, there was a necrotized chin region and mandible body on the left. He was repeatedly admitted with abscesses and phlegmon in the cervicofacial region. The necrotic fragments of the mandible were removed by the sequesters over a period of 4 years, resulting in a bone and soft tissue defect.

Through the defect of the buccal plateau, saliva is removed from the oral cavity (Fig. 1), leading to functional disorders (mastication, swallowing, and phonation), aesthetic disorders (facial asymmetry, presence of scars in the



a **a**

Fig. 1. Necrosis of the chin region (a) and mandible body on the left (b) (amphetamine consumption over 15 years).

submandibular region), and morphological disorders (lack of bone continuity, lack of teeth). Placement of the defect with surrounding soft tissues was performed. As a result of being treated at home for synesthesia, most patients present to us with a variety of complications, including deforming scars, massive defects, pronounced facial asymmetry, and functional disorders.

D. K., a 50-year-old man. In the anamnesis, he presents long-term consumption of an amphetamine drug; at present, he is using Methadone.

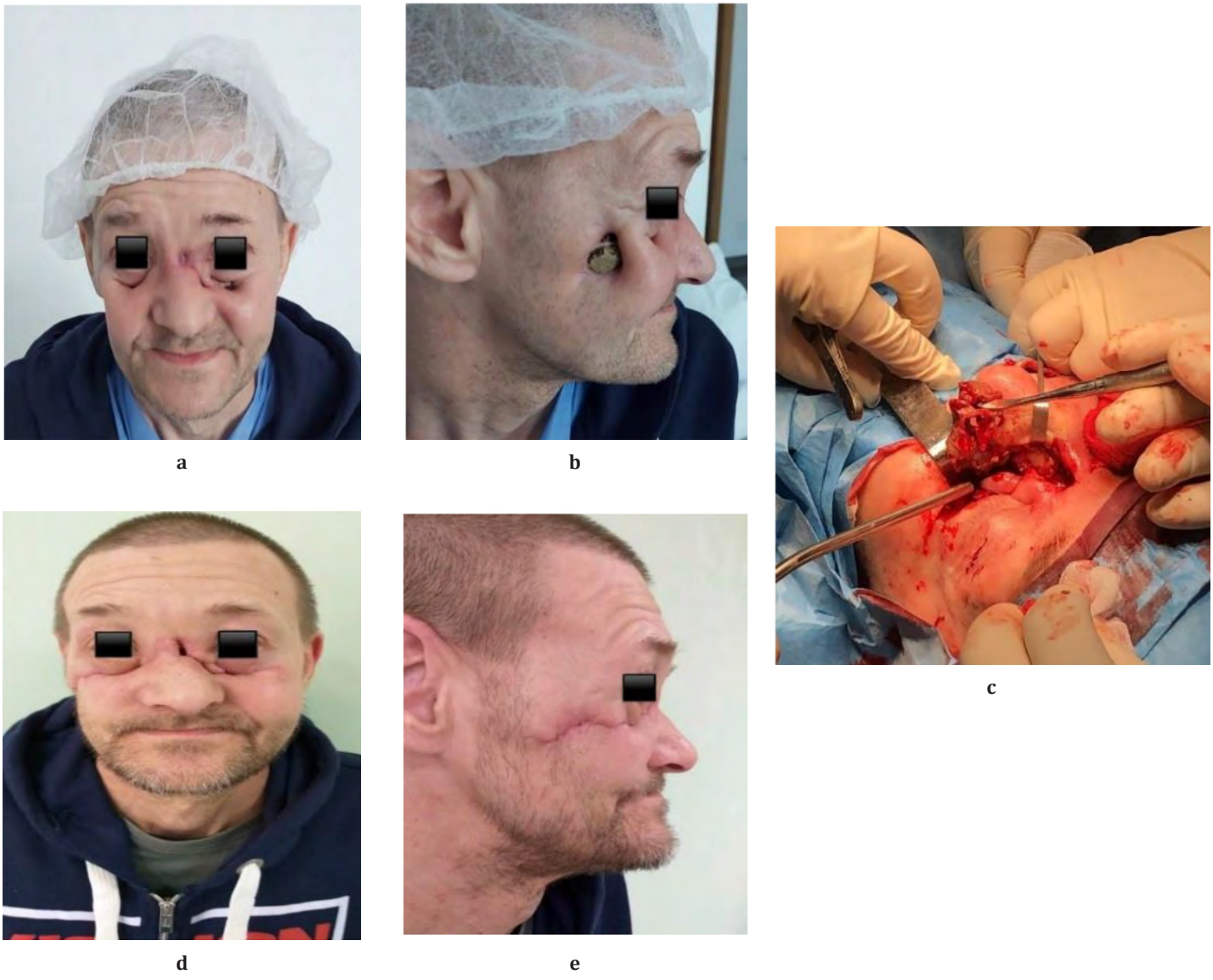


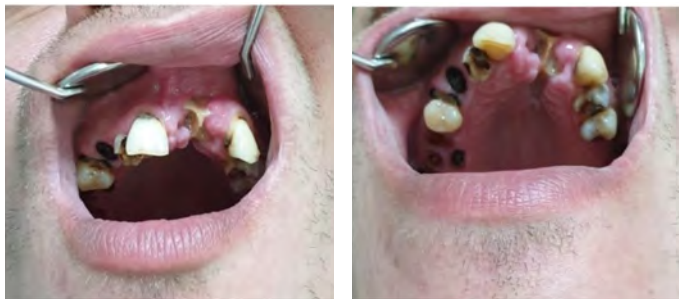
Fig. 2. Facial bone necrosis (a, b, c, d, e).

The entire upper jaw was necrotic, with damage to the maxillary sinuses and zygomatic bones and damage to the orbital plane and nasal bones (Fig. 2). After stopping amphetamine drug administration, the portions affected by necrosis (alveolar process with teeth, the hard palate entirely, and the zygomatic and nasal bones) were removed. Radical cure of the maxillary sinuses was performed without placement of the communications. Due to the chronic inflammatory process of the mucosa, dehiscences of the operative wound were formed, and as a result, repeated oro-sinus communications, functional disorders (mastication, phonation), and morphological disorders occurred. In view of what has been reported, it is very important that patients with toxic osteomyelitis of the jaws be treated simultaneously by several specialists, namely the oro-maxillofacial surgeon, psychologist, narcologist, and therapist. Equally important for their psycho-emotional, morpho-functional, and aesthetic rehabilitation is their referral for check-ups

and multiple, sometimes quite complicated and lengthy surgeries.

D. B., a 33-year-old man, has a medical history of amphetamine use and has recently used α-PVP.

The frontal part of the upper jaw was necrotized, i.e., the part where the drugging took place by friction of the preparation in the mucosa of the nostril was more pronouncedly affected (Fig. 3). This patient is undergoing rehabilitation in a narcology clinic and is preparing for surgical treatment.



a **b**

Fig. 3. Necrosis of the upper jaw after drug use of α-PVP (a, b).

Discussions

The study of the composition of used substances is an important factor in the definition and development of the given disease's cause and mechanism. According to the patient's account, this disease appeared after the use of the drug amphetamine. This drug contained the main substance, ephedrine, and also red phosphorus and iodine, which accumulate and cause trophic changes. Almost all organisms' systems are affected by amphetamine intoxication. Given that only surgical treatment has any effect on any of the patients in this group, we devised a conservative presurgical treatment plan. Lavages of the mouth cavity are performed on a daily basis, and necrectomy is eventually performed. The elaborated scheme of conservative and surgical treatment yielded positive results in the treatment of toxic jaw osteomyelitis.

Conclusions

1. Based on the data from the literature studied as well as the clinical data, it can be concluded that jaw necrosis occurs against the background of various narcotic drugs containing red phosphorus, as this specific chemical component leads to necrosis of the facial bones.

2. Analyzing over the years the clinical and paraclinical data of patients with toxic osteomyelitis of the jaws, we can state that positive results of treatment were obtained only in patients who totally refused drug use, overcame drug dependence, and had the desire to recover.

3. When amphetamine and α-PVP users are compared, it can be concluded that α-PVP causes more rapid and extensive irreversible processes in the jaws and other facial bones.

Declaration of conflict of interest

Nothing to declare.

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Vă rugăm să indicaţi contribuţiile specifice efectuate de fiecare autor (înscrieţi iniţialele autorilor, urmate de numele lor, de exemplu: *A. Belîi, Gh. Rojnoveanu*). Numele fiecărui autor trebuie să apară cel puţin o dată în fiecare dintre cele trei categorii, menţionate mai jos.

Categoria 1

Concepţia şi design-ul studiului: _____, _____, _____, _____;

Achiziţia de date: _____, _____, _____, _____;

Analiza şi/sau interpretarea datelor: _____, _____, _____, _____.

Categoria 2

Elaborarea (*drafting*-ul) manuscrisului:_____, _____, _____, _____;
Revizuirea semnificativă a manuscrisului, cu implicare intelectuală semnificativă: _____, _____.

Categoria 3

Aprobarea versiunii „gata pentru tipar" a manuscrisului (trebuie menţionate numele tuturor autorilor):

_____, _____, _____, _____, _____,
_____, _____, _____, _____, _____.

Mulţumiri:

Toate persoanele care au adus contribuţii importante la lucrul raportat în manuscris (de exemplu, ajutor tehnic, scris şi asistenţă la editare, suport general), dar care nu îndeplinesc criteriile de autor, sunt menţionate în secţiunea *„Mulţumiri",* iar acestea şi-au dat acordul în scris ca să fie menţionate. Dacă secţiunea *„Mulţumiri"* lipseşte din manuscris, atunci acest fapt semnifică că nu au existat contribuţii substanţiale din partea non-autorilor.

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Prezenta declaraţie este semnată de către toţi autorii:

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Manuscript title: _____
_____
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Authorship contributions:

Please indicate the specific contributions made by each author (list the authors' initials followed by their surname(s), e.g., *A. Belîi, Gh. Rojnoveanu*). The name of each author must appear at least once in each of the three categories below.

Category 1

Conception and design of study: _____, _____, _____, _____;
Acquisition of data: _____, _____, _____, _____;
Analysis and/or interpretation of data:_____, _____, _____, _____.

Category 2

Drafting the manuscript: _____, _____, _____, _____;
Revising the manuscript critically for important intellectual content:_____, _____.

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Approval of the version of the manuscript to be published (the names of all authors must be listed):
_____, _____, _____, _____, _____,
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Acknowledgements:

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and edit- ing assistance, general support), but who do not meet the criteria for authorship, are named in the „*Acknowledgements*" and have given us their written permission to be named. If we have not included an „*Acknowledgements*", then that indicates that we have not received substantial contributions from non-authors:

_____, _____, _____, _____, _____,

This statement is signed by all the authors:

(*a photocopy of this form may be used if there are more than 6 authors*):

Author's name (typed)	**Author's signature**	**Date**
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MJHS Moldovan Journal of Health Sciences
REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

SCRISOARE DE ÎNSOŢIRE

Titlul manuscrisului: _____
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Relevanţa manuscrisului pentru scopul promovat de Revistă: _____
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Ce aduce nou manuscrisul domeniului (specialităţii) în care este publicat: _____
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Modul în care manuscrisul adaugă valoare la literatura științifică de specialitate: _____
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Noi, autorii subsemnaţi ai manuscrisului, declarăm că (bifaţi):

- ☐ lucrarea menţionată este originală;
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- ☐ lucrarea menţionată nu este depusă pentru publicare în altă revistă;
- ☐ toţi autorii subsemnaţi au contribuit la elaborarea manuscrisului;
- ☐ de la subiecţii incluşi în studiu a fost obţinut consimţământul informat;
- ☐ toţi autorii subsemnaţi au aprobat versiunea finală a manuscrisului;
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- ☐ au fost declarate orice potenţiale conflicte de interes.

Prin prezenta, autorii sunt de acord să transfere drepturile de proprietate (copyright) Revistei de Ştiinţe ale Sănătăţii din Moldova – Moldovan Journal of Health Sciences, în caz că manuscrisul va fi publicat.

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1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____

Locul şi data: _____

Datele de contact ale autorului corespondent:

Instituţia: _____
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Adresa: _____
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COVER LETTER

Manuscript title: _____
_____

Relevance of the manuscript for the Journal purposes: _____
_____
_____
_____

Contributions of the manuscript for to the research field: _____
_____
_____
_____

What is the added value of the manuscript to the already published scientific literature: _____
_____
_____
_____

We, the undersigned authors of the manuscript, declare that (please, tick):

- ☐ the paper contain original data;
- ☐ the paper has not been published before;
- ☐ the manuscript is not submitted for publication to another journal;
- ☐ all authors have contributed to the manuscript;
- ☐ the informed consent were obtained from all study subjects;
- ☐ all coauthors approved the final version of the manuscript;
- ☐ we agree for checking of the manuscript for plagiarism;
- ☐ any potential conflicts of interest were disclosed.

With this, the authors agree to transfer property rights (copyright) to the *Moldovan Journal of Health Sciences – Revista de Stiinte ale Sanatatii din Moldova*, in the event that the manuscript will be published.

Authors (name, surname, signature):

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5. _____
6. _____
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Place and date: _____

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Revista de Ştiinţe ale Sănătăţii din Moldova

Moldovan Journal of Health Sciences

Ghidul autorului

Criterii pentru publicare

Articolele originale trebuie să conţină cercetări noi (originale), rezultatele cărora contribuie la acumularea de noi cunoştinţe în domeniul publicat şi cu condiţia că rezultatele prezentate nu au mai fost publicate înainte sau nu sunt depuse, în paralel, la o altă revistă, în vederea publicării.

Manuscrisele prezentate trebuie să corespundă standardelor STROBE (http://www.strobe-statement.org).

Prezentarea manuscrisului

Manuscrisele trebuie să fie prezentate doar în formă electronică, în limba română sau engleză. Dacă manuscrisul a fost depus doar în limba română, odată ce a trecut procedura de recenzare internă, acesta va fi tradus integral de către autori în limba engleză, pentru a putea trece procedura de recenzare externă. În acelaşi manuscris se permite utilizarea *US English* sau *British English*, dar nu mixt. Varianta tipărită (hârtie) nu va fi acceptată. Doar autorul corespondent va putea depune manuscrisul la redacţie; tot el va deţine responsabilitatea completă de procesul de depunere, de corespondenţa cu redacţia pe durata procesului de publicare.

Procesul de publicare poate fi amânat, întrerupt sau anulat, la discreţia autorului corespondent. Odată manuscrisul depus, autorul corespondent va primi un cod electronic de identificare a manuscrisului, pe care îl va folosi în corespondenţa ulterioară cu redacţia.

În scopul menţinerii integrităţii editoriale şi a standardelor internaţionale de calitate, Redacţia *Moldovan Journal of Health Sciences – Revista de Ştiinţe ale Sănătăţii din Moldova* utilizează un sistem de detectare a plagiatului şi va supune manuscrisul unei verificări antiplagiat. Depunerea manuscrisului pentru publicare înseamnă, implicit, acordul tuturor autorilor cu verificarea lui antiplagiat. În cazul suspectării că manuscrisul depus a încălcat politicile de publicare, acesta poate fi suspendat sau respins, indiferent de etapa procesului de publicare.

Scrisoarea de însoţire

La depunere, autorul corespondent va anexa la manuscris o scrisoare de însoţire. Formularul tipizat al Scrisorii de însoţire este oferit de către Redacţie. Scrisoarea de însoţire include: (1) titlul manuscrisului; (2) o scurtă descriere despre relevanţa manuscrisului pentru scopul promovat de Revistă; (3) contribuţiile aduse de manuscris pentru domeniul său; (4) modul în care manuscrisul adaugă valoare la literatura ştiinţifică de specialitate; (5) numele şi semnăturile tuturor coautorilor; (5) datele complete de contact ale Autorului corespondent, cu menţionarea instituţiei şi adresei instituţionale, nr. de telefon, nr. de fax şi adresa e-mail.

Instructions for Authors

Criteria for publication

Original articles should contain new (original) results, which bring new knowledge in the field. The submitted manuscripts should contain data unpublished before and not submitted in parallel for publication to another journal.

Manuscripts submitted must meet STROBE standards (http://www.strobe-statement.org).

Manuscript submission

Manuscripts must be submitted only in electronic form in Romanian or English. Once past the internal reviewing procedure, the manuscript was submitted only in Romanian will be fully translated by the authors in English to pass the external reviewing procedure. In the manuscript are allowed to use U.S. English or British English, but not mixed. Printed version (paper) will not be accepted. Only the corresponding author may submit the manuscript. The corresponding author holds full responsibility of the submission and correspondence with the editor during reviewing and publication process.

The publication of the manuscript may be postponed, stopped or canceled at the request of the corresponding author. Once the manuscript is submitted, the corresponding author will receive an electronic identification code of the manuscript, which should be used for subsequent correspondence with the editor.

In order to maintain editorial integrity and international quality standards, editor of the Moldovan Journal of Health Sciences reserves the right to use a plagiarism detection system. Thus the submitted manuscript will be checked for plagiarism. Manuscript submission involves agreement of all coauthors for checking for plagiarism. If the submitted manuscript violates copyright policies; it can be suspended or dismissed, regardless of the stage of the publishing process.

Cover letter

A submitted manuscript should be accompanied by a Cover letter. A template of Cover letter is provided by editor. Cover letter should include: (1) the title of the manuscript; (2) a short statement regarding the relevance of the manuscript for the journal proposes; (3) contributions of the manuscript for to field; (4) what is the added value of the manuscript to the already published scientific literature; (5) the names and signatures of all coauthors; (5) the full contact details of corresponding author, indicating the institution and institutional address, no. telephone, no. fax and e-mail.

In the Cover letter, the corresponding author should clearly indicate that: (1) the paper contain original data; (2) the paper has

În scrisoarea de intenție, Autorul corespondent trebuie să indice în mod clar că: (1) lucrarea menționată este originală; (2) lucrarea menționată nu a fost publicată anterior; (3) lucrarea menționată nu este depusă pentru publicație în altă revistă; (4) toți autorii subsemnați au contribuit la elaborarea manuscrisului; (5) de la subiecții incluși în studiu a fost obținut consimțământul informat; (6) toți autorii subsemnați au aprobat versiunea finală a manuscrisului; (7) acordul implicit de verificare antiplagiat al manuscrisului; (8) au fost declarate orice potențiale conflicte de interes. De asemenea, Autorul corespondent poate include orice informație suplimentară în Scrisoarea de intenție, dacă consideră că aceasta poate fi utilă pentru Redacție.

Consimțământul informat

Orice manuscris care comunică rezultate experimentale, obținute de la subiecți umani, trebuie să fie bazat pe studii, în care a fost obținut consimțământul informat de la subiect (ți) și/sau tutore (i). În scrisoarea de intenție, autorul corespondent trebuie să indice în mod clar obținerea consimțământului informat. În caz de necesitate, Redacția este în drept să solicite probe suplimentare, care atestă obținerea consimțământului informat.

Comitetul de Etică

Pentru orice studiu experimental, efectuat pe oameni sau animale, este necesar de a menționa evaluarea etică a proiectului de cercetare. În acest sens, în articol vor fi menționate numărul procesului verbal și data ședinței Comitetului de Etică, când a fost aprobat proiectul de cercetare.

Permisiuni

În conformitate cu ghidurile Comitetului Internațional al Editorilor Revistelor Medicale (*ICMJE Guidelines*), în cazul când în manuscrisul prezentat este folosită sau reprodusă o informație publicată anterior, sau un material cu drepturi de autor, este de responsabilitatea Autorului corespondent să obțină permisiunea în scris a deținătorului de drepturi (*Copyright*) și să citeze corect sursa originală. Cu scopul de a menține transparența, se recomandă ca această permisiune, sub formă de copie, să fie depusă împreună cu manuscrisul.

Fotografii cu pacienți identificabili

În conformitate cu ghidurile internaționale ale Comitetului de Etică a Publicațiilor (*COPE Guidelines*), în cazul când în imaginile prezente în manuscris (fotografii, radiograme, rezultate de laborator, rezultatele investigațiilor paraclinice, înregistrări video sau sonore ș. a.) o persoană este identificabilă fizic, de la aceasta trebuie obținută o permisiune în scris de utilizare a imaginii date. Se recomandă ca permisiunea dată să fie depusă împreună cu manuscrisul, iar în manuscris să fie stipulat în mod clar, că această permisiune a fost obținută.

Specificarea medicamentelor și dispozitivelor

În manuscris se vor utiliza nume generice de medicamente, urmate, dacă este cazul, de denumirea lor comercială între paranteze. Pentru medicamente și dispozitive, includeți numele producătorului și localizarea acestuia (țara de origine).

Formatul fișierelor

Se acceptă următoarele formate de text pentru manuscrisul principal: Microsoft Word (97, 2003, 2007, 2010) și formatele „.rtf", „.doc", „.docx". Se acceptă următoarele formate pentru imag-

not been published before; (3) the manuscript is not submitted for publication to another journal; (4) all authors have contributed to the manuscript; (5) the informed consent were obtained from all study subjects (6) all coauthors approved the final version of the manuscript; (7) agreement for checking of the manuscript for plagiarism; (8) any potential conflicts of interest were disclosed. Corresponding author may include in the Cover letter any other additional information which could be useful for the editor.

Informed consent

Manuscripts that report experimental results obtained on human subjects must be based on studies in which informed consent was obtained from study subjects and/or their legal representative. The corresponding author should clearly indicate in his letter of intention about the obtaining of the informed. Editor reserved the right to request additional evidence attesting the obtaining of the informed consent.

Ethic Committee

For any experimental study conducted on humans or animals, it is necessary to mention in the article the ethical evaluation of the research project (such as date of evaluation and reference number of approval).

Permissions

In accordance with the guidelines of the International Committee of Medical Journals Editors (ICMJE Guidelines) if the submitted manuscript used or reproduced information/material previously published or copyrighted is the responsibility of the corresponding author to obtain a written permission from the owner of the copyright and properly cite the original source. In order to maintain transparency, it is recommended to submit the permission, as a copy, along with the manuscript.

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In accordance with international guidelines of the Publications Committee of Ethics (COPE Guidelines), if the manuscript contains pictures (photographs, radiograms, laboratory results, results of laboratory investigations, videos or sound etc.) which allows physical identification of the person, it must be obtained a written permission for the use of the image data. It is recommended to submit the permission along with the manuscript. Also in the manuscript text should be clearly stated that permission was obtained.

Drugs and devices specifications

In manuscript generic names of drugs, followed by their trade name in parentheses (if appropriate) should be used. For drugs and devices, manufacturer's name and location (country of origin) should be mentioned.

Files format

The following file formats for manuscript text are accepted: Microsoft Word (97, 2003, 2007, 2010) ".rtf", ".doc", ".docx". Pictures should be submitted in one of the following formats: ".jpeg", ". tiff", ".eps ", ".ppt", , ".pptx". The images could be transmitted also, in a format item ".ppt" or ".pptx" (one image one slide). Scanning

ini: „.jpeg“, „.tiff“, „.eps“, „.ppt“. „.pptx“. Este posibil ca imaginile articolului să fie transmise în format „.ppt“ sau „.pptx“ (o imagine – un slide). Calitatea imaginilor, indiferent de format, trebuie să fie, minim: pentru desene – 800 dpi, pentru imagini cu detalii fine – 1000 dpi, pentru imagini alb-negru – de 300 dpi.

Structura manuscrisului

Publicaţia Periodică *Moldovan Journal of Health Sciences – Revista de Ştiinţe ale Sănătăţii din Moldova* respectă recomandările STROBE de raportare a cercetărilor observaţionale biomedicale. Pentru a vă uşura procesul de elaborare şi structurare a manuscrisului, vă recomandăm să consultaţi informaţia respectivă, disponibilă online, pe site-ul www. strobe-statement.org.

Volumul textului unui manuscris nu trebuie să depăşească 6000 de cuvinte. Cu toate că numărul figurilor şi tabelelor în manuscris rămâne la discreţia autorilor, se recomandă ca numărul lor să fie limitate la 5, pentru a nu reduce din lizibilitatea articolului pe paginile Revistei.

Structura unui articol original trebuie să respecte următoarea consecutivitate:

- Titlul lung (formulat în conformitate cu ghidurile STROBE)
- Numele şi prenumele complete ale autorului (autorilor)
- Afilierile autorului (autorilor)
- Datele de contact ale autorului corespondent
- Titlul scurt (va fi utilizat în calitate de colontitlu pe paginile Revistei)
- Elementele scoase în evidenţă din articol:
  - Ce nu este, deocamdată, cunoscut la subiectul abordat (descris în 1-3 fraze)
  - Ipoteza de cercetare (formulată în 1-2 fraze)
  - Noutatea adusă de articol literaturii ştiinţifice din domeniu (limitată la 1-3 fraze).
- Rezumatul articolului (compus din: introducere, materiale şi metode, rezultate, concluzii), limitat la maximum 350 de cuvinte.
- Cuvinte cheie
- Introducere
- Materiale şi metode
- Rezultate
- Discuţii
- Concluzii
- Lista abrevierilor utilizate (dacă este cazul)
- Declaraţia de conflict de interese
- Contribuţiile autorilor
- Mulţumiri şi finanţare (dacă este cazul)
- Referinţe bibliografice
- Tabele şi legende la tabele (dacă este cazul)
- Ilustraţii şi figuri (dacă este cazul)
- Legendele figurilor (dacă este cazul)
- Descrierea datelor suplimentare, anexe (dacă este cazul)

Pe pagina de titlu a manuscrisului trebuie să fie prezente următoarele elemente:

- **Titlul manuscrisului:** formulat în conformitate cu ghidurile STROBE, trebuie să fie laconic, relevant pentru conţinutul manuscrisului, să reflecte tipul (*design*-ul) studiului şi să nu depăşească 25 de cuvinte. Nu se admit prezenţa abrevierilor în titlu.
- **Titlul scurt** (ce va fi utilizat drept colontitlu pe paginile Revistei) reprezintă o versiune scurtă, de esenţă, a titlului complet.

resolution should be as follows: drawings – at least 800 dpi, fine line images – 1000 dpi and greyscale images – at least 300 dpi.

Structure of the manuscript

Moldovan Journal of Health Sciences follows STROBE recommendations for reporting observational biomedical research studies. To facilitate the development of the manuscript, please consult this information available online at www.strobe-statement.org.

The volume of the manuscript text should not exceed 6000 words.

Although, the number of figures and tables in the manuscript is at the discretion of the authors, in order to not reduce article legibility it is recommended to limit their number to five.

Structure of original article must comply with the following sequence:

- Full title (according to the STROBE guidelines)
- Full authors' name
- Authors' affiliations
- Contact details of corresponding author
- Short title (to be used as a running head on the journal)
- Article highlights:
  - What is not yet known on the issue addressed in the submitted manuscript (described in 1-3 sentences)
  - The research hypothesis (described in 1-2 sentences)
  - The novelty added by manuscript to the already publishedscientific literature (limited to 1-3 sentences).
- Abstract (consisting of background, materials and methods, results and conclusions), to not exceed 350 words.
- Keywords
- Introduction
- Materials and methods
- Results
- Discussions
- Conclusions
- List of abbreviations used (if applicable)
- Declaration of conflict of interests
- Authors' contributions
- Acknowledgements and funding (if applicable)
- References
- Tables and tables' captions (if applicable)
- Pictures and figures (if applicable)
- Figures' legends (if applicable)
- Description of additional data, appendices (if applicable)

The cover page of the manuscript should include:

- **Title of the manuscript:** written according to the STROBE guidelines, should be concise, relevant to the content of the manuscript, and reflect the study design. The title length should not exceed 25 words. It is not allowed the presence of abbreviations in the title.

- **Short title:** (to be used as a running title) is a short version of the essential of the full title. Short title will be limited to 40 characters, including spaces.

- **Author(s) name:** Authors list must include only those persons who had a substantial contribution to the work. Exam-

Va fi limitat la 40 de caractere, inclusiv spaţiile.

• **Numele autorului (autorilor).** Autori sunt numiţi doar acele persoane, care au avut o contribuţie substanţială la lucrare. Exemple de contribuţie esenţială la lucrare sunt: elaborarea *design*-ului studiului, recrutarea pacienţilor, participarea în colectarea datelor, analiza datelor, interpretarea rezultatelor, scrierea propriu-zisă a articolului, realizarea tehnică a testelor, investigaţiilor, realizarea imaginilor, formularea concluziilor. Pot fi citaţi până la 10 autori individuali. În cazul când grupul de lucru depăşeşte 10 autori individuali, vor fi citaţi în secţiunea „Numele şi prenumele autorilor" doar primii doi, iar restul vor fi menţionaţi la sfârşitul articolului, la secţiunea „Mulţumiri şi finanţare".

Membrii grupului de lucru, care nu îndeplinesc criteriile formale de autor enumerate, dar au avut o oarecare contribuţie la lucrare, pot fi menţionaţi în secţiunea „Mulţumiri şi finanţare".

Notă: Pentru a diferenţia autorul corespondent şi autorii care au contribuit în aceeaşi măsură la lucrare, folosiţi caractere speciale, ca exponenţi, la sfârşitul numelor lor:

(*) – pentru Autorul corespondent;

(†) – pentru Autorii care au avut o contribuţie egală. (De exemplu: Adrian Belîi*, Adrian Belîi†)

Nu se vor menţiona gradele şi titlurile ştiinţifice şi cele ştiinţifico-didactice.

• **Afilieri.** Afilierea autorilor se va scrie după secţiunea „Numele autorului (autorilor)". În acest sens, se va menţiona numele complet al instituţiei de afiliere a autorului (autorilor), localitatea şi ţara.

Afilierea se marchează cu cifre arabe, în superscript (de exemplu: Adrian Belîi[1])

• Elementele scoase în evidenţă din articol:
  - o Ce nu este, deocamdată, cunoscut la subiectul abordat (descris în 1-3 fraze)
  - o Ipoteza de cercetare (formulată în 1-2 fraze)
  - o Noutatea adusă de articol literaturii ştiinţifice din domeniu (limitată la 1-3 fraze).

Din pagină nouă:

Rezumatul

Rezumatul trebuie să fie scris la timpul trecut, persoana a treia. Acesta trebuie să ofere un sumar concis al scopului, obiectivelor, rezultatelor semnificative şi concluziilor studiului, în limitele la 350 de cuvinte, organizate în următoarele secţiuni:

- **Introducere** – unde se va reflecta, pe scurt, contextul şi scopul principal al studiului;
- **Materiale şi metode –** cum a fost realizat studiul şi ce teste statistice au fost aplicate;
- **Rezultate** – prezintă rezultatele principale ale studiului;
- **Concluzii** – o scurtă trecere în revistă a constatărilor făcute, cu posibile implicări pentru studii ulterioare.

Nu utilizaţi abrevieri şi citaţii în rezumatul articolului.

Cuvintele cheie

Enumeraţi 4-10 cuvinte cheie, care sunt reprezentative pentru conţinutul articolului. Pentru a uşura găsirea articolului Dvs. de către motoarele de căutare ale bazelor de date, folosiţi termeni recomandaţi din lista de titluri cu subiect medical de pe http://nlm.nih.gov/ mesh.

Înregistrarea trialului clinic

În caz dacă articolul Dvs. comunică rezultatele unui trial clinic,

ples of essential contribution to the work are: developing of the study design, patients recruitment, participation in data collection, data analysis, interpretation of results, writing of the manuscript, performing of the tests, pictures taking, drawing conclusions. The authors list should not exceed 10 persons. If the research group exceed 10 individual authors, in the "Authors name" section first two will be cited, all others should be mentioned at the end of the article, in the "Acknowledgements and funding" section.

Members of the research group who do not meet the formal criteria of the authorship, but have had some contribution to the paper, may be mentioned in the "Acknowledgements and funding" section.

Note: To differentiate the corresponding author, as well as authors who have an equal contribution to the work, using special characters as a superscript index at the end of their names is recommended:

(*) – Corresponding author;

(†) – Authors with equal contribution. (e.g. Adrian Belii*, Adrian Belii†)

• **Affiliation:** Please state the full name of institution, city and country to which the author(s) is affiliated. Affiliation should be marked with Arabic numerals in superscript after the author(s) name (e.g. Adrian Belii[1])

- **Article highlights:**
  - o What is not yet known on the issue addressed in the submitted manuscript (described in 1-3 sentences)
  - o The research hypothesis (described in 1-2 sentences)
  - o The novelty added by manuscript to the already published scientific literature (limited to 1-3 sentences).

From new page:

Abstract

The abstract should be written using the past tense, third person. It should provide a concise summary of the purpose, objectives, significant results and conclusions of the study. The summary text should not exceed 350 words organized into the following sections:

- **Introduction** – reflect in short the context and purpose of the study;
- **Materials and methods** – describe how the study was conducted and specify the applied statistics;
- **Results** – present the key results of the study;
- **Conclusions** – a brief overview of the findings, with possible implications for further studies.

Do not use abbreviations or citations in the abstract of the article.

Key words

List 4-10 keywords that are representative for the contents of the article. To facilitate finding of your article by search engines of electronic databases, use MESH keywords list (available on http://nlm. nih.gov/mesh).

Registered clinical trial

In case if your article reported the results of a clinical trial, please indicate Trial Register and the unique registration number of the trial.

vă rugăm să indicaţi Registrul trialului şi numărul unic de înregistrare a trialului.

Exemplu: *„Current Controlled Trials ISRCTN61362816”*. Atenţie! Nu trebuie să existe niciun spaţiu între literele şi cifrele numărului unic de înregistrare a trialului. Pentru mai multe informaţii, va rugam să accesaţi http://www.isrctn.org (*International Standard Randomised Controlled Trial Number*) şi http://www.icmje.org (*International Committee of Medical Journal Editors*).

Din pagină nouă:

Introducerea

Introducerea, scrisă la timpul trecut, persoana a treia, trebuie:

- să ofere informaţii care ar permite cititorilor din afara domeniului să intre în contextul studiului, să-i înţeleagă semnificaţia;
- să definească problema abordată şi să explice de ce aceasta este importantă;
- să includă o scurtă trecere în revistă a literaturii recente din domeniu;
- să menţioneze orice controverse sau dezacorduri relevante în domeniu;
- să formuleze ipoteza de cercetare şi să prezinte parametrul principal şi cei secundari de rezultat;
- să concludă cu scopul lucrării şi cu un comentariu care să ateste dacă scopul propus a fost atins.

Materiale şi metode

În secţiunea „Materiale şi metode” trebuie să fie descrise cu detalii suficiente procedurile efectuate. Aici se vor menţiona protocoalele detaliate privind metodele utilizate precum şi informaţii justificative. Se vor include: *design*-ul studiului, descrierea participanţilor şi materialelor implicate, descrierea clară a tuturor intervenţiilor şi comparaţiilor efectuate, precum şi testele statistice aplicate. Se vor specifica denumirile generice de medicamente. Atunci când în cercetare sunt folosite branduri, se indică în paranteze denumirea lor comercială. În cazul studiilor pe subiecţi umani sau pe animale, trebuie să fie menţionată aprobarea etică (data şi nr. procesului verbal al şedinţei Comitetului de Etică, preşedintele CE şi denumirea instituţiei, în cadrul căreia activează CE), precum şi consimţământul informat al persoanelor.

Rezultate

Rezultate şi discuţiile vor fi prezentate în secţiuni separate.

Autorii trebuie să prezinte rezultate clare şi exacte. Rezultatele prezentate trebuie explicate (nu justificate sau comparate, în această secţiune) cu constatări fundamentale, evident, referitoare la ipoteza care a stat la baza studiului. Rezultatele trebuie redate concis şi logic, cu accentuarea celor noi.

Discuţii

Se va descrie impactul, relevanţa şi semnificaţia rezultatelor obţinute în domeniul respectiv. Rezultatele obţinute se vor compara cu cele provenite din studiile anterioare din domeniu şi se vor trasa potenţiale direcţii viitoare de cercetare. Discuţiile trebuie să conţină interpretări importante ale constatărilor şi rezultatelor, în comparaţie cu studiile anterioare. De asemenea, se vor menţiona limitele studiului şi factorii potenţiali de *bias*.

Concluzii

Această secţiune trebuie să concludă laconic întregul studiu şi

E.g.: “Current Controlled Trials ISRCTN61362816”

Attention! There should be no space between letters and numbers of the unique record number of the trial. For more information, please visit http://www.isrctn.org (International Standard Randomized Controlled Trial Number) and http://www.icmje.org (International Committee of Medical Journal Editors).

From new page: Introduction

The Introduction section should be written using past tense, third person, and should:

- provide information that would allow readers outside of the field to enter the context of the study, to understand its meaning;
- define the problem addressed and explain why it is important;
- include a brief review of recent literature in the field;
- mention any controversy or disagreement existing in the field;
- formulate research hypothesis and present the main and secondary assessed outcomes;
- conclude with the research’ propose and a short comment whether the purpose has been achieved.

Materials and methods

“Materials and methods” section should present in sufficient details all carried out procedures. Here should be described protocols and supporting information on the used methods. It will include study design, subjects’ recruitment procedure, clear description of all interventions and comparisons and applied statistics. In the manuscript text the generic names of drugs should be used. When drug brands are used their trade name will be shown in parentheses. For studies on humans or animals a statement about ethical approval and informed consent of study subjects should be include. Please specify date and number of Ethics Committee (EC) decision, chair of the EC as well as institution within EC is organized.

Results

Results and discussion should be presented in separate sections. Authors must present results in a clear and accurate manner. Results should be explained (not justified or compared in this section) and include fundamental statements related to hypothesis behind the study. The results should be presented concisely and logically, emphasizing on new original data.

Discussions

Describe the impact, relevance and significance of the obtained results for the field. The results are compared with those from previous publications and draw potential future research directions. Discussions should include important interpretations of the findings and results compared with previous studies. Also, study limitations and potential bias should be mentioned.

Conclusions

This section should conclude laconically entire study, and highlight the added-value brought on the studied issue. The conclusions should not provide new information or double (repeat) those presented in the “Results” section.

să specifice, care este plus-valoarea adusă la informaţiile disponibile despre subiectul abordat. În concluzii nu se vor oferi informaţii noi şi nu se vor dubla (repeta) cele prezentate în secţiunea „Rezultate".

Abrevieri

Folosiţi numai abrevieri standard. De asemenea, pot fi formulate şi alte abrevieri, cu condiţia că acestea vor fi descifrate în text atunci când sunt utilizate pentru prima dată. Abrevierile din figuri şi tabele vor fi descifrate în legendă. Abrevierile trebuie folosite cât mai rar posibil.

Declaraţia de conflict de interese

După publicare, persoanele sau organizaţiile implicate în studiu vor deveni publice şi astfel poate fi influenţată reputaţia lor. Prin urmare, autorii trebuie să dezvăluie relaţia financiară sau non-financiară cu persoane sau organizaţii şi să declare conflictele de interese pentru datele şi informaţiile prezentate în manuscris. În conformitate cu ghidurile ICMJE, Autorul (autorii) trebuie să completeze o declaraţie privind Conflictele de interese, care va fi prezentată la sfârşitul articolului publicat.

Completând declaraţia referitoare la Conflictele de interes, se vor lua în consideraţie:

Pentru Conflicte de interese financiare

- specificaţi dacă vreo organizaţie are relaţie financiară cu lucrarea ştiinţifică reflectată în manuscris, inclusiv de finanţare, salariu, rambursări;
- menţionaţi, dacă articolul are un impact asupra organizaţiei date, ce ar genera pierderi sau profituri după publicare, în prezent sau în viitor;
- autorul (autorii) trebuie să precizeze dacă deţin cote de proprietate în orice organizaţie care ar putea să suporte pierderi sau să aibă profituri după publicare, în prezent sau în viitor. De asemenea, se recomandă să se specifice dacă autorul (autorii) deţin(e) sau aplică pentru orice drepturi de proprietate (brevet) în legătură cu conţinutul utilizat în manuscris;
- precizaţi dacă există oricare alte conflicte de interese.

Pentru Conflicte de interese non-financiare

- Vă rugăm să specificaţi oricare conflicte de interese non-financiare legate de politică, individuale, religioase, ideologice, educaţionale, raţionale, comerciale etc., care au legătură cu manuscrisul.

Contribuţia autorilor

Această secţiune a manuscrisului are rolul de a specifica contribuţia şi gradul de implicare a fiecărui autor. În acest sens, vă rugăm să respectaţi formatul exemplului propus: *„HW a conceput studiul, a participat la design-ul studiului şi a ajutat la redactarea manuscrisului. MG a efectuat procesarea exemplarelor, a metodelor de cultură ale ţesutului şi a elaborat manuscrisul. TK a efectuat testele de imunofluorescenţă. PN a participat la colorarea probelor şi la analiza citometrică prin flux. AR a participat la elaborarea design-ului studiului şi a efectuat analiza statistică. Manuscrisul final a fost citit şi aprobat de către toţi autorii".*

Fiecare Autor trebuie să aibă o contribuţie individuală în desfăşurarea cercetării, pregătirii manuscrisului şi publicării lucrării. Un Autor trebuie să contribuie semnificativ la conceptul şi *design*-ul lucrării, la efectuarea procedurilor experimentale, la colectarea datelor, la compilarea, analiza, interpretarea şi validarea rezultatelor.

Conform recomandărilor Comitetului Internaţional al Editorilor Revistelor Medicale, ICMJE, (www.icmje.org), drept autor poate fi considerată persoana care se încadrează în toate cele 4 criterii:

Abbreviations

Use only standard abbreviations. Other abbreviations may be defined and provided when are used for the first time in the manuscript. Abbreviations in the figures and tables will be explained in legend. Abbreviations should be used as rare as possible.

Declaration of conflict of interests

Following publication, persons or organizations involved in the study become public and thus their reputation may be influenced. Therefore, authors must disclose financial and non-financial relationship with people or organizations and to declare conflicts of interest related to the data presented in the manuscript. In accordance with the ICMJE guidelines, authors must fulfill a statement of conflicts of interest, which will be published at the end of the article.

Complementing the declaration of conflicts of interest the following will be taken into consideration

For financial conflicts of interest

- specify whether any organization has financial relationship with research presented in the manuscript, including funding, salary, reimbursements;
- mentioned, if the article has any impact on the eventually involved organization and could generate losses or profits after publication, now or in the future;
- authors must indicate if they have shares ownership in any organization that may incur losses or take profits after publication, now or in the future. Also, you should specify whether the author (s) own (s) or apply to any property rights (patent) on the content used in the manuscript;
- indicate if there are any other conflicts of interest.

For non-financial conflicts of interest

- Please specify any non-financial conflicts of interest: political individual, religious, ideological, educational, rational, commercial etc. related to manuscript.

Authors' contributions

This section of the manuscript is to specify the input and involvement of each author. In this regard, please follow the suggested format: *"HW conceived the study and participated in study design and helped drafting the manuscript. MG performed the processing of specimens and tissue culture methods and drafted the manuscript. TK performed immunofluorescence tests. PN participated in staining and flow-cytometry. AR participated in the study design and performed the statistical analysis. Final manuscript was read and approved by all authors".*

Each author must have an individual contribution to the research, manuscript preparation and work publication. An author should contribute substantially to one of the following: the concept and design of the work, performing of the experimental procedures, data collection, compilation, analysis, interpretation and validation of results.

According to the International Committee of Medical Journals Editors, ICMJE (www.icmje.org), as author may be a person who fit all four of following criteria:

o has made a substantial personal contribution in desi-gning,

- o a adus o contribuţie individuală substanţială conceperii, elaborării design-ului cercetării, sau a colectat, analizat sau interpretat datele;
- o a elaborat manuscrisul sau l-a revăzut în mod critic, aducând o contribuţie intelectuală importantă;
- o a aprobat versiunea finală a manuscrisului, gata pentru publicare;
- o este de acord să fie responsabilă pentru toate aspectele legate de cercetarea efectuată şi de manuscrisul depus pentru publicare şi să dea asigurare, că toate întrebările referitoare la acurateţea sau integritatea lucrării vor investigate şi rezolvate în mod corespunzător.

Notă: Persoanele, care au contribuit la realizarea lucrării, însă nu se încadrează în toate cele 4 criterii enunţate mai sus, nu pot fi considerate drept autori; contribuţia acestora va fi menţionată în secţiunea „mulţumiri şi finanţare" a manuscrisului. De asemenea, persoanele care au fost implicate doar în colectarea datelor, supraveghere, asistenţă tehnică şi finanţare, nu deţin drept de Autor, dar ei pot fi menţionaţi în secţiunea „mulţumiri şi finanţare". Simpla deţinere a funcţiei de şef de unitate, departament sau instituţie, în cadrul căreia s-a efectuat cercetarea, fără îndeplinirea tuturor celor 4 recomandări ale ICMJE, nu oferă dreptul de a fi (co)autor al lucrării.

Mulţumiri şi finanţare

Persoanele care au contribuit la elaborarea design-ul studiului, colectarea datelor, analiza şi interpretarea acestora, la pregătirea manuscrisului şi la redactarea lui critică, au oferit suport general sau tehnic, au contribuit cu materiale esenţiale pentru studiu, dar care nu îndeplinesc criteriile ICMJE de Autor, nu vor fi considerate drept Autori, dar contribuţia lor va fi menţionată în secţiunea „mulţumiri şi finanţare". Tot în această secţiune se vor menţiona sursele de finanţare ale lucrării. Menţionarea persoanelor fizice sau juridice, care au contribuit la realizarea lucrării şi manuscrisului, poate fi făcută doar după obţinerea unei permisiuni de la fiecare dintre ele.

Tabelele

Fiecare tabel va fi creat cu dublu-spaţiere şi amplasat pe o pagină separată, după textul manuscrisului. Enumerarea tabelelor va fi consecutivă, cu cifre arabe, în ordinea primei lor citări în text, scris cu caractere grase **(bold)**, alinierea – pe stânga, deasupra tabelului. Fiecare tabel va avea un titlu laconic, care va fi scris cu caractere normale (regular) sub numărul tabelului. Nu utilizaţi caractere bold în interiorul tabelului. Urmaţi exemplul prezentat:

Tabelul 1
Evenimente adverse intra-anestezice şi imediat post-extubare

	Lot experimental (n=100)	Lot control (n=100)	p
Disritmii	6,0%	3,0%	0,49
Instabilitate hemodinamică	7,0%	1,0%	0,034
Trezire prelungită*	11,0%	4,0%	0,19
GVPO† post-extubare	8,0%	27,0%	0,007
Durere intensă la trezire	17,0%	19,0%	1,0

Notă: * – trezire neobişnuit de lentă, după ce concentraţia cerebrală a reziduurilor de anestezice a trecut sub pragul de inducere a hipnozei; † – greaţă şi vomă postoperatorie. Analiza statistică utilizată: testul Fisher.

developing research protocol, or collected, analyzed and interpreted data;
- o developed or reviewed critically the manuscript bringing a significant intellectual contribution;
- o approved the final version of the manuscript ready for publication;
- o agrees to be responsible for all aspects of the conducted research and submitted manuscript and to assure that all questions relating to accuracy or completeness of the work was adequately assessed and resolved.

Note: Persons who have contributed to the work, but not fit the four criteria mentioned above cannot be considered as authors. Their contribution will be mentioned in the "Acknowledgment and funding section" of the manuscript. Also, people who have only been involved in data collection, monitoring, technical assistance and funding, are not eligible as coauthors, but they may be mentioned in the "Acknowledgements and funding" section. Mere position of head of unit, department or institution, on which the research was conducted, without fulfilling all four ICMJE criteria, doesn't provide the right to be a coauthor of the work.

Acknowledgements and funding

People who contributed to the study design, data collection, analysis and interpretation, manuscript preparation and editing, offered general or technical support, contributed with essential materials to the study, but do not meet ICMJE authorship criteria will not be considered as authors, but their contribution will be mentioned in section "Acknowledgements and funding". Also in this section must be specified the sources of work funding. Mention of persons or institutions who have contributed to the work and manuscript can be made only after obtaining permission from each of them.

Tables

Content of each table should be double-spaced and placed on a separate page after the text of the manuscript. Tables numbering will be done using consecutive Arabic numerals in the order of their first citation in the text; it is should be written in **bold**, align to left and place above the table. Each table should have a concise title that will be written in bold (regular) under table number. Do not use bold within the table. Please follow the example:

Tabelul 1
Intra-anesthetic and immediately post-extubation adverse events

	Experimental Cohort (n=100)	Control Cohort (n=100)	p
Dysrhythmia	6,0%	3,0%	0,49
Hemodynamic instability	7,0%	1,0%	0,034
Prolonged awakening*	11,0%	4,0%	0,19
PONV† post-intubation	8,0%	27,0%	0,007
Strong pain on awakening	17,0%	19,0%	1,0

Note: * – Unusually slow awaking, after that cerebral concentration of the anesthetic reach the under hypnotic level; † – postoperative nausea and vomiting. Used statistical analysis: Fisher's exact test.

Legendele şi notele explicative vor fi făcute sub tabel. Toate abrevierile non-standard se vor explica în notele de subsol, folosind următoarele simboluri, în următoarea ordine: * , † , ‡ , § , | | , , ** , † † , ‡ ‡ , § § , | | | | , ¶ ¶ etc.

Menţionaţi, de asemenea, testele statistice aplicate şi tipul de date prezentate. Asiguraţi-vă că fiecare tabel este citat în text. Dacă utilizaţi date din altă sursă publicată sau nepublicată, trebuie să obţineţi permisiunea şi să declaraţi pe deplin sursa sub tabel.

Figurile

Figurile vor fi prezentate atât în manuscris, cât şi pe fişiere separate. În manuscris, figurile vor fi prezentate după textul lucrării, fiecare pe pagină separată şi vor fi numerotate consecutiv, cu cifre arabe, în ordinea citării lor în text. Numerotarea va fi scrisă abreviat (**Fig. 1**), cu caractere grase (**bold**), alinierea – pe stânga, sub figură. Fiecare figură va avea un titlu laconic, care va fi scris cu caractere normale (regular) în dreptul numerotării.

Figurile trebuie să fie calitative, vizibile în detaliu. Fotografiile cu persoane potenţial identificabile trebuie să fie însoţite de permisiunea scrisă de a utiliza fotografia. În caz contrar, faţa persoanelor trebuie acoperită cu o bandă neagră. În cazul în care o figură a fost publicată anterior, faceţi referinţă la sursa originală şi prezentaţi permisiunea scrisă de la deţinătorul drepturilor de autor pentru a reproduce figura. Permisiunea poate fi luată atât de la autorul figurii, cât şi de la editor, cu excepţia documentelor din domeniul public.

Pentru figuri, sunt acceptate următoarele formate de fişiere:

- o TIFF
- o JPEG
- o EPS (format preferat pentru diagrame)
- o PowerPoint (figurile trebuie să fie de mărimea unui singur diapozitiv)

Titlul fişierului va consta din numărul figurii şi un titlu scurt, identificabil.

Legendele figurilor

Legenda figurii va fi scrisă în continuare, imediat după titlul figurii. Descrierea figurii nu trebuie să repete descrierea din textul manuscrisului. Când sunt folosite simboluri, săgeţi, numere sau litere pentru a identifica, descrie părţi ale ilustraţiilor, identificaţi-le şi explicaţi-le pe fiecare în mod clar în legendă. Explicaţi scala internă şi identificaţi metoda de colorare în microfotografii.

Vă rugăm să reţineţi că este de responsabilitatea autorului (autorilor) de a obţine permisiunea de la deţinătorul drepturilor de autor pentru a reproduce figuri sau tabele care au fost publicate anterior în altă parte. Imaginile color vor fi tipărite din contul autorilor.

Referinţele bibliografice

Toate referinţele bibliografice trebuie să fie numerotate consecutiv, între paranteze pătrate [ ], în ordinea în care sunt citate în text. Citatele de referinţă nu trebuie să apară în titluri sau subtitluri. Fiecare referinţă trebuie să aibă un număr individual. Citările multiple din cadrul unui singur set de paranteze trebuie să fie separate prin virgulă şi spaţiu. În cazul în care există trei sau mai multe citări secvenţiale, acestea ar trebui să fie indicate sub formă de serie. Exemplu: [1, 5-7, 28].

Vă rugăm să evitaţi folosirea excesivă a referinţelor. În cazul în care se folosesc sisteme automate de numerotare, numerele de

Legends and notes will be place under the table. All non-standard abbreviations should be explained in footnotes, using the following symbols, in the following order: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡, § §, | | | |, ¶ ¶ etc.

Applied statistical tests and the type of presented data should be also mentioned. Make sure that each table is cited in the text. If you use data from another published or unpublished source, you must obtain permission and cited the source below the table.

Figures

Figures will be included in the main manuscript, and also submitted as separate files. The manuscript figures should be presented, each one on a separate page and should be numbered consecutively with Arabic numerals in the order of their citation in the text. Figure numbering will be written abbreviated (Fig. 1), using bold fonts, left alignment, and placed under the figure. Each figure should have a laconic title that will be written using regular font and place in the right of the figure's number. Figures' quality should assure the visibility of details. Pictures of persons potentially identified must be accompanied by written permission to use it. If a figure has been previously published, please cite the original source and submit the written permission to reproduce the figure from the copyright owner. Permission can be taken from both the author and the publisher, except the documents of public domain.

For figures, the following file formats are accepted:

- o TIFF
- o JPEG
- o EPS (preferred format for diagrams)
- o PowerPoint (figures should be of the size of a single slide)

The file title should include the figure number and an identifiable short title.

Figures' legends

Figure's legend should be written immediately after the figure's title. Figure's description should not repeat the description in the text of the manuscript. When used symbols, arrows, numbers or letters to describe parts of the figure, explain clearly each one of them in the legend. Explain the internal scale and identify the staining method of the photomicrographs.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have been published previously elsewhere. Color images will be printed at the expense of the manuscript authors.

References

All references must be numbered consecutively, in square brackets [ ], in the order they are cited in the text. Reference citations should not appear in titles or subtitles. Each reference should have an individual number. Multiple citations within a single set of brackets must be separated by commas and spaces. If there is a sequence of three or more citations, they have to be given as a range (e.g. [1, 5-7, 28]).

Please avoid excessive use of references. If an automatic system of citation is used, reference numbers must be finalized and the bibliography must be fully formatted before submission. Reference list should include all authors. Journals' abbreviation must be in accordance with Index Medicus/MEDLINE. It may be cited only

referinţă trebuie să fie finalizate, iar bibliografia trebuie formatată complet înainte de depunere. Lista de referinţă trebuie să conţină toţi autorii. Abrevierea revistelor trebuie să fie în conformitate cu Index Medicus / MEDLINE. Pot fi citate doar articolele sau rezumatele care au fost publicate şi care sunt disponibile, accesibile prin intermediul serverelor publice. Orice rezumate sau articole nepublicate sau cu caracter personal nu trebuie să fie incluse în lista de referinţă, dar pot fi incluse în text şi citate în mod corespunzător, indicând cercetătorii implicaţi. Obţinerea permisiunii printr-o scrisoare de la autori pentru a le cita comunicările sau datele nepublicate sunt în responsabilitatea autorului corespondent al articolului.

Formatul referinţelor

Autorii sunt rugaţi să furnizeze cel puţin un link pentru fiecare referinţă bibliografică (preferabil PubMed).

o *Referinţă la revistă*

Numele şi iniţialele autorului sau al autorilor, separate prin virgulă (regular). Titlul articolului (regular). Forma abreviată a denumirii revistei (italice), urmat de anul, numărul volumului: numărul paginilor (regular). Articolele în curs de publicare citate vor fi menţionate cu „***In press***" (italic, bold), după numărul paginilor. Se vor menţiona toţi autorii articolului.

Ex: „1. Belîi A., Cobâleţchi S., Casian V., Belîi N., Severin G., Chesov I., Bubulici E. Les aspects pharmaco-economiques dans la gestion de la douleur perioperatoire. Mise au point. *Ann Fr Anesth Réanim*, 2012; 31: 60-66."

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