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Хірургія

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NEW APPROACHES TO THE TREATMENT OF ACUTE PERITONITIS

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The high prevalence of acute peritonitis, its unpredictable course, and the rapid development of systemic dysfunctions necessitate further study of the disease. It is relevant to use the principle of personalized medicine, which is based on the selection of diagnostic, therapeutic and preventive means taking into account the patient's genetic, physiological, biochemical and other characteristics. The paper presents data on the diagnosis and treatment of acute peritonitis in 246 patients who, in addition to standard clinical, biochemical, immunoenzymatic and genetic studies, were conducted to determine the role of proinflammatory cytokines (IL1β) in the pathogenesis of the inflammatory process and the development of its complications. The dependence of the manifestations of inflammation and it's spread on the concentration of IL1β in the blood and variants of the IL1β gene (–511C/T), which regulates its secretion, is shown. The processes of peroxidic oxidation, antioxidant protection, unlimited proteolysis, fibrinolytic activity in the implementation of systemic reactions in peritonitis were studied, and their individual variability was shown. On the basis of the conducted research, the stages of surgical interventions, drug treatment schemes and proposed methods of prevention of various complications have been improved. This approach to diagnosis, forecasting the course of acute peritonitis, and the choice of treatment tactics is personalized and provides an opportunity to significantly improve the results of treatment of such patients and reduce mortality.

Keywords: *peritonitis, genetic studies, systemic inflammatory reactions, prognosis.*

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Introduction

Acute peritonitis is one of the most urgent problems in abdominal surgery [1–3]. This is due to its prevalence [4; 5], unpredictable course, rapid development of systemic dysfunctions [5]. The low effective-

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ness of existing methods of treating peritonitis necessitates new research into its pathogenesis, the mechanisms of implementation of systemic reactions, their genetic determinism, which will make it possible to multidisciplinary assess the role of these processes in the progression of the inflammatory process, the development of life-threatening homeostasis disorders [6–9]. It is possible to achieve this by using the principles of personalized medicine, which is based on the selection of diagnostic, therapeutic and preventive means taking into account the patient's genetic, physiological, biochemical and other characteristics [4].

The purpose of the study – to increase the effectiveness of treatment of patients with acute peritonitis by means of a multidisciplinary assessment of the causes and nature of the mechanisms of damage, development of personalized treatment tactics.

Material and methods

246 patients with manifestations of acute peritonitis were included in the study. The research was conducted in compliance with the main provisions of the GSP (1996), the Council of Europe Convention on Human Rights and Biomedicine (1997), the Helsinki Declaration of the World Medical Association on Ethical Principles of Scientific Medical Research with Human Participation (1964–2008), and the Order of the Ministry of Health of Ukraine No.960 dated September 23, 2009.

The age of the examined patients ranged from 18 to 86 years and averaged 58.4±2.14 years. All patients underwent a generally accepted clinical, laboratory, biochemical and instrumental examination.

In addition, the levels of interleukin 1β in blood serum were determined by enzyme-linked immunosorbent assay, using reagents from the company "DRG" (Germany).

The peroxidic oxidation of lipids was studied by the content of malonaldehyde in erythrocytes (Vladimirov Yu.A., Archakov A.I., 1972); determined the activity of glutathione peroxidase glutathione-S-transferase, reduced glutathione (Meschyshen I.F., Gerush I.V., 1998).

Enzymatic (FFA), non-enzymatic (NFA), total fibrinolytic activity (SFA) blood plasma and proteolytic activity of blood plasma were evaluated (by lysis of azoalbumin, azocasein and azocollagen using reagents of the company "Danish Ltd." (Ukraine)).

Alleles of polymorphic regions of IL1β genes (-511C/T) were studied by isolating genomic DNA from leukocytes of peripheral blood stabilized with EDTA as an anticoagulant ("Merk®", Germany), followed by amplification of the polymorphic region using polymerase chain reaction (PCR). The fragments were visualized using a UV-emitter in the presence of a marker of molecular weights of 100–1000 bp.

Statistical processing of research results was carried out using Microsoft® Office Excel spreadsheets (build 11.5612.5703) and the program for statistical processing Statgraphics Plus 5.1 Enterprise edition (®Statistical Graphics corp., 2001).

Research results and their discussion

Among the causes that led to acute peritonitis in the examined patients were: acute destructive appendicitis – in 87 patients (35.36%), destructive cholecystitis – in 48 patients (19.51%), perforated ulcer of the stomach or duodenum – in 56 patients (22.76%), intestinal obstruction – in 34 patients (13.82%), gynecological pathology – in 21 patients (8.55%).

The prevalence of the inflammatory process in the peritoneal cavity was determined according to the classification of Polyanskyi I.Yu. et al. (2012). Local peritonitis was detected in 22 (8.95%) patients, diffuse – in 68 (27.64%), spilled – in 97 (39.43%), general – in 59 (23.98%).

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It is known about the important role of cytokines in the mechanisms of development of peritonitis. We found a directly proportional relationship between the spread of the inflammatory process in the peritoneal cavity and the concentration of IL1β in the blood. Thus, in patients with local peritonitis, it was 180.35±0.74 pg/ml, with diffuse peritonitis – 186.13±3.27 pg/ml, and in patients with diffuse peritonitis – 231.44 ± 4.67 pg/ml, general peritonitis – 238.15±9.85 pg/ml. This is evidence of the leading effect of IL1β on the progression of the inflammatory process in the peritoneal cavity.

It is known that the secretion of cytokines is genetically determined. When studying the relationship between variants of the IL1β gene polymorphism (–511C/T) and IL1β blood concentration, it was established that the lowest concentration was observed in the SS variant (182.48± ±4.27 pg/ml), probably higher in the ST variant (200.4±8.47 pg/ml; $p<0.05$) and the highest – with the TT variant of the genotype (225.33±6.34 pg/ml; $p<0.01$).

Genetic studies established that all patients with local peritonitis had the SS variant IL1β (–511C/T), in patients with diffuse peritonitis the SS variant was found in 94.12% of patients, and ST – in 5.88%. In patients with spilled peritonitis, the favorable SS-variant occurred only in 10.31% of cases, ST – in 71.12% of cases, and TT-variant in 18.57% of patients. With general peritonitis, none of the patients had the SS variant, 55.93% had the ST variant and 44.07% had the TT variant.

According to the theory of chances, the probability of the development of local or diffuse peritonitis is probable with the SS-variant of the IL1β gene (–511C/T) ($t=0.75$; $p<0.01$), and with the TT-variant – widespread peritonitis ($t=0.84$; $p<0.001$).

This became the basis for the developed method of predicting the course of peritonitis: if the patient has a ST- and, especially, a TT-variant of the IL1β gene (–511C/T), we predict the development of widespread peritonitis. In such patients, treatment tactics should be aimed at preventing the progression of the inflammatory process in the peritoneal cavity and its elimination through more intensive intra- and postoperative sanitation of the peritoneal cavity with local application of anticytokine agents.

It is known that not only microorganisms but also a whole cascade of systemic reactions plays a role in tissue and structure damage during peritonitis. One of them is pronounced microcirculatory disorders that arise as a result of hypercoagulation. This leads to secondary ischemic lesions of tissues, contributes to the spread of destructive processes in the visceral and parietal peritoneum. We found a significant increase in the total fibrinolytic activity, proportional to the spread of the inflammatory process in the peritoneum. It is characteristic that the activation of fibrinolysis occurs mainly due to non-enzymatic fibrinolysis, which is realized due to the complexation of various biologically active substrates with heparin. Excessive fibrinolytic activity, on the one hand, contributes to the improvement of microcirculation, on the other hand, prevents the formation of fibrinous boundaries of the affected areas, promotes the spread of the inflammatory process. This became the basis for the inclusion of low molecular weight heparins and antifibrinolytic drugs in the complex treatment of such patients.

Manifestation of systemic reactions in peritonitis is the activation of peroxide oxidation processes. We found not only a progressive increase in the concentration of malonaldehyde in erythrocytes, but also a decrease in the activity of antioxidant protection enzymes (glutathione peroxidase, glutathione-S-transferase). This is a sign of an imbalance in the redox system, the severity of which correlates with variants of the IL1β gene (–511C/T). In this regard, we include in the complex treatment

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of such patients antioxidant therapy, the intensity of which depends on the severity of the imbalance of pro- and antioxidant systems.

Processes of unlimited proteolysis play an important role in the pathogenesis of peritonitis. Excessive activation of proteolytic activity is evidenced by the increase in proteolysis for azoalbumin (to low-molecular structures), for azocasein (to medium-molecular structures) and a decrease in proteolysis for azocol (to high-molecular structures). This became the basis for the inclusion of antiproteolytic agents in the complex treatment of such patients.

Treatment tactics in patients with acute peritonitis depends on its form, prevalence of the inflammatory process, prognostic criteria for the course of peritonitis and the development of complications. Thus, for effective rehabilitation of the peritoneal cavity, it is important to take into account not only the existing nature and localization of the inflammatory process at the time of surgery, but also the predicted propensity for inflammation to spread. Local irrigation of the peritoneum with anti-cytokine drugs, drainage of the peritoneum departments in which the spread of inflammation is predicted, use of prolonged rehabilitation according to the developed methods [12], extension of indications to the use of programmed laparotomy for repeated rehabilitation, evaluation of the nature of the inflammatory process, viability of structures is expedient. This, especially in persons with a likely predicted unfavorable variant of the course of indefinite peritonitis, allows to prevent the progression of the inflammatory process, the occurrence of various complications, and in case of their development, to detect and eliminate these complications in a timely manner.

Such a multidisciplinary, personalized approach to diagnosis, prediction of the course of acute peritonitis, selection of treatment tactics taking into account the severity of systemic disorders, improvement of the stages of surgical intervention and drug influence on the leading mechanisms of the inflammatory process made it possible to significantly improve treatment results and reduce mortality to 6.84%.

At the same time, it is obvious that it is impossible to achieve recovery of all peritonitis patients with complex treatment. Prevention of its occurrence through planned surgical treatment of those surgical diseases that can be complicated by peritonitis, timely diagnosis and early adequate treatment of acute surgical pathology is a real way to solve this problem.

Conclusions

1. Genetic studies make it possible to predict the course of the inflammatory reaction, its severity and the development of various complications.

2. An unfavorable prognosis makes it necessary to change treatment tactics, which should be preventive in nature, aimed at preventing damaging mechanisms and reducing their manifestations.

3. Manifestations of systemic reactions in peritonitis necessitate a multidisciplinary approach to their assessment and purposeful correction.

The authors declare **no conflict of interest.**

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НОВІ ПІДХОДИ ДО ЛІКУВАННЯ ГОСТРОГО ПЕРИТОНІТУ

Висока поширеність гострого перитоніту, непередбачуваний його перебіг, швидкий розвиток системних дисфункцій зумовлюють необхідність подальшого вивчення захворювання. Актуальним є використання принципу персоналізованої медицини, яка базується на підборі діагностичних, лікувальних і профілактичних засобів з урахуванням генетичних, фізіологічних, біохімічних та інших особливостей пацієнта. У роботі наведені дані про діагностику та лікування гострого перитоніту у 246 хворих, яким окрім стандартних клінічних, біохімічних, методів проведені імуноферментні та генетичні дослідження для визначення ролі прозапальних цитокінів (IL1β) у патогенезі запального процесу та розвитку його ускладнень. Показана залежність проявів запалення, його розповсюдження від концентрації в крові IL1β та варіантами гену IL1β (–511C/T), що регулює його секрецію. Досліджені процеси пероксидного окиснення, антиоксидантного захисту, необмеженого протеолізу, фібринолітичної активності у реалізації системних реакцій при перитоніті, показана їх індивідуальна варіабельність. На основі проведених досліджень вдосконалено етапи оперативних втручань, схеми медикаментозного лікування та запропоновані методи профілактики різних ускладнень. Такий підхід до

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діагностики, прогнозування перебігу гострого перитоніту, вибору лікувальної тактики носить персоналізований характер і дає можливість значно покращити результати лікування таких хворих, знизити летальність.

Ключові слова: *перитоніт, генетичні дослідження, системні реакції запалення, прогнозування.*

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