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CONTENT

PUBLIC HEALTH AND EPIDEMIOLOGY

L. V. Levytska, V. V. Yurkiv, M. M. Korda PREDICTORS OF LOW FUNCTIONAL RESERVES IN REHABILITATION OF PATIENTS WITH MYOCARDIAL INFARCTION COMPLICATED BY COMORBID PATHOLOGY.....	5
--	---

T. V. Lunova, I. M. Klishch GENDER DIFFERENCES IN THE INFLUENCE OF COMORBID CONDITIONS ON THE LONG-TERM OUTCOMES OF PATIENTS WITH ACUTE CORONARY SYNDROME.....	11
---	----

SURGICAL DISEASES

S. Y. Zaporozhan, D. B. Fira, O. V. Pokryshko ANTIBACTERIAL THERAPY FOR PATIENTS WITH BURN INJURIES.....	18
---	----

I. Y. Galaychuk ONCOPLASTIC CONE-SHAPED REMOVAL OF MELANOMA IN SITES WITH LIMITED SKIN RESOURCES.....	25
---	----

V. V. Nair, P. Sharma, N. Rajendran, S. Raja, P. P. Rao, R. Mehta CASE REPORT ON RARE OUTCOME OF A RETROPERITONEAL MASS: MANAGEMENT CHALLENGES AND LESSONS LEARNT.....	31
--	----

T. B. Singh, R. Kumar, A. Nigam, T. R. Devi AN OBSERVATIONAL STUDY TO FIND RELATIONSHIP OF ACUTE APPENDICITIS TO MENSTRUATION CYCLE IN NORTHERN AND NORTHEASTERN PART OF INDIA.....	37
---	----

I. Ya. Dzyubanovskyy, A. D. Bedeniuk, S. Y. Grytsenko CLINICAL OUTCOMES OF REVERSAL OF HARTMANN'S PROCEDURE.....	44
---	----

I. K. Venher, S. Ya. Kostiv, B. P. Selskyi, D. V. Khvalyboha, M. Yu. Orlov, I. V. Faryna, N. I. Tsiupryk ENDOVASCULAR ANGIOPLASTY FOR MULTI-LEVEL STENOTIC-OCCLUSIVE LESIONS OF THE FEMORAL-DISTAL ARTERIAL BED IN CASES OF STENOTIC-OCCLUSIVE PROCESS OF THE TIBIAL ARTERIES	48
---	----

J. S. Randhawa, N. Rajendran, J. Husain, R. Shankaran, V. V. Nair, S. Dorai B. SHORT TERM STUDY ON CLINICAL RELEVANCE AND OUTCOMES OF FOETAL HYDRONEPHROSIS.....	55
--	----

PSYCHIATRY

R. Jahagirdar ATTITUDE TOWARDS PSYCHIATRY AND PSYCHIATRISTS AMONG MEDICAL STUDENTS IN TERTIARY HEALTH CARE HOSPITAL	62
---	----

BIOMEDICAL SCIENCES

M. V. Danchyshyn, O. V. Lototska

ANTIOXIDANT PROTECTION IN WHITE RATS ON THE BACKGROUND

OF DRINKING WATER USE WITH EXCESSIVE NITRATE CONCENTRATION..... 67

I. M. Klishch, A. V. Dovbush, H. O. Havryliuk-Skiba, O. P. Andriyishyn

SUBMICROSCOPIC CHANGES IN HEMOCAPILLARIES OF ADRENAL GLAND

AND PANCREATIC ISLETS OF LANGERHANS IN CASES

OF IMMOBILIZATION STRESS WITH UNDERLYING HYPOTHYROIDISM..... 74

M. Marushchak, O. Mialiuk, M. Kaskiv, M. Demjanchuk, I. Krynytska

STRUCTURAL ORGANIZATION OF RAT TISSUES IN EXPERIMENTAL

COMBINED TRAUMA OF THE CHEST AND BOTH THIGHS 81

PREDICTORS OF LOW FUNCTIONAL RESERVES IN REHABILITATION OF PATIENTS WITH MYOCARDIAL INFARCTION COMPLICATED BY COMORBID PATHOLOGY

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Background. Myocardial infarction (MI) is one of the leading causes of death in working age population; the risk of cardiovascular complications for survivors of acute MI complicated by comorbid pathology (CP) is very high.

Objective. The study is aimed to search for reliable prognostic markers for risk of reducing the functional reserves of the cardiovascular system in myocardial infarction with comorbid pathology.

Methods. The prospective study involved 371 patients with MI, who received non-invasive therapy and were observed for a 90-day period after admission to the hospital. All patients were examined and treated according to current protocols.

Results. It was found that 6-minute walk test (6MWT) is a specific and highly sensitive prognostic marker of functional reserves for patients with MI with CP (specificity – 100%, sensitivity – 63%, prognostic value of a positive result – 100%) with the Charlson comorbidity index (CCI) ≥ 2 . The correlation of 6MWT performed on the 10th, 30th and 90th day of rehabilitation was revealed with the age of patients, SpO₂, respiratory rate, systolic blood pressure, heart rate, left ventricular ejection fraction, levels of troponin T, creatinine, the number of lymphocytes in the peripheral blood, CCI ($p < 0.05$).

Conclusions. During the 90-day rehabilitation period of a patient with MI complicated by CP, the markers of reduced exercise tolerance to be monitored are: blood pressure levels, respiratory rate, troponin T, creatinine, cholesterol, low-density lipoprotein, SpO₂, the number of lymphocytes in the peripheral blood. To improve control over the process of rehabilitation in patients with MI complicated by CP the 6MWT and CCI should be used.

KEYWORDS: myocardial infarction; comorbid pathology, Charlson comorbidity index, 6-minute walk test, predictors of functional reserves.

Introduction

Myocardial infarction (MI) is the main cause of cardiovascular mortality in the human population [1, 2]. To date, there is no single strategy for the use of clinical, laboratory, imaging parameters to predict risks in the treatment and rehabilitation of patients with MI. The task of risk prevention in patients with MI with comorbid pathology (CP) is particularly difficult [3, 4]. The objectives of this study were to identify and evaluate the predictors of severe MI with CP in the stages of rehabilitation.

Methods

The prospective study involved 371 patients with MI, who received non-invasive therapy and were observed for a 90-day period from ad-

mission to the hospital in 2014-2019. All patients were examined and treated according to the current protocols. Clinical, laboratory and instrumental examinations were performed on the 1st, 10th, 30th and 90th days. Cardiovascular functional reserves were determined by the degree of heart failure (Killip and NYHA), echocardiography and 6-minute walk test (6MWT) on the 10th, 30th and 90th days of MI. Risk assessment was performed according to the GRACE scale and the AACPR cardiovascular risk scale. The Charlson Comorbidity Index (CCI) was used to estimate the degree of comorbidity [5, 6, 7]. Statistical analysis was performed using software products MSExcel 2000, EVIEWS 5.1. and SPSS.

Results

There were 67.4% of men and 32.6% of women aged (66.2 $\pm$ 10.4) years involved in the study. Comorbid pathology was detected in

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93.8 % of the patients: arterial hypertension – in 84.9%; diabetes mellitus – in 25.1%; vascular pathology – in 35.6%. Analysis of exercise tolerance and rehabilitation potential in the study cohort showed that inpatients had predominantly high heart failure and reduced cardiac reserves. Thus, the six-minute walk test performed in patients on the 10th day after admission was (76.1±35.2) m; on the 30th and 90th days – (133.8±49.6) m and (207.6±74.1) m, respectively. Their NYHA functional class was high (2.9±0.7), and the risk on the GRACE scale and the AACPR risk scale was high and very high (2.9±0.3) and (2.7±0.6), respectively. Rehabilitation and hemodynamic potentials, reflected by the functional class according to the rehabilitation classification and parameters of left ventricular systolic function, also indicated a significant depletion of functional reserves of the cardiovascular system. Thus, the functional class according to echocardiography was (2.9±0.8) points, and the class according to the rehabilitation classification was (3.3±0.7).

The possible correlations between the degrees of cardiovascular risk according to the GRACE, AACPR scales, functional classes according to the rehabilitation classification, functional classes of heart failure (Killip, NYHA) and the presence and severity of comorbid pathology were assessed. High reliability ($p<0.0001$) relationships were found between the presence of CP and the categorical indicators of functional class of heart failure according to Killip, NYHA and the degree of risk according to AACPR (Table 1).

The proportion of patients at maximum risk for GRACE was significantly higher in patients with MI with CP than in those without CP (Z-test = -4.399; $p<0.0001$). Risk levels for GRACE in patients with MI with CP directly correlated with age ($r=0.267$; $p<0.0001$), respiratory rate ($r=0.248$; $p=0.001$), glucose levels ($r=0.2$; $p=0.007$) and CCI ($r=0.275$; $p<0.0001$). High

specificity (92.5%) and sensitivity (87.1%) of the GRACE calculator and the AACPR risk scale (94.2% and 71.0%, respectively) with a high prognostic value of a positive result (97% for both risk scales) and CCI ≥ 2 was determined. The obtained data allow using the GRACE calculator and the AACPR risk scale to predict early risks and possible negative consequences of the standard rehabilitation program at the hospital stage, as well as stratification of comorbid patients into individualized rehabilitation programs in the acute phase of rehabilitation.

The correlation of high reliability of CCI with risk levels according to GRACE ($r=0.542$ according to the association coefficient), functional class according to NYHA and 6MWT on the 10th, 30th and 90th days of rehabilitation was revealed; ($r_{6MWT10}=-0.318$; $r_{6MWT30}=-0.397$; $r_{6MWT90}=-0.425$) ($p<0.0001$).

It was established that the six-minute walk test is a specific and highly sensitive prognostic marker of functional reserves for patients with MI and CP (specificity – 100%, sensitivity – 63 %, prognostic value of a positive result – 100%), CCI ≥ 2 . The correlation of 6MWT performed on the 10th, 30th and 90th days of rehabilitation (6MWT₁₀, 6MWT₃₀ and 6MWT₉₀) was revealed regarding the age of patients ($r_{6MWT10}=-0.199$; $r_{6MWT30}=-0.287$; $r_{6MWT90}=-0.410$ respectively; $p<0.05$), SpO₂ ($r_{6MWT10}=0.399$; $r_{6MWT30}=0.265$; $r_{6MWT90}=0.248$; $p<0.05$), respiratory rate ($r_{6MWT10}=-0.318$; $r_{6MWT30}=-0.357$; $r_{6MWT90}=-0.298$; $p<0.0001$), systolic blood pressure ($r_{6MWT10}=0.179$; $r_{6MWT30}=0.205$; $p<0.05$), heart rate ($r_{6MWT10}=-0.259$; $r_{6MWT30}=-0.179$; $p<0.05$), left ventricular ejection fraction ($r_{6MWT10}=0.706$; $r_{6MWT30}=0.706$; $r_{6MWT90}=0.583$; $p<0.0001$), levels of troponin T ($r_{6MWT10}=-0.210$; $r_{6MWT30}=-0.312$; $p<0.05$), creatinine ($r_{6MWT10}=-0.148$; $p<0.05$), lymphocyte count in peripheral blood ($r_{6MWT10}=-0.303$; $r_{6MWT30}=-0.278$; $r_{6MWT90}=-0.294$; $p<0.0001$), CCI ($r_{6MWT10}=-0.323$; $r_{6MWT30}=-0.398$; $r_{6MWT90}=-0.427$; $p<0.0001$).

Table 1. **Dependence of functional categorical indicators in patients with myocardial infarction on the presence of comorbid pathology**

Index	FC according to Killip	FC according to NYHA	Risk degree according to AACPR	FC according to rehabilitation classification
Pearson's coefficient of mutual conjugation	0.258	0.237	0.370	0.286
Chuprov coefficient of mutual conjugation	0.189	0.206	0.334	0.251
Cramer's coefficient of mutual conjugation	0.267	0.244	0.398	0.299
χ^2 (p-value)	<0.0001	<0.0001	<0.0001	<0.0001

According to the results obtained, most of these dependence factors are repeated at all three stages of rehabilitation; therefore, their significant impact on exercise tolerance during the 90-day period of the cardiorehabilitation program is obvious. In general, the patients with MI with CP and high age indices, RR, heart rate, creatinine, troponin T and Charlsson comorbidity index, as well as low SBP in the acute period of MI, SpO₂ and LVEF have significantly lower tolerance to physical activity at all stages of rehabilitation. Therefore, the above parameters can be considered to be the main functional clinical, hemodynamic and laboratory markers of reduced tolerance to exercise; they should be used to monitor the response to increased physical activity and predict the tolerability of rehabilitation measures in patients with MI associated with comorbid pathology.

Discussion

Profound disturbances of functional reserves in this category of patients were associated with late treatment (20.34±15.11 hours), and, accordingly, the lack of timely revascularization of the infarct-related artery. The age category of patients (mean age (66.16±10.41) years) and the presence of comorbid pathology in most patients (93.8%) were also significant. This profile of infarct patients, which is characterized by late treatment, and, consequently, the loss of timely revascularization of infarct-related artery, the presence of comorbid pathology and old age of patients, is still common in Ukraine and requires special approaches unprescribed in the current protocols of rehabilitation. Most studies [8-13] confirm the significant negative impact of comorbid pathology on the functional state and reserve capacity of the cardiovascular system in patients with MI with a high efficiency of adequate rehabilitation programs.

The study confirms the possibility of using the Charlsson index to quantify the degree of comorbidity in patients with MI and various comorbid pathologies and predict their reaction to exercise tolerance in the rehabilitation stages. So, the interdependence of the degree

of Charlsson comorbidity and the six-minute walk test in the stages of rehabilitation was analyzed [14, 15]. It was established that 6MWT₁₀, 6MWT₃₀ and 6MWT₉₀, which reflect exercise tolerance, in the acute (inpatient) and subacute (early and late outpatient) phases of rehabilitation process in the patients with a higher degree of comorbidity were significantly lower ($p<0.0001$), $r_{6MWT10}=-0.318$; $r_{6MWT30}=-0.397$; $r_{6MWT90}=-0.425$, respectively.

Analysis of the specificity and sensitivity of the six-minute walk test on the 10th day of rehabilitation of postinfarction patients with the parameters of the Charlsson comorbidity index ≥ 2 showed high specificity and prognostic value of a positive result of this marker for comorbid patients (Table 2, Fig. 1). According to the results of the ROC analysis, it was established that the best quality of the model for 6MWT₁₀ (AUC=0.75, 95% CI (0.672-0.828) provides a threshold value (distribution point) <83.5 m with the specificity of 100%, sensitivity – 63%, and the prognostic value of a positive result – 100%.

The corresponding values for 6MWT performed on the 30th and 90th days after the beginning of MI were also with the maximum specificity (100%) and prognostic value of a positive result (100 %) for 6MWT₃₀ values in the range from 147 to 166.5 m (95% CI (0.766-0.904), $p=0.005$; area under the ROC curve 0.835) and 6MWT₉₀ in the range of 199.5-227.5 m (95% CI (0.741-0.933), $p=0.005$; area under ROC curve 0.837). Thus, the analysis of the specificity and sensitivity of the six-minute walk test on the 10th, 30th and 90th days of rehabilitation of postinfarction patients with CCI values ≥ 2 showed maximum specificity (100%) and prognostic value of a positive result (100 %) of this marker in comorbid patients. Accordingly, the 6MWT targets by the end of the first decade of the rehabilitation period in patients with MI with the Charlsson comorbidity index ≥ 2 were in the range of 83.5-98 m, by the end of the first month of rehabilitation – 147.0-166.5 m and by the end of the first trimester after the index date – 199.5-227.5 m. The results suggest that the Charlsson comorbidity index and the six-

Table 2. Matrix for sensitivity and specificity of 6MWT₁₀ at CCI values ≥ 2

6MWT ₁₀ value	Sensitivity	Specificity	Prognostic value of a positive result
83.5	0.63	1	1
98.0	0.80	0.33	0.97
100.5	0.81	0.33	0.97

Note. 95% CI (0.672-0.828), $p=0.038$.

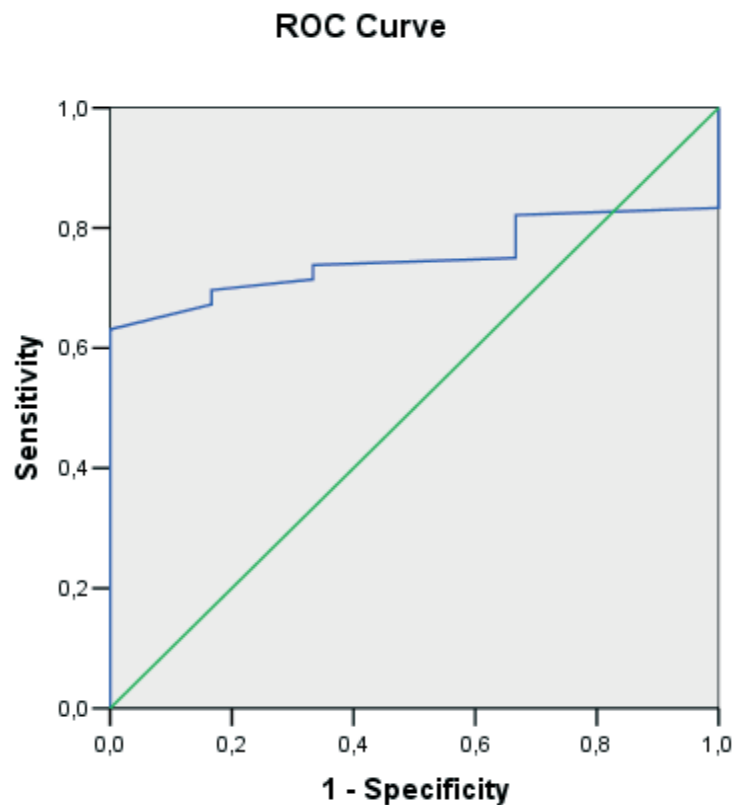


Fig. 1. ROC-curve of sensitivity and specificity of 6MWT₁₀ at values of CI >2 (area under the curve 0.75, standard error 0.040; p=0.038).

minute walk test are highly specific and sensitive prognostic markers of exercise tolerance in patients with MI with comorbid pathology at all stages of rehabilitation.

Conclusions

During the 90-day rehabilitation period of a patient with myocardial infarction and CP, the markers of reduced exercise tolerance to be monitored are blood pressure levels, heart rate, respiratory rate, SpO₂, troponin T, creatinine, the number of lymphocytes in the peripheral blood. The basic test for monitoring functional reserves in patients with MI and CP during the 90-day period is 6MWT. To improve control over

the process of rehabilitation in patients with MI and CP, the Charlson comorbidity Index should be used in addition to GRACE and AACPR cardiovascular risk scales.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Larysa V. Levytska – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Viktoriia V. Yurkiv* – data curation, writing – reviewing and editing; *Mykhaylo M. Korda* – investigation, formal analysis, writing – reviewing and editing.

ПРЕДИКТОРИ НИЗЬКИХ ФУНКЦІОНАЛЬНИХ РЕЗЕРВІВ У ХВОРИХ НА ІНФАРКТ МІОКАРДА, УСКЛАДНЕНИЙ КОМОРБІДНОЮ ПАТОЛОГІЄЮ

*Л. В. Левицька, В. В. Юрків, М. М. Корда

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,
ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Інфаркт міокарда (ІМ) є однією з головних причин смертності у працездатному віці, а ризик серцево-судинних ускладнень для тих, хто виживає в гострий період ІМ з коморбідною патологією (КП), є дуже високим.

Мета. Пошук надійних прогностичних маркерів ризику зниження функціональних резервів серцево-судинної системи при інфаркті міокарда з коморбідною патологією.

Методи. У проспективне дослідження було включено 371 хворого на інфаркт міокарда, які отримували неінвазивне лікування та спостерігалися протягом 90 днів з моменту надходження до стаціонару. Усі пацієнти були обстежені та проліковані згідно з діючими протоколами.

Результати. Встановлено, що тест шестихвилинної ходьби (ТШХ) є специфічним і високочутливим прогностичним маркером функціональних резервів у хворих на ІМ з КП (специфічність – 100%, чутливість – 63%, прогностичне значення позитивного результату – 100%) з ІКЧ ≥ 2 . Виявлено кореляцію ТШХ, проведеного на 10, 30 і 90 день реабілітації, з віком пацієнтів, частотою дихання (ЧД), SpO_2 , систолічним артеріальним тиском, частотою серцевих скорочень (ЧСС), фракцією викиду лівого шлуночка (ФВ), рівнями тропоніну Т, креатиніну, кількістю лімфоцитів в периферичній крові та індексом коморбідності Чарльсон ІКЧ ($p < 0,05$).

Висновки. Протягом 90-денного періоду реабілітації хворих на інфаркт міокарда з коморбідною патологією маркерами зниженої толерантності до фізичних навантажень, які потребують моніторингу, є рівні артеріального тиску, ЧСС, ЧД, SpO_2 , тропоніну Т, креатиніну, кількість лімфоцитів в периферичній крові. Для покращення контролю за процесом реабілітації у хворих на ІМ з КП доцільно використовувати ТШХ та ІКЧ.

КЛЮЧОВІ СЛОВА: інфаркт міокарда; коморбідна патологія, індекс коморбідності Чарльсон, тест 6-хвилинної ходьби, предиктори функціональних резервів.

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GENDER DIFFERENCES IN THE INFLUENCE OF COMORBID CONDITIONS ON THE LONG-TERM OUTCOMES OF PATIENTS WITH ACUTE CORONARY SYNDROME

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Background. Gender differences in the baseline characteristics of patients with the acute coronary syndrome (ACS) have been widely acknowledged. Women are known to be generally older with a higher prevalence of comorbidities.

Objectives. Gender differences in the baseline characteristics of patients with the acute coronary syndrome (ACS) have been widely acknowledged. Women are known to be generally older with a higher prevalence of comorbidities. At the same time, it is now yet clear which comorbid conditions have the most significant impact on the long-term outcomes of patients with ACS and if there are any gender differences in this respect.

Methods. We performed a retrospective cohort study of 167 patients (109 men and 58 women) admitted to the acute coronary unit of Ternopil Municipal Hospital with ACS in 2016-2017. All relevant clinical information has been recorded in the pre-designed data charts. The incidence of repeated major adverse cardiovascular events (MACEs) has been assessed over 36 months after the hospital discharge via an e-Health electronic system.

Results. In this cohort, female patients with ACS had a higher prevalence of comorbid conditions: 15.5% of women vs. 11% of men with ACS had ≥ 5 comorbidities, 65.5% of women and 60% of men had 2-4 comorbid conditions, and 19% of women vs. 29% ≤ 1 concomitant disease. The comorbidity structure also differed between genders. Women more often had concomitant cerebrovascular diseases (17.2% vs. 7.3%, $p=0.05$), dementia (15.5% vs. 5.5%, $p=0.03$), connective tissue disorders (17.25% vs. 6.42%, $p=0.03$) and thyroid disease (12.1% vs. 2.8%, $p=0.02$). Men more often suffered from peptic ulcer (13.7% vs. 3.4%, $p=0.05$). The incidence of MACEs during the follow-up period rose sharply with age and was higher in females (55% vs. 33%, $p=0.003$). In the multivariable model, PAD (OR 9.5, 95% CI: 1.7-52.3, $p=0.01$) and thyroid disease (OR 7.2, 95% CI: 1.19-43.2, $p=0.03$) demonstrated the most significant impact on the long-term event-free survival of females in the cohort. In turn, a solid metastatic tumor was the most significant predictor of poor prognosis in men (OR 6.3, 95% CI: 2.13-18.9, $p=0.001$).

Conclusions. We observed significant gender differences in the prevalence of comorbid conditions and their influence on the three-year event-free survival of patients with ACS. The predictive value of comorbidities should be further investigated, preferably, with the involvement of larger cohorts.

KEYWORDS: acute coronary syndrome; gender; outcomes.

Introduction

Cardiovascular disease (CVD) remains the number one cause of death of males and females all around the world with coronary heart disease (CHD) representing the major proportion [1]. The common misconception about CHD being predominantly "male" disease has been confronted few decades ago, and gender differences in clinical presentation and treatment strategies have been widely acknowledged. Significant body of evidence suggests that females presenting with acute coronary syndrome (ACS) are usually older and more often have concomitant arterial hyper-

tension (AH) and diabetes mellitus (DM) [7]. It is also known that female patients with ACS have generally worse short-term and long-term outcomes as compared with males [3-6]. Studies indicate that such disparities may be attributed to older age and higher prevalence of comorbidities in female patients [5, 6]. Nevertheless, it is still not well-established which comorbid conditions have the most significant impact on the long-term outcomes of men and women with ACS.

In this study, we analyzed existing gender differences in the prevalence of comorbid conditions in patients with ACS. We also aimed at identifying which comorbidities had the most significant impact on the long-term prognosis of men and women with ACS.

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Methods

We performed a retrospective cohort study of 167 patients admitted to the acute coronary unit of Ternopil Municipal Hospital with ACS in 2016-2017. Study sample was divided into two gender groups (109 males and 58 females). Relevant clinical data has been extracted from medical records and indicated in pre-designed data charts. Comorbidity structure in the following cohort has been assessed drawing on Charlson Comorbidity Index. The 3-year follow-up of the patients has been conducted through e-Health system and in rare cases patients have been contacted by phone. The incidence of repeated major adverse cardiovascular events (MACEs) throughout 36 months after hospitalization has been assessed which included all-cause death, acute myocardial infarction and unstable angina.

ACS included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Comorbid conditions of patients were mentioned in their medical records or diagnosed during their hospital stay according to the guideline-based diagnostic criteria. Such comorbidities from Charlson Comorbidity Index were analyzed in the study: prior acute myocardial infarction (prior AMI), congestive heart failure (HF), AH, peripheral artery disease (PAD), chronic kidney disease (CKD), liver disease, chronic obstructive pulmonary disease (COPD), leukemia, hemiplegia, metastatic solid tumor, AIDS, lymphoma, connective tissue disorders, cerebrovascular disease, dementia, DM, peptic ulcer. Additionally, we analyzed the prevalence of thyroid disease and anemia in selected patients.

All statistical information has been processed using IBM SPSS Statistics 22.0 software. Continuous variables were expressed as mean± standard deviation (SD). Numbers and percentages were used for categorical data. Differences between groups were analyzed using Student's *t*-test for continuous data and Pearson's Chi-square test for categorical variables. A *p*-value of <0.1 was considered significant. The evaluation of prognostic impact of particular comorbidities was performed in multivariable

analysis adjusting to various confounders, such as age, cardiogenic shock, elevated cardiac troponin levels. The predictors of MACE were presented as adjusted odds ratios (OR). The analysis was performed separately for two gender groups.

Results

Women in the following cohort were in general 10 years older than men (69.5±21.5 vs. 59.5±28.5, *p*<0.001). Female patients with ACS more often experienced nausea, vomiting, palpitations and fatigue instead of typical chest pain. They were also more likely to be hospitalized more than 12 hours after the symptom onset (64% vs. 41%, *p*=0.006). Men were more often smokers while women were more often obese. Female patients with ACS more often than male had preserved ejection fraction (55.0% vs. 38.0%, *p*=0.04), but at the same time, they more often developed cardiogenic shock (12.0% vs. 3.7%, *p*=0.04). STEMI was more often diagnosed in male patients (55% vs. 36%, *p*=0.02), while NSTEMI and UA more often occurred in females (64% vs. 45%, *p*=0.02).

We observed significant gender differences in clinical profiles of patients in the following cohort. In general, female patients with ACS had higher prevalence of comorbid conditions: 15.5% of women vs. 11% of men with ACS had ≥5 comorbidities, 65.5% of women and 60% of men had 2-4 comorbid conditions and 19% of women vs. 29% ≤1 concomitant disease (Table 1).

In the following cohort of patients with ACS, women more often had concomitant cerebrovascular diseases (17.2% vs. 7.3%, *p*=0.05), dementia (15.5% vs. 5.5%, *p*=0.03) and connective tissue disorders (17.25% vs. 6.42%, *p*=0.03). Thyroid disease was also more often diagnosed in female patients (12.1% vs. 2.8%, *p*=0.02). Men more often suffered from peptic ulcer (13.7% vs. 3.4%, *p*=0.05). We did not observe statistically significant gender differences in the prevalence of arterial hypertension (AH), peripheral artery disease (PAD), prior myocardial infarction (prior AMI), chronic kidney disease (CKD), liver disease and COPD in the selected cohort. Diabetes mellitus was more often found in female pa-

Table 1. Gender differences in the prevalence of comorbid conditions

Number of comorbidities	1 group (men)	2 group (women)
≤1	32 (29%)	11 (19%)
2-4	66 (60%)	38 (65.5%)
≥5	12 (11%)	9 (15.5%)

tients (34.5% vs. 25%), but the difference was not considered significant ($p=0.1$). Gender differences in the comorbidity structure are demonstrated in the table 2.

The incidence of MACEs during the follow-up period was significantly higher in females than in males (55% vs. 33%, $p=0.003$). The probability of adverse outcomes rose sharply with age. Among female patients with ACS aged 65 and older, the cumulative MACEs rate was

significantly higher than in younger women (66% vs. 30%). Similarly, 27% of men younger than 65 years old experienced recurrent MACEs within the following 3 years after hospital discharge and 44% of men, aged 65 and older. Kaplan-Meier analysis identified significant gender differences in the 3-year event-free survival of patients older than 65 years old and no sex differences in the prognosis of younger patients (Figure 1, 2).

Table 2. Gender differences in the comorbidity structure

Comorbid condition	1 group (men) n=109	2 group (women) n=58	p-value
Prior Acute Myocardial Infarction	n=32 (29%)	n=18 (31%)	$p=0.8$
Congestive heart failure	n=16 (15%)	n=10 (17%)	$p=0.5$
Peripheral artery disease	n=11 (10%)	n=5 (9%)	$p=0.9$
Dementia	n=6 (5.5%)	n=9 (15.5%)	$p=0.03$
Diabetes Mellitus	n=27 (25%)	n=20 (34.5%)	$p=0.1$
Cerebrovascular disease	n=8 (7%)	n=10 (17%)	$p=0.05$
COPD	n=6 (5.5%)	n=3 (5%)	$p=0.9$
Connective tissue disorders	n=7 (6%)	n=10 (17%)	$p=0.03$
Peptic ulcer	n=15 (14%)	n=2 (3%)	$p=0.05$
Chronic kidney disease	n=17 (16%)	n=8 (14%)	$p=0.7$
Hemiplegia	n=0 (0%)	n=0 (0%)	–
Leukemia	n=1 (1%)	n=0 (0%)	–
Lymphoma	n=0 (0%)	n=0 (0%)	–
Metastatic solid tumor	n=6 (5.5%)	n=1 (2%)	$p=0.2$
Liver disease	n=26 (24%)	n=14 (24%)	$p=0.9$
AIDS	n=0 (0%)	n=0 (0%)	–
Arterial hypertension	n=89 (82%)	n=53 (91%)	$p=0.1$
Other comorbidities			
Thyroid disease	n=3 (3%)	n=7 (12%)	$p=0.02$
Anemia	n=13 (12%)	n=7 (12%)	$p=0.2$

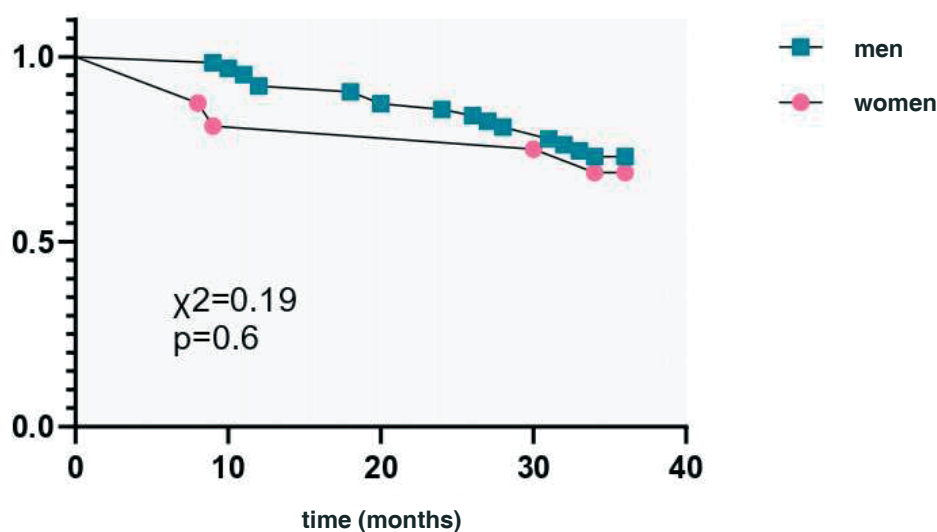


Fig. 1. Event-free survival (36 months) of patients older than 65 years.

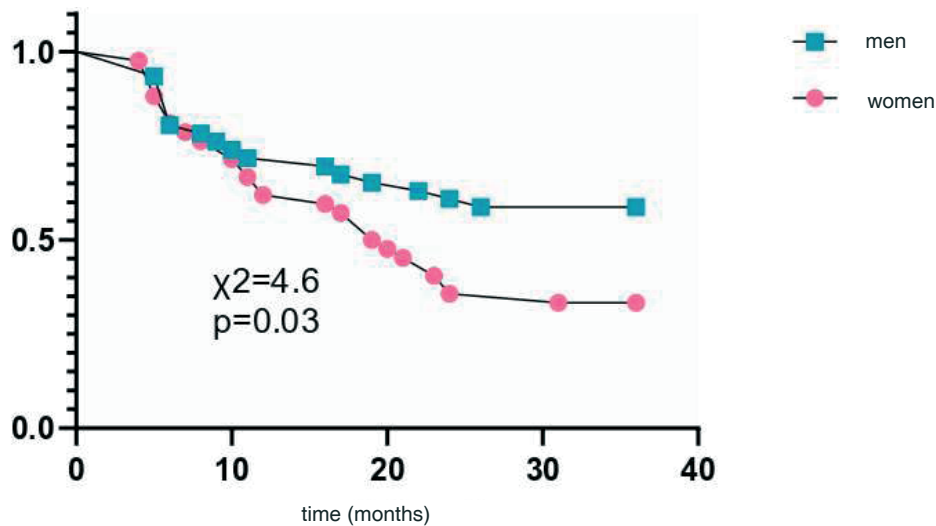


Fig. 2. Event-free survival (36 months) of patients younger than 65 years.

Multivariable analysis identified 7 comorbid conditions that most significantly influenced the prognosis in men (Table 3). According to obtained results, the greatest negative impact on the event-free survival of male patients in this cohort had metastatic solid tumor (OR 6.3, 95% CI: 2.13-18.9, $p=0.001$). Cerebrovascular disease, peptic ulcer, dementia and CKD were associated with more than twice higher chances of MACEs in the future while PAD and prior MI with 1.5 times higher probability of MACEs.

In the multivariable model, PAD (OR 9.5, 95% CI: 1.7-52.3, $p=0.01$) and thyroid disease (OR 7.2, 95% CI: 1.19-43.2, $p=0.03$) demonstrated the most significant impact on the long-term event-free survival of females in this cohort. Con-

gestive HF (OR 2.92, 95% CI: 0.6-14.2, $p=0.06$), prior MI (OR 1.86, 95% CI: 0.6-5.7, $p=0.075$) and AH (OR 2.3, 95% CI: 0.4-12.0, $p=0.06$) also negatively affected the prognosis of women with ACS. Higher incidence of recurrent MACEs was found in females with ACS and gynecological diseases, such as endometriosis, polycystic ovary syndrome, dys hormonal states of the reproductive system, uterine extirpation, etc. (OR 5.4, 95% CI: 0.9-10.3, $p=0.04$), (Table 4).

Discussion

This article provides an additional insight into gender-related differences in the prevalence of comorbidity in patients with ACS as well as the prognostic impact of comorbid conditions

Table 3. Multivariable analysis of the prognostic impact of comorbid conditions in men with ACS

Variables	SE	p-value	OR	95% CI	
				Lower	Upper
Age	0.017	0.510	1.011	0.979	1.045
Elevated cardiac troponin levels*	0.380	0.849	1.075	0.511	2.264
Ectopic rhythm	0.493	0.563	0.752	0.286	1.975
Cardiogenic shock	0.045	0.501	1.054	0.453	1.843
Prior MI	0.424	0.090	1.403	0.612	3.219
Congestive HF	0.577	0.740	0.826	0.267	2.558
PAD	0.580	0.084	1.901	0.610	5.925
Dementia	0.948	0.096	2.591	0.404	16.606
DM	0.550	0.077	0.781	0.129	1.110
Cerebrovascular disease	0.951	0.098	2.555	0.396	16.475
Peptic ulcer	0.496	0.065	2.493	0.943	6.585
CKD	0.533	0.083	2.088	0.734	5.935
Metastatic tumor	0.556	0.001	6.343	2.132	18.868

Table 4. Multivariable analysis of the prognostic impact of comorbid conditions in women with ACS

Factors				95% CI	
	SE	p-value	OR	Lower	Upper
Age	0.034	0.001	1.22	1.050	1.198
Prior MI	0.574	0.075	1.860	0.604	5.724
Congestive HF	0.805	0.060	2.925	0.604	14.166
PAD	0.870	0.010	9.498	1.725	52.303
Liver disease	0.634	0.880	0.909	0.262	3.149
AH	0.843	0.063	2.301	0.441	12.010
Thyroid disease	0.916	0.031	7.188	1.194	43.253
Gynecological diseases	0.675	0.044	5.412	0.895	10.342

in male and female patients. According to the results obtained, female patients with ACS more often experienced nausea, vomiting, palpitations and fatigue instead of typical chest pain. They were also more likely than men to be hospitalized >12 hours after the symptom onset. In the following cohort, STEMI was more often diagnosed in men and NSTEMI or UA more often occurred in women.

A substantial body of evidence suggests that female patients with ACS are usually older and have more comorbid conditions, such as diabetes mellitus (DM) and arterial hypertension (AH) [2, 7-10]. At the same time, limited number of scientific articles analyzes the prevalence of other comorbidities. In accordance with previous studies, women in the following cohort were also older and had generally worse risk profiles. Nevertheless, we did not observe significant gender differences in the prevalence of DM and AH in our study. Instead, women more often than men had concomitant cerebrovascular diseases, dementia, connective tissue disorders and thyroid disease. In turn, men more often suffered from peptic ulcer (13.7% vs. 3.4%, $P=0.05$).

Female patients with ACS showed significantly higher 3-year cumulative MACEs rates, as compared with their male counterparts. Nevertheless, such gender difference was mainly attributed to the higher incidence of recurrent events in older patients (>65 years old). Kaplan-Meier analysis did not identify any significant gender differences in the prognosis of younger patients (< 65 years old). The above mentioned results reflect the general trend in the outcomes of women with ACS. It is widely acknowledged that premenopausal women are generally protected with the anti-atherogenic and vasoprotective effects of estrogen [11, 12]. The situation changes dramatically when females reach the menopause. In such women,

we observe not only a sharp increase in the incidence of de novo CVD cases, but also a worse overall prognosis after acute ischemic events [13].

According to the results of numerous studies, female patients with ACS have generally worse unadjusted short-term and long-term mortality rates after ACS. Nevertheless, after adjustment for various factors, the gender difference was attenuated [3-6, 14]. Scientists suggest that the mortality is most likely attributed to the older age and higher prevalence of comorbidity in female patients [5, 6]. In this study, we analyzed the prognostic impact of comorbid conditions, which were included to Charlson Comorbidity Index. We also investigated the prognosis of patients with concomitant thyroid disease and the prognosis of females with gynecological diseases.

The greatest impact on the 3-year event-free survival of male patients with ACS in this cohort demonstrated solid metastatic tumor. This comorbid condition was associated with six-fold risk of MACEs during the follow-up period. Men with ACS and concomitant cerebrovascular disease, peptic ulcer, dementia and CKD had more than twice higher chances of MACEs as compared with men with no such conditions. Finally, PAD and prior MI increased the probability of recurrent MACEs in 1.5 times in male patients with ACS. The influence of other comorbidities on the long-term prognosis of men in this cohort was less significant.

PAD and thyroid disease demonstrated the most significant impact on the long-term event-free survival of women with ACS in this cohort. Females with gynecological diseases also had significantly higher incidence of recurrent MACEs within 3 years after ACS as compared with females with no history of gynecological issues. Congestive HF, prior MI and AH also negatively affected the prognosis of female

patients with ACS in this cohort. The prognostic impact of other comorbid conditions was not considered statistically significant.

Conclusions

We observed significant gender differences in the clinical profiles and the prevalence of comorbidity in patients with ACS. The cumulative incidence of 3-year MACEs was higher in women than in men. At the same time, statistically significant gender difference in the long-term outcomes has been observed exceptionally in the cohort of older patients. The influence of comorbid conditions on the event-free survival of patients with ACS differed between genders. The predictive value of comorbidities should be further investigated, preferably, with an involvement of larger cohorts.

Limitations

First of all, this is a retrospective study and the cohort of patients involved is relatively

small. That is why we deem it reasonable to conduct further research on this subject with an involvement of larger patient samples. Second, the selected patients never (or very rarely) developed leukemia, AIDS, hemiplegia and lymphoma; hence, it was impossible to investigate the influence of these conditions on the long-term prognosis in the following cohort. Third, we did not have a chance to observe the 3-year event-free survival in female patients with diagnosed metastatic tumor due to a small number of cases.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Tetiana Lunova – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Ivan Klishch* – data curation, writing – reviewing and editing.

ГЕНДЕРНІ ВІДМІННОСТІ ВПЛИВУ КОМОРБІДНИХ СТАНІВ НА ВІДДАЛЕНІ НАСЛІДКИ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ

*Т. В. Луньова, І. М. Кліщ

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Вплив статі на клінічний перебіг гострого коронарного синдрому (ГКС) у пацієнтів є широко відомим. Жінки з таким діагнозом зазвичай старші та мають більше супутніх захворювань.

Мета. У даній роботі ми мали на меті дослідити, які фактори впливають на довготривалий прогноз та віддалені наслідки у пацієнтів з ГКС.

Методи. Ретроспективне когортне дослідження включало 167 пацієнтів (58 жінок та 109 чоловіків), які проходили лікування на базі Тернопільської міської комунальної лікарні № 2 у 2016-2017 рр. з діагнозом ГКС. Уся інформація була записана у спеціально створені карти пацієнтів. Частоту повторних серцево-судинних подій оцінювали протягом 36-ти місяців після виписки зі стаціонару.

Результати. Жінки у цій когорті були старшими та мали вищу частоту супутніх захворювань: 15,5% жінок та 11% чоловіків з ГКС мали ≥ 5 коморбідностей, 65,5% жінок і 60% чоловіків мали 2-4 коморбідності, і 19% жінок та 29% чоловіків ≤ 1 коморбідне захворювання. Жінки частіше мали супутні цереброваскулярні захворювання (17,2% проти 7,3%, $p=0,05$), деменцію (15,5% проти 5,5 %, $p=0,03$), хвороби сполучної тканини (17,25% проти 6,42%, $p=0,03$) і захворювання щитоподібної залози (12,1% проти 2,8%, $p=0,02$). Чоловіки частіше мали виразкову хворобу (13,7% проти 3,4%, $p=0,05$). Частота повторних серцево-судинних подій була вищою у жінок (55% проти 33%, $p=0,003$). Хвороба периферичних артерій (OR 9,5, 95% CI: 1,7-52,3, $p=0,01$) хвороби щитоподібної залози (OR 7,2, 95% CI: 1,19-43,2, $p=0,03$) продемонстрували найбільший вплив на прогноз у жінок. Онкологічні захворювання мали найбільший вплив на виживання у чоловіків (OR 6,3, 95% CI: 2,13-18,9, $p=0,001$).

Висновки. Ми спостерігали суттєві гендерні відмінності у структурі коморбідностей та вільному від подій виживанні пацієнтів з ГКС. Доцільно провести подальші дослідження із залученням більших когорт пацієнтів.

КЛЮЧОВІ СЛОВА: гострий коронарний синдром; стать; прогноз.

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ANTIBACTERIAL THERAPY FOR PATIENTS WITH BURN INJURIES

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Background. Treatment of burn wound infection is an urgent issue of contemporary medicine, including surgery, combustiology and microbiology. It is established that infectious complications are a challenge for burn patients. In the course of wound reparation, infectious complications may worsen. Along with surgical treatment, mechanical removal of pathogens from burn wounds is also important as well as antimicrobials for patients with severe burns.

Objective. The aim of the study was to define the most common pathogens of purulent-inflammatory complications of burn wounds and their susceptibility to antibiotics.

Methods. The study involved patients treated at the Center of Thermal Trauma and Plastic Surgery of Lviv I-Territorial Medical Association, the unit of St. Luke Hospital of Lviv. Collection of material from wound secretions of burn wounds was performed with sterile swab. The study was performed before prescription of antibiotics, at the end of the first and second weeks of the disease. The pathogens were isolated and identified. Antibiotic susceptibility was studied using standard research methods. The obtained results were analyzed by means of the software package of the microbiological monitoring system WHONET 5.2 (WHO Collaborating Centre for Surveillance of Antimicrobial Resistance) and the program Microsoft Office Excel 2007.

Results. The study of smears from burn wounds proved that 240 strains of gram-positive and gram-negative microorganisms that caused purulent-inflammatory processes were isolated. Among the selected causative agents of a burn wound complicated by a purulent-inflammatory process, gram-negative bacteria predominated (60.8% of all detected microorganisms). Gram-positive flora of *S. epidermidis* and *S. aureus* were more common in the wound surface during the first week of the disease. In most patients with severe burns, bacterial associations were isolated from the wound surface (66.3%) in two and three weeks, and in three weeks *Candida* spp. were isolated. Non-fermenting rods *A. baumannii* and *P. aeruginosa* dominated among the gram-negative flora isolated from the wound surface of burns. The analysis of susceptibility of microorganisms isolated from patients with burns to antibiotics showed that almost all of the cultures were polyresistant.

Conclusions. Gram-negative microorganisms, strains of non-fermenting bacteria predominated among the pathogens isolated from burn wounds complicated by purulent inflammation; *Staphylococcus aureus* prevailed among the gram-positive ones. The most significant clinical strains were highly polyresistant to antibiotics.

KEYWORDS: smears from burn wounds; strains of microorganisms; antibiotics; resistance.

Introduction

According to the WHO, injuries, burns, poisonings, etc. are the third in the structure of human mortality. Every year about 840 million people suffer from burns and about 180 thousand people die in the world. In Ukraine, more than 100,000 cases of burns are registered annually, and 60-80% of those burned have superficial burns of the skin of II-III A degree, which do not require surgical intervention [1, 2, 3, 4].

Treatment of burn wound infection is an urgent issue of contemporary medicine, in particular, surgery and combustiology. Accord-

ing to literature [5, 6], despite the constant improvement of wound healing methods, the frequency of its infectious complications in surgery is 30%. Traditional remedies and treatments for infected burns are often ineffective. This necessitates further search for new and improvement of existing medications and treatment that stimulate reparative processes in infected wounds, as well as in-depth study of the mechanisms of action of antibiotics [7]. Today, there is a wide range of medications for conservative treatment of burns, but none of them is sufficiently effective.

It is established that infectious complications are a challenge for patients with burns. According to the literature, their frequency correlates with the depth and area of burns. Complications

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in patients with burns are caused by disturbance of barrier function of the skin, reduction of its protective properties due to the action of traumatic factors and suppression of the immune system of these patients [8, 9, 10].

The most common cause of patient mortality is infection, which accounts for about 76.3% of burn mortality. In cases of thermal damage, coagulation necrosis of the epidermis, of various layers of the dermis and adjacent tissues develops that creates favorable conditions for massive microbial invasion. Infectious complications worsen the course of reparative processes in the wound. In patients with severe burns antimicrobial therapy is important together with surgical treatment aimed at mechanical removal of pathogens from burn wounds [11, 12, 13].

The aim of the study was to define the most common pathogens of purulent-inflammatory complications of burn wounds and their susceptibility to antibiotics.

Methods

The study involved patients treated at the Center of Thermal Trauma and Plastic Surgery of Lviv I-Territorial Medical Association, the unit of St. Luke's Hospital of Lviv. Collection of material from the wound secretions of burn wounds was performed with sterile swab. burn wounds in all patients were studied before prescription of antibiotics, at the end of the first and second weeks of the disease, which included isolation of pathogens, their identification by morphological, cultural and biochemical properties.

Antibiotic susceptibility was studied using standard research methods according to the Order of the Ministry of Health of Ukraine No. 167 "On approval of guidelines for Determination of susceptibility of microorganisms to antibacterials", dated April 05, 2007 and the recommendations of the International Committee of Clinical Standards (NCCLS, 2002).

Statistical processing and analysis of the results was performed using the software package of the microbiological monitoring system WHONET 5.2 (WHO Collaborating Centre for Surveillance of Antimicrobial Resistance) and Microsoft Office Excel 2007 [14].

Results

The results of the studies showed that in patients with burn trauma during the first week of the disease gram-positive flora of *S. epidermidis* and *S. aureus* were more common

according to microbiological examination of smears from wound surfaces. *Candida* spp. were isolated in patients with severe burns on the third week of the disease, which might have been associated with immunosuppression due to thermal trauma and development of antibacterial resistance [15]. Depending on this, susceptibility of the main pathogens to antibacterials was evidenced. The study found that *S. aureus* showed high resistance to ceftriaxone (78-80%) and carbapenems (70-73%), high susceptibility to fluoroquinolones, including ciprofloxacin (71.5%) and levofloxacin (67.5%). *P. aeruginosa* strains were susceptible to carbapenems, in particular to meropenem (80 %) and imipenem (95%).

On day 18-20 from the moment of the injury, *Pseudomonas aeruginosa* was isolated from the wound in 65-70% of patients. Strains of *Pseudomonas aeruginosa* were moderately resistant, retaining susceptibility to carbapenems.

As a result of microbiological examination of smears from burn wounds, etiologically significant pathogens of infectious complications in patients with dermal burns were isolated. A total of 240 strains of gram-positive and gram-negative microorganisms were isolated from burn wound surfaces, which led to development of purulent-inflammatory processes.

On the seventh day after burns in 62.3% of cases, microorganisms were isolated from patients in monoculture, and only 37.7% – in associations. In two and three weeks of the disease, most patients with severe burns had bacterial associations isolated from the wound surface (66.3%), and on the third week of the disease *Candida* spp. were isolated due to possible immunosuppression on the background of thermal trauma.

Acinetobacter baumannii (30.0%), *Pseudomonas aeruginosa* (20.4%) and *Staphylococcus aureus* (15%) are leading in the spectrum of isolated clinical strains (Fig. 1). Most often, they formed associations from the second week of the disease.

Among the isolated pathogens of purulent-inflammatory complications of burn wounds, gram-negative bacteria predominated (60.8 % of all isolated microorganisms) (Fig. 2).

Non-fermenting rods *A. baumannii* and *P. aeruginosa* (48.3% and 34.9%, respectively) dominated in the gram-negative flora isolated from the burn wound surface; they were most often isolated after the first week of the disease. In contrast, Enterobacteria accounted for only 17.1 % (Fig. 3); *Escherichia coli* (8.7 % of isolated

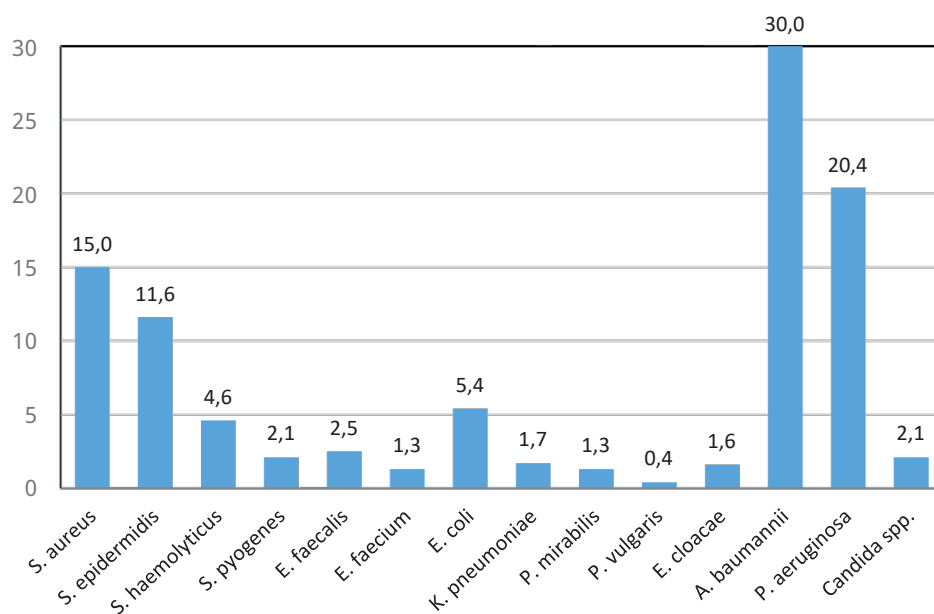
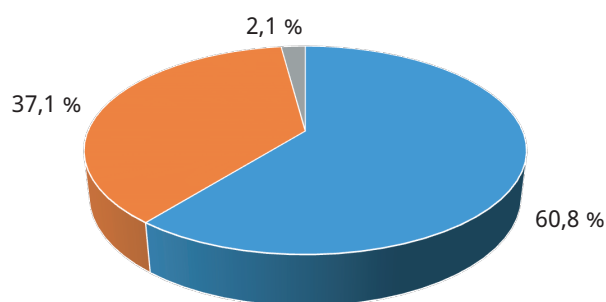


Fig. 1. The range of microorganisms isolated from burn surfaces,%.



■ gram-negative bacteria ■ gram-positive bacteria ■ yeast fungi

Fig. 2. The range of microorganisms isolated from purulent-inflammatory surfaces of burn wounds,%.

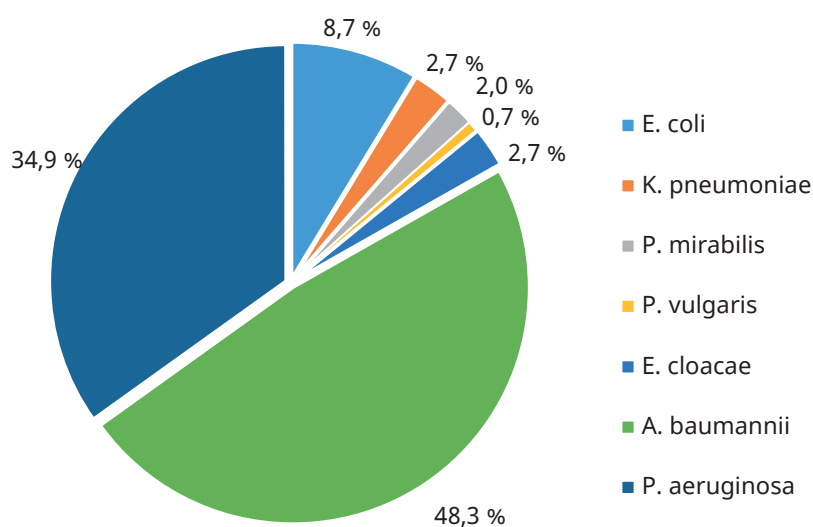


Fig. 3. Species of gram-negative bacteria isolated from burn surfaces,%

gram-negative rods), *Enterobacter cloacae* (2.7 %), *Klebsiella pneumoniae* (2.7 %), *Proteus mirabilis* (2.0%), *Proteus vulgaris* (0.7%) were isolated among them.

Gram-positive cocci were isolated 1.6 times less (37.1%) (Fig. 4). Staphylococci were predominant among them. They accounted for 75 % of isolated strains of cocci, and cultures of *S. aureus* (40.4% of all identified strains of cocci) were most often isolated among them. Coagulase-negative cocci were represented by cultures of *S. epidermidis* and *S. haemolyticus* (31.5 % and 12.4%, respectively). Enterococci were represented by strains of *Enterococcus faecalis* and *Enterococcus faecium*, which accounted for 10.1 % of the coccal flora, respectively. *Streptococcus pyogenes* was isolated only in 5.6%. Enterococci were more often isolated in the first week of the disease, staphylococci in the following weeks.

Candida spp. accounted for only 2.1 % of all isolated microorganisms.

The analysis of the susceptibility of microorganisms isolated from patients with burn disease to antibiotics showed that these clinical strains had high resistance to antibacterials, especially those that most often infect the wound surfaces. Almost all isolated strains were polyresistant.

The identified strains of *P. aeruginosa* were low susceptible to cephalosporins, in particular: cefepime (92.3%), ceftriaxone (86.5%), ceftazidime (80.8%), cefotaxime (69.2%). Almost half of the isolated cultures of *Pseudomonas*

aeruginosa were resistant to aminoglycosides: to gentamicin – in 46.2% cases, to amikacin – 42.3 %. Meropenem and imipenem showed also low effectiveness, although they were reserve antibiotics. Clinical strains of *P. aeruginosa* showed resistance in 51.9 % and 82.7 % cases, respectively. The most effective antimicrobial against *Pseudomonas aeruginosa* was doxycycline. Resistance to it was only 19.2 %.

Like *P. aeruginosa* strains, isolated cultures of *A. baumannii* had a high level of antibiotic resistance. Cephalosporin antibiotics, in particular ceftazidime (97.2 %), ceftriaxone (95.8 %), cefepime (91.7 %), cefotaxime (86.1 %), were ineffective against acinetobacteria. Strains of *A. baumannii* to gentamicin and amikacin (73.6 % and 79.2 %, respectively) were highly resistant. They were also low susceptible to fluoroquinolones, i.e.: levofloxacin (76.4 %), ciprofloxacin (68.1%), gatifloxacin (63.9%). Meropenem and imipenem were more effective than other groups of antibacterials against acinetobacteria, only in 31.9% and 40.2% of resistant cultures of *A. baumannii*.

Isolated cultures of *S. aureus* were resistant to oxacillin (63.9%) that indicated methicillin resistance of these strains, as well as cephalosporin antibiotics, in particular: cefepime, ceftazidime, ceftriaxone (from 19.4 % to 33.3 %, respectively). *Staphylococcus aureus* was highly resistant to azithromycin (66.7 %) and lincosamides such as clindamycin (72.2 %) and doxycycline (52.8 %). Fluoroquinolones were also low effective, i.e.: ciprofloxacin (58.3 %) and

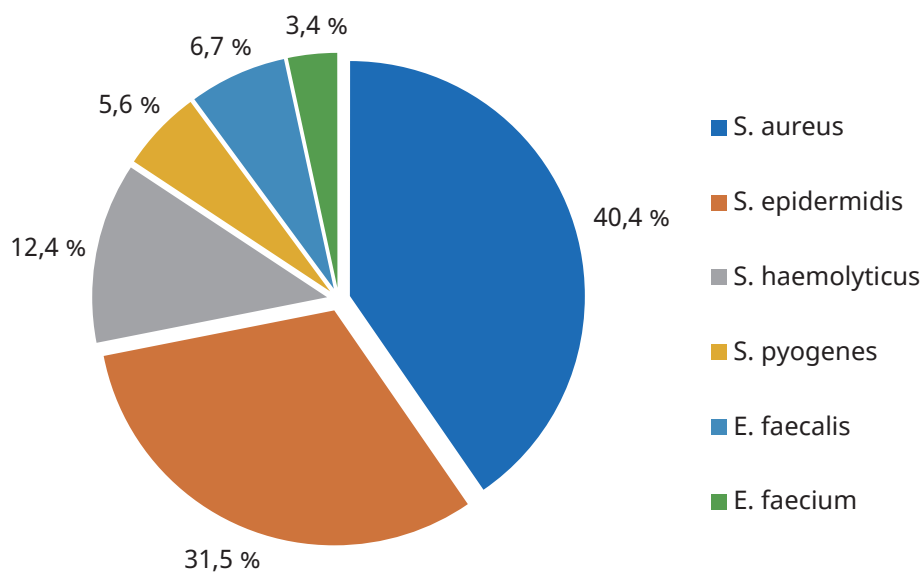


Fig. 4. Species of gram-positive bacteria isolated from burn surfaces,%

levofloxacin (25.0-44.4 %), as well as aminoglycosamides: gentamicin (30.6 %) and amikacin (38.9 %). In contrast to non-fermenting bacteria, clinical strains of *S. aureus* were the most susceptible to carbapenems: meropenem and imipenem resistant cultures of *Staphylococcus aureus* were only 8.3% and 5.6% of strains.

Discussion

Burns destroy the first barrier of human innate immunity that protect tissue from the colonised external world, and microorganisms can easily spread and infiltrate necrotic tissue [15, 16]. Our data confirmed many published studies, which have reported gram-negative bacteria as the commonest microorganisms that colonize burn wounds [17]. Initial burn wounds are sterile. However, within a few days, Gram-positive strains, such as *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and *Streptococcus spp.*, start to colonize the wounds from deeper structures (hair follicles and glands). In the second phase, a Gram-negative shift takes place, where *P. aeruginosa*, *E. coli*, and *Proteus* are the predominant isolates [18, 19, 20]. If left untreated, this colonization can lead to infection [20, 21]. Our data confirmed the steps of infectious process developing on burn wounds. The study had established that *S. aureus* among gram-positive microbes and *P. aeruginosa* among gram-negative microbes were the most frequent microbial isolates in our patients (40.4% and 34.9% respectively). Similar observation was seen in the study by Tsolakidis S. et. al. [18].

In our study, we found a variable percentage of antibiotic resistance among the cultured bacteria. The analysis of the studied isolates susceptibility to antibiotics showed that most often infecting the wound surfaces clinical strains had high resistance to antibacterials. Almost all isolated bacteria were multiresistant. 63.9% of identified *S. aureus* belong to MRSA staphylococci. This had less incidence with other studies on MRSA in burn patients by Mandal [21]. Isolates of *S. aureus* (more than 70 % of all of them) were found as highly resistant to cephalosporins, including cefepime, ceftazidime, ceftriaxone, to lincosamides, such as clindamycin (72.2 %) and doxycycline

(52.8 %). *S. aureus* was highly resistant to fluoroquinolones, i.e.: ciprofloxacin (58.3 %) and levofloxacin (25.0-44.4 %), as well as aminoglycosamides: gentamicin (30.6 %) and amikacin (38.9 %). However, isolates of *S. aureus* were susceptible to fluoroquinolones, including ciprofloxacin (71.5 %) and levofloxacin (67.5%). In contrast to non-fermenting bacteria, clinical strains of *S. aureus* were the most susceptible to carbapenems: meropenem and imipenem; only 8.3 % and 5.6 % of strains of *S. aureus* were resistant to these antibiotics.

P. aeruginosa strains as well as *S. aureus* were resistant to cephalosporins, in particular: cefepime (92.3 %), ceftriaxone (86.5 %), ceftazidime (80.8 %), cefotaxime (69.2 %); to aminoglycosides: gentamicin (46.2 %), amikacin (42.3 %); to meropenem and imipenem (almost half of the isolated cultures of *P. aeruginosa*). and moderate resistant to carbapenems, in particular: to meropenem (80 %) and imipenem (95 %). The most resistant antibiotics found in most of studies were cephalosporins and quinolones [7, 8, 23, 24, 25]. In contrast, some authors reported no isolated bacteria found resistant to gentamicin [24], or susceptible to aminoglycosides [25].

Conclusions

It was established that among the pathogens isolated from complicated purulent-inflammatory burn wounds, gram-negative microorganisms of non-fermenting bacteria predominated and *Staphylococcus aureus* among gram-positive ones. The most significant clinical strains were highly multiresistant to antibiotics.

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This research received no external funding.

Conflict of interest

The authors declare no conflict of interests in this study.

Author's Contributions

Stepan Zaporozhan – conceptualization, writing – original draft; *Dmytro Fira* – formal analysis, writing – original draft, writing – reviewing and editing; *Olena Pokryshko* – data curation, writing – reviewing and editing.

АНТИБАКТЕРІАЛЬНА ТЕРАПІЯ У ХВОРИХ ІЗ ОПІКОВОЮ ТРАВМОЮ

С. Й. Запорожан, Д. Б. Фіра, О. В. Покришко
ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО,
ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Лікування опікової ранової інфекції є актуальною проблемою сучасної медицини, зокрема хірургії, комбустіології й мікробіології. Відомо, що у хворих з опіками інфекційні ускладнення становлять серйозну проблему. Інфекційні ускладнення погіршують перебіг репаративних процесів у рані. Водночас із хірургічними методами лікування, спрямованими на механічне видалення збудників з опікових ран, важливе значення має застосування антимікробних лікарських засобів у хворих із тяжкими опіками.

Мета. Визначити найбільш поширені збудники гнійно-запальних ускладнень опікових ран у хворих та їх чутливість до антибіотиків.

Методи. Дослідження проводилось у пацієнтів, що перебували на стаціонарному лікуванні у центрі термічної травми і пластичної хірургії КНП «І-е територіальне медичне об'єднання м. Львова» відокремленого підрозділу «Лікарня святого Луки» м. Львів. Забір матеріалу із ранових виділень опікових ран здійснювали за допомогою стерильного тампону. Дослідження проводили у хворих до початку застосування антибіотиків, наприкінці першого і другого тижня захворювання. Виділяли збудники, ідентифікували їх. Чутливість до антибіотиків вивчали за допомогою стандартних методів дослідження. Отримані результати піддавали аналізу, який включав пакет програм системи мікробіологічного моніторингу "WHONET 5.2" (WHO Collaborating Centre for Surveillance of Antimicrobial Resistance) та програму «Microsoft Office Excel 2007».

Результати. У результаті проведеного дослідження мазків з опікових ран виділено 240 штамів грампозитивних та грамнегативних мікроорганізмів, які спричиняли гнійно-запальні процеси. Серед виділених збудників гнійно-запальних ускладнень опікових ран переважали грамнегативні бактерії (60,8% усіх виділених мікроорганізмів). Впродовж першого тижня захворювання у рановій поверхні частіше зустрічалися грампозитивна флора *S. epidermidis* та *S. aureus*. Після двох і трьох тижнів захворювання у більшості пацієнтів із важкою опіковою травмою з ранової поверхні висівали асоціації бактерій (66,3%) та на третьому тижні захворювання виділяли ще й гриби роду *Candida spp.* У грамнегативній флорі, висіяній із ранової поверхні опіків, домінували неферментуючі палички *A. baumannii* та *P. aeruginosa*. Результати аналізу чутливості мікроорганізмів, виділених від хворих із опіковою хворобою, до антибіотиків показали, що практично всі висіяні культури були полірезистентними.

Висновки. Серед виділених збудників гнійно-запальних ускладнень опікових ран переважали грамнегативні мікрорганізми, штами неферментуючих бактерій, серед грампозитивних – золотисті стафілококи. Найбільш значущі клінічні штами були високо полірезистентними до антибіотиків.

КЛЮЧОВІ СЛОВА: мазки з опікових ран; штами мікроорганізмів; антибіотики; резистентність.

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ONCOPLASTIC CONE-SHAPED REMOVAL OF MELANOMA IN SITES WITH LIMITED SKIN RESOURCES

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Background. According to the existing recommendations of the NCCN, 2-cm margins are optimal for surgical excision of skin melanoma (SM).

Objective. A method of cone-shaped oncoplastic surgery of SM in sites with limited skin-plastic resources is presented.

Methods. In the study 30 patients (11 men, 19 women) underwent cone-shaped removal of primary SM on arm and shin, epigastria and subclavicular sites. Oncosurgical approach involves the following: primary SM is excised with 2 cm margins around with transforming this round wound into conical using additional incisions; then conical wound is closed by transverse displacement of lateral skin-fatted flap. The postoperative seam looks like hook-shaped line. SM thickness is measured by sonography before surgery. Morphological verification is obtained by cytological examination of smears after superficial scraping biopsy.

Results. Postoperative histology confirmed melanomas in all cases with "clear margins" in all surgical specimens, and postoperative staging was as follows: pT2bN0M0 – in 3 patients, pT2bN1-2M0 – 4 patients, pT3bN0M0 – 9 patients, pT4bN0M0 – 7 patients, and pT4bN1-2M0 – in 7 patients. Partial marginal necrosis of displaced flaps was of 4 patients (13.3%). There were no recurrences of melanoma at site of postoperative scar. 3-years disease free survival (DFS) rate was 76.6%, and 5 years DFS rate – 60.0%.

Conclusions. Cone-shaped radical excision of primary melanoma is an appropriate surgery for patients with SM on the forearms, shoulders, epigastria and subclavicular sites and legs. The one-step oncoplastic radical surgery without intermediate biopsy prevents local recurrence in site of surgery as well as iatrogenic metastasis to regional lymph nodes.

KEYWORDS: skin melanoma; surgical margins; oncoplastic surgery.

Introduction

Surgery of primary cutaneous melanoma is very important because radical surgical elimination of clinically visible melanoma is the main treatment method to which various adjuvant methods are added. Recently, a revolution in the systemic treatment of melanoma took place. Successful development of immuno- and targeted therapies has changed the context of melanoma treatment in general. However, surgical resection is an important treatment consideration even in the systemic therapy era [1-3].

Over the last two decades, a number of clinical studies have been conducted to determine the extent of surgical removal of primary cutaneous melanoma. There was no consensus

regarding optimal surgical excision margins. The removal limits of a 1-cm versus 3-cm, a 1 vs 2-cm, and 2 vs 4-cm, etc. have been compared. It is established that a 2 cm excision margin of localized cutaneous melanoma is adequate and safe for patients [4-6].

The recommendations by the NCCN in the Principles of surgical margins for wide excision of primary melanoma are the same: if tumor has thickness 1-2 mm – the clinical margins should be 1-2 cm, if thickness 2-4 mm – margins 2 cm, and if thickness >4 mm – margins 2 cm [7]. However, the patients diagnosed with shave and punch biopsy techniques are significantly more likely to have positive margins on the wide local excision specimen [8]. Otherwise, wide excision sites require reconstruction with a skin graft or local flap at all locations, especially the extremities and head and neck. Also, in these

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cases the rate of perioperative surgical adverse events increases as well as wound complications [4, 6, 9]. Therefore, oncoplastic surgery for melanoma in areas with limited plastic resources is still relevant.

Thus, a method of cone-shaped oncoplastic surgery of melanoma in sites with limited skin-plastic resources (arm, shin, epigastria and other) is presented in the study.

Methods

A design of radical surgery with full plastic replacement of surgical wound is shown on Fig. 1. When planning the operation, the margins of wide removal of melanoma are marked on the skin with the tumor location in the center of a circle (O') with radius r_1 . A line $O'O$ ($O'O=2.5 r_1$) is drawn along the axis of the limb. The cone is formed by drawing the lines OD and OE . The transverse flap is marking as two adjacent arcs from the base of the cone – one arc of a circle of radius r_2 ($r_2=4/5 r_1$), the second arc of a circle of radius r_3 ($r_3=3/5 r_1$). The cone-shaped melanoma removal procedure is planning within OECD figure. Then, the tissue flap separated along perimeter OEBAFO moves in the oblique-transverse direction towards to the edge (OD) of the surgical wound so that the

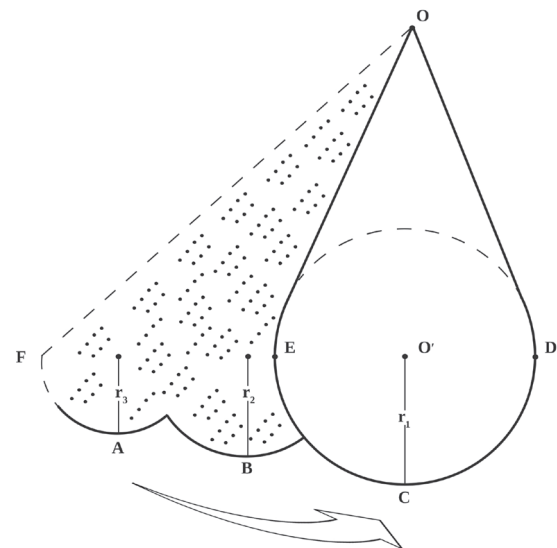


Fig. 1. Surgery design.

flap arc with radius r_2 closes the main surgical wound (r_1), and the flap arc r_3 cover the place of the displaced flap r_2 [18].

The stereometric design of the surgery may vary slightly depending on the location of a melanoma and the volume of soft tissue in the area.

Clinical cases:

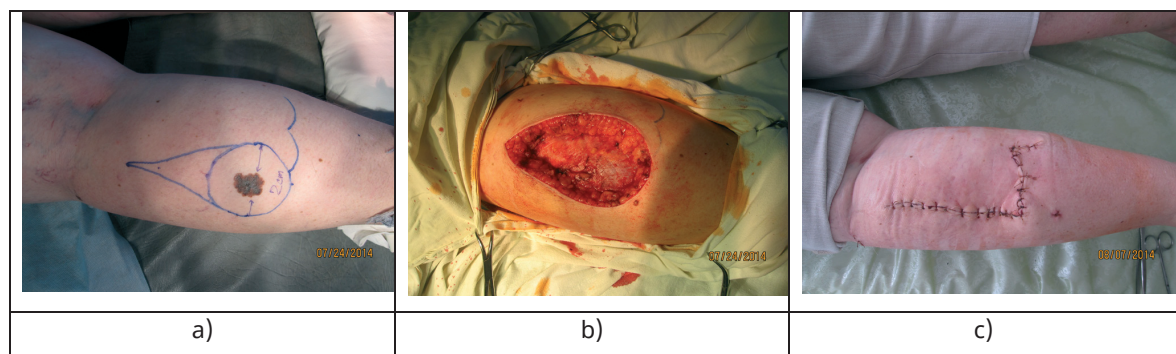


Fig. 2. Patient R., 58 years old, female; skin melanoma pT2bN0M0, stage IIA. Disease free survival (DFS) – 7 years (2014–2021).

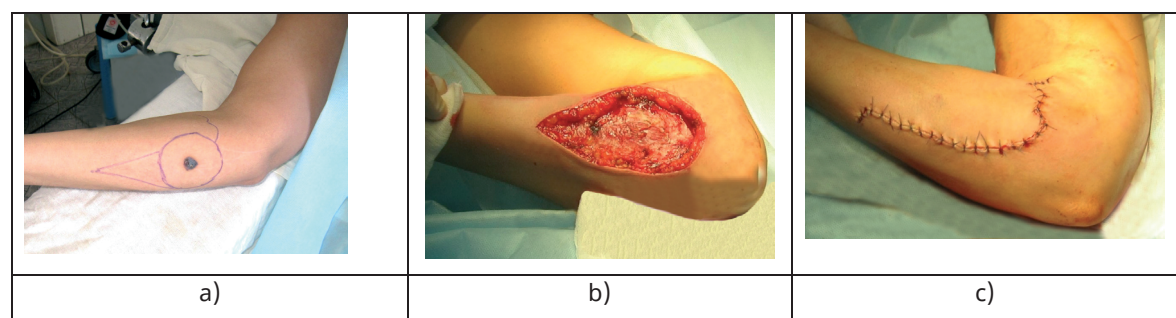


Fig. 3. Patient B., 43 years old, female; Skin melanoma pT2bN2cM0, stage IIIB. DFS – 5 years. (2013–2018).

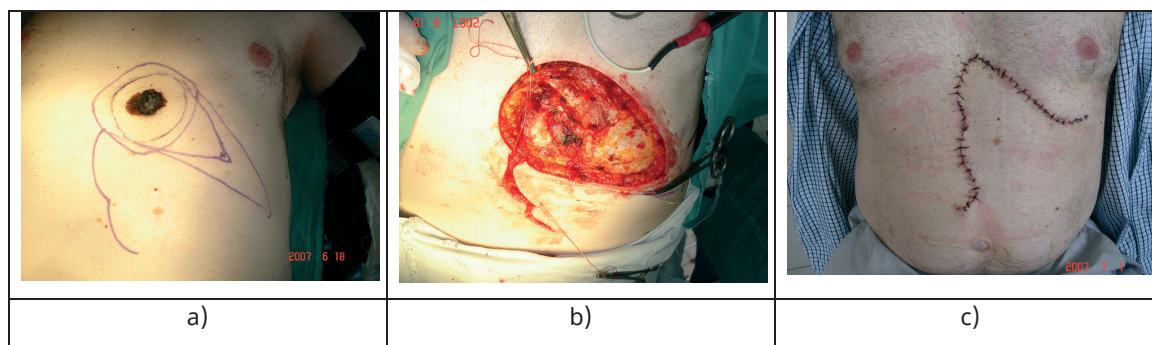


Fig. 4. Patient M., 56 years old, male; Skin melanoma pT4bN0M0, stage IIC. DFS – 9 years (2007–2016); right axillary lymph nodes dissection of melanoma metastases in 2016; no disease recurrence up to the end of 2021.

Cone-shaped operation was performed in 30 patients with primary skin melanoma. There were 11 males and 19 females aged from 30 to 75. The sites of cutaneous melanoma: forearm – 4 cases, shoulder – 5, shoulder joint – 3, epigastria – 3, subclavica – 4, and shin – 11 cases. The study was approved by the Ethical Committee of I. Horbachevsky Ternopil National Medical University, and accordingly, the patients provided a written informed consent.

The algorithm of preoperative diagnosis consisted of clinical evaluation of pigmented lesions, dermoscopy in case of superficial spreading melanomas, and ultrasound measurement of melanoma thickness (*in vivo*) with sonography of regional lymph nodes. Chest/abdomen staging CT was performed for patients with node-positive disease. Morphological verification of melanoma was obtained by superficial scraping biopsy with cytological examination of smears. The preoperative diagnosis of melanoma was consistent with the clinical cTNM classification.

In practice, the surgery is carried out in the way according to Fig. 2a, b. After marking, a scalpel at a distance of 2 cm from the edge of the melanoma cut the skin and subcutaneous fat perpendicularly. The conical skin-fatted flap is removed along with the superficial muscular fascia and then the edges of the wound are mobilized around its perimeter. Next, at the base of the cone with a scalpel an oblique cross-sectional wave with two arcs of larger and smaller radius are made. This skin-fatted flap above the muscular fascia continues to be mobilized, and then the mobilized tissue in the oblique-transverse direction is moved to the opposite edge of the conical wound, sutures and drainage are put. As a result of plastic replacement of surgical wound the hook-like seam occurred; its longer part is located along the axis of the

limb and the shorter one – across it (Fig. 2c). Healing usually takes place by primary tension.

Results

Histological examinations, which were performed after radical surgery, confirm melanomas in all cases. Also, the “clear margins” were confirmed in all surgical specimens. Distribution by Breslow thickness: pT2b – 7 melanomas, pT3b – 9, and pT4b – 14; by Clark’s invasion: level III – in 11 specimens, levels IV – 12, and levels V – 7. Lymph node metastases (N1 and N2) were confirmed histologically after lymph nodes dissection in 11 patients.

Postoperative staging was as follows: pT2bN0M0 – in 3 patients, pT2bN1-2M0 – 4 patients, pT3bN0M0 – 9 patients, pT4bN0M0 – 7 patients, and pT4bN1-2M0 – 7 patients.

Local complications: partial marginal necrosis of the displaced flaps was evidenced in 4 elderly patients (13.3%). There were no recurrences of melanoma at the site of postoperative scar.

A 3-year disease free survival (DFS) rate was 76.6% (23 patients), and a 5-year DFS rate – 60.0 % (18 patients).

This method of melanoma removing has shown its effectiveness not only in the extremities, where there is usually a lack of plastic resources, but also in sites where bone contours (e.g., costal arch, clavicle) limit plastic wound closure by the method of Limberg. In general, the method of radical removal of melanoma with the formation of a cone-shaped surgical wound has proven its effectiveness. Despite the fact that a larger surgical wound is formed, it is possible to plastically close this wound with adjacent tissues using their transverse displacement. Thus, this type of radical surgery allows obtaining satisfactory cosmetic and functional results.

Discussion

The discussion about surgical margins of melanoma lasts for several decades including many clinical trials. However, the same methodological principles were inherent for all these clinical studies: biopsy is the first surgery, and next surgery is wide local excision (WLE) of postbiopsy scar. According to the published results and recommendations of the AAD, ESMO and NCCN, the primary melanoma should be removed by excisional biopsy within 1-3 mm from the edge of the tumor using local anesthesia [7, 10, 11]. The WLE is recommended after complete histological examination of the biopsy-removed melanoma. Moreover, it takes 4-6 weeks between two surgeries. In our opinion, the second surgery at distance 2.0 vs 4.0 cm (or 1 vs 3 cm) has nothing with melanoma for the simple reason that it (melanoma) has already been removed 4-6 weeks earlier. In fact, the linear post-biopsy scar is excised during the second operation. Usually the pathologist does not detect signs of melanoma in fresh scar tissue.

Thus, with this methodological approach, we can predict that results of treatment will not differ. Indeed, there were no significant differences in melanoma-specific and overall survival of the patient groups comparing the wide (3-5 cm) and narrow (1-2 cm) margins of biopsy-scar removing. The overall local recurrences including in-transit metastases were remarkably similar between 1 cm and 3 cm groups [4, 5, 9, 12, 13].

Such data were obtained in most clinical studies from 2001 to 2019. This creates illusion that the surgical margins for removal of primary melanoma do not matter (2.0 or 4.0 cm; 1.0 or 3.0 cm), because the survival rate in the comparative groups is just about the same [4, 6, 12, 14, 15]. However, in 20-35% of patients with stage II melanoma ($pT2b$, $pT3a/b$, $pT4a/b$) metastatic lesions in regional lymph nodes were evidenced during the second surgery [4, 16, 17], which indirectly confirmed the fact that excisional biopsy may affect development of locoregional metastases.

Our clinical study shows the true surgical margins in excision of primary melanoma. In these cases, the term *oncosurgical* is used to refer the one-step radical removal of skin melanoma compare to the dermatological approach [19].

What do we gain from the *oncosurgical* approach? The first surgery with full plastic replacement of surgical wound becomes a radical surgery of primary melanoma. We get rid of two-stage surgery with an interval of 4-6 weeks; the time of treatment is reduced, which has a positive effect on the emotional state of the patient.

Primary WLE of melanoma most likely involves microsatellites; that is why there were no recurrences at the postoperative scar in the study, while the incidence of local recurrence for shave, excisional, incisional, and punch biopsy was 4.9%, 6.5%, 14.3%, and 6.1 % respectively [8]. In addition, primary WLE decreases the iatrogenic dissemination of malignant cells into regional lymph nodes compare to excisional biopsy under local anesthesia. However, the careful ultrasonic monitoring of the regional lymph nodes should be carried out during the follow-up of these patients.

Conclusions

This clinical experience shows that cone-shaped radical excision of cutaneous melanoma is a reasonable surgery for patients with melanoma on the forearms, shoulders, epigastria and subclavicular sites and legs.

From the edge of the primary melanoma it is necessary to make a 2 cm marking for a wide local excision of this melanoma. The one-step oncoplastic radical surgery of primary melanoma without the intermediate biopsy prevents local recurrence in the site of surgery and also it prevents iatrogenic metastases to regional lymph nodes.

Decision making for radical resection of primary skin melanoma may be based on its cytological verification and ultrasound measurement of melanoma thickness *in vivo*.

Conflict of Interests

The author declares no conflict of interest.

РАДИКАЛЬНЕ КОНУСОПОДІБНЕ ВИДАЛЕННЯ МЕЛАНОМИ В МІСЦЯХ З ОБМЕЖЕНИМИ ПЛАСТИЧНИМИ РЕСУРСАМИ ШКІРИ

І. Й. Галайчук

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,
ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Відповідно до існуючих рекомендацій NCCN, 2-сантиметрові краї резекції є оптимальними для хірургічного видалення меланоми шкіри (МШ).

Мета. Представити хірургічну методику радикального конусоподібного видалення меланоми в місцях з обмеженими пластичними ресурсами шкіри.

Методи. У 30 хворих (чол. – 11, жін. – 19) застосовано методику конусоподібного видалення первинної МШ, локалізованої на верхніх і нижніх кінцівках, епігастрії та підключичних ділянках. Методика операції полягала в тому, що МШ вирізали з 2-см краями резекції навколо, утворену округлу операційну рану за допомогою додаткових розрізів перетворювали в конічну. Пластичне закриття конічної рани здійснювали шляхом поперечного зміщення бічного шкірно-жирового клаптя. Після пластики рани утворювався гачкоподібний післяопераційний шов. Перед операцією товщину МШ вимірювали за допомогою УЗД, а морфологічну верифікацію отримували шляхом цитологічного дослідження мазків з поверхні меланоми.

Результати. Післяопераційні гістологічні дослідження підтвердили наявність меланоми в усіх випадках із «чистими краями резекції» у всіх хірургічних зразках. Були встановлені наступні стадії захворювання: pT2bN0M0 – у 3-х хворих, pT2bN1-2M0 – 4 хворих, pT3bN0M0 – 9 хворих, pT4bN0M0 – 7 хворих і pT4bN1-2M0 – 7 хворих. Частковий крайовий некроз зміщених клаптів був відмічений у 4 хворих (13,3%). Рецидивів меланоми в ділянці післяопераційного рубця не було протягом часу спостереження. 3-річна безрецидивна виживаність становила 76,6%, а 5-річна – 60,0%.

Висновки. Радикальне конусоподібне висічення первинної меланоми є доцільним хірургічним втручанням у хворих з локалізацією МШ на передпліччях, плечах, епігастрії та підключичних ділянках і гомілкях. Одноетапна онкопластична радикальна операція без проміжної біопсії унеможливорює виникнення локального рецидиву меланоми в ділянці операції, а також запобігає ятрогенному метастазуванню в регіонарні лімфатичні вузли.

КЛЮЧОВІ СЛОВА: меланома шкіри; краї резекції; онкопластична операція.

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CASE REPORT ON RARE OUTCOME OF A RETROPERITONEAL MASS: MANAGEMENT CHALLENGES AND LESSONS LEARNT

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Background. *Gastrointestinal stromal tumours (GIST) are non-epithelial mesenchymal solid neoplasm with varied presentation. The study reports the case of a retroperitoneal GIST in a 21-year-old male presented with an abdominal lump for six months. The lesion was initially thought to be a retroperitoneal sarcoma. Exploratory laparotomy revealed an abdominopelvic mass covering the entire right side of abdomen and pelvis. The tumour was adherent to the terminal ileum and ascending colon. There were dense adhesions between the retroperitoneum with involvement of the middle third of the right ureter. The tumour was resected with right hemicolectomy with ileotransverse anastomosis. Post-operative histopathology revealed it as high-grade spindle cell type GIST. The patient is presently on post-operative chemotherapy with Imatinib mesylate.*

Objective. *Atypical presentations of GIST are seldom discussed but frequently encountered in clinical practice. This article depicts different challenges the surgeon has to face while diagnosing such atypical entity.*

Methods. *Case report of atypical GIST presenting as retroperitoneal lump.*

Results. *The patient underwent surgical resection and is presently on post-operative chemotherapy with good overall outcome for a one year follow up.*

Conclusions. *GISTs presenting as retroperitoneal lumps are very rare, they should be considered in their differential diagnosis of an atypical retroperitoneal mass.*

KEYWORDS: GIST; atypical presentation; retroperitoneal tumour; abdominal lump.

Introduction

Gastrointestinal stromal tumours (GIST) are intra-abdominal benign mesenchymal neoplasia arising from the interstitial cell of Cajal. The most common sites are the stomach and the intestine. Mostly GIST presents as a slow-growing intra-abdominal mass appreciated as a lump abdomen. They can also present as gastrointestinal bleed or intestinal obstruction. However, there are many incidences where they present atypically. This article is about the diagnostic challenges and analysis of various rare presentations of GIST.

Case Report

A 21-year-old male presented with a 6-month history of lump abdomen in the umbilical and right lumbar region. The lump was insidious in onset and gradually progressive. There was no history of vomiting, constipation or obstipation. He also denies any history of

trauma to the abdomen. There were no hepatic or urinary complaints. On clinical examination a nontender, smooth surfaced firm 20×15 cm lump was palpated in the right lumbar region extending to the umbilicus crossing 3 cm lateral to the midline. The lump was fixed to retroperitoneum. There was no palpable hepatosplenomegaly, and digital rectal examination was normal.

The patient underwent extensive preoperative investigation for diagnosis. On admission his haemoglobin was 13.5 g%, Total leukocyte count was 6.200/mm³ with a normal differential count, platelet count and coagulogram. The random blood sugar was 98 mg%. The renal and liver function tests were normal. The abdomen ultrasonogram revealed large heterogeneous mass of 16×11.4 cm in the pelvis region on the right side. Possibility of Lymphoma / lymphoproliferative disorder should be ruled out. Mild fullness of pelvic/colic system on right side and mild hepatosplenomegaly presented. Keeping a working diagnosis of a retroperitoneal tumour, a contrast enhanced computerised

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tomography scan revealed 13.2×9.9×13.4 cm round to oval, predominantly isodense lesion in lower abdomen and pelvis (Fig. 1).

On the right side, it appeared to involve the mesentero-peritoneal space. Patchy mesenteric fat stranding was seen. Mass effect with displacement of bowel loops and indentation of urinary bladder was evidenced. Another 3.2×3.1×9.7 cm iso to hyperdense lesion was present predominantly in iliopsoas muscle. An ill-defined isodense lesion of 2.2×1.3×1.2 cm was revealed in subcutaneous tissue of anterior abdominal wall in right paraumbilical region. Multiple sub centimetric sized mesenteric lymph nodes was seen. Posterior end of left lower ribs appeared thickened and showed mild deformity. The tumour was locally aggressive with multiple intramuscular, and subcutaneous enhancing nodular lesion was revealed. Non enhancing hyperdense band like lesions was evidenced in iliacus and paraspinalis muscles. There was an Expansile lesion of the 7th and 8th ribs on the left side. The differential diagnosis of desmoplastic fibroma/fibrous dysplasia of the retroperitoneum was contemplated. Fine needle aspiration cytology from the lesion showed no evidence of malignant cells.

A CT angiogram further revealed the same locally aggressive lesion in right lumbar and iliac region with extension into pelvis. The arterial supply of the lesion was seen to arise

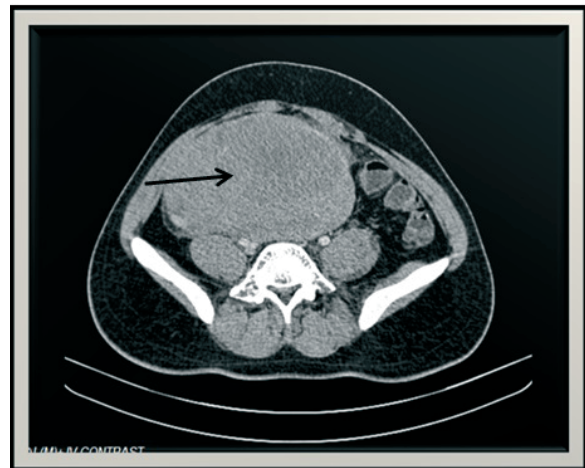


Fig. 1. GIST ** CECT Abdomen and pelvis showing predominantly solid abdominopelvic mass measuring 10×15×16 cm with heterogeneous enhancement. Right sided Grade III hydroureteronephrosis noted.

from hypertrophic ileo-colic-right colic trunk. The diameter of ileo colic – right colic trunk at origin was 4 mm. A CT guided Trucut biopsy revealed histomorphological features suggestive of spindle cell tumour of borderline malignant potential (Fig. 2).

On exploratory laparotomy there was an intrabdominal mass covering the entire right side of abdomen and right side of pelvis (Fig. 3).

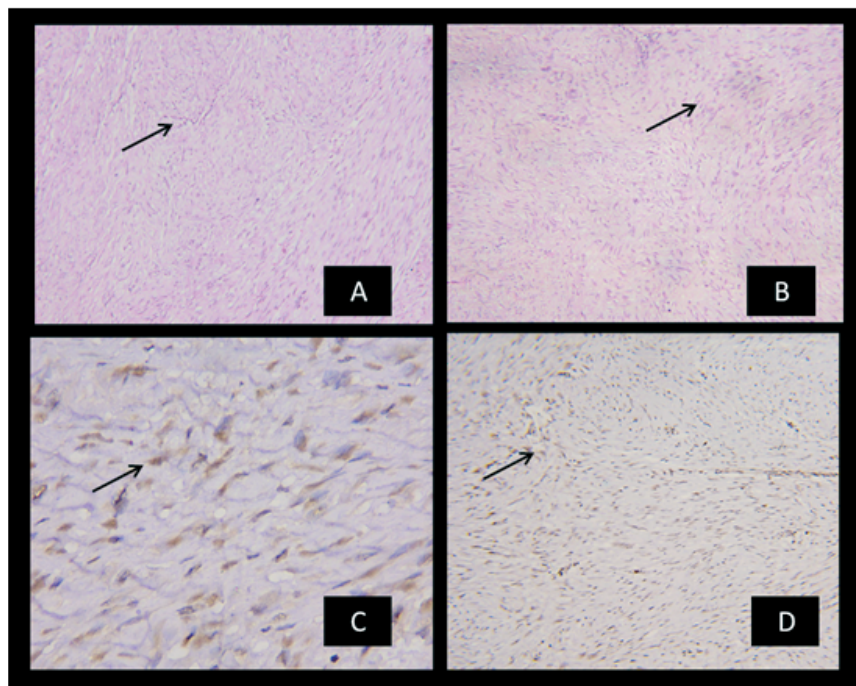


Fig 2. GIST ** A&B: H&E stained section shows interlacing benign spindle cells embedded in myxoid stroma; C&D: Immunohistochemical staining with C kit antibody showing cytoplasmic positivity.

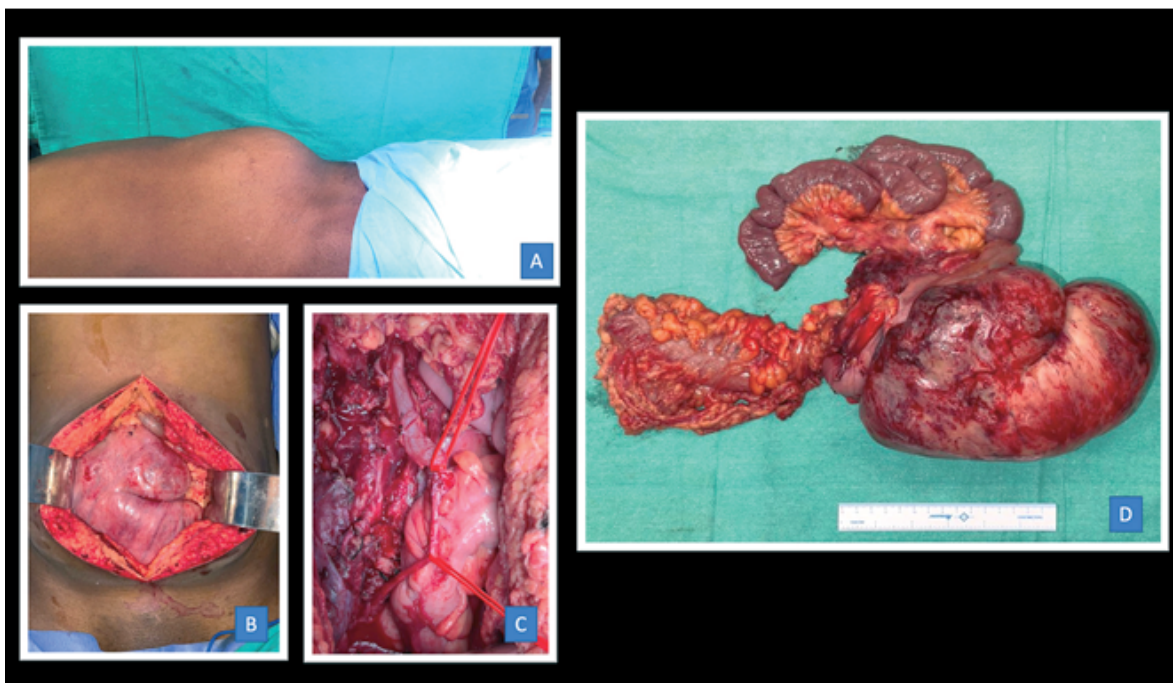


Fig 3. GIST ** A: Preoperational image showing abdominopelvic lump in lateral view; B: Intra pic showing 13×13 cm hard lump; C: Intra op pic showing Right ureter with hydronephrosis; D: Resected specimen showing terminal ileum and transverse colon along with the lump.

The tumour was adherent to the terminal ileum and ascending colon. The tumour was resected with right hemicolectomy and ileo-transverse anastomosis. There was dense adhesion between the retroperitoneum with involvement of right middle ureter. The involved part of right ureter was resected and re-anastomosed with double J stent (Fig. 4).

On the 5th postoperative day, the patient developed increased frequency of stools, which

subsided over next few days. He was discharged in 10 days with initiation of chemotherapy with tablet imatinib mesylate 400 mg once daily.

The post-operative specimen Histopathology showed Gastrointestinal stromal tumour, spindle cell type, high grade, pT4N0Mx. On immunohistochemistry DOG 1 and CD 17 were positive. CD 34, Desmin, S100 and SMA were negative. Ki 67 score was 8 to 10%. Cut end of the left ureter showed small focus of tumour abutting the adventitia wall. On the follow up in 30 days, the abdominal wall wound healed well and chemotherapy was tolerated without any side effects. DJ stent was removed in six weeks. Review ultrasound examinations over three and sixth month showed no recurrence of growth. Presently the individual has got back to the normal life activities and is perusing a master's course in university.



Fig 4. Post op X-ray Pelvis showing Right sided double J stent in place.

Discussion

The largest series of retroperitoneal GIST reported in literature comes from Miettinen et al. [1]. They analysed data for a period of 26 years and studied 112 cases of retroperitoneal GIST. Equal incidence was evidenced in both sexes and more common in the elderly population. A vast majority of these tumours were from extraintestinal site with 35 cases from

unspecific sites. All tumours were positive for immunohistochemistry markers for GIST.

Regarding the analysis of the unusual presentation of GIST, many articles are available in the literature. Raja et al. reported a case of GIST presenting as intra peritoneal bleed in a 31-year-old male [2]. The highly malignant nature of the GIST caused ulceration and bleed into the peritoneal cavity and presenting as hemo peritoneum.

Sometimes GIST arising from the retroperitoneum presents with nonspecific symptoms of vomiting, weight loss, low grade fever, anaemia and asthenia. There will be no mass/lump palpable in the abdomen. Thus, imaging technique and biopsy will reveal mass retroperitoneum classified as extraintestinal GIST (E-GIST). Yan et al. reported one of the rare occurrences of pancreatic GIST [3]. This was one of the first two such cases reported in the literature. The diagnosis was made by tissue biopsy using endoscopic ultrasound. A malignant GIST was similarly diagnosed by Rao et al. as a growth in the head of pancreas in a 40-year-old patient [4]. Similarly, Harindhanavudhi et al. [5] reported GIST presenting as haemorrhagic cyst in the head of pancreas.

Another rare location with varied presentation for retroperitoneal GIST is duodenum.

The largest series was by Vassos et al. [6]. In their 1-year review of 13 patients this site was amenable to surgical resection. Both local excision and pancreaticoduodenectomy showed comparable results in experience centres. This article also stressed the use of TKI imatinib mesylate in overall long-term prognosis.

Gorelik et al. [7] reported another rare presentation of GIST. The patient presented in bacteraemia with liver abscess. The unusual presentation arose from a fistula between the small intestine and the tumour. Similarly Virgilio et al. [8] studied 15 cases of GIST presenting as mass in the inguinal canal.

Finally, in the review of literature by Gupta [9] 9 cases of gall bladder GIST were reported. These symptoms may be presumed as a sign of mimic cholangitis and are often seen in women. Almost all of these tumours are malignant and require urgent surgical excision.

Finally, a similar case was reported by Ashoor et al. [10] as an incidental finding in a 67-year-old man reported for benign prostrate hyperplasia. The tumour measuring 15 cm was arising from the retroperitoneal aspect of right inguinal fossa. This is the last presentation of incidental findings in radiological evaluation for other problems in this study.

Table 1. Some of the varied presentations of GIST are as tabulated further down

No.	Year	Topic	Author	Presentation
A)	2014	Atypical Presentation of Gastrointestinal Stromal Tumours: A Case Report	Kalpana Raja et al.	Hemangioma
B)	2020	Atypical presentation of gastrointestinal stromal tumor as multiple intra-abdominal cysts: a case report	Ram Prakash Gurram et al.	Gastric cyst
C)	2004	Atypical presentation of gastrointestinal stromal tumor as multiple intra-abdominal cysts: a case report	Ke Kang Sun et al.	Intra-abdominal cyst
D)	2015	Atypical presentation of gastrointestinal stromal tumor masquerading as a large duodenal cyst: a case report	Ameet Kumar et al.	Duodenal cyst
E)	2019	Unusual presentation of a large gist in an extraintestinal site: a challenging diagnosis dilemma	Arwa Ahmed Ashoor et al.	Jejunal mesentery
F)	2018	An Ulcerated Ileal Gastrointestinal Stromal Tumor Disguised as Acute Appendicitis	Ashish Lal Shrestha et al.	Ileal GIST presenting as appendicitis
G)	2017	Ileal gist presenting with bacteremia and liver abscess: a case report and review of literature	Gorelik et al.	Bacteraemia with liver abscess
H)	2021	Inguinal gist: a systematic literature review of primary and metastatic cases	Virgilio et al.	Mass in the inguinal canal
I)	2014	Malignant extra-gastrointestinal stromal tumor of the pancreas: report of two cases and review of the literature	Yan et al.	Pancreatic gist
J)	2019	Gallbladder gist: a review of literature	Gupta et al.	Gall bladder gist

Conclusions

Gastrointestinal stromal tumours are mostly benign neoplasm arising from gastrointestinal tissues. They seldom become malignant and metastasis is rare. There are many atypical variations in clinical presentation for these tumours. The surgeon always needs to keep this diagnosis in mind while evaluating atypical cases of intra-abdominal or retroperitoneal mass.

Limitations

Single centre study.

Conflict of Interests

All authors declare no conflict of interest.

Author's Contributions

Vipin V. Nair, Pawan Sharma, Nagamahendran R. – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; Santosh Raja, Pankaj P. Rao – data curation, writing – reviewing and editing; Ritu Mehta – investigation, formal analysis.

КЛІНІЧНИЙ ВИПАДОК РІДКІСНОГО ЗАОЧЕРЕВИННОГО УТВОРЕННЯ: ТРУДНОЩІ ЛІКУВАННЯ ТА НАБУТИЙ ДОСВІД

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Вступ. Шлунково-кишкові стромальні пухлини (ШКСП) — це неепітеліальні мезенхімальні солідні новоутворення з різноманітними проявами. У цьому дослідженні описано випадок заочеревинної ШКСП у 21-річного чоловіка, у якого протягом шести місяців спостерігалася припухлість в ділянці живота. Утворення спочатку вважали заочеревинною саркомою. Діагностична лапаротомія виявила черевно-тазову пухлину, що охоплювала всю праву частину живота та таза. Пухлина була спаяна з термінальним відділом клубової та висхідної ободової кишки. Виникли щільні спайки між заочеревинним простором із ураженням середньої третини правого сечоводу. Пухлину видалено з правосторонньою геміколектомією з ілео-поперечним анастомозом. Післяопераційна гістопатологія показала, що це веретенноклітинна ШКСП високого ступеня диференціювання. Зараз пацієнт проходить післяопераційну хіміотерапію імаїнібу мезилатом в таблетках.

Мета. Атипові прояви ШКСП рідко обговорюються, але часто зустрічаються в клінічній практиці. Ця стаття описує різні проблеми, з якими доводиться зустрічатися хірургу під час діагностики такого нетипового утворення.

Методи. Опис випадку атипового ШКСП, який проявлявся у вигляді заочеревинної припухлості.

Результати. Пацієнту була проведена хірургічна резекція, зараз він отримує післяопераційну хіміотерапію з хорошим загальним результатом після року спостереження.

Висновки. ШКСП, які проявляються у вигляді заочеревинних утворень, зустрічаються дуже рідко, їх слід враховувати при диференціальній діагностиці атипової заочеревинної пухлини.

КЛЮЧОВІ СЛОВА: ШКСП; атипове положення; заочеревинна пухлина; ущільнення в животі.

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AN OBSERVATIONAL STUDY TO FIND RELATIONSHIP OF ACUTE APPENDICITIS TO MENSTRUATION CYCLE IN NORTHERN AND NORTHEASTERN PART OF INDIA

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Background. Diagnosing acute appendicitis correctly in a female patient is a challenge for a practicing surgeon. Rate of misdiagnosis of acute appendicitis is very high among female patients. There are many studies carried out to find incidence of acute appendicitis as per various phases of menstruation cycle but the results were conflicting.

Objective. The study was conducted to find the relationship of acute appendicitis with the different phases of the menstruation cycle.

Methods. This research was an observational study carried out in two regional hospitals in northern and north-eastern part of India. Duration of study was 24 months between 01 June 2019 and 31 May 2021. Inclusion Criteria were for all female patients, non-pregnant and menstruating, who were histopathologically confirmed as acute appendicitis. All pathologically proven negative appendectomy patients were excluded from this study. All female patients taking oral contraceptive pills (OCP) were excluded from the study.

Results. A total of 96 females were hospitalized in both hospitals during the study period; 12 of them did not attain menarche (12.5%), 6 had menopause (6.3%) and 78 were menstruating (81.25%). Of those 78 patients, who had physiological menstrual cycles, 6 were in menstrual phase (7.6%), 18 were in proliferative phase (23%), and 54 in luteal phase (69.2%). In our study, there were only 6 cases of acute appendicitis during menstruation. therefore, the expected ratio of cases was $6/14=0.42$. The corresponding expected rate for the proliferative phase was $2.78 \times 9=25$ cases, whereas for the luteal phase it was $2.78 \times 14=38.92$. The expected ratio was $18/25=0.72$ for the proliferative phase and $54/39=1.38$ for the luteal phase. There was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value <0.05 . Mean age of the study participants was 28.31 ± 9.56 .

Conclusions. According to the result of the study, the incidence of acute appendicitis significantly differs in different phases of menstruation cycle with highest incidence in luteal phase. Hence, female hormones (estrogen and progesterone) are significant in causing acute appendicitis.

KEYWORDS: acute appendicitis; menstruation phase; proliferative phase; luteal phase.

Introduction

Diagnosing an acute appendicitis in female patients is a challenge for a practicing surgeon. The rate of misdiagnosis is comparatively high in female patients especially in reproductive age group. The lifetime risk of appendicitis is 6.7% for females [1]. Diseases of the female internal reproductive organs that may erroneously be diagnosed as appendicitis in approximately descending order of frequency include pelvic inflammatory disease, ruptured

graafian follicle, twisted ovarian cyst or tumor, endometriosis and ruptured ectopic pregnancy [1]. Timely diagnosis and early treatment can prevent complications associated with the disease. The sonographic diagnosis of acute appendicitis has reported sensitivity of 55% to 96% and a specificity of 85% to 98% [1]. Appendicitis is also associated with gastrointestinal symptoms like nausea (sensitivity, 58%; specificity, 36%), vomiting (sensitivity, 51%; specificity, 45%), and anorexia (sensitivity, 68%; specificity, 36%) [1]. Gastrointestinal symptoms that develop before the onset of pain suggest a different etiology such as gastroenteritis [1].

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The ratio of cases of appendicitis to cases of pelvic inflammatory disease is low in females in the early phase of the menstrual cycle and high during the luteal phase [1]. Many studies showed different results. Arnbjörnsson et al. showed that appendicitis is more common during the luteal phase of the cycle [2] whereas Robinson et al. showed that acute appendicitis is equally common in all phases of the cycle [3]. The aim of the current study was to find out the relationship of acute appendicitis to menstruation cycle.

Methods

This study was an observational study carried out in two regional hospitals in northern and north-eastern parts of India. The study was aimed to assess the relationship of phases of menstruation cycle to acute appendicitis. Duration of study was 24 months between 01 June 2019 and 31 May 2021.

Inclusion Criteria: all female patients, non-pregnant and menstruating, who were histopathologically confirmed as acute appendicitis.

Exclusion Criteria: all pathologically proven negative appendectomy patients were excluded

from this study. All female patients, who were consuming in OCP, were excluded from the study.

Menstrual cycle was divided into 3 phases:

1. Menstruation phase; 2. Proliferative phase; 3. Luteal phase.

Duration of two phases was considered as constant (a) menstruation phase: 05 days of menstruation in physiological cycle from the beginning of bleed; (b) luteal phase: last 14 days of cycle (calculated retrospectively 14 days from the first day of menstruation bleed of next cycle excluding the day 1 of bleed). Hence, the period of proliferative phase was variable. It was also considered that ovulation occurred at the 14th day of the cycle.

Results

A total of 96 females were hospitalized in both hospitals during the study period (Table 1); 12 of them did not attained menarche (12.5%), 06 had menopause (6.3%), and 78 were menstruating (81.25%). Of those seventy-eight patients, who had physiological menstrual cycles, 6 were in menstrual phase (7.6%), 18 were in proliferative phase (23%), and 54 – in luteal phase (69.2%).

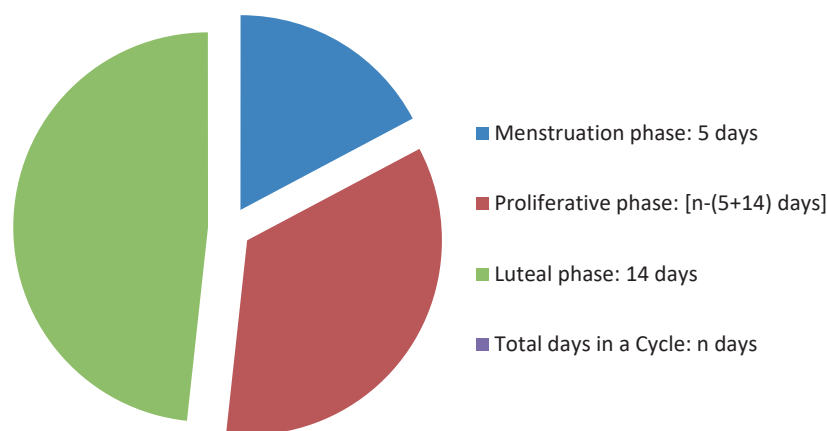


Fig. 1. Phases of menstruation cycle.

Table 1. Acute appendicitis cases (total number and percentage) as per phases of menstruation

	Number of females	Percent
Not attained menarche	12	12.5
Menstrual phase	6	6.3
Proliferative phase	18	18.8
Luteal phase	54	56.3
Post menopause	6	6.3
Total	96	100.0

Four out of seventy-eight acute appendicitis cases (Table 2) in menstruating females were complicated type, whereas none in non-menstruating female group had any complications.

The expected daily occurrence of acute appendicitis for patients with physiological menstrual cycles (for a 28-day cycle) would have been $78/28 = 2.78$ cases/day. The expected rate for cases of acute appendicitis during menstruation (accepting that menstruation lasts for 5 days), would have been $2.78 \times 5 = 14$ cases. In current study there were only 06 cases of acute appendicitis during menstruation. The obser-

ved: expected ratio of cases therefore was $06/14 = 0.42$. The corresponding expected rate for the proliferative phase was $2.78 \times 9 = 25$ cases, whereas for the luteal phase it was $2.78 \times 14 = 38.92$. The observed: expected ratio therefore was $18/25 = 0.72$ for the proliferative phase and $54/39 = 1.38$ for the luteal phase.

There was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value < 0.05 .

The mean age of the study participants was 28.31 ± 9.56 .

Table 2. Total complicated and non-complicated cases

	Menstruating	Non Menstruating	Total
Complicated	4	0	4
Non Complicated	74	18	92
Total	78	18	96

Table 3. Observed frequency, expected frequency and P value with respect to different phases of menstruation cycle

Phase of menstrual cycle	Observed frequency	Expected frequency	P value
Menstrual	6	14	P value 0.034066
Proliferative	18	25	
Luteal	54	39	
Chi-square statistic 6.7589			

Table 4. Mean, Median, Std deviation and Ranges

Statistics		
N	Valid	78
Mean		28.31
Median		28.00
Std. Deviation		9.558
Range		39
Minimum		13
Maximum		52

Discussion

The previous studies by Arnbjornsson [2] and Eldar et. al. [4] reported that incidence of histologically confirmed acute appendicitis was less common during menstruation phase [1] but the difference were not statistically significant. On literature search before these current studies, there were conflicting observations. Some studies [1, 4] showed higher incidence of acute appendicitis in luteal phase whereas some other [2] - in proliferative and menstruation phase. Another study by Robinson et. al. failed to show any difference [3].

The study had established that there was a significant increase in number of cases of acute appendicitis among the menstruating women in luteal phase with p value < 0.05 . Similar result was shown in the studies by Eldar et. al. The cause of this significant raise in incidence of acute appendicitis may be because of low estrogen level and high progesterone level modulating immune response and increasing susceptibility for gut infections.

Souza et. al. [5] reported increased NK activity in follicular phase as compared with luteal phase. Progesterone receptors and progesterone induced apoptosis of NK cells and suppresses IL-12-induced IFN- γ production of Killer Ig-like receptor (KIR)+ NK cells [6]. Whereas estrogen has been reported in many studies to prevent B cell apoptosis, enhance survival and activation of autoreactive cells [7], and increase expression of CD4+ T cell chemokine receptors [8]. Estrogen exerts immune regulation via estrogen receptors (ERs) on the lymphocytes, and receptors for estrogen, progesterone, androgen, and glucocorticoid are found in lymphoid organs and/or lymphocytes [9, 10].

Hall et. al described that concentrations of progesterone fluctuated over the life course in females, with increased concentrations at puberty, cyclical changes during the menstrual cycle, and a steady rise during pregnancy followed by a sharp decline post-partum [11]. At menopause, concentrations steadily declined to levels that are similar to those prior to puberty [11].

Progesterone hormone level started rising after ovulation on the 14th day of cycle and reached its highest level during mid-luteal phase (Fig. 2). Speroff et al. in his study mentioned that serum levels of progesterone fluctuate during the menstrual cycle with a peak of 20 ng ml⁻¹ during the luteal phase and the nadir (<1ng ml⁻¹) during the follicular phase [12].

Progesterone generally inhibits inflammatory innate immune responses [11]. In vitro studies by Hardy et. al. and Jones et. al. showed that progesterone can suppress activation of macrophages and dendritic cells [13, 14]. When progesterone is bound to its receptor, it directly interferes with the transcription factor nuclear factor-kappa B (NF- κ B) through transrepression and inhibits gene transcription downstream of the NF- κ B pathway, including cyclooxygenase-2 to decrease inflammation [13, 15]. Progesterone can also decrease inflammation by inhibiting the production of proinflammatory cytokines (e.g., TNF- α , IFN- γ , and IL-12) and increasing

production of anti-inflammatory cytokines, including IL-10 [14, 16].

Raised level of progesterone also suppresses Th1 response and enhances IL-10 producing Th2 cells. Miyaura et. al. in his study mentioned that progesterone was established to suppress Th1 response and enhance IL-10 producing Th2 cells [17]. Ehring et. al. in his study had showed that progesterone suppressed immune functions of T cells by a non-genomic mechanism, which was the blocking of K⁺ channel, Ca²⁺ signaling and NF of activated T cells driven gene expression [18]. Siiteri et. al. had demonstrated in vivo the immunosuppressive effects of progesterone in his study by prolonged survival of xenografts near silastic implants containing progesterone at concentrations typically found in the placenta [19]. Hence, such high progesterone level in luteal phase may have caused unfavorable immunity changes leading to more susceptibility to gut infection and causing highest incidence of acute appendicitis in luteal phase.

Estrogen hormone increases its level from menstruation phase and reaches its peak at late proliferative phase. Estrogen then decline its level and reaches minimum level at late luteal phase. Hence, maximum proliferation of both lymphocytes and macrophages occurs during proliferative phase whereas minimum proliferation of both lymphocytes and macrophages occurs during luteal phase.

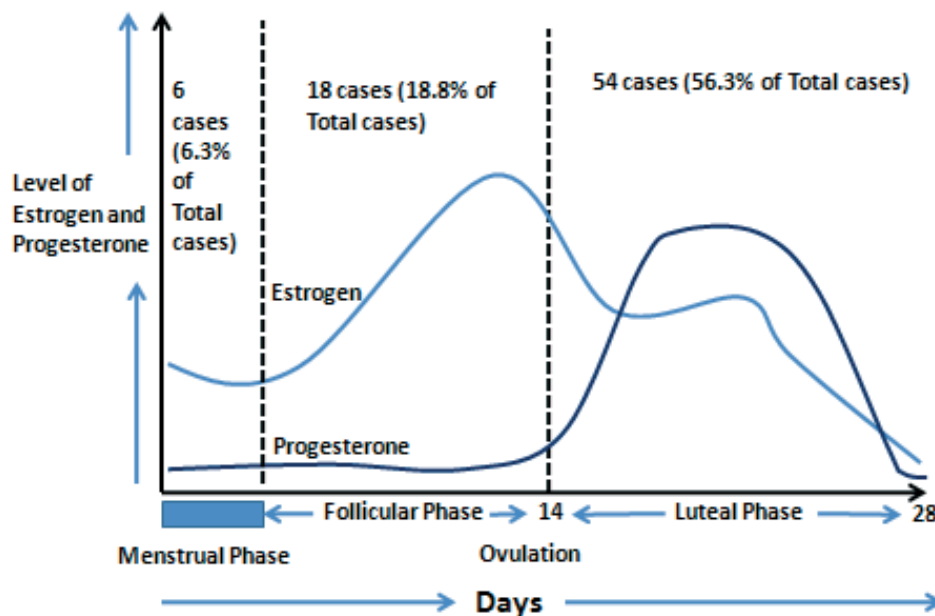


Fig. 2. Relationship between different level of estrogen and progesterone with percentage of acute appendicitis in different phases of menstruation cycle.

Whitacre et. al. stated in his study that the effects of estrogen were pleotropic on immune cell function and estrogen had been shown to significantly stimulate the proliferation of both lymphocytes and macrophages [20]. In many studies, estrogen has been shown to regulate immune response by impairing negative selection of high affinity auto-reactive B cells, modulating B cell function and leading to Th2 response [21, 22]. Estrogen also influences physiological functions via ERs which are expressed in brain, gut epithelial cells, lymphoid tissue cells as well as immune cells [23, 24]. R. Mo et. al has stated that estrogen also induces T cell homing by enhancing the expression of C-C chemokine receptor type 5 (CCR5), a homing marker [8]. Many studies has also shown that estrogen regulates immune response via modulation of endosomal TLRs and TLR8 expression thus hormonal balance determines the overall response to infection in females [25, 26, 27]. Hence, such low estrogen level with high progesterone level in luteal phase may cause unfavorable immunity changes leading to more susceptibility to gut infection and causing highest incidence of acute appendicitis in luteal phase and vice versa in proliferative phase.

Conclusions

According to the results of the study, it can be concluded that the incidence of acute appendicitis significantly differs in different phases of menstruation cycle with highest incidence in luteal phase. Hence, female hormones (estrogen and progesterone) are significant in causing acute appendicitis. This relationship can be used as additional guiding tool or information when there is diagnostic dilemma for acute appendicitis in females.

Limitations

Small sample size.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Thokchom Bishwajit Singh, Ranjan Kumar – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; Ankur Nigam – investigation, formal analysis; Tekcham Roshini Devi – data curation, writing – reviewing and editing.

ВЗАЄМОЗВ'ЯЗОК ГОСТРОГО АПЕНДИЦИТУ ТА ФАЗИ МЕНСТРУАЛЬНОГО ЦИКЛУ У ЖИТЕЛІВ ПІВНІЧНОЇ ТА ПІВНІЧНО-СХІДНОЇ ЧАСТИНИ ІНДІЇ

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Вступ. Діагностування гострого апендициту у пацієнта може бути проблемною для практикуючого хірурга. Частота неправильної діагностики гострого апендициту дуже висока серед пацієнтів. Існує багато досліджень, проведених для виявлення частоти гострого апендициту відповідно до різних фаз циклу менструації, але їх результати є суперечливими.

Мета. Дане дослідження проводилося для встановлення та оцінки взаємозв'язку гострого апендициту з різними фазами менструального циклу.

Методи. Дослідження було спостережним, проведеним у двох регіональних лікарнях у північній та північно-східній частині Індії. Тривалість дослідження становила 24 місяці з 01 червня 2019 року по 31 травня 2021 року. Критерії включення: Усі пацієнти, які не порушень менструального циклу та які мали гістопатологічне підтвердження діагнозу гострий апендицит. Критерії виключення: Усі пацієнти яким не проводилася апендектомія чи які приймали оральні контрацептиви, були виключені з дослідження.

Результати. Всього 96 жінок були госпіталізовані в обох лікарнях протягом періоду дослідження. З них 12 не досягли менархе (12,5%), 6 мали менопаузу (6,3%), а 78 – мали менструальні цикли (81,25%). З тих 78 пацієнтів, які мали фізіологічні менструальні цикли; 6 були в менструальній фазі (7,6%), 18 - у

проліферативній фазі (23%) та 54 у лютеїновій фазі (69,2%). У нашому дослідженні під час менструації було лише 6 випадків гострого апендициту. Таким чином, спостережуване: очікуване співвідношення випадків становило $6/14 = 0,42$. Відповідна очікувана цифра для проліферативної фази становила $2,78 \times 9 = 25$ випадків, тоді як для лютеїнової фази було $2,78 \times 14 = 38,92$. Таким чином, спостережуване/очікуване співвідношення становило $18/25 = 0,72$ для проліферативної фази та $54/39 = 1,38$ для лютеїнової фази. Спостерігалось значне збільшення кількості випадків гострого апендициту серед менструальних жінок у лютеїновій фазі ($p < 0,05$). Середній вік учасників дослідження становив $28,31 \pm 9,56$.

Висновки. За результатами нашого дослідження можна зробити висновок, що захворюваність на гострий апендицит значно відрізняється різними фазами циклу менструації з найвищою частотою в лютеїновій фазі. Отже, жіночі гормони (естроген та прогестерон) відіграють важливу роль у виникненні гострого апендициту.

КЛЮЧОВІ СЛОВА: гострий апендицит; фаза менструації; проліферативна фаза; лютеїнова фаза.

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CLINICAL OUTCOMES OF REVERSAL OF HARTMANN'S PROCEDURE

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Background. Reversal of Hartmann's procedure (HP) is one of the most complex surgical interventions in abdominal surgery with high morbidity rates of up to 58% in the patients after HP and mortality of up to 3.6%.

Objective. This was a retrospective observational study to analyze the Hartmann's reversal (HR) outcomes.

Methods. The study involved 31 patients (16 males and 15 females), average age 59.6 ± 10.31 (range 26-80), who underwent HR at Ternopil Regional Hospital in 2010 - 2021. The reasons for the HP were: cancer in 20 (64.5%) cases, perforation of the diverticulum – 6 (19.3%), traumatic rupture – 3 (9.7%) and Crohn's disease - 2 (6.4%) cases.

Results. Median time from Hartmann's procedure to reversal was 11.13 ± 9.24 months (interval 3-38). Intraoperative time was 210.33 ± 56.91 minutes (range 120-330). HR was performed in 30 (96.8 %) patients. Dense pelvic adhesions of the stump of the rectum was diagnosed in 13 (41.9%) patients. Hand-sewn anastomosis was performed for 22 (71%) patients, stapler anastomosis – 4 (12.9%), pull-through technique – 3 (9.7%) patients. AL occurred in 3 (9.7%) patients on the 15th, 23rd and 35th postoperative days. pseudomembranous colitis was diagnosed in 2 (6.4%) patients with AL. The mortality rate was 1 (3.3%) as a result of septic complications due to AL; this case was not operated by a colorectal surgeon due to administrative issue in the hospital.

Conclusions. Hartmann's reversal is still one of the most difficult operations in colorectal surgery with high incidence of postoperative complications. Sound selection of patients with low comorbidity and in suitable time period is crucial for successful HR.

KEYWORDS: Hartmann's procedure; reversal; anastomotic leakage.

Introduction

A century has passed since Henry Hartmann firstly performed the widely known operation, but it has not lost its relevance and is frequently used around the world to prevent anastomotic leakage (AL), which remains an eternal problem in colorectal surgery [1]. Reversal of Hartmann's procedure (HP) is one of the most complex surgical interventions in abdominal surgery with high morbidity rates of up to 58% in the patients after HP and mortality of up to 3.6% [6, 8]. Multifactorial technical difficulties particular to reversal include dense pelvic adhesions, pelvic infection, adhesions, difficulty in identification of rectal stump and performing of colorectal anastomosis with short rectal stump [1, 7]. As a result, more than two-thirds of patients remain with a permanent stoma following Hartmann's procedure, either due to inability to perform reversal or due to anastomotic leak and stoma

restoration [1, 6, 7]. The majority of ostomy patients become socially and psychologically maladapted need to manage the physical and psychological challenges associated with a stoma [7].

Methods

This was a retrospective observational study to analyze the Hartmann's reversal (HR) outcomes. The study involved thirty-one patients (16 males and 15 females) of average age 59.6 ± 10.31 (range 26-80), who underwent HR at Ternopil Regional Hospital in 2010-2021. The median BMI was 25.2 (range 18-39). Most of the patients (80.6 %) had an ASA score 3-4. Median time from Hartmann's procedure to reversal was 11.13 ± 9.24 months (interval 3-38). Intraoperative time was 210.33 ± 56.91 minutes (range 120-330). Blood loss was 331.67 ± 191.4 ml (range 150-1000). The reasons for the HP were: cancer in 20 (64.5%) cases, perforation of the diverticulum – 6 (19.3%), traumatic rupture – 3 (9.7%) and Crohn's disease – 2 cases (6.4%) (Table 1).

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Quantitative variables were calculated with the median. All calculations were performed using the Statistica 64 software.

Results

HR was performed for 30 (96.8 %) patients. Mobilization of the splenic flexure was performed for 5 (16.1%) patients. Dense pelvic adhesions of the stump of the rectum was diagnosed in 13 (41.9%) patients. Hand-sewn anastomosis was performed for 22 (71%) patients, stapler anastomosis – 4 (12.9%), reduction – 3 (9.7%) patients. paracolostomy hernia was diagnosed in 7 (22.6%) patients. The mean hospital stay was 14.03 ± 11.3 days (interval 7-62).

AL developed in 3 (9.7%) patients on the 15th, 23rd and 35th postoperative days (Table 2). pseudomembranous colitis was diagnosed in 2 (6.4%) patients with AL. 1 patient after HR was affected with Covid-19 on the 12th postoperative day, probably it was one of the major favorable factors of AL development which was diagnosed on the 35th postoperative day due to systemic infection and reducing the reactivity of the immune system. The mortality rate was 1 (3.3%) as a result of both sepsis and purulent peritonitis due to AL; this case was not operated by a colorectal surgeon due to administrative issue in the hospital.

Discussion

Adequate patient selection and preoperative planning are extremely important for HR pro-

cedures to reduce the risk of postoperative complications [1]. Patients with a benign disease, aged under 69 years old and with low comorbidity are more likely of undergoing HR [6, 8]. In our study AL was diagnosed in 3 (9.7%) patients aged 63-80 years old and ASA score 3-4.

Chronic infection (cured abscess and infected pelvis infiltratis) is one of the major factors influencing HR outcome and usually creates technical difficulties during surgery in the form of dense pelvic adhesions [4, 7]. These challenges made performing HR impossible in one patient in our study.

One of the important factors is the optimal interval between HP and HR. According to the literature the best time to perform HR is at least 6 months after the surgery [5, 7]. In our study the interval between HP and HR was 11.13 ± 9.24 months (interval 3-38), however, such results were obtained by inclusion of 3 patients, who underwent HR at 36-38 months after HP. Other authors show that timing of surgery (more than 6 months) do not affect surgical complications rate or severity or the length of hospital stay [5]. In the study paracolostomy hernia was evidenced in 7 (22.6%) patients, nevertheless at the same time it did not increase the complication rate.

Laparoscopic HR has significant privilege under open HR with less short-term complications regarding the overall morbidity, less frequency of wound infection and postoperative ileus [2, 3].

Table 1. Indications for Hartmann's procedure

Indications for Hartmann's procedure	n	%
Colorectal cancer	20	64.5
Perforation of the diverticulum	6	19.3
Traumatic rupture	3	9.7
Crohn's disease	2	6.7

Table 2. Analasis of patients with AL

Clinical data/patients	1	2	3
Age	80	63	69
Sex	female	female	female
Indications for HP	perforation	colorectal cancer	perforation
Months between HP and HR	4	14	13
Relaparotomy	+	+	+
AL on ... postoperative day	15	23	37
Hand-sewn anastomosis	+	+	+
Pseudomembranous colitis	-	+	+
Covid-19	-	-	+
Hospital discharge/death	19(death)	42	56

Conclusions

Hartmann's reversal is still one of the most difficult operations in colorectal surgery with a high incidence of postoperative complications. Sound selection of patients with low comorbidity and in period of 6-12 months after HP is crucial for successful HR.

Conflict of Interests

Authors declare no conflict of interest.

Authors' Contributions.

Ihor Dzyubanovsky – conceptualization, writing – reviewing and editing; Anatoliy Bedeniuk – methodology, formal analysis; Stepan Grytsenko – investigation, data curation, writing – original draft.

КЛІНІЧНІ РЕЗУЛЬТАТИ ЗАКРИТТЯ СТОМИ ПІСЛЯ ОПЕРАЦІЇ ГАРТМАНА

І. Я. Дзюбановський, А. Д. Беденюк, С. Й. Гриценко

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Закриття стоми після операції Гартмана є однією з найскладніших хірургічних втручань в абдомінальній хірургії з високим рівнем захворюваності до 58% і смертністю до 3,6%.

Мета. Це ретроспективне обсерваційне дослідження з метою аналізу клінічних результатів закриття стоми після операції Гартмана.

Методи. Тридцять один пацієнт (16 чоловіків та 15 жінок) із середнім віком $59,6 \pm 10,31$ років (діапазон 26-80), які проходили курс лікування у Тернопільській обласній лікарні з 2010 по 2021 рік. Причинами операції Гартмана були: рак у 20 (64, 5%) випадків, перфорація дивертикула – 6 (19,3%), травматичний розрив – 3 (9,7%) та хвороба Крона – 2 (6,4%).

Результати. Середній час між операцією Гартмана та реконструктивно-відновною операцією становив $11,13 \pm 9,24$ місяця (інтервал 3-38). Інтраопераційний час становив $210,33 \pm 56,91$ хв (діапазон 120-330). Реконструктивно-відновну операцією виконано у 30 (96,8 %) пацієнтів. Щільні тазові спайки кулки прямої кишки діагностовано у 13 (41,9%) хворих. 22 (71%) пацієнтам накладено ручний анастомоз, степлерний анастомоз у 4 (12,9%), низведення у 3 (9,7%). Неспроможність анастомозу виникла у 3 (9,7%) пацієнтів на 15, 23 та 35 добу після операції. У 2 (6,4%) хворих з неспроможністю анастомозу діагностовано псевдомембранозний коліт. Летальність у 1 (3,3%) випадку внаслідок септичних ускладнень зумовлених неспроможністю анастомозу, цей випадок неоперований колоректальним хірургом.

Висновки. Закриття стоми після операції Гартмана залишається однією з найскладніших операцій в колоректальній хірургії з високим відсотком післяопераційних ускладнень. Правильний відбір пацієнтів з низьким рівнем супутньої патології та в правильний період часу є важливим ключем до успішного виконання реконструктивно-відновної операції.

КЛЮЧОВІ СЛОВА: операція Гартмана; закриття стоми; неспроможність анастомозу.

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ENDOVASCULAR ANGIOPLASTY FOR MULTI-LEVEL STENOTIC-OCCLUSIVE LESIONS OF THE FEMORAL-DISTAL ARTERIAL BED IN CASES OF STENOTIC-OCCLUSIVE PROCESS OF THE TIBIAL ARTERIES

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Background. Occlusive-stenotic lesions of the lower extremity arteries are the second in the structure of cardiovascular diseases, after only coronary heart disease. Surgical treatment of patients with infrainguinal atherosclerotic lesions of the arterial segment is challenging in a number of cases. At the same time, revascularizing surgical interventions on the femoral-distal artery and especially on the tibial arteries in chronic critical ischemia is the only chance to avoid amputation of the lower limb. In this regard, the search and study of optimal methods of revascularizing surgery on the infrainguinal artery for stenotic-occlusive lesions of the arteries of the tibial segment is urgent.

Objective. This study is aimed at promotion of endovascular and hybrid technology in cases of stenotic-occlusive process of the tibial arteries and choosing the optimal surgical treatment tactics in this case.

Methods. Endovascular interventions of the femoral-distal arterial bed in cases of stenotic-occlusive process of the tibial arteries performed for 135 patients at the Department of Vascular and Cardiac Surgery of Ternopil Regional Clinical Hospital have been analysed.

Results. In most cases, endovascular angioplasty of two tibial arteries in hybrid and endovascular methods of revascularization of multilevel atherosclerotic process of the femoral-distal arterial segment of the lower extremity prevents development of thrombosis in tibial segment and allows maintaining the patency of the reconstruction segment and preservation of the lower extremity in 97.57% and 93.44% of cases, respectively.

Conclusions. Endovascular angioplasty of two tibial arteries provides a better result than angioplasty of one isolated tibial artery and allows maintaining the patency of the reconstructed segment for more than 90 percent compare to one isolated angioplasty.

KEYWORDS: vascular surgery; endovascular angioplasty; stenotic-occlusive process; atherosclerosis; revascularization.

Introduction

Occlusive-stenotic lesions of the lower extremity arteries are the second in the structure of cardiovascular diseases, only after coronary heart disease [1]. More than 55% of atherosclerotic lesions of the femoral-distal arterial segments were detected [2]. Occlusive-stenotic lesions of the infrainguinal artery in 35-65% of cases lead to chronic critical ischemia [3]. Surgical treatment of patients with infrainguinal atherosclerotic lesions of the arterial bed is challenging in a number of cases [4]. The complexity of surgical interventions in the femoral-distal arterial area is due to multilevel atherosclerotic lesions of the arterial bed, the

spread of lesions to adjacent arterial basins, collateral arterial basins and the state of outflow pathways – tibial arteries. At the same time, revascularizing surgical interventions on the femoral-distal artery and especially on the tibial arteries in chronic critical ischemia is the only chance to avoid amputation of the lower limb [13]. In this regard, the search and study of optimal methods of revascularizing surgery on the infrainguinal artery for stenotic-occlusive lesions of the tibial arteries is urgent.

Methods

Endovascular angioplasty of the femoral-distal arterial bed in cases of stenotic-occlusive process of the tibial arteries was performed for 135 patients. According to Fontaine's classification, 50 patients were diagnosed with stage

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IIb of chronic arterial insufficiency (CAI), 63 patients – stage III of CAI, 22 patients – stage IV. The method of hybrid revascularization was applied for 74 patients, and 61 patients underwent endovascular angioplasty of the infrainguinal arterial bed of the lower extremity.

To diagnose occlusive-stenotic lesions of the aorta and main arteries of the lower extremities, computed tomography with angio-amplification was performed by Philips Brilliance CT64 (Philips Medical Systems, the Netherlands) and ultrasound Doppler SonoScape S8 Exp (Italy) for examination of the arterial bed of lower extremities, angiography in the settings of the endovascular X-ray operating room, by angiograph Siemens Axiom Artis (Germany).

Before endovascular surgery double disaggregating therapy was prescribed to all patients were: acetylsalicylic acid drugs one day (160-300 mg/d) and thieperidine drugs (clopidogrel 75 mg/d). One hour before the operation, premedication was prescribed. Promedol 2%, 1.0 ml was most often administered intramuscularly or 30-40 minutes prior intramuscular injection of sol. Relanii or sol. Seduxeni 2.0.

Endovascular interventions were performed under local anaesthesia: 20.0-40.0 ml of 0.5% solution of Novocaine. Before the operation, after access, Heparin solution was administered at a dose of 70-80 U/kg of the patient body weight (5000-7500 U). To prevent arterial spasm of the tibial arteries, it was effective to prescribe Nifedipine 10 mg under the tongue for 15-20 minutes in combination with intravenous administration of 2.0 ml of 2% solution of Papaverine under control of blood pressure.

Check-Flo Performer by Cook Incorporated (USA) and Balton (EU), size 4-7 Fr were used to ensure the change of the balloon catheter and the free introduction of contrast. During the endovascular stage of hybrid surgery, intraluminal angioplasty of the tibial arteries was performed, and in 14 – subintimal angioplasty and subsequent stenting. In all cases, long cylinders (80-150 mm) Armada 35 LL by Abbott Vascular (USA) and Amphirion Deep (Medtronic) Coyote (Boston Scientific), stents CompleteSE (Medtronic), Smart (Cordis) were used.

In all cases, long cylinders (80-150 mm) Armada 35 LL by Abbott Vascular (USA) and Amphirion Deep (Medtronic) Coyote (Boston Scientific), stents CompleteSE (Medtronic), Smart (Cordis) were used.

Retrograde transfemoral access was applied for endovascular manipulations on the

femoral-popliteal-tibial arterial bed. The puncture site of the CFA was placed 2-3 cm below the inguinal fold. Subsequently, endovascular manipulations on the arteries of the femoral-popliteal segment were performed through the 6F introducer. Endovascular angioplasty of the stenotic-occlusive process of the femoral segment was performed with balloon catheters Pan Medical (PEKICO), OPTA PRO (Cordis).

After hybrid and endovascular angioplasty, unfractionated heparin was administered at a dose of 70-80 U/kg of body weight immediately after surgery with continued use until 12-24 hours of the early postoperative period. In 12 to 24 hours, thromboprophylaxis was continued with low molecular weight heparin. Disaggregating therapy with acetylsalicylic acid 100 mg and clopidogrel 75 mg was prescribed.

The criteria for inclusion of patients in the group for surgery was the presence of a multilevel atherosclerotic stenotic-occlusive lesions of the infrainguinal artery. The atherosclerotic process in the tibial arteries was extensive, parietal with segmental stenotic-occlusive lesions of the vascular lumen, the length of which was within 2.8-4.3 cm. Thus, endovascular angioplasty of two tibial arteries was performed to form a functionally suitable outflow pathway in the tibial arteries in cases of stenotic-occlusive process.

Statistical analysis was performed using the statistical software package STATISTICA 6.0 for Windows (StatSoft, Inc. Tulsa OK, USA) and Microsoft Excel (Microsoft office 2013, USA) with data in the form of mean and standard deviation ($M \pm SD$). Spearman correlation analyses were conducted to evaluate correlations between resistance index and type of angioplasty.

Results

Hybrid revascularization of the infrainguinal artery in cases of stenotic-occlusive lesions of the tibial arteries was performed for 74 patients. According to Fontaine's classification of stages of chronic arterial insufficiency, stage IIb of CAI was detected in 26 patients, in 34 patients – stage III; in 14 patients with stage IV of CAI trophic changes on the toes were found.

Atherosclerotic lesions of the arterial bed of the lower extremity was multilevel. It was established that occlusive process in one tibial artery with simultaneous development of stenotic lesions of the other two was detected in 6 (9.83%) cases. The occlusive process of two tibial arteries was established in 59 (79.73%)

cases. In 9 (14.76%) cases, segmental occlusive process was detected simultaneously in all tibial arteries. In 17 (22.97%) cases, atherosclerotic occlusion spread from the level of bifurcation of the common femoral artery (CFA) to the superficial femoral artery; in 38 (51.35%) cases the superficial femoral artery (SFA) was affected; in 7 (9.46%) cases the occlusive process spread from the initial segment of the middle third of the SFA to the level of the first section of the popliteal artery (PA), in 12 (16.22%) – to the II-III section of PA. Ultrasound duplex examination in 17 (22.97%) cases revealed stenosis at the level of 54-68% of the mouth (first section) of the deep femoral artery (DFA).

Hybrid surgery included open reconstruction of the femoral-popliteal segment and endovascular angioplasty of the tibial arteries and was staged one-step. Surgical treatment began with isolation of the femoral and popliteal arteries at typical access sites. In all cases, the distal anastomosis of the autovenous conduit was formed at the level of PA, and in 51 (68.92%) cases it was formed by the end-to-end type from autovein to PA. Subsequently, the autovenous conduit was moved anatomically through the canal along the vascular-nerve bundle to the selected level of the femoral artery. The proximal anastomosis of the autovenous bypass in 17 (22.97%) cases was formed at the level of CFA bifurcation. In these cases, the formation of the proximal anastomosis preceded the profundoplasty. In 57 (77.03%) cases, the proximal anastomosis was formed at the level of SFA: in 38 (66.67%) cases – at the level of the upper third of SFA, in 19 (33.33%) – at the level of the initial section of the middle third of SFA.

Prior to the completion of the first stage of the hybrid operation, a venous stump was formed at the level of the proximal anastomosis of the autovenous conduit to fix the introducer. This was achieved as follows: in the formation of the proximal anastomosis autovein was taken with an excess length of 3-4 cm, the stump was formed from it. An introducer was inserted into it, which was fixed with a tourniquet and was passed through a puncture at a distance of 5-6 cm from the edge of the wound to the skin surface. The venous stump to insert an introducer was used in 65 cases. In 9 cases, the introducer was performed at the level of the proximal anastomosis through the venous branch of the autovenous bypass. Thus, 122 endovascular angioplasties of the tibial arteries were performed: angioplasty of only one of the

tibial arteries was performed in 26 (35.13%) cases, and angioplasty of two vessels simultaneously – in 48 (64.87%) cases.

In 14 patients with stage IV of CAI, trophic changes were found on the toes: in 10 cases superficial trophic changes of the skin of the toes were detected; in 3 cases – deep ulcer of the toes, which involved subcutaneous adipose tissue, tendons and muscles; in one case – a deep ulcer involving subcutaneous adipose tissue, tendons, muscles with bone lesions, 1-3 fingers with spreading to their base. At the end of revascularization on the infrainguinal arterial segment, surgical treatment of trophic changes of the distal segments of the feet was performed in 4 cases. In cases of deep ulcer, which involved subcutaneous adipose tissue, tendons and muscles, exarticulation of the second and third toes was performed, and in one case of deep ulcer involving subcutaneous adipose tissue, tendons, muscles with bone lesions – metatarsal amputation of the distal segment of the foot. So, endovascular revascularization interventions on the infrainguinal artery in stenotic-occlusive lesions of the tibial arteries were performed for 61 patients.

Instrumental examination of a vascular bed of the lower extremity showed multilevel stenotic-occlusive atherosclerotic lesion of the infrainguinal arterial bed. It was established that atherosclerotic lesions of the arteries of the tibial segment were parietal with the spread of the process along the entire length of the artery, which narrowed its lumen and led to segmental occlusion. The length of occluded segments in the tibial arteries was 2.7-3.5 cm. The occlusive process in one vessel was found only in 6 (9.83%) cases with stenotic lesions of the other two tibial arteries. In the vast majority of cases, 42 (68.85%), the occlusive process of two tibial arteries with stenotic lesions of the third of the tibial arteries was revealed. In 9 (14.75%) cases the occlusive process was established simultaneously in all tibial arteries. Tibioperoneal trunk occlusion was revealed in 4 (6.56%) cases.

The results of computed tomography and ultrasound Doppler of the arterial bed of the lower extremities were taken as the basis for the choice of endovascular method of revascularization of the stenotic-occlusive process of the infrainguinal arterial bed of the lower extremity.

After balloon angioplasty, self-opening stents Smart Control (Cordis) were used in 8 cases, Carbostent (Flype) in 6 cases, and Vascu-

lar stent (BARD) in 11 cases. That is, in 40.98% of cases, self-opening stents were used to ensure the effectiveness of endovascular angioplasty of the femoral segment.

The second stage of endovascular intervention on the femoral-popliteal-tibial artery was angioplasty of the tibial arteries. Intraluminal angioplasty of the tibial arteries was performed in 48 cases, and subintimal angioplasty – in 13 cases, followed by stenting. Thus, in total 108 endovascular angioplasties of the tibial arteries were performed: angioplasty of only one of the tibial arteries was performed in 6 (5.56%) cases, and two tibial vessels at the same time – in 51 (83.61%) cases. Endovascular angioplasty of the tibioperineal trunk was performed in 4 cases.

Among 61 patients who underwent endovascular revascularization methods, trophic changes of the toes were revealed in 8 (13.15%) patients with stage IV of CAI; superficial ulcer was found in 5 of them, in 2 cases – a deep ulcer in which subcutaneous adipose tissue, tendons and muscles were involved in the process; and in one case – a deep ulcer involving subcutaneous adipose tissue, tendons, muscles with bone damage. At the end of revascularization manipulations on the infrainguinal arterial bed, surgical treatment of trophic changes of the toes was performed; in 3 cases the toes (2-3 toes) were amputated.

Complications were diagnosed during hybrid revascularization of the infrainguinal artery in cases of stenotic-occlusive lesion of the tibial arteries in 74 patients; 6 of them (8.11%) were diagnosed with complications in the early postoperative period. In 5 (6.76%) cases, thrombosis of the reconstruction segment was revealed, and in one (1.35%) – ineffectiveness of surgery.

After endovascular revascularization of the femoral-distal artery in cases of stenotic-occlusive lesions of the tibial arteries in 61 patients, complications were diagnosed in 5 (8.17%) cases. In 4 (6.56%) cases, thrombosis of the reconstruction segment was revealed and in one (1.64%) – ineffectiveness of surgery.

After hybrid and endovascular revascularization of multilevel atherosclerotic lesions of the femoral-distal arterial bed of the lower extremity thrombosis of the revascularization segment developed in 9 (6.67%) patients: in 8 cases – thrombosis of the popliteal segment, in 1 case – thrombosis of the femoral-popliteal segment.

In 8 patients with thrombosis of the popliteal segment, a minimally invasive thrombec-

tomy method was used [14]: rheological thromboextraction with the Angiojet rheological thromboextraction device (Possies, USA). In two cases rethrombosis of the reconstruction segment developed in the early postoperative period of the minimally invasive method of thrombectomy. Thrombolytic and active conservative therapies were ineffective that led to amputation of the lower extremity.

In 1 case thrombosis of the femoral-popliteal segment developed on the 6th day after two-level endovascular revascularization of atherosclerotic lesions of the femoral-distal arterial segment. In cases of acute arterial insufficiency of the stage IIb, according to Savelyev's classification, open femoral-popliteal autovenous bypass and thrombectomy from the tibial segment were performed. The postoperative period was without complications.

In two (1.48%) cases, both hybrid and endovascular methods of revascularization of the infrainguinal artery were not successful: after surgery, the preservation and progression of lower extremity ischemia was evidenced. Intensive conservative therapy for 7-9 days did not stop development of ischemia that led to amputation of the lower limb.

Discussion

At the moment, there are various opinions regarding the choice of method of revascularization of the infrainguinal arterial bed of the lower extremity: open, endovascular or hybrid [7]. The main purpose of revascularizing surgical interventions is to use the optimal method of revascularization in multilevel atherosclerotic lesions of the femoral-distal arterial bed of the lower extremity and prevent development of a number of postoperative complications [8]. At the same time, many researchers point to development of postoperative complications, including thrombosis of the revascularization segment, the lack of effectiveness of surgery, which are more common when using endovascular revascularization methods [9, 10].

In a number of studies on revascularization of the multilevel stenotic-occlusive process of the femoral-distal arterial bed in cases of stenotic-occlusive lesions of the tibial arteries, endovascular angioplasty of only one tibial artery was used [11, 12]. It is possible that in these circumstances revascularization of only one tibial artery cannot fully perform the tract outflow, which leads to development of thrombosis of the reconstruction segment.

The choice of the extent of surgery was based on the recommendations of the international classification TASC-II (2007) and the European recommendation for the management of patients with the lesions of aortic/iliac-femoral-popliteal arterial bed (2014). According to the European recommendation, the following types were singled out: Type A – single stenosis or single occlusion of the femoral segment up to 10 cm – 38 cases; Type B – multiple lesions of the femoral segment, each of which <5 cm, single lesion <5 cm above the slit of the knee joint, any lesions in the absence of patency of the tibial arteries <5 cm, single stenosis of the popliteal artery – 17 cases; Type C – multiple lesions of the femoral segment with a length of >15 cm, without or with calcification, restenosis or reocclusion after two endovascular interventions – 5 cases; Type D – chronic stenotic-occlusive process of the femoral segment >20 cm with spread to the popliteal artery – 1 case.

The criterion for inclusion in the study was the presence of multilevel atherosclerotic stenotic-occlusive lesion of the infrainguinal artery with underlying stenotic-occlusive lesion of the tibial arteries. Atherosclerotic process in the tibial arteries had extensive, parietal character with segmental stenotic-occlusive lesions of the vascular lumen at the level of 2.8 to 4.3 cm. So, there was a need to form a functionally suitable outflow pathway in the tibial segment. This can be achieved by endovascular angioplasty of the two arteries of the tibia. In the study of the level of blood flow at the level of the popliteal artery the patients underwent endovascular revascularization of multilevel atherosclerotic stenotic-occlusive lesions of femoral-distal arterial bed with endovascular angioplasty of one or two tibial arteries. Resistance index (RI) in the patients with endovascular angioplasty of one tibial artery was at the level of 0.88 ± 0.09 – 0.86 ± 0.10 unit, while RI in patients with endovascular angioplasty of two tibial arteries was 0.67 ± 0.13 unit, which is 1.3 in times lower ($p < 0.05$) than RI in endovascular angioplasty of one tibial artery. The results of the study have proved that endovascular angioplasty of the two tibial arteries produces satisfactory functional conditions of the outflow tract in the tibial segment.

A similar level of incidence of postoperative complications was achieved due to the fact that in revascularization of multilevel atherosclerotic lesions of the femoral-distal arterial bed of the

lower extremity by both hybrid and endovascular methods, mainly endovascular angioplasty of two tibial arteries was performed in 64.87% and 83.61% of cases, respectively. Complications of the early postoperative period developed in those cases when endovascular angioplasty of only one of the tibial arteries was performed during revascularization of the infrainguinal artery.

The analysis of the results of revascularization surgeries during the first month of the early postoperative period has proved that a high clinical level of effectiveness is achieved by hybrid and endovascular methods of revascularization of the stenotic-occlusive process of infrainguinal arterial bed in cases of atherosclerotic lesions of the tibial arteries, endovascular angioplasty of the two tibial arteries in 64.87% and 83.61% of cases, respectively. The preservation of the patency of the reconstruction segment as well as saving the lower extremity was obtained by hybrid methods and endovascular revascularization in 97.57% and 93.44% of cases, respectively.

Conclusions

In most cases, endovascular angioplasty of two tibial arteries in hybrid and endovascular methods of revascularization of multilevel atherosclerotic process of the femoral-distal arterial segment of the lower extremity prevents development of thrombosis in tibial segment and allows maintaining the patency of the reconstruction segment and preservation of the lower extremity in 97.57% and 93.44% of cases, respectively.

Conflict of Interests.

Authors declare no conflict of interests.

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ЕНДОВАСКУЛЯРНА АНГІОПЛАСТИКА ПРИ БАГАТОРІВНЕВОМУ СТЕНОТИЧНО-ОКЛЮЗИВНОМУ ПРОЦЕСІ СТЕГНО-ДИСТАЛЬНОГО АРТЕРІАЛЬНОГО РУСЛА В ПОЄДНАННІ З СТЕНОТИЧНО-ОКЛЮЗИВНИМ ПРОЦЕСОМ ГОМІЛКОВИХ АРТЕРІЙ

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,
ТЕРНОПІЛЬ, УКРАЇНА

Вступ. У структурі серцево-судинних захворювань стенотично-оклюзійні ураження артерій нижніх кінцівок посідають друге місце, поступаючи лише ішемічній хворобі серця. Хірургічне лікування хворих з атеросклеротичним ураженням інфраінгвінального артеріального сегмента у ряді випадків є складним завданням. У той же час ревазуляризуючі оперативні втручання на стегново-дистальному артеріальному руслі, особливо на гомілкових артеріях при хронічній критичній ішемії залишаються єдиним шансом уникнути ампутації нижньої кінцівки. У зв'язку з цим пошук і апробація оптимальних методів ревазуляризуючого хірургічного втручання на гомілкових артеріях спрямовані на ліквідацію стенотично-оклюзивного ураження артерій гомілки.

Мета. Це дослідження спрямоване на популяризацію ендоваскулярних та гібридних хірургічних втручань при стенозно-оклюзійному процесі гомілкових артерій та вибір оптимальної тактики та об'єму лікування в цьому випадку.

Методи. Проведено та проаналізовано результати 135 пацієнтів яким були проведені ендоваскулярні втручання на стегно-дистальному руслі в умовах стенотично-оклюзивного процесу гомілкових артерій на базі відділенні серцево-судинної хірургії Комунального некомерційного підприємства «Тернопільська обласна клінічна лікарня» Тернопільської обласної ради.

Результати. У більшості випадків проведення ендоваскулярної ангіопластики двох гомілкових артерій при гібридних та ендоваскулярних методах ревазуляризації багаторівневих атеросклеротичних уражень стегно-дистального сегменту нижньої кінцівки, запобігає розвитку тромбозу гомілкового сегмента та дозволяє підтримувати прохідність сегменту реконструкції та збереження нижньої кінцівки у 97,57% та 93,44% випадків відповідно.

Висновки. Проведення ендоваскулярної ангіопластики двох гомілкових артерій дає достовірно кращий результат, ніж ангіопластика однієї ізольованої гомілкової артерії і дає можливість зберегти прохідність сегменту реконструкції більше ніж на 90 відсотків при порівнянні з однією ізольованою ангіопластикою.

КЛЮЧОВІ СЛОВА: судинна хірургія; ендоваскулярна ангіопластика; стенотично-оклюзивний процес; атеросклероз; ревазуляризація.

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SHORT TERM STUDY ON CLINICAL RELEVANCE AND OUTCOMES OF FOETAL HYDRONEPHROSIS

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Background. Hydronephrosis is the most common urinary tract pathology detected on antenatal screening by Ultrasound. The detection of fetal hydronephrosis by ultrasound presents a treatment dilemma to the treating surgeon and parental anxiety.

Objective. This study aims to examine the role of serial ultrasounds in antenatally detected fetal hydronephrosis to know the disease progression, and to assess indications and timing of surgery in these patients to preserve renal function.

Methods. This is an observational study of 30 cases of foetal hydronephrosis conducted at a tertiary care paediatric surgery centre. A foetal renal pelvic Antero-posterior diameter (APD) >7 mm at 32 weeks of gestation is considered to indicate Foetal hydronephrosis. These patients are followed up for a period of two years from 2018 to 2020. Progression of disease and need for surgical intervention is noted.

Results. The study comprised 30 cases of antenatal foetal hydronephrosis (42 renal units). Of 26 renal units with mild hydronephrosis, all are resolved in the post-natal period. Of 10 renal units with moderate hydronephrosis, 3 (30%) resolved and 7 (70%) worsened and required surgical intervention. Of 6 renal units with severe hydronephrosis, all required surgical intervention and underwent surgery between 12 to 18 months of age.

Conclusions. These results suggest a grading system with antero-posterior diameter of renal pelvis distinguishes those cases with moderate and severe degrees of hydronephrosis that are at higher risk of surgery.

KEYWORDS: antero-posterior renal pelvic diameter; antenatal fetal hydronephrosis; pyeloplasty.

Introduction

Antenatal ultrasound surveillance detects significant fetal anomaly in 1% of pregnancies; 20-30% of them are genitourinary cases, and 50% – manifest as hydronephrosis [1]. Much of the controversy arises from diagnostic dilemmas and difficulties in distinguishing lesions which are obstructive and potentially harmful to the developing fetal kidney. Controversy remains on the efficacy of therapeutic intervention due to limited knowledge of the underlying natural history and determining appropriate outcome measures. Furthermore, early diagnosis of hydronephrosis may cause anxiety to parents in rest of the pregnancy. Early onset of fetal hydronephrosis is directly related to prognosis [2]. Antenatally detected hydronephrosis is diagnosed if the renal pelvic

AP diameter equals or exceeds 4 mm before 28 weeks or 7 mm thereafter [3].

The study took place at the Tertiary Care Paediatric Surgery Centre to assess the progression and disease course of antenatally detected fetal hydronephrosis. The issue which is still ambiguous at present and is the area of much study is how to differentiate a dilated but non obstructed system from a dilated and obstructed system [4]. To alleviate this pitfall, an integrated approach right from antenatal ultrasonogram to the latest available investigation techniques including DMSA, scintigraphy scan was performed to deepen the understanding of progression of disease in patients with suspected PUJ obstruction [5].

Follow up of antenatally detected fetal hydronephrosis with serial ultrasounds was carried out to identify the disease progression in terms of antero-posterior diameter of renal pelvis. Clinical and imaging parameters were

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analyzed in antenatal and postnatal period to assess the functional status of Urinary system. The indication and right time for surgical intervention was assessed to preserve renal function. This understanding of the functional status of the urinary system also guides in timely surgical intervention.

Methods

This observational study was done at the Tertiary Care Centre in the Department of Paediatric Surgery after due permission from the Institutional Ethics Committee and after taking written informed consent from the patients. Once the patients were enrolled for the study, a thorough history and physical examination was done as per proforma (Table 1).

The complete profile with clinical, radiological imaging and renal scan details were taken as per study proforma and were followed up and outcomes were assessed for complete resolution, partial resolution and persisting cases requiring surgical intervention (Fig. 1).

The antenatal USG at around 32 weeks was performed to diagnose ANH, and renal pelvic anteroposterior diameter (APD) between <7mm was taken as mild, 7-10 mm was taken as moderate and >10mm was taken as severe hydronephrosis (Table 2, 3).

Imaging with ultrasound: all new-borns with history of ANH underwent postnatal USG between days 3-7 of life (Table 4).

Neonates with suspected posterior urethral valves, oligohydramnios or severe bilateral hydronephrosis underwent ultrasonography within 24-48 hours of birth [6]. Subsequent ultrasounds were done at 4-6 weeks, 3 months, 6 months, and 6 monthlies thereafter till resolution/correction. Two consecutive normal ultrasounds were considered as the criteria for resolution.

Voiding Cystourethrogram: VCUG was performed for cases with moderate to severe hydronephrosis, if hydronephrosis worsens on follow up USG, presence of ureteral dilatation, features of lower urinary tract obstruction and in urinary tract infection.

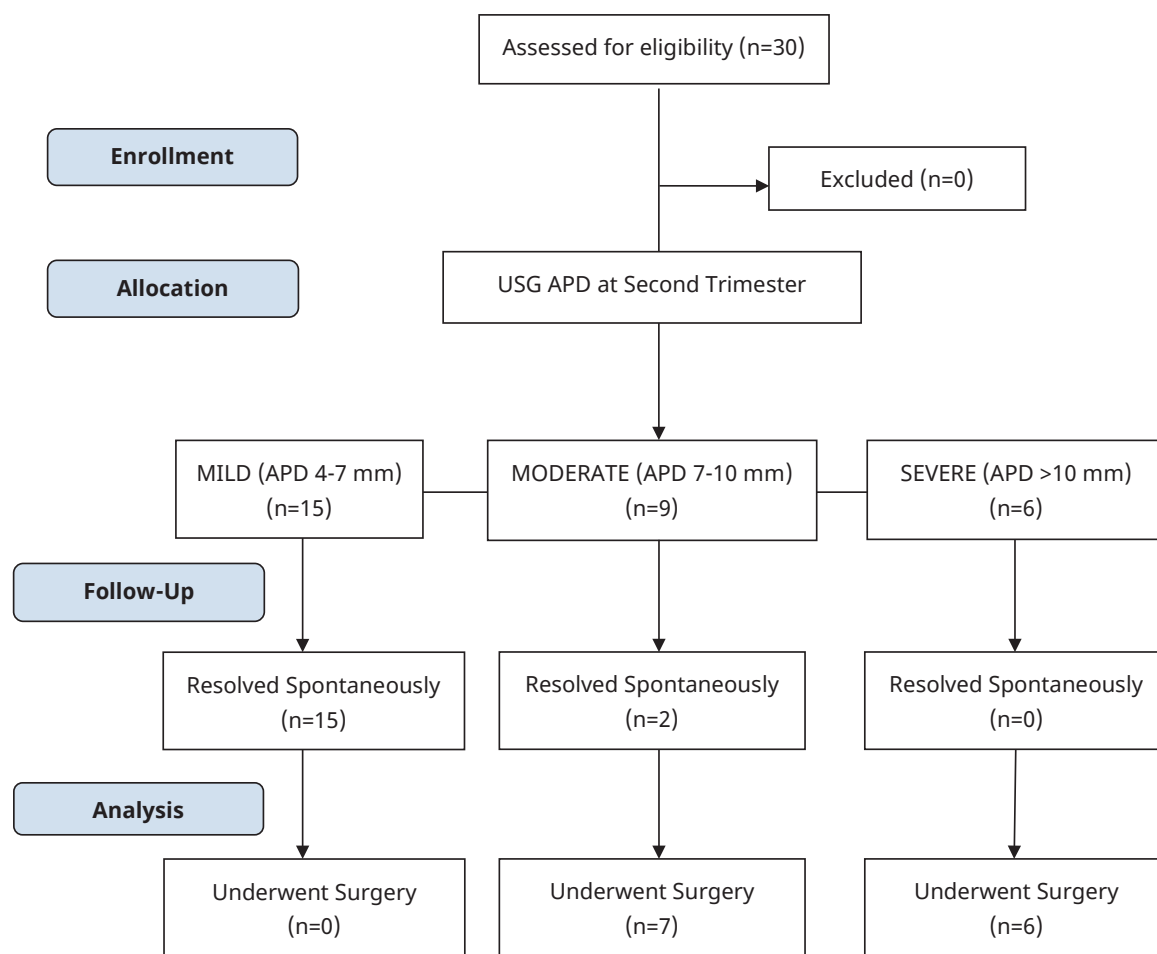


Fig 1. Consort flow diagram.

Table 1. Demographic data

Parameter		No. of patients	No. of kidneys
Gender	Female	8 (26.67 %)	10
	Male	22 (73.33 %)	32
Affected side	Left	12 (40 %)	12
	Right	6 (20 %)	6
	Bilateral	12 (40 %)	24
Second Trimester USG	Mild	15 (50 %)	26
	Moderate	9 (30 %)	10
	Severe	6 (20 %)	6
Third Trimester USG	Resolved	13 (43.33 %)	24
	Mild	4 (13.3 %)	4
	Moderate	5 (16.66 %)	6
	Severe	8 (26.66 %)	8

Table 2. Severity of ANH, second trimester (kidneys=42)

U/L VS B/L	Mild 4-7 mm (n=26)	Moderate 7-10 mm (n=10)	Severe >10 mm (n=6)
	No of kidneys	No of kidneys	No of kidneys
Unilateral	4 (15.38%)	8 (80%)	6 (100%)
Bilateral	22 (84.62%)	2 (20%)	0 (0%)

Table 3. Severity of ANH, third trimester (kidneys=42)

U/L VS B/L	Resolved (n=24)	Mild 4-7 mm (n=4)	Moderate 7-10 mm (n=6)	Severe >10 mm (n=8)
	no of kidneys	no of kidneys	no of kidneys	no of kidneys
Unilateral	2 (8.33%)	4 (100%)	4 (66.67%)	8 (100%)
Bilateral	22 (91.67%)	0 (0%)	2 (33.33%)	0 (0%)

Table 4. Severity of ANH, post-natal (kidneys=42)

U/L VS B/L	Resolved (n=26)	Mild 4-7 mm (n=0)	Moderate 7-10 mm (n=4)	Severe >10 mm (n=10)
	no of kidneys	no of kidneys	no of kidneys	no of kidneys
Unilateral	4 (15.38%)	0 (0%)	2 (50%)	10 (100%)
Bilateral	22 (84.62%)	0 (0%)	2 (50%)	0 (0%)

Radioisotope Studies: diuretic renography was done at 6-8 weeks of life. Radioisotope studies were done in moderate to severe hydronephrosis, worsening hydronephrosis and dilated ureter on USG.

Antibiotic Prophylaxis: The postnatally confirmed ANH of moderate grade, severe grade or with dilated ureters were put on antibiotic prophylaxis with Syp. Cephalexin 10 mg/kg/day as per our institution protocol till evaluation were complete (Table 5).

Table 5. Descriptive analysis of UTI in study population (n=30)

Urine C/S	Frequency	Percentages
No growth	23	76.67%
Growth	7	23.33%
E. Coli	4	57.14%
Kelbsiella pneumoniae	1	14.29%
Mixed growth	1	14.29%
Staph hominis	1	14.29%

Surgery: The progression of disease was screened by postnatal ultrasound. In cases of persistent and severe hydronephrosis, after assessing the functional status of kidneys, surgery was planned according to the etiology (Table 6, 7).

The type of surgery performed and the ideal timing of surgery were assessed (Table 8, 9).

Quantitative data was presented by the mean and standard deviation. Comparison among the study groups was performed by the unpaired t test as per results of normality test. Qualitative data was presented via the frequency and percentage table. Association among the study groups was assessed by the Fisher test, Student' t-test and Chi-Square test. P value less than 0.05 was taken as significant.

Table 6. Post-natal analysis of operated vs non-operated cases

Severity	Operated	Non-operated
Mild (n=15)	0 (0%)	15 (100%)
Moderate (n=9)	7 (77.78%)	2 (22.22%)
Severe (n=6)	6 (100%)	0 (0%)

Table 7. Operated post-natal pathology (n=13)

Pathology	Operated cases	Percentage
PUJ obstruction	9	69.23%
Vesico ureteric reflux	2	15.38%
Posterior urethral valve	1	7.69%
VUJ obstruction	1	7.69%

Table 8. Descriptive analysis of time of surgery in the study population (n=13)

Time of Surgery	Frequency	Percentages
Within 10 days	1	7.69%
10 days to 6 months	3	23.07%
6 months to 12 months	3	23.07%
12 months to 18 months	6	46.15%

Table 9. Descriptive analysis of surgical procedure done in the study population (n=30)

Post-surgical outcome	Frequency	Percentages
Underwent surgery	13	43.33%
Underwent MAH	9	69.23%
Ureterostomy with ureter reimplantation	3	23.07%
Fulguration	1	7.69%

Results

There was significant male preponderance in the study population; 73% of the study population was comprised by male gender. While comparing right and left APD in cases of unilateral hydronephrosis, left APD was significantly more than the right. Post-natal APD mean difference was also the highest with left sided hydronephrosis. As the trimester increases, distension of urinary bladder was on rise and it was directly proportional to the degree of ANH in the early trimester. Oligohydramnios was an indirect marker for severe congenital ANH with almost 50% of the antenatal mothers had oligohydramnios during

their pregnancy. In our study, out of 30 patients, 17 cases underwent spontaneous resolution.

Those cases with mild hydronephrosis, all were resolved postnatally. In the moderate hydronephrosis cases, some of them were resolved, and in the severe hydronephrosis group, further evaluation and surgical intervention was done in all cases. It was further observed that, for those cases, where outlet obstruction was suspected, radio nuclide studies were completed to assess the excretory function of kidney. 13 patients with persistent severe hydronephrosis in post-natal period underwent further evaluation with MCU and MRU. In those patients, E. coli remained the

most common infectious organism in urine amounting to 57% of cases in patients with symptomatic UTI. Pelvi ureteric junction obstruction was the commonest indication for surgery amounting to 61%.

In the study, most of the infants born with persistent and severe hydronephrosis underwent corrective surgery in 12 months. This complies with the institution protocol of more conservative and follow up approach for definitive period before a surgical decision was taken. Among the operated 13 cases, left sided modified Anderson Hyne's pyeloplasty was the commonest procedure amounting to 62.5% of the cases operated. In the surgical patients, left sided poor functioning kidney was maximum with less than 50 % split function in more than 80 % of the surgical group. There was significant male preponderance in our study population. 73% of the study population was comprised by male gender. While comparing right and left APD in cases of unilateral hydronephrosis, left APD was significantly more than the right. Post-natal APD mean difference was also the highest with left sided hydronephrosis. As the trimester increases, distension of urinary bladder was on rise and it was directly proportional to the degree of ANH in the early trimester. Oligohydramnios was an indirect marker for severe congenital ANH with almost 50% of the antenatal mothers suffering from oligohydramnios during their pregnancy. In the study, out of 30 patients. 17 cases underwent spontaneous resolution.

All cases with mild hydronephrosis were resolved postnatally. In the moderate hydronephrosis cases, some of them resolved and in the severe hydronephrosis group, further evaluation and surgical intervention was done for all cases. It was further observed that, those cases where outlet obstruction was suspected, radio nuclide studies were performed to assess the excretory function of kidney. 13 patients with persistent severe hydronephrosis in post-natal period underwent further evaluation with MCU and MRU. In those patients, E. coli was the most common infectious organism in urine amounting to 57% of cases. Pelvi ureteric junction obstruction was the commonest indication for surgery amounting to 61%.

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Discussion

The study reports on the independent association of grading of anteroposterior diameter of renal pelvis and its direct association with the risk for surgical intervention. The results support the use of prenatal and post-natal ultrasonograms in assessment of disease progression. While the renal pelvic APD varies with gestation; bladder distension was also an objective parameter in assessing severity of hydronephrosis. If ANH is detected, a followed up with ultrasound including evaluation for lower urinary tract, renal dysplasia, and extra renal structural malformations is carried out [7]. Two follow up ultrasounds were performed, one in third trimester and the other in postnatal period irrespective of severity of hydronephrosis. In the study 100% of severe hydronephrosis and 77.78% of moderate hydronephrosis needed surgical management. Hence, frequent ultrasound evaluation is suggested in cases with moderate and severe hydronephrosis in 6-8 weekly interval to assess disease progression.

We recommend that all newborns with history of ANH irrespective of any trimester should undergo postnatal ultrasound examination within the first week of life. In neonates with moderate or severe hydronephrosis, ultrasonography should be performed within first or second day of birth. We suggest that a micturating cystourethrogram (MCU) being performed within 4 days of life in patients with unilateral or bilateral, moderate and severe hydronephrosis [8].

Our institution performs diuretic renography after 10 weeks of age in persistent severe and progressing moderate hydronephrosis and repeats the same in the 6th month of post-natal life. Our indication for surgical intervention is persistent severe hydronephrosis with obstruction and with evidence of reduced differential renal function on repeat evaluation [6]. As per our institution protocol, in 12th month of birth, we repeat the diuretic renography and watch for disease progression and worsening of split renal function to decide on surgical correction [9]. The patients were started on oral antibiotics

for all cases of moderate and severe hydronephrosis with Syp Cephalixin as the incidence of UTI in these groups of patients was maximum and E coli was the most commonly isolated organism in urine [10].

Conclusions

The prenatal diagnosis of uropathies is today the main contributor to the evolution of individuals suffering from this disease. When faced with a diagnosis of pyelocalyceal dilation, postnatal observation should be planned in order to minimize parental anxiety and to monitor progression of nephrourological pathology. Because of the extremely elastic nature of the fetal renal system, it was established that an evaluation of antenatal hydronephrosis via ultrasound should be conducted on more than one occasion via a standardized methodology

[11]. The APD grade may be used as reliable predictor of the outcome of fetal hydronephrosis, and may be an independent indicator for postpartum surgery.

Limitations

Single centre observational study

Conflict of Interests

The authors declare no conflict of interest.

Author's Contributions

J. S. Randhawa, Nagamahendran R., Jafar Husain – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; Vipin V. Nair, Shankaran R. – data curation, writing – reviewing and editing; Shakthi Dorai B. – investigation, formal analysis.

КОРОТКОСТРОКОВЕ ДОСЛІДЖЕННЯ КЛІНІЧНОЇ ЗНАЧУЩОСТІ ТА НАСЛІДКІВ ГІДРОНЕФРОЗУ ПЛОДА

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Вступ. Гідронефроз - найпоширеніша патологія сечовивідних шляхів, яка виявляється при допологовому обстеженні за допомогою УЗД. Виявлення гідронефрозу плода за допомогою УЗД ставить перед лікуючим хірургом дилему лікування та викликає занепокоєння у батьків.

Мета. Це дослідження мало на меті вивчити роль серійних ультразвукових досліджень при антенатально виявленому гідронефрозі плода, щоб визначити прогресування захворювання, а також оцінити показання та терміни хірургічного втручання у цих пацієнтів для збереження функції нирок.

Методи. Спостережне дослідження 30 випадків гідронефрозу плода, проведене в центрі дитячої хірургії третинної медичної допомоги. Передньо-задній діаметр ниркової миски плода розміром понад 7 мм на 32 тижні вагітності вважається ознакою гідронефрозу плода. Пацієнти перебували під спостереженням протягом двох років з 2018 по 2020 рік. Відзначалось прогресування захворювання та необхідність оперативного втручання.

Результати. Дослідження охопило 30 випадків антенатального гідронефрозу плода (42 нирки). З 26 нирок з легким гідронефрозом всі одужали в післяпологовому періоді. З 10 нирок із помірним гідронефрозом 3 (30%) одужали, а у 7 (70%) стан погіршився, що вимагало хірургічного втручання. З 6 нирок з важким гідронефрозом всі вимагали хірургічного втручання і були прооперовані у віці від 12 до 18 місяців.

Висновки. Результати свідчать про те, що система класифікації за передньо-заднім діаметром ниркової миски дозволяє розрізняти випадки з помірним і важким ступенями гідронефрозу, які мають вищий ризик хірургічного втручання.

КЛЮЧОВІ СЛОВА: передньо-задній діаметр ниркової миски; антенатальний гідронефроз плода; пієлопластика.

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ATTITUDE TOWARDS PSYCHIATRY AND PSYCHIATRISTS AMONG MEDICAL STUDENTS IN TERTIARY HEALTH CARE HOSPITAL

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Background. *Psychiatry is a medical subject; many medical students ignore its importance in medicine. Regarding mental illness, many medical professionals and students are less aware as mental illness is very important in affecting the quality of care the patient receives and in choosing psychiatry as a career. This study specializes in psychiatry based on many factors, however undergraduate students' attitude towards career choice is the most important.*

Objective. *This study aims to explore attitude towards psychiatry subject among undergraduate medical students.*

Methods. *This is a Descriptive cross-sectional study done at Vikhe Patil Medical College, Ahmednagar. The total of 295 volunteer students from all phases of MBBS (Bachelor of Medicine and Bachelor of Surgery) were enrolled by purposive sampling, a 30-item self-administered questionnaire, ATP-30 (Attitude towards Psychiatry) was used to measure the attitude of medical students. Data collected was analysed using SPSS version 24. The results were reported as percentage and frequencies.*

Results. *In the study, 47.4% of the respondents were males and 52.6% were females. Out of total study participants 52.3% of our study respondents strongly agreed that psychiatry was a respected branch of medicine; 56.7% strongly agreed that psychiatry should be an important part of medical curriculum; 19.4% of study respondents considered it in the list of the career choice while the majority did not think that it should be in their career list options.*

Conclusions. *In the study, the students from the later phases of MBBS showed positive attitude than that of the initial phases. Many students found it as respected subject and essential field of medicine for their choice of profession. However, shortcoming knowledge and awareness was observed in the responses pertaining to present available treatment and recent trends in the field.*

KEYWORDS: attitude; undergraduate medical students; psychiatry; India.

Introduction

According to the World Health Organization (WHO), mental disorders and mental illness are today the most significant part of the global burden of diseases [1]. Psychiatric disorders affect 10% of adult population [2]. Whereas mental disorders are either ignored by majority of people in their life or hesitated to share having very few psychiatrists. Globally, psychiatry as a subject, psychiatrists as professionals, and patients with psychiatric disorders are subjected to cultural stereotypes and negative attitude by the general population. The alarming concern is that these prejudices exist within the medical community as well [3, 4].

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This information has serious implications on psychiatry.

Most mental illness in people are undiagnosed or underdiagnosed as people with mental disorders hesitate and remain silent to pursue medical care due to presenting stigma and discrimination to them [5].

Stigma exists even in the health care system and even students carry prejudices to choose and enter into psychiatry, which affects medicine. In this aspect, evaluation of undergraduate students for their attitude towards mental health issues is important as they are future of nation and going to influence directly or indirectly the health system [6]. Psychiatric teaching in the undergraduate medical curriculum appears negligible and short due to insufficient number of allotted lectures, no

available qualified teaching staff as well as lack of proper clinical positions, which results to inadequate exposure of medical students to psychiatry [7, 8, 9].

This study aims at evaluating the current attitudes towards psychiatry as a subject, which can further help in revising the curriculum, teaching and learning methods of undergraduates in order to improve the understanding of mental health issues in community and medical profession.

Methods

This descriptive study was done after approval from the ethical committee, was conducted at Vikhe Patil Medical College, Ahmednagar for 6 months duration from July to December 2019. The study includes 295 medical students from all phases of MBBS (Bachelor of Medicine and Bachelor of surgery) selected with purposive sampling. Purpose of the present study was informed to participants about research and voluntary participation was invited. Informed consent was taken and confidentiality was maintained and ensured for every participant though questionnaire did not included any information for identification. Those not giving consent and not willing to participate were excluded from study. Modified short ATP-30 (Attitude towards Psychiatry developed in Canada by Burra et al (1982) a 30 item self-administered questionnaire was used to measure the attitude of medical students in this study [10].

This scale measured the attitude of respondents such as towards psychiatry patients, psychiatry illness, psychiatry knowledge, psychiatry treatment including drugs, psychiatrists, psychiatry career choice, and psychiatry training. The ATP Uses a 5-Point Likert type Scale: 1; Strongly Agree, 2; Agree, 3; Neutral Opinion, 4; Strongly Disagree, And 5; Disagree. Total score on the scale indicates positive or negative attitude, with a high total score indicating positive and low score indicating negative attitudes toward different aspects of psychiatry. Data was analysed using SPSS version 24.

Results were entered in Microsoft excel and were presented as frequencies and percentages.

Results

All 295 students were analysed in order to assess their attitude towards psychiatry by a questionnaire. The distribution of the respondents according to gender and professional year is presented in Table 1.

Among all 295 participants involved for the analysis, 53.98% (n=159) were males and 46.10% (n=136) were females. The highest number of participants were from final year of study (n=110, 37.2%), followed closely by the second professional phase (n=139, 34.4%) and the 1st year of study (n=119, 29.45%). Apart from the 1st year students, all other participants (n=212, 71.5%) had been exposed to psychiatry postings and lectures as per the current MBBS curriculum.

The majority of students (n=185, 63%) considered psychiatry to be a respected branch of medicine and 79.9% (n=230) thought that psychiatric illnesses deserve as much attention as physical illnesses. 240 respondents (81.1%) agreed that psychiatry should have been an important part of school curriculum (Table 2).

Discussion

The interlinking has always existed between mental and physical health in all individuals. Undergraduate attitude towards mental health has significant influence in their future medical practice and the quality of life of patients. All MBBS undergraduates of all phases of study were involved into the study fairly. The formal students of pre and para clinical subjects did not receive any formal introduction to psychiatry while the other students studied psychiatry either in the forms of lectures or clinical postings. The majority of our study respondents are from the final phase of study (37.2%) among the respondents involved. The analysis of the study results shows that the majority of students has positive attitude towards psychiatry. 47.5% of our study respondents strongly agree that psychiatry is a respected branch of medicine; 40.7% believe most patients do not go

Table 1. Demographic Data of Sample Population

Year of study	Males n (%)	Females n (%)	Total n (%)
First	48 (57.83)	35 (42.16)	83 (28.1)
Second	52 (50.98)	50 (49.01)	102 (34.5)
Final	59 (53.63)	51 (46.36)	110 (37.2)
Total	159 (53.89)	136 (46.10)	295(100)

Table 2. Results of ATP-30 questionnaire

Item	Strongly agree		Agree		Neutral		Strongly agree		Disagree	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatry is a respected branch of medicine	115	39.0%	70	23.7%	45	15.3%	25	8.5%	41	13.6%
People taking up psychiatry are running away from “real” medicine	27	9.2%	35	11.9%	42	14.2%	73	24.7%	118	40.0%
Psychiatric disorders deserve as much attention as physical illness	158	53.6%	75	25.4%	40	13.6%	17	5.8%	5	1.7%
Psychiatry is unscientific and imprecise	7	2.4%	18	6.1%	45	15.3%	55	18.6%	170	57.6%
Psychiatry is an important part of the medical school curriculum	164	55.6%	77	26.1%	28	9.5%	19	6.4%	7	2.4%
There has been significant advancement in the understanding and treatment of psychiatric disorders in recent years	157	53.2%	71	24.1%	29	9.8%	20	6.8%	18	6.1%
With the treatment available today, most psychiatric patients experience improvement	160	54.2%	74	25.1%	34	11.5%	22	7.5%	5	1.7%
I find it hard to believe that patient’s symptoms can improve by “talk therapy”	100	33.9%	95	32.2%	54	18.3%	39	13.2%	7	2.4%
Genes and family history are important in the theology of mental illnesses	144	48.8%	86	29.2%	31	10.5%	24	8.1%	10	3.4%
I believe that spiritual healer can help the mentally illnesses	4	1.4%	24	8.1%	45	15.3%	97	32.9%	125	42.4%
I believe that ghosts (Jinn) and magic (Jadoo) can cause mental illnesses	5	1.7%	11	3.7%	42	14.2%	100	33.9%	137	46.4%
Mental illness can be a punishment for past sins	4	1.4%	12	4.1%	49	16.6%	95	32.2%	135	45.8%
Most psychiatric patients are violent and dangerous	15	5.1%	18	6.1%	52	17.6%	81	27.5%	129	43.7%
Psychiatric hospitals are like prisons	7	2.4%	9	3.1%	24	8.1%	98	33.2%	157	53.2%
Psychiatrists are mentally unstable compare to other doctors	2	0.7%	7	2.4%	21	7.1%	105	35.6%	160	54.2%
If I was asked to name three most exciting medical specialties, psychiatry would be in the list	21	7.1%	26	8.8%	15	5.1%	94	31.9%	139	47.1%
Psychiatrists are less respected than other specialists	19	6.4%	29	9.8%	15	5.1%	92	31.2%	140	47.5%
Psychiatrists get less satisfaction from their work than other specialists	31	10.5%	32	10.8%	15	5.1%	103	34.9%	115	39.0%
Psychiatrists earn less than other doctors	76	25.8%	71	24.1%	36	12.2%	58	19.7%	54	18.3%
Most patients do not go to a psychiatrist even if they have mental problems	120	40.7%	70	23.7%	24	8.1%	44	14.9%	37	12.5%
There is an acute shortage of psychiatrists in our country	88	29.8%	124	42.0%	18	6.1%	34	11.5%	31	10.5%

PSYCHIATRY

to a psychiatrist even if they have mental health problems.

Many students strongly agree that psychiatry should be an important part of medical curriculum (81%).

In certain aspects of the study, positive outcomes were noted regarding positive attitude toward psychiatrists. Many of the students thought of psychiatry as an important stimulating discipline and psychiatric practice perceived to have promising prospects. Our study findings were positively surprising compare to previous ones, which had reported same numbers with fewer respondents viewing psychiatry and psychiatrists in a positive light [11, 12]. However, a few studies in UK, Australia and France shows opposing results [13, 14]. In fact, many students believe in magic, ghosts and family history [15].

Thus, the study results are consistent with the research findings of the respondents, who consider psychiatry as exciting specialty and in the list of their future career choice, while a few has neutral opinion and some students con-

sider it in the list of top specialties that they will likely to choose in the future [16].

Conclusions

Even though lack of sufficient knowledge about the reasons behind mental problems students have positive attitude towards psychiatrists and psychiatry because of its importance in medicine. The study highlights the attitude of medical students towards psychiatry as their future preference of choice. This might be because a majority of students find psychiatry to be a respected and essential field of medicine. The study also focuses on the need for further development of theoretical and clinical teaching of psychiatry at the undergraduate level to overcome these faults.

Conflicts of interest

The author declares no conflict of interest.

Acknowledgements

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СТАВЛЕННЯ ДО ПСИХІАТРІЇ ТА ПСИХІАТРІВ СЕРЕД СТУДЕНТІВ-МЕДИКІВ У ЗАКЛАДАХ ТРЕТИННОЇ МЕДИЧНОЇ ДОПОМОГИ

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Вступ. Психіатрія є медичним предметом, проте багато студентів-медиків ігнорують її важливість у галузі медицини. Щодо психічних захворювань, багато медичних працівників і студентів-медиків є менш обізнаними, незважаючи на те, що психічні захворювання відіграють дуже важливу роль у впливі на якість лікування, яке отримує пацієнт, а також у виборі психіатрії як професії.

Мета. Це дослідження мало на меті вивчити ставлення до предмету психіатрії серед студентів-медиків.

Методи. Це описове перехресне дослідження, проведене медичним коледжем імені Vikhe Patil у місті Ахмеднагар. В експерименті взяло участь 295 студентів-добровольців з усіх курсів MBBS (бакалавр медицини та бакалавр хірургії), для оцінювання ставлення студентів-медиків використовувався опитувальник із 30 пунктів самостійного заповнення, ATP-30 (ставлення до психіатрії). Зібрані дані були проаналізовані за допомогою SPSS версії 24. Результати були представлені у відсотках і частотах.

Результати. У цьому дослідженні 47,4% респондентів були чоловіками та 52,6% жінками. Із загальної кількості учасників дослідження 52,3% респондентів повністю згодні з тим, що психіатрія була шанованою галуззю медицини, а 56,7% повністю згодні з тим, що психіатрія також має бути важливою частиною медичної навчальної програми, ще 19,4% респондентів дослідження розглядають її як кар'єрний вибір, тоді як більшість не вважала, що психіатрія має бути в списку варіантів кар'єри.

Висновки. У цьому дослідженні студенти старших курсів MBBS демонструють більш позитивне ставлення до психіатрії ніж студенти молодших курсів. Багато студентів вважали цей предмет шанованим і важливою галуззю медицини для свого вибору професії. Однак у відповідях, що стосуються наявного лікування та останніх тенденцій у цій галузі, спостерігався недолік знань та обізнаності.

КЛЮЧОВІ СЛОВА: ставлення; студенти бакалаврату медичного факультету; психіатрія; Індія.

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ANTIOXIDANT PROTECTION IN WHITE RATS ON THE BACKGROUND OF DRINKING WATER USE WITH EXCESSIVE NITRATE CONCENTRATION

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Background. *The problem of nitrate pollution in terms of its scale and consequences has reached a global level. Approximately one-third of groundwater bodies for which information is currently available exceed the maximum allowable concentrations of nitrates in drinking water.*

Objectives. *The aim of the research is to study the features of antioxidant protection in the body of white rats on the background of drinking water with excessive concentrations of nitrates for 30 days regarding the age.*

Methods. *The experiment was performed on 2 groups of outbred white female rats of different age (mature and immature), 30 animals each, divided into 5 subgroups, which differed in the quality of drinking water they consumed independently. In a 30-day study, nitrates were given to rats with drinking water at a dose of 50, 150, 250, 500 mg of sodium nitrate per liter. The animals of the control group drank water from the city water supply. The effect of nitrates on superoxide dismutase (SOD), catalase (CAT) and ceruloplasmin (CP) in the serum of rats was evaluated.*

Results. *The research has shown increased SOD, CAT and CP in blood serum on the background of drinking water with a nitrate concentration of 150 to 500 mg/l in the experimental groups of animals of both ages. According to the research, the most significant changes in parameters are caused by drinking water with nitrates at a concentration of 500 mg/l. More significant changes were in immature animals than the mature ones.*

Conclusions. *Excessive concentrations of nitrates in drinking water adversely affect the body of experimental animals causing activation of the studied parameters of the antioxidant system.*

KEYWORDS: drinking water; nitrates; superoxide dismutase; catalase; ceruloplasmin.

Introduction

The problem of nitrate pollution in terms of its scale and consequences has reached the global level. It consists in total pollution of the biosphere, deterioration of plant agricultural products and drinking water, negative impact on the human body, especially young children and farm animals. Approximately one third of the groundwater bodies, for which information is currently available, exceeds the maximum permissible concentrations (MPC) of nitrates in drinking water that is equal to 50 mg/dm³. Monitoring of nitrate levels in groundwater in different districts of Ternopil region showed that the maximum concentration ranges from 1.1 to 7.3 times or from 55 to 365 mg/l and even more [1, 2]. This is due to the widespread use of nitrogen-containing organic and inorganic fertilizers in agriculture. However, unfortunately, residents of houses have been using such water for drinking for many years, because nitrates,

even their excessive concentrations are not felt or tasted by humans.

Nitrates are non-toxic, but entering the gastrointestinal tract they are reduced to nitrites, which due to their oxidizing properties are ten times more toxic than nitrates. Nitrites are absorbed into the blood, and consequently reach tissues. The main mechanism of nitrite toxicity is the oxidation of Fe²⁺ to Fe³⁺, the conversion of hemoglobin into methemoglobin (MetHb) [3].

The use of nitrates with drinking water affects the nervous and cardiovascular systems, development of embryos; it can cause colorectal cancer, thyroid disease and neural tube defects [4, 1]. When systematically ingested, they can lead to disorders of the endocrine and central nervous system, blood circulation, etc. [5].

In addition, it is established that nitrites in the presence of amines can form N-nitrosamines, which have carcinogenic activity. Nitrates can also inhibit the enzyme systems involved in tissue respiration. As a result, a large number of free radicals is formed. At the same time, at

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the cellular level the processes of free radical oxidation of phospholipids of biological cell membranes take place that lead to development of oxidative stress [6].

This can be overcome by reducing the intensity of lipid peroxidation (LPO) in the body with antioxidant system (AOS) which controls and inhibits all stages of reactions of free radicals capable of damaging the cell from their initiation to formation of hydroperoxides and malonic dial [7].

This protective system combines a number of substances of different nature; each of them acts in close contact with its other structural elements, harmoniously complements, and in many cases enhances the action of each other. The main antioxidants of blood plasma are superoxide dismutase (SOD), catalase (CAT) and ceruloplasmin (CP) [8, 9]. When an organism is in unfavorable living conditions, in particular ecological, or when it is exposed to adverse factors the activity of these antioxidants increases sharply [10].

Therefore, the aim of the research was to study the features of antioxidant protection in the body of white rats on the background of drinking water with excessive concentrations of nitrates for 30 days regarding the age.

Methods

The study was conducted on 60 outbred white female rats which were kept on the standard diet of the vivarium of I. Horbachevsky Ternopil National Medical University. Animals were divided into 2 age categories: the 1st category – 30 mature animals weighing 180-200 g and the 2nd – 30 immature animals weighing 60-80 g. The experimental animals of each age category were divided into 5 groups with 6 rats in each. The groups were selected by randomization. The animals of control group drank drinking water from the city water supply. The rats of the 1st group drank drinking water with nitrate content of 50 mg/l, the 2nd – 150 mg/l, the 3rd – 250 mg/l, the 4th – 500 mg/l. To create model aqueous solutions, drinking water from city water supply was used; taking into account background concentrations, sodium nitrate (NaNO_3) was added into it to create aqueous solution with nitrates at a dose of 50, 150, 250, 500 mg per liter. The experiments were performed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Research Purposes (Strasbourg, 1986) [12] and the norms of biomedical ethics and the "General Ethical Principles of Animal Expe-

riments" adopted by the First National Congress on Bioethics (Kyiv, 2001).

The animals were taken out of the experiment by bloodletting under thiopental-sodium anesthesia in 30 days after the beginning of the experiment.

The activity of catalase (CAT), ceruloplasmin (CP) and superoxide dismutase (SOD) was determined in the serum by means of a semi-automatic biochemical analyzer Humalyzer 2000 using standard kits by HUMAN diagnostics (Wiesbaden, Germany). The kits used for evaluation of CAT, CP and SOD were adapted for their determination in animal serum. The results were statistically processed using computer programs STATISTICA 10.0 and Excel 2010. The choice of statistical research method was based on the correct distribution of the studied features. Further pairwise comparison of groups was performed using the Mann-Whitney U-test, the statistical significance $p < 0.05$.

Results

The results of our studies showed that when drinking water with different concentrations of nitrates, the AOS of the experimental animals of both ages underwent significant changes.

The key enzyme of AOS is SOD. It was found that the level of SOD, CAT and CP in the 1st experimental group of both age categories did not differ significantly from the data in the control group.

The increase in SOD activity in other groups of experimental rats of both ages compare to the controls was directly proportional to the concentration of nitrates in water. The level of SOD in the 2nd group of mature animals increased significantly by 43.7%, in the 3rd – by 56.2% and in the 4th – by 62.5% (Fig. 1).

In the immature animals, a more significant increase was evidenced. Thus, in the 2nd group the activity of SOD significantly increased by 61.1%, in the 3rd – by 94.4%. However, the activity of SOD increased the most in the 4th group – by 116.6% (Fig. 2).

SOD always works in conjunction with CAT, which converts hydrogen peroxide to water and molecular oxygen. When determining the activity of CAT in the serum of mature animals it increased by 16.0% in the 2nd group, in the 3rd – by 30.5% ($p < 0.05$), and in the 4th group – by 97.2% ($p < 0.05$) compare to the control (Fig. 3).

In the immature animals, insignificant increase in the activity of this parameter was found in the 2nd and 3rd groups (by 6.7% and 18.3%, respectively). However, in the animals

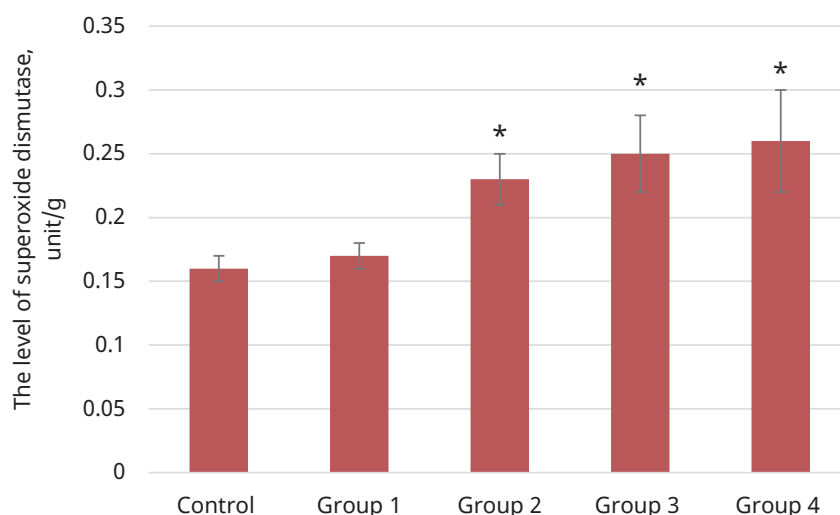


Fig. 1. The level of superoxide dismutase in the serum of mature experimental animals when drinking water with different concentrations of nitrates (unit/g).

Note: * – the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

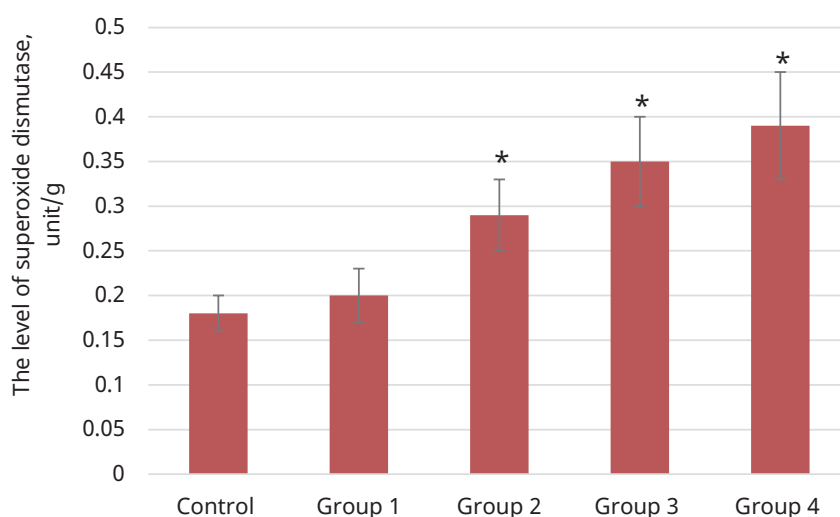


Fig. 2. The level of superoxide dismutase in the serum of immature experimental animals when drinking water with different concentrations of nitrates (unit/g).

Note: * – the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

of the 4th group the parameter increased by 28.8% ($p < 0.05$) compare to the control group (Fig. 4).

The nonenzymatic part of AOS was assessed for the presence of CP in the blood serum, which is also one of the main antioxidants in the human's body. A main feature of this protein is its high stability to the toxic action of reactive oxygen species which allows it to maintain biological activity under conditions of their intensive generation [7, 8].

Increased level of CP in both age categories was established; it differed not much. In the 2nd

group of mature animals the parameter increased by 22.1%, in the 3rd group – by 23.4%, in the 4th group – by 53.3% ($p < 0.05$) (Fig.5).

The number of SR in the immature animals of the 2nd group increased by 28.4%, in the 3rd – by 39.0% ($p < 0.05$), in the 4th – by 61.0% ($p < 0.05$) (Fig. 6).

Discussion

According to the literature the antioxidant substance in the cell is present at low concentrations and significantly reduces or prevents oxidation of the oxidizable substrate. The most

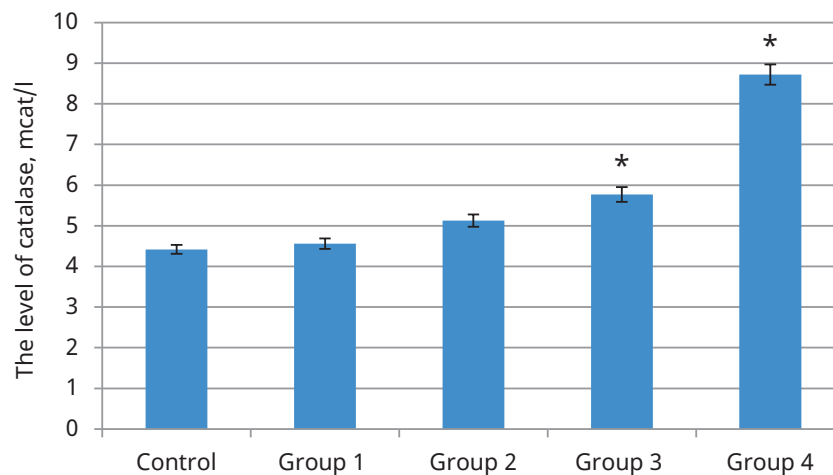


Fig. 3. The level of catalase in the serum of mature animals when drinking water with different concentrations of nitrates (mcat/l).
 Note: * - the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

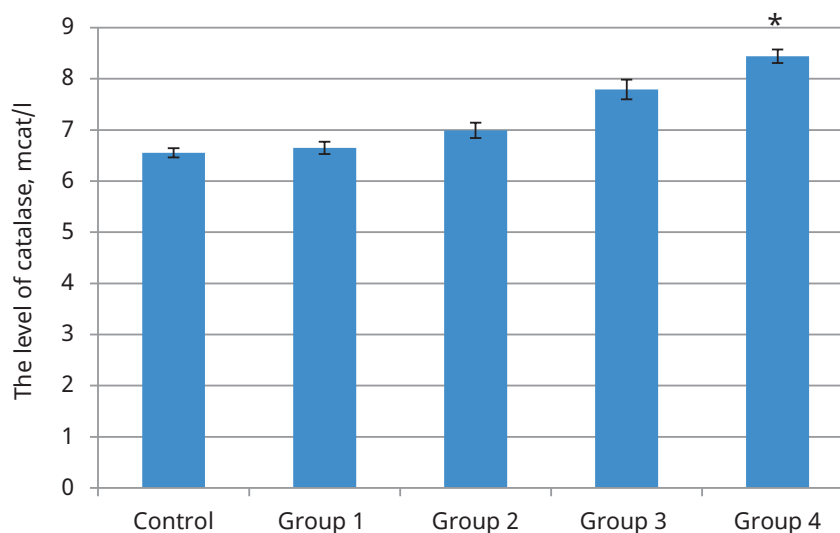


Fig. 4. The level of catalase in the serum of immature animals when drinking water with different concentrations of nitrates (mcat/l).
 Note: * - the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

efficient enzymatic antioxidants contain glutathione peroxidase, catalase and superoxide dismutase. SOD is one of the most potent intracellular enzymatic antioxidants, and it catalyzes the conversion of superoxide anions to dioxygen and hydrogen peroxide. The hydrogen peroxide is removed by catalase. This enzyme is present in the peroxisome of aerobic cells and is very efficient in promoting the conversion of hydrogen peroxide to water and molecular oxygen [13]. An increase in the activity of CAT and SOD is usually observed in cases of environmental pollutants since SOD-CAT system represents the first line of defense

against oxidative stress [14, 15]. According to Krishnamoorthy and Sangeetha [16], sodium nitrite (300 mg/kg body weight) significantly increased the lipoperoxidation and the activities of liver marker enzymes such as alanine aminotransferase, aspartate aminotransferase, acid phosphatase and lactate dehydrogenase.

Analyzing the dynamics of changes in the activity of AOS in the serum of rats, significantly higher SOD against CAT and CP were established. The SOD interrupts the chains of oxygen-dependent free radical reactions, causing dismutation of the superoxide anion radical with the release of hydrogen peroxide, which may

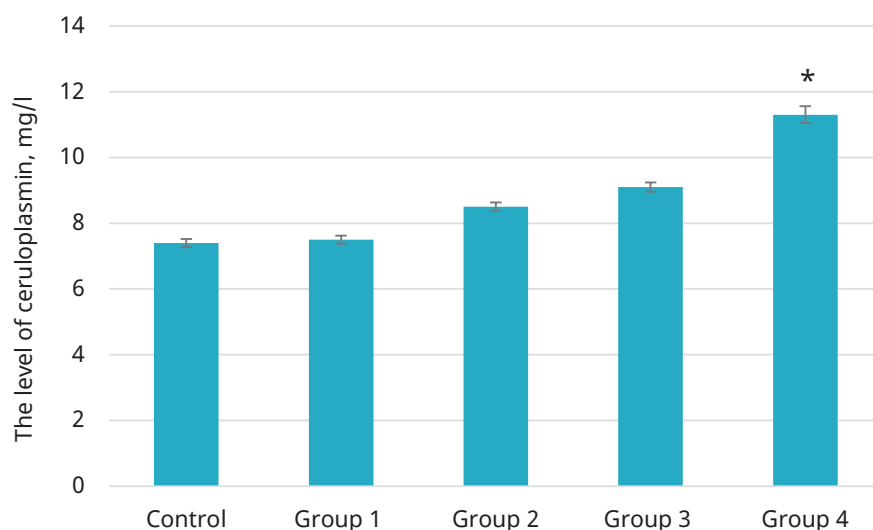


Fig. 5. The level of ceruloplasmin in the serum of mature animals when drinking water with different concentrations of nitrates (mg/l).

Note: * – the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

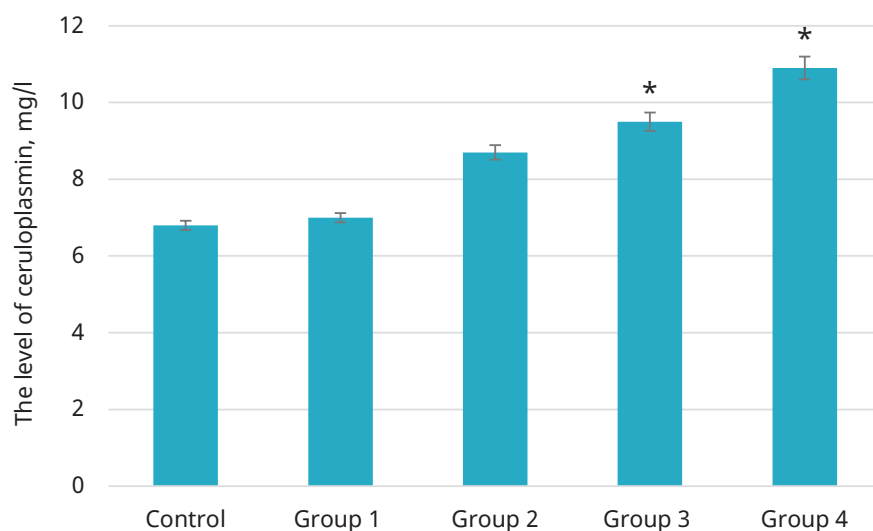


Fig. 6. The level of ceruloplasmin in the serum of immature animals when drinking water with different concentrations of nitrates (mg/l).

Note: * – the differences are significant comparing to the control group ($p < 0.05$). Error bars indicate $\pm$ standard deviation of the mean after three replicates.

precede formation of the most toxic hydroxyl radical ($\text{OH}^\cdot$) and triplet oxygen [10]. Increased activity of SOD is an additional damaging factor and may cause pathological processes as a result of increased cytotoxic action of hydrogen peroxide, formed as a result of dismutation of superoxide [8]. The increase of CAT in serum does not exclude the presence of cytolysis on the background of drinking water with different concentrations of nitrates, because CAT is an intracellular enzyme and its increased activity

in the blood occurs in cases of increased permeability of cell membranes.

CP neutralizes free radicals and protects cell membranes due to its ability to inhibit lipid peroxidase. It prevents activation of the floor, formation of toxic iron ions and damage to cell membranes. This enzyme acts as an “extracellular superoxide dismutase” neutralizing superoxide anions in the extracellular environment, blood, amniotic and cerebrospinal fluid, muscle, kidney and myocardium. CP increases with iron deficiency and excessive

copper, in response to hypoxia, insulin, thrombin, estradiol, proinflammatory cytokines [11].

Increased oxidation processes are extremely crucial in the genesis of many pathological conditions, including inflammatory lesions of various tissues. In case of increased intake of xenobiotics, depletion of antioxidant depots and influence of negative factors, oxidative stress develops; it is characterized by pro-oxidant and antioxidant disbalance and development of oxidative damage [17].

Conclusions

The study allowed drawing the conclusion that excessive concentrations of nitrates in drinking water adversely affected the body of experimental animals causing activation of the studied parameters of the antioxidant system. As a result, the increased activity of SOD, CAT

and CP in blood serum against consumption of drinking water with concentration of nitrates from 150 to 500 mg/l within 30 days in the experimental groups of both age categories has been revealed. The most pronounced changes in the parameters were regarding drinking water with nitrates at a concentration of 500 mg/l. The changes were more pronounced in immature animals than in the mature ones.

Conflict of Interests

The authors declare no conflict of interest.

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Authors' Contributions

Maryana Danchyshyn – investigation, data curation, formal analysis, writing – original draft, writing – reviewing and editing; *Olena Lototska* – conceptualization, methodology, writing – reviewing and editing.

ОСОБЛИВОСТІ АНТИОКСИДАНТНОГО ЗАХИСТУ В ОРГАНІЗМІ БІЛИХ ЩУРІВ НА ТЛІ ВЖИВАННЯ ПИТНОЇ ВОДИ З ПОНАДНОРМАТИВНОЮ КОНЦЕНТРАЦІЄЮ НІТРАТІВ

М. В. Данчишин, О. В. Лотоцька

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,
ТЕРНОПІЛЬ, УКРАЇНА

Вступ. Проблема забруднення довкілля нітратами за своїми масштабами та наслідками вийшла на глобальний рівень. Приблизно в одній третині підземних водних об'єктів, щодо яких наразі доступна інформація, перевищено гранично допустимі концентрації вмісту нітратів у питній воді.

Метою цієї роботи стало вивчення особливостей антиоксидантного захисту в організмі білих щурів на тлі вживання питної води з понаднормативною концентрацією нітратів впродовж 30 днів в залежності від віку.

Матеріали. Експеримент проводили на 2 групах безпородних білих самок-щурів різного віку (статевозрілих та статевонезрілих) по 30 особин у кожній, розділених на 5 підгруп, які відрізнялися за якістю питної води, яку вони споживали самостійно. У 30-денному дослідженні нітрати давали щурам у питній воді в дозі 50, 150, 250, 500 мг нітрату натрію на літр. Тварини контрольної групи пили воду з міського водопроводу. Оцінювали вплив нітратів на активність супероксиддисмутази (СОД), каталази та церулоплазміну (СР) в сироватці крові щурів.

Результати. У результаті досліджень виявлено підвищену активність СОД, каталази та СР у сироватці крові на тлі вживання питної води з концентрацією нітратів від 150 до 500 мг/л у піддослідних групах обох вікових категорій. Встановлено, що найбільш виражені зміни показників викликає вживання питної води з нітратами у концентрації 500 мг/л. Більш виражені зміни були у статевонезрілих тварин.

Висновки. Присутність нітратів у питній воді у понаднормативних концентраціях негативно впливає на організм піддослідних тварин, викликаючи активацію досліджуваних показників антиоксидантної системи.

КЛЮЧОВІ СЛОВА: питна вода; нітрати; супероксиддисмутаза; каталаза; церулоплазмін.

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SUBMICROSCOPIC CHANGES IN HEMOCAPILLARIES OF ADRENAL GLAND AND PANCREATIC ISLETS OF LANGERHANS IN CASES OF IMMOBILIZATION STRESS WITH UNDERLYING HYPOTHYROIDISM

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Background. Today, among the increasing number of various diseases, stress is a trigger in the development of diseases and mortality among the population.

Objective. To establish submicroscopic changes in the hemocapillaries of the islets of Langerhans of the pancreas and adrenal glands in the presence of immobilization stress with underlying hypothyroidism.

Methods. The experiment was carried out on 20 mature white male rats. Hypothyroidism was modeled by daily per os injection with a probe of the pharmacopoeial mercazole thyreostatics at a dose of 25 mg/kg for 21 days. Acute immobilization stress was modeled by tying the experimental rats in a supine position in 4 limbs without restricting head mobility for 3 hours. The study was conducted 2 hours later (anxiety stage) after the end of the stress impact. The material was collected for electron microscopy and tissue processing was performed according to generally accepted methods.

Results. Electron microscopic examination of the blood capillaries of the islets of Langerhans in the pancreas and the hemocapillaries of the adrenal cortex after the action of the stress factor in cases of hypothyroidism showed slightly enlarged lumens and moderate perivascular edema. The basement membrane was moderately thickened but clearly contoured. Endotheliocyte nuclei were mostly hypertrophied, euchromatin was uniformly located in the nucleoplasm, and nucleoli were defined. The karyolemma was clearly contoured, the number of nuclear pores was small, and the perinuclear lumen was locally widened. Endoplasmic reticulum with moderately expanded and short tubules, moderately thickened cisterns of the Golgi complex were observed in the cytoplasm of endotheliocytes. There were two types of mitochondria: hypertrophied with an electron-light matrix, single cristae, and with clear visible cristae and a moderately electron-dense matrix. In addition to the capillaries mentioned above, there were also single narrowed microvessels that had perivascular edema and vaguely contoured fenestrae.

Conclusions. When modeling a stressor in cases of hypothyroidism, structural changes of all components of the walls of blood capillaries of the pancreas and adrenal glands take place.

KEYWORDS: stress, pancreas, adrenal gland, submicroscopic changes, hemocapillaries.

Introduction

Today, among the increasing number of various diseases, stress is a trigger in the development of diseases and mortality among the population. Stress is a non-specific reaction of the body in response to a very strong effect or stimulus from the environment, which can significantly affect the body increasing the chances of development of pathological conditions and diseases [1, 2, 3, 4]. It is established that the thyroid gland hormones have a significant influence on the functions of the body as a whole; therefore, their dysfunction – hypothyroidism (reduced production of thyroid hormones) is one of the main endocrine pathology [5, 6]. The

cells of the endocrine part of the pancreas and endocrinocytes of the adrenal glands produce a complex of hormones that regulate most of the vital functions of the body, provide metabolic processes responsible for maintaining body homeostasis in general and stressful conditions in particular. As a result of the action of the stress factor, a structural rearrangement of both the components of the organs and their microcirculatory bed take place; the blood-filled, dilated vessels and remodeling of the hemocapillary wall are the signs of microcirculation disorders. In recent decades, the negative effect of the stress factor on various human organs has already been proven. However, the state of the hemocapillaries of the endocrine glands in cases of immobilization stress with underlying hypothyroidism is studied insuf-

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ficiently and necessitates detailed research [5, 6, 7, 8, 9].

Therefore, the aim of our work was to establish submicroscopic changes in the hemocapillaries of the islets of Langerhans of the pancreas and adrenal glands in cases of immobilization stress with underlying hypothyroidism.

Methods

The experimental part was carried out on 20 mature white male rats with a body weight of 200-250 g, which were kept in the vivarium of I. Horbachevsky Ternopil National Medical University. The object of the study was the pancreas and adrenal glands. Hypothyroidism was modeled by daily per os injection with a probe of the pharmacopoeial mercazole thyreostatics (Health, Ukraine) at a dose of 25 mg/kg for 21 days. The completeness of hypothyroidism was monitored by measuring the concentration of triiodothyronine and thyroxine in blood serum, as well as by the dynamics of the animals' weight and their motor activity. Acute immobilization stress (AIS) was modeled by tying the experimental rats in a supine position in 4 limbs without limiting the mobility of the head for 3 hours. The study was conducted 2 hours later (anxiety stage) after the end of the stress impact [10, 11]. All studies on animals were carried out in compliance with the international rules and principles of the "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes" (Strasbourg, France, 1986) and the Law of Ukraine No. 3447-IV "On Protection of Animals from ill-treatment", dated 21.02.2006.

For electron microscopy, pieces of the pancreas and adrenal glands were fixed in a 2.5% glutaraldehyde solution with an active reaction medium of pH 7.3-7.4. After fixation, they were washed with a buffer solution for 30 minutes. Postfixation was carried out with a 1% osmium tetroxide solution in the Millonig's buffer for 60 minutes; after that it was dehydrated in alcohols and propylene oxide and embedded into a mixture of epoxy resins. Sections were made on the LMB 4801 A ultramicrotome contrasted with uranyl acetate, lead citrate according to the Reynolds method and studied using an electron microscope PEM-125K [12].

Results

During the electron microscopic study in the blood capillaries of the pancreatic islets of Langerhans 2 hours after the end of the action

of the stressor factor in cases of hypothyroidism, the ultrastructural rearrangement of the hemocapillary wall was insignificant. Moderate perivascular edema of fenestrated hemocapillaries was observed. Their lumens were slightly widened, they showed aggregation of erythrocytes and leukocytes. The basement membrane was moderately thickened, but clearly contoured; pericytes with compacted nuclei were adjacent to it. The plasmolemas of endotheliocytes were not clearly defined, and some areas of the luminal surface contained cytoplasmic outgrowths, fenestrae were defined in the peripheral cytoplasmic areas, some were vaguely contoured. Endotheliocyte nuclei were mostly hypertrophied, of a round shape; euchromatin was uniformly located in the nucleoplasm, but heterochromatin was marginally accumulated, and nucleoli were identified. The karyolemma was clearly contoured, the number of nuclear pores was small, the perinuclear lumen was locally widened. In the cytoplasm of endotheliocytes, there were areas of lightening, swollen mitochondria with a compacted matrix and clear cristae, slightly expanded tubules of the endoplasmic reticulum with a moderate number of ribosomes; and moderately thickened cisterns of the Golgi complex were observed. The number of micropinocytotic vesicles decreased in the cytoplasmic areas (Fig. 1).

Electron microscopic studies of the hemocapillaries of the adrenal cortex in 2 hours after the action of the stress factor in cases of hypothyroidism showed structural changes in the walls of microvessels. The lumens of some hemocapillaries were slightly dilated, filled with blood, in addition to erythrocyte stasis, a few leukocytes were also present. Platelets sometimes were attached to the luminal surface of the endothelium. There were no signs of diapedesis of the formed blood elements into the perivascular space. The nuclei of some endothelial cells were of elongated shape, the inner and outer nuclear membranes were clearly contoured, but they formed deep intussusceptions in some areas. The karyoplasm was mostly electron-bright due to the predominance of euchromatin in it, but there were also clumps of heterochromatin, which was mostly present in the area of the karyolemma. Nucleoli were small or absent. The endoplasmic reticulum was represented by expanded and short tubules. The number of pinocytotic vesicles and free ribosomes in the cytoplasm was insignificant and moderately distributed in the cytoplasm. Some mitochondria located near the nucleus

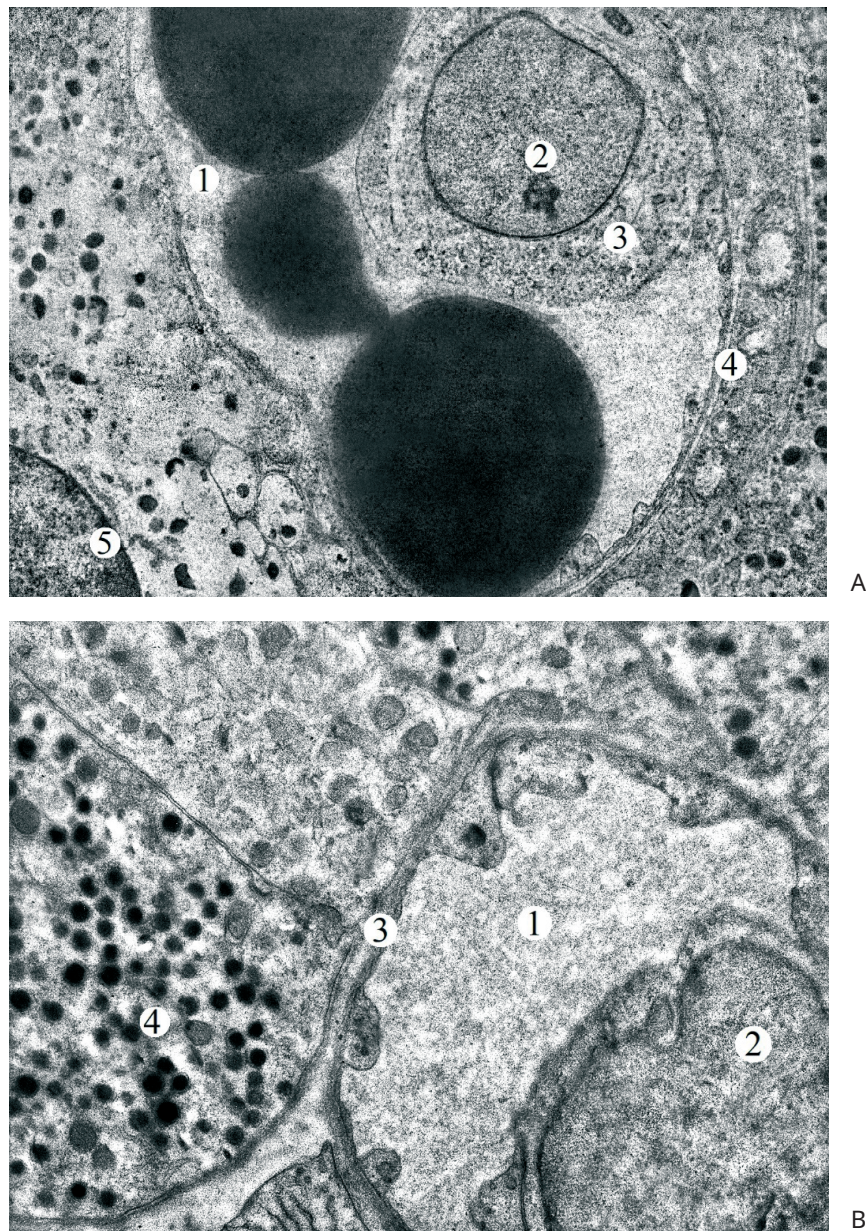


Fig. 1. Ultrastructural changes in the hemocapillary of the rat pancreas in 2 hours (anxiety stage) after the end of the exposure to a stressor in cases of hypothyroidism.

A. 1 – capillary lumen with erythrocytes, 2 – endotheliocyte nucleus, 3 – endotheliocyte cytoplasm, 4 – basement membrane, 5 – endocrinocyte fragment. TEM $\times 12,000$.

B. 1 – lumen of a capillary, 2 – endotheliocyte, 3 – basement membrane, 4 – fragment of an endocrinocyte. TEM $\times 14,000$.

had signs of swelling, were hypertrophied, with an electron-light matrix and single cristae. However, there were also mitochondria with clear visible cristae and a matrix of moderate electron density.

The Golgi complex was formed by fragmented, shortened cisternae and vacuoles. Peripheral areas of the cytoplasm had both thinned and sometimes locally thickened zones; fenestrae were clearly defined. The basement

membrane of blood capillaries contained both locally thickened and thinned areas, moderate perivascular edema was observed in some places. Pericytes were found around the hemocapillaries; their processes were located in the splits of the basal membrane. The cytoplasm of pericytes contained indistinct tubules of the endoplasmic reticulum and cisterns of the Golgi complex; mitochondria were of a round-oval shape, ribosomes were single.

Osmiophilic cell nuclei were of an oval or round shape. In the cortex of the adrenal glands, in addition to capillaries with an enlarged lumen and the presence of clear fenestrae in the endothelium, there were also single narrowed microvessels with perivascular edema and vaguely contoured fenestrae. The nuclei of the endothelial cells of these hemocapillaries were of a chimeric shape; the membranes of the karyolemma formed numerous intussuscep-

tions. The electron-light cytoplasm of such endotheliocytes contained rare destructively altered organelles: some mitochondria were enlarged, with signs of swelling, the tubules of the endoplasmic reticulum were shortened and expanded, and the cisterns of the Golgi complex were rare. The basement membrane was indistinct and contained areas of uneven thickness. Pericytes also showed signs of edema (Fig. 2).

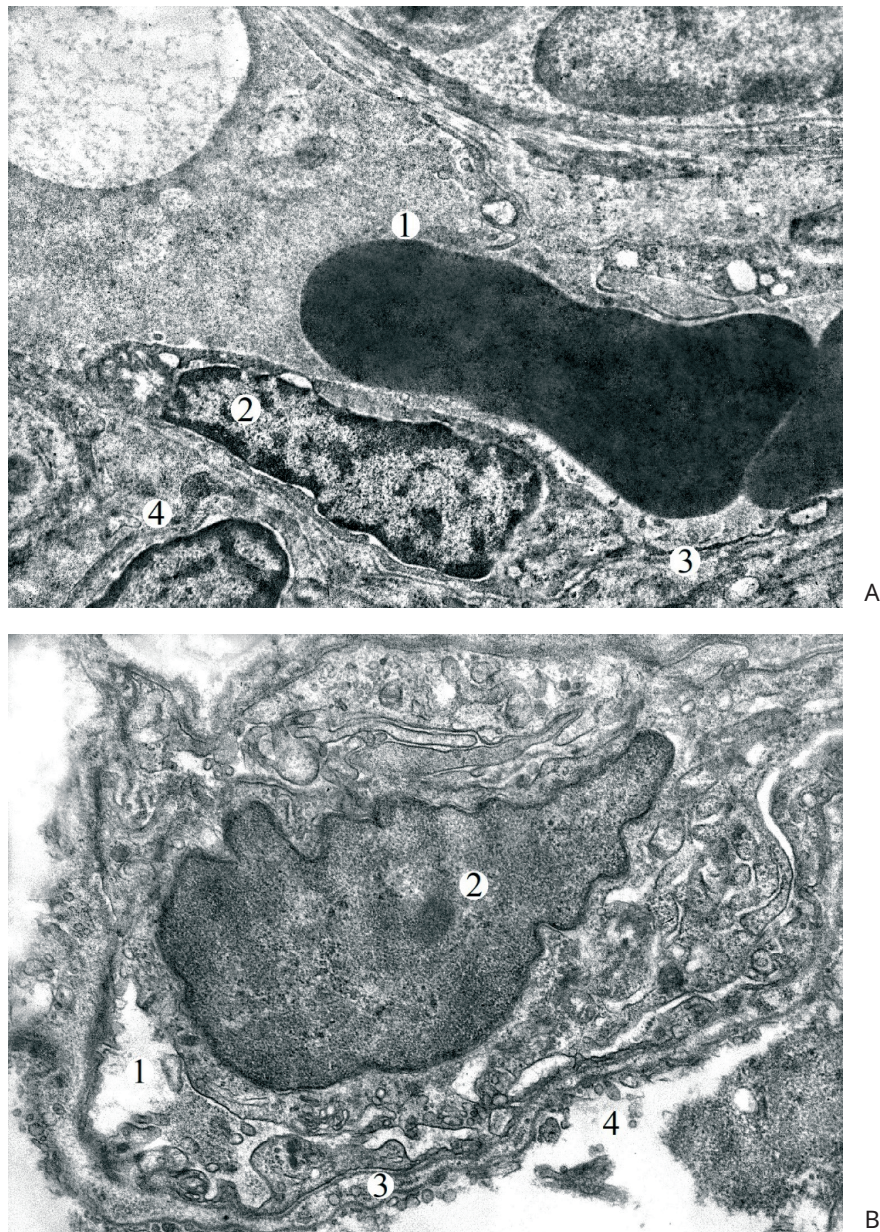


Fig. 2. Ultrastructural changes in hemocapillaries of the zona fasciculata of the rat adrenal cortex in 2 hours (anxiety stage) after exposure to a stressor in cases of hypothyroidism.
A. 1 – capillary lumen with erythrocytes, 2 – endotheliocyte nucleus, 3 – basement membrane, 4 – a fragment of an endocrinocyte. TEM $\times 12,000$.
B. 1 – narrow capillary lumen, 2 – endotheliocyte nucleus, 3 – basement membrane, 4 – perivascular edema. TEM $\times 16,000$.

Discussion

The study of hemocapillaries of the endocrine part of the pancreas and adrenal cortex in cases of immobilization stress with underlying hypothyroidism showed some similar changes in the structure of the walls of microvessels. Thus, the presence of a moderate perivascular edema, erythrocyte aggregation in the lumen of fenestrated hemocapillaries, a thickened basement membrane, and the presence of swollen mitochondria in the cytoplasm of endotheliocytes showed typical changes characteristic of the organ response in the stage of anxiety after stress factor exposure. However, unlike the pancreas, the adrenal glands were characterized by the presence of capillaries with both widened and narrowed lumens, which clearly indicated the significance of these glands in the body response to stress and the release of hormones into the blood.

According to some studies [13] the use of only short-term immobilization is partially consistent with our results as a stress factor does not cause negative changes in the rats' body. However, other authors [2] believe that the body of rats begins responding to stress in the early stages and later enters the adaptation state. Similar research for morphological changes [3] established that the use of additional stressful factors (for example, a change in the temperature regime) were manifested by cardinal changes in the organs; however, the impact of the additional stress factor turned out to be a more damaging factor than the increased immobilization load (the longer and more diverse the stress, the more significant changes in internal organs) that is consistent with the results of our research.

Schur MB [14], in the study of the effect of experimental hypothyroidism on the microcirculatory bed in the retina of rats, describes the presence of typical dilated hemocapillaries of vascular walls with aggregation of erythrocytes and platelets in the lumen of vessels with destructively altered nuclei of endotheliocytes that had deep invaginations of karyolemmas and densely packed adjacent heterochromatin. Hemocapillaries with a narrowed lumen and perivascular edema were also present in the retina that is consistent with our research and proves development of destructive changes

caused by experimental pathology of the thyroid gland. Similar changes were evidenced in the research [15] of hemocapillaries of the lateral pterygoid muscle in hypothyroidism. Thus, the most significant manifestation of changes in the structure of hemocapillary walls were edematous and dystrophic changes in the dynamics of the experiment. Thus, deformation of the lumen of the most capillaries was observed; the basement membrane was disintegrated and thickened; the perivascular area was expanded and vacuolated, that is also partially consistent with our research.

Conclusions

The study showed that when simulating a stressor in cases of hypothyroidism, structural changes of all components of the walls of blood capillaries of the pancreas and adrenal glands took place. However, the blood capillaries in the adrenal glands underwent more intensive changes compare to the capillaries of the pancreatic islets, which indicated the significance of these glands in the organ response to stress. The changes had adaptive-compensatory and partially alternative disturbances, which were manifested by blood filling or narrowing of their lumens as a result of slight swelling of the capillary wall components. The nuclei changed their shape, the content of heterochromatin in the karyoplasm increased, and the perinuclear space expanded locally. Clearing of the cytoplasm with slightly changed organelles, decreased number of fenestrae in the cytoplasmic areas, and uneven thickening of the basement membrane were established. The detected changes indicate disturbed microcirculation in the organ, which probably led to dysfunction of the organs and the body as a whole.

Conflict of Interests

The authors declare no conflict of interest.

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Author's Contributions

Ivan Klishch – conceptualization, writing – reviewing and editing; *Andriy Dovbush* – investigation, writing – original draft; *Halyna Havryliuk-Skiba* – methodology, formal analysis; *Oleksandra Andriyishyn* – investigation, data duration.

СУБМІКРОСКОПІЧНІ ЗМІНИ ГЕМОКАПІЛЯРІВ НАДНИРКОВОЇ ЗАЛОЗИ ТА ОСТРІВЦІВ ЛАНГЕРГАНСА ПІДШЛУНКОВОЇ ЗАЛОЗИ ЗА УМОВ ІММОБІЛІЗАЦІЙНОГО СТРЕСУ НА ТЛІ ГІПОТИРЕОЗУ

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1 – ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО
МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

2 – НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ О. О. БОГОМОЛЬЦЯ, КИЇВ, УКРАЇНА

Вступ. У сучасному світі серед зростаючої кількості різноманітних захворювань, стрес є пусковим механізмом у розвитку захворювань та смертності серед населення.

Мета. встановлення субмікроскопічних змін гемокapілярів острівців Лангерганса підшлункової залози та надниркових залоз за умов іммобілізаційного стресу на тлі гіпотиреозу.

Методи. Експеримент проведений на 20 статевозрілих білих щурах самцях. Гіпотиреоз моделювали щоденним введенням *per os* фармакопейного тиреостатика мерказолілу у дозі 25 мг/кг протягом 21-ї доби. Гострий іммобілізаційний стрес моделювали шляхом прив'язування піддослідних щурів у положенні на спині за 4 кінцівки без обмеження рухливості голови тривалістю 3 години. Дослідження проводили через 2 години (стадія тривоги) після завершення дії стресорного фактора. Для електронної мікроскопії забір матеріалу та його проведення здійснювали згідно загальноприйнятих методик.

Результати. При електронномікроскопічному дослідженні кровоносних капілярів острівців Лангерганса підшлункової залози та гемокapілярів кори надниркових залоз після дії фактору стресу на тлі гіпотиреозу спостерігались незначно розширені просвіти та помірний периваскулярний набряк. Базальна мембрана помірно потовщена, але чітко контурована. Ядра ендотеліоцитів переважно гіперторфовані, в нуклеоплазмі рівномірно розташований еухроматин, визначалися ядерця. Каріолема чітко контурована, кількість ядерних пор невелика, перинуклеарний просвіт локально розширений. В цитоплазмі ендотеліоцитів спостерігали ендоплазматичну сітку з помірно розширеними та короткими канальцями, помірно потовщеними цистернами комплексу Гольджі. Наявні два типи мітохондрій: гіперторфовані з електроннопрозвітленим матриксом, поодинокими кристами та з чіткими кристами і матриксом помірної електронної щільності. Крім вище згаданих капілярів були також поодинокі звужені мікросудини, що мали периваскулярний набряк та нечітко контуровані фенестри.

Висновки. При моделюванні стресорного фактора на тлі гіпотиреозу зміни відбуваються у всіх структурних компонентах стінок кровоносних капілярів підшлункової та надниркових залоз.

КЛЮЧОВІ СЛОВА: стрес; підшлункова залоза; надниркова залоза; субмікроскопічні зміни; гемокapіляри.

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STRUCTURAL ORGANIZATION OF RAT TISSUES IN EXPERIMENTAL COMBINED TRAUMA OF THE CHEST AND BOTH THIGHS

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Background. In cases of severe trauma, fractures of long bones are the most often combined with trauma of the chest, head, and abdomen, as well as development of hemorrhagic shock. Therefore, it is reasonable to study the combined trauma of the chest and lower extremities in details, as well as the post-traumatic multiple organ dysfunction especially in early manifestation stage.

Objective. The aim of the study was to identify the features of structural organization of the lungs, heart and liver with underlying combined trauma of the chest and both thighs on the 7th day of the post-traumatic period.

Methods. The experimental study involved 22 adult nonlinear white male rats with body mass of 200-210 g, kept on a standard diet at animal facility with food and drinking regimes recommended by the standards for laboratory animals. All animals were divided into 2 groups: the control group (1st, n=10), the experimental group (the 2nd) chest trauma and both thighs trauma, observation for 7 days (n=12). The animals of the experimental group were simulated for right-sided closed pneumothorax with a rib fracture by a trocar under thiopental-sodium anesthesia (40 mg/kg of body weight of the rat, intraperitoneally); it was combined with a fracture of the left and right femurs. Skeletal injury was modeled on each thigh that caused a closed fracture by a single dosed blow with a specially designed device. The blow energy was 0.375 J that corresponds to a severe injury. The associated injury was simulated by successive infliction of both injuries.

Results. Examination of the liver of animals on the 7th day of the experiment revealed a rapid growth of lesions in their parenchyma. The central veins were poorly visible and contained single erythrocytes; the vessels of medium caliber of myocardial stroma were dilated and blood-filled, which was manifested by the development of perivascular oedema. In the lungs of experimental animals, a moderate decrease of interstitial tissue oedema of the interalveolar septa was present, while cellular infiltration of mast cells, macrophages and lymphocytes also decreased significantly.

Conclusions. Multiple organ injuries, which are characterized by structural changes in the liver, heart and lungs in the combined trauma of the thorax and thighs on the 7th day of experiment were evidenced.

KEYWORDS: combined trauma; lungs; heart; liver; morphology.

Introduction

At the present time, the significant increase of multiple and combined traumatic injuries is one of the major health problems in Ukraine as well as in many countries around the world, [1] that leads to polysystemic and multiorgan lesions, which in turn increase mortality rate [2, 3]. The most common injuries and major causes of death are traumatic brain injury [4] and chest injury [5]. According to other research, limb fractures predominate in the structure of polytrauma [6, 7]. In the case of severe trauma, fractures of long bones of the extre-

mities are most often combined with trauma of the chest, head, and abdominal organs, as well as development of hemorrhagic shock [8]. It is established that among patients with trauma, the frequency of polytrauma is 13.7%, and polytrauma with combined multiple fractures of long bones of the lower extremities is 0.5% [9]. The same authors note that more than 70% of chest injuries, traumatic brain injuries, and injuries of the musculoskeletal system (16.7% of patients have fractures of the lower extremities) dominate as for the localization. Therefore, it is reasonable to study the combined trauma of the chest and lower extremities, as well as the post-traumatic multiple organ dysfunction especially in early manifestation stage (on the 7th day).

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The aim of the study was to define the features of the structural organization of the lungs, heart and liver with underlying combined trauma of the chest and both thighs on the 7th day of the post-traumatic period.

Methods

The experimental study involved 22 adult nonlinear white male rats weighing 200-210 g, which were kept on a standard diet of vivarium with food and drinking regimes at the level recommended by the standards for laboratory animals. All animals were divided into 2 groups: the control group (1st, 10 animals); the experimental group (2nd) – chest trauma and both thighs trauma (CT + 2T), observation during 7 days (12 animals). The animals of the experimental group were simulated right-sided closed pneumothorax with a rib fracture by a trocar under thiopental-sodium anesthesia (40 mg/kg of the body weight of the rat, intraperitoneally); it was combined with a fracture of the left and right femurs. Skeletal injury was modelled on each thigh that caused a closed fracture by applying a single dosed blow by a specially designed device [10]. The blow energy was 0.375 J, which corresponds to a severe injury. The associated injury was simulated by successive infliction of both injuries. While working with animals, the rules of handling experimental animals were followed. Mortality rate of animals was 16.7%.

Samples of heart, liver and lung tissues, under the conditions of simulated associated trauma and correction, were fixed with 1.5% solution of glutaraldehyde in 0.2 M cacodylate buffer (pH 7.2) at $t=4^{\circ}\text{C}$ for 1 h. The samples were washed with cacodylate buffer and additionally fixed with a 2% solution of osmium tetroxide in the same buffer for 1 h ($t=4^{\circ}\text{C}$). The preparations were washed from the fixatives and dehydrated in increasing concentrations of ethyl alcohol (50%, 70%, 90% and 100%). Additionally, they were dehydrated in 2 changes of propylene oxide and placed in epoxy resin epon-812. The sections were obtained using an ultramicrotome UMT-6 and a diamond knife, they were contrasted with 2% uranyl acetate solution for 15 min and additionally with lead citrate according to Reynolds. Sections were observed and photographed using an electron transmission microscope PEM-100.

All animal studies have been approved by the appropriate bioethics committee of I. Horbachevsky Ternopil State Medical University (protocol № 41 of June 1, 2017).

Results

In the most severe period of the maximum probability of complications (from 3 to 10 days) development of respiratory hypoxia, cardiovascular disorders, metabolic acidosis, programmed and induced cell death is possible. During this period the syndrome of multiple organ dysfunction is diagnosed. Therefore, liver, heart and lungs were investigated as target organs in multiple organ dysfunction during associated trauma in 7 days of the experiment. Examination of the liver of animals in 7 days of the experiment revealed a rapid growth of lesions in its parenchyma. The central veins were poorly visible and contained single erythrocytes. The lumens of the sinusoids were practically not visualized, but erythrocytes were traced in their single preserved areas (Fig. 1). The lobular organization of hepatocytes was disturbed, the vast majority of cells did not have a clear structure, their contours were not clear, the size was difficult to visualize. The cytoplasm of hepatocytes of all parts of the lobe was devastated, enlightened, or granular (Fig. 1), which indicated development of severe protein hyaline-droplet and hydropic dystrophy with transition to focal necrosis (Fig. 1). The vast majority of nuclei was crumpled, became smaller, or disappeared, but in some cells they were visualized with loose chromatin, multiple nucleoli. Intercellular connections were largely lost.

Uneven blood supply and focal lympho- and histiocytic perivascular infiltration were observed in the vessels of the portal tracts.

In 7 days of the experiment, the vessels of medium calibre of myocardial stroma were still dilated and blood-filled, which was manifested by development of perivascular oedema. Dilated capillaries and diapedesis of erythrocytes were found in the fibre thickness. Cardiomyocytes were well visualized in the vast majority of visual fields, but focal intracellular myocytolysis and pyknotically altered nuclei were evidenced in some of them, indicating the presence of focal dystrophic-necrotic changes. The perivascular stroma was loosened due to oedema, which also spread to the intercellular spaces, disintegrating the muscle layer (Fig. 2).

In 7 days of the experiment in the lungs of the experimental animals a moderate decrease of interstitial tissue oedema of the interalveolar septa was evidenced, while cellular infiltration of mast cells, macrophages and lymphocytes also decreased significantly. Signs of dystelectasis (partial decline) were still present

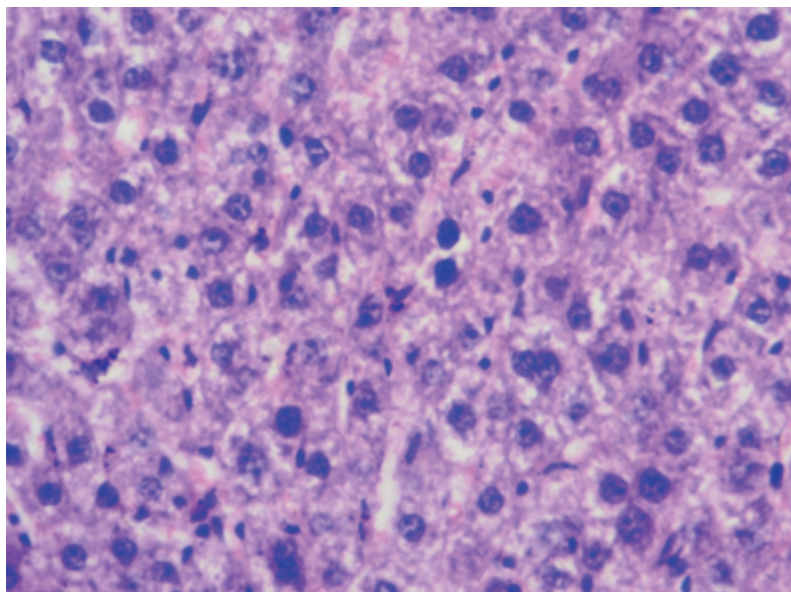


Fig. 1. Structural changes in the liver in cases of simulation of combined trauma in 7 days of the experiment (acute hyaline-drip and hydropic dystrophy with transition to focal necrosis). Hematoxylin and eosin staining. ×200.

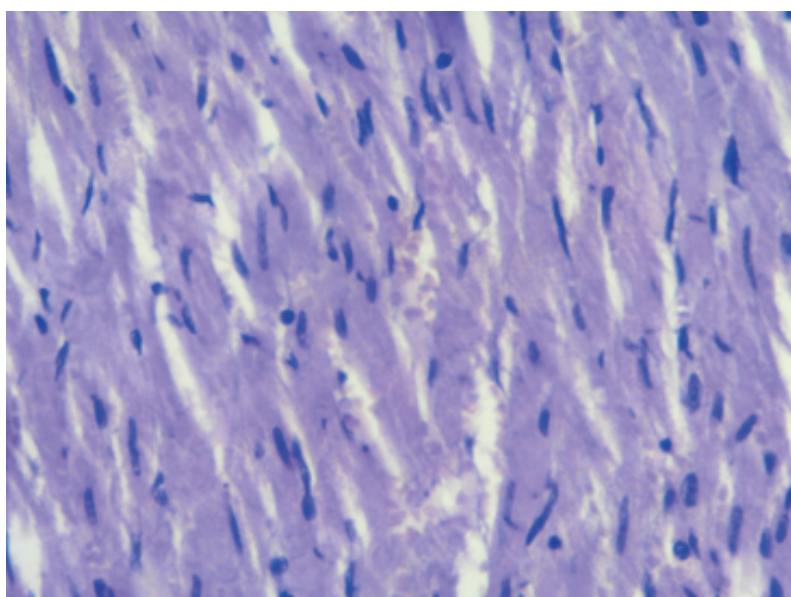
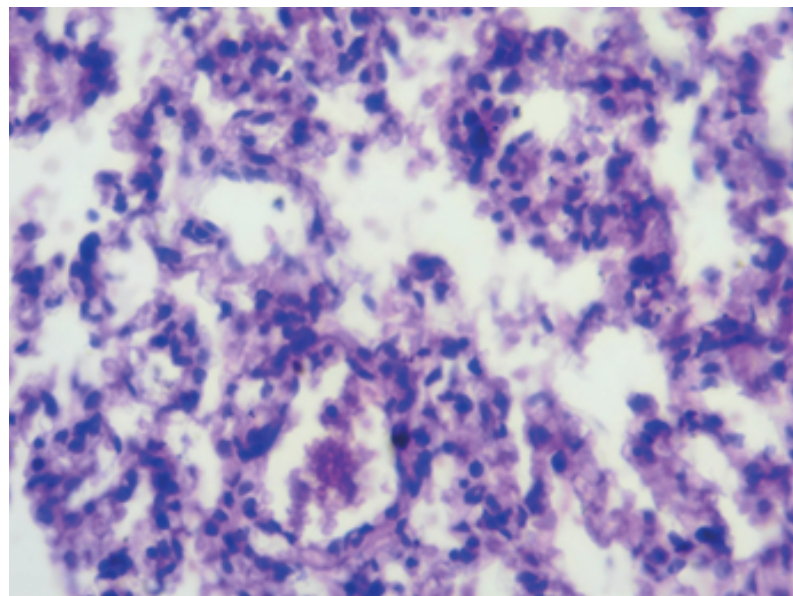


Fig. 2. The structure of cardiomyocytes in the simulation of associated trauma in 7 days of the experiment (pericellular oedema combined with erythrodiapedesis, focal dystrophic changes in cardiomyocytes). Hematoxylin and eosin staining. ×200.

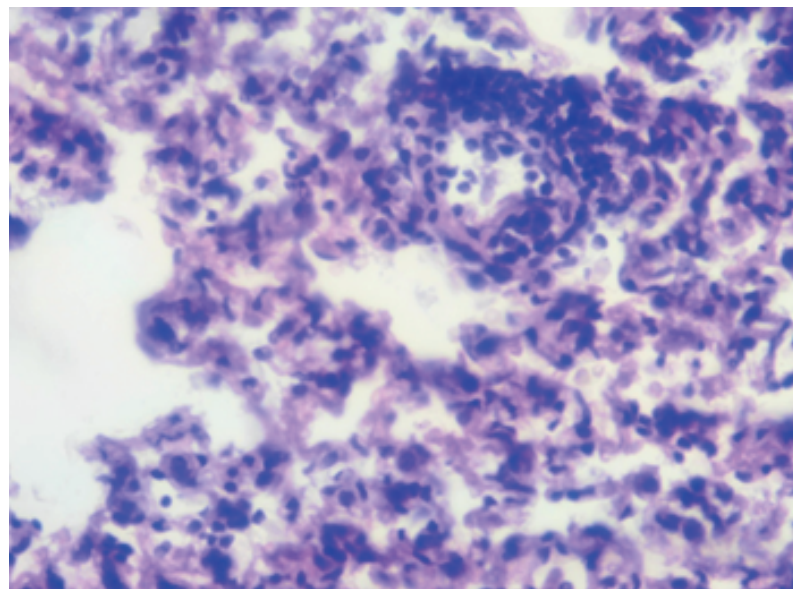
that led to a decrease in the airiness of the lung tissue. Some pneumocytes underwent dystrophic-necrotic changes, and a small amount of exfoliated epithelium and serous exudate appeared in the lumens of the alveoli (Fig. 3). The blood supply to the vessels was still uneven, with a predominance of venous capillary ones. Leukocytes focally accumulated in the perivascular spaces (Fig. 3).

Discussion

The severity of the patient's condition with trauma is largely determined by development of various metabolic disorders in organs and tissues with underlying severe endotoxiosis [11]. These pathological phenomena cause development of deregulatory pathology, one of the manifestations of which is multiorgan



A



B

Fig. 3. Structural changes of the lung in cases of simulation of combined trauma in 7 days of the experiment: A (perivascular accumulation of leukocytes), B (uneven vascular blood supply, dystrophic-necrotic changes of epitheliocytes, slight effusion in the lumen of the alveoli, dystelectasis, focal perivascular leukocyte infiltration). Hematoxylin and eosin staining. $\times 200$.

failure involving lungs, heart and liver into the pathological process.

According to the pathogenesis shortly after the injury the systemic inflammatory response syndrome is established. A number of studies have shown that oxidative stress is crucial in activation of inflammation. From a genetic point of view, oxidative stress modulates inflammation by regulating the activity of certain transcription factors, such as nuclear kappa factor B (NF- κ B), signal transducer and activator of transcription 3 signal transducer and

activator of transcription 3 (STAT 3), hypoxia induction factor 1 alpha (HIF-1- alpha), and protein-1 activator (AP-1) [12]. Activation of peroxidation processes is one of the factors destabilizing the membranes. It is established that when hydroxyl radicals influence on diene conjugates of fatty acids, lipid hydroperoxides are formed, which cause conformational disturbances in the cell membranes. The data obtained indicate that the intensity of peroxidation in different tissues of the body depends on the type of injury. Analysis of the scientific

sources shows that oxidative stress in the patients with various injuries develops almost immediately after the initial injury moving from the macroscopic level to the cellular and molecular one [13-15]. Currently, scientists have proven that the maximum of lipoperoxidation coincides with the intensity of the body's response to inflammation [16]. Thus, Kozak DV notes that the intensity of lipoperoxidation due to hip injury and blood loss is fluctuating with a period of development to the 3rd day, a period of temporary well-being in 14 days and a re-increase in 21 days [17]. The results of the study of oxidative processes in the case of combined trauma of the chest and both thighs show that the most intense free-radical processes occur in the lungs on the 7th and 14th days of observation. On the 3rd day of the experiment, the production of mitochondrial superoxide anion radical increases equally in the tissues of the heart and lungs, while in the tissues of the liver this rate increases to a maximum within 3-14 days [18-20]. It has been established that acute hyperproduction of reactive oxygen species by leukocytes in 1 day of the experiment causes disorganization of bioelectrical activity of mitochondrial membranes, which is characterized by a dynamic increase in the ratio of leukocyte cells suspension with reduced transmembrane potential and the ratio of leukocytes with signs of apoptosis with a maximum in 7 days [21].

In cases of extensive metabolic changes in the body tissues of rats with simulated com-

bined trauma, structural changes in the liver, heart and lungs after 1-3 days of the experiment were evidenced. These changes were manifested by severe circulatory disorders, erythrostatics and development of dystrophic-necrotic changes, especially in epithelial structures [22]. According to our study, these structural changes progressed in the lungs, heart and liver up to the 7th day of observation that is comparable to the severity of oxidative stress in the body tissues and apoptotic death of leukocytes.

Conclusions

In cases of combined trauma of the thorax and thighs of the experimental animals, structural changes develop in the liver, heart and lungs on the 7th day of observation. These changes are characterized by severe hyaline-drip and hydropic dystrophy with transition to focal necrosis of liver tissue, pericellular oedema and dystrophic-necrotic changes of pneumocytes.

Conflict of interest

Authors declare no conflict of interest.

Author contributions

Mariya Marushchak, Inna Krynytska – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Mykhailo Demjanchuk, Oksana Mialiuk* – data curation, investigation, formal analysis; *Marjana Kaskiv* – writing, original draft.

ОСОБЛИВОСТІ СТРУКТУРНОЇ ОРГАНІЗАЦІЇ ТКАНИН ЩУРА ЗА УМОВ ПОЄДНАНОЇ ТРАВМИ ГРУДНОЇ КЛІТКИ ТА ОБОХ СТЕГОН

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*1 – ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО
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РІВНЕНСЬКОЇ ОБЛАСНОЇ РАДИ, РІВНЕ, УКРАЇНА*

Вступ. За умови тяжкої травми переломи довгих кісток кінцівок найчастіше поєднуються з травмою грудної клітки, голови, органів черевної порожнини, розвитком геморагічного шоку. Тому, обґрунтованим є дослідження поєднаної травми грудної клітки та нижніх кінцівок, а також поліорганність їх ураження, особливо у фазу маніфестації.

Мета. Виявити морфологічні особливості структурної організації легень, серця і печінки на тлі поєднаної травми грудної клітки та обох стегон через 7 діб моделювання травми.

Методи. Експериментальне дослідження виконано на 22 дорослих нелінійних білих щурах-самцях масою 200–210 г, яких утримували на стандартному раціоні віварію з підтриманням харчового і питного режимів на рівні, рекомендованому нормами утримання лабораторних тварин. Усіх тварин

було поділено на 2 групи: контрольну (1-а, 10 тварин), дослідну групу: 2-а – травма грудної клітки й обох стегон (ТГК+2С), спостереження 7 діб (12 тварин). Тваринам дослідної групи під тіопентал-натрієвим наркозом (40 мг/кг маси тіла щура внутрішньочеревно) за допомогою троакара моделювали правобічний закритий пневмоторакс із переломом ребра та поєднували їх з переломом лівої і правої стегнових кісток. Скелетну травму моделювали шляхом нанесення однократного дозованого удару спеціально розробленим пристроєм по кожному стегну, який викликав закритий перелом (Kozak, 2011). Енергія удару становила 0,375 Дж, що відповідало травмі важкого ступеня тяжкості. Поєднану травму моделювали шляхом послідовного нанесення обох ушкоджень.

Результати. Дослідження печінки тварин через 7 діб експерименту встановило різке зростання ураження її паренхіми. Центральні вени проглядалися слабо, містили поодинокі еритроцити, судини середнього калібру стромі міокарда залишалися розширеними та наповненими кров'ю, що проявилось розвитком перивакулярного набряку. У легенях піддослідних тварин спостерігалось помірне зменшення набряку інтерстиціальної тканини міжальвеолярних перегородок, а також значно зменшилась клітинна інфільтрація тучними клітинами, макрофагами та лімфоцитами.

Висновки. При поєднаній травмі грудної клітки та стегон експериментальних тварин структурні зміни в печінці, серці та легенях на 7 добу спостереження, що характеризуються вираженою гіаліново-крапельною та гідропічною дистрофією з переходом у вогнищеві некрози тканин печінки, перичелюлярним набряком, поєднаним з еритродіapedезом, вогнищевими дистрофічними змінами кардіоміоцитів та дистрофічно-некротичними змінами пневмоцитів.

КЛЮЧОВІ СЛОВА: поєднана травма; легені; серце; печінка; морфологія.

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