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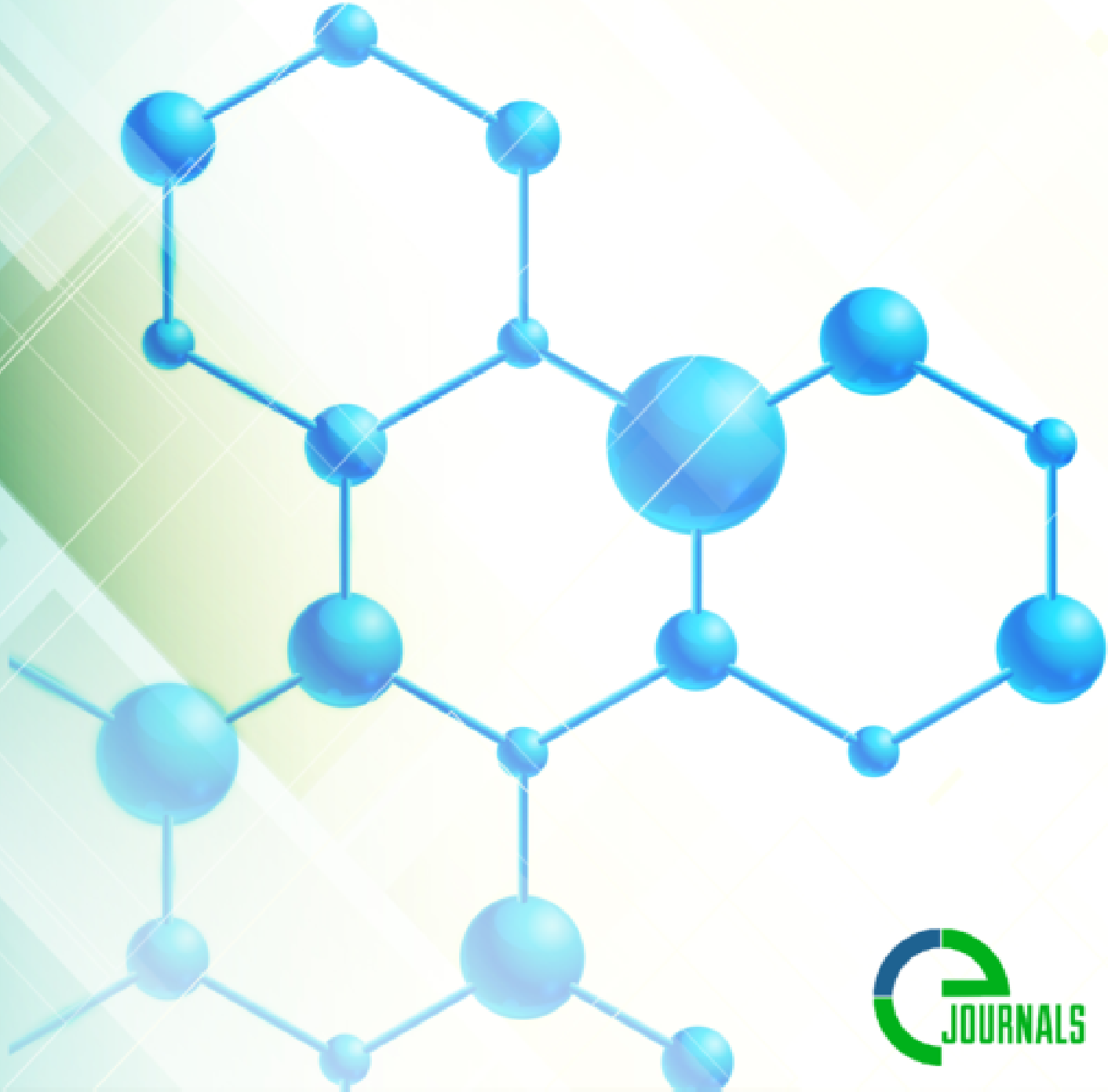

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ANALYSIS OF THE LEVEL OF ENDOGENOUS INTOXICATION IN CHILDREN WITH WIDESPREADM APPENDICULARM PERITONITISOM

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Abstract: The aim of this article was to assess the intensity of endogenous intoxication syndrome in children with advanced appendicular peritonitis. To achieve this goal, 402 children with advanced appendicular peritonitis were examined. Clinical and laboratory studies included interpretation of general blood analysis data, including calculation of the leukocyte intoxication index, neutrophil nuclear segmentation index, and spontaneous white blood cell agglomeration ниndex on the 1st, 2nd, 3rd, and 4th days of the disease. The degree of endogenous intoxication was judged by the level of average plasma molecules. The activity of superoxide dismutase and catalase in blood serum were determined. Studies of hemostasis parameters were also conducted.

As a result of the conducted studies, it was found that the pronounced inflammatory process and endotoxicosis that inevitably accompanies RAP have a direct effect on the platelet link of hemostasis, which can be a prerequisite for disorders in the microcirculation system, aggravating both the damage to the peritoneum and increasing the risk of intra - and postoperative complications.

Keywords: advanced appendicular peritonitis, endogenous intoxication, hemostasis, antioxidant system, children.

According to the conducted studies, the most severe complication of acute appendicitis in childhood is widespread appendicular peritonitis (RAP), which occurs in 8-10% of all cases of the disease. [1, 3, 11]. Mortality in these complications is on average 25%, while in severe forms with endogenous intoxication (EI) accompanied by bacterial-toxic shock, it reaches 76% [7, 10, 15].

Endogenous intoxication, which occurs in acute purulent-inflammatory diseases of the abdominal cavity, is the result of intestinal insufficiency, significantly complicates the course of the postoperative period in 30-50% of patients. [6, 8].

As many authors point out, the mortality rate in children with RAP depends on the development of septic complications, the initial manifestations of which are EI [12]. EI is characterized by a cascade of stages, which plays an important role in the progression of the generalized process. The presence of a generalized process contributes to the

accumulation of toxic substances in high concentrations in the bloodstream, exceeding the functional capabilities of natural neutralization systems with subsequent pathological changes in the organs, as well as in the body system of children [2, 4].

Based on the above, it can be concluded that, despite the conducted studies, widespread appendicular peritonitis in children remains one of the most pressing problems, and many issues require in-depth study, in particular, the criterion of severity and the role of an integral assessment of the degree of endogenous intoxication.

Objective: to assess the intensity of endogenous intoxication syndrome in children with RAP.

Materials and methods: the study is based on the survey data of 402 children with advanced appendicular peritonitis. The control group consisted of 40 children who did not have acute inflammatory and surgical diseases and were hospitalized for minor non-local planned surgical interventions (circumcision, herniation).

The groups compared were statistically comparable in age, type, and severity of the disease. There were 248 boys (61.7%) and 154 girls (38.3%). Of the 207 patients with diffuse and 195 diffuse peritonitis included in the study, only a tenth were admitted to the clinic in the reactive stage of the disease, which definitely indicates gaps in the work of the primary health care system in terms of early diagnosis and differential diagnosis of acute appendicitis in children.

It should be emphasized that approximately one quarter of our patients were operated on in the terminal stage, which is characterized by high mortality rates, which once again demonstrates the relevance of the problem under consideration.

Taking into account that the study included only patients with advanced peritonitis, 92.8% of patients were admitted to our clinic up to 7 days after the onset of the attack.At the same time, 24 patients were diagnosed with peritonitis 8-10 days ago, and 3 patients were diagnosed with peritonitis more than 10 days ago.

As a rule, in children with advanced peritonitis, we observed general somatic complications such as toxic pneumonia, encephalopathy and myocarditis.As a result of late hospitalization, only one quarter of the patients are considered to have a moderate condition, while three - quarters (three-quarters) are considered to have a severe or extremely severe condition.

Data analysis showed that 40.0% of children were admitted to the reactive stage of the disease, and almost one-third of patients had a toxic stage of the disease, and 25.4% had end-stage peritonitis, which should be taken into account when drawing up a program of perioperative complex intensive care.

Of the 195 patients with diffuse peritonitis, 95% were admitted to the clinic in the toxic and terminal stages of the disease, which is associated with a prognostically unfavorable course of the disease.With diffuse peritonitis, a more favorable course of the disease was noted: 72.9% of children were admitted with a reactive stage of the disease, 27.1% were diagnosed with a toxic stage of the disease.

In proportion to the above, we observed a significant correlation between the stage of peritonitis and its prevalence: as the disease progressed from the reactive stage to the terminal stage, the proportion of patients with diffuse process increased from 5.1% to 52.3%, while the proportion of patients with diffuse peritonitis decreased from 72.9% to 27.1%.

A general blood test was performed according to the standard method, the leukocytogram was counted in stained smears, and the leukocyte intoxication index (LII) was calculated using the formula Ya.Ya. Kalf-Kalifa. The neutrophil nuclear segmentation index (NNR) and the spontaneous leukocyte agglomeration index (PSAL) were determined by the method of A.M. Shamsiev et al. (2002) N.A. 1st, 2nd, 3rd, 4th

day of the disease. The degree of endogenous intoxication was judged by the level of average plasma molecules (SMP), which were determined by Gabrielyan N. I. et al. (1985).

Determination of malonovodialdehyde (MDA) in blood serum was carried out according to the method of I. D. Stalnoy et al. (1977); activity of superoxide dismutase (SOD) in blood-according to the method of R. N. Mirsa, I. Fridovich modified by O. S. Brusov et al. (1976); activity of catalase in blood - according to M. A. Korolyuk and et al. (1988).

The study of the hemostatic system included screening tests: activated partial thromboplastin time(APTT), prothrombin time (PV), and fibrinogen concentration, which were performed according to generally accepted methods: the determination of activated partial thromboplastin time (APTT) was carried out using standard kits from Cypress Diagnostics, Belgium; prothrombin time was studied using Techplatin-test kits manufactured by Techplatin-test. "Technology-standard "(Barnaul, Russia); the concentration of fibrinogen in plasma was measured according to R. A. Rutberg; platelet count was performed according to Phoni.

The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package, including the use of built-in statistical processing functions.

Research results and discussion: Research results and discussion: according to our results, all children with RAP showed a significant increase in the number of total white blood cells (1.7-2.3 times) relative to the control group, a shift in the leukocyte formula to the left, and a number of patients had myelocytes and metamyelocytes, which reflected a significant increase in the number of total white blood cells relative to the control group. index of leukocyte intoxication-LII(Table 1).

Table 1
Indicators of leukocytosis and LII in children with RAP

Indicator	Control group, n=40	Diffuse peritonitis, n=207	Diffuse peritonitis, n=195	Total group-RAP n=402
Leukocytes, $\times^{109}$/l	5,36±0,21	9,42±0,991*	12,23±1,11*	11,03±0,99*
Stick-based systems,%	1,2±0,1	9,4±0,66*	12,5±1,6*,**	6,1±0,4*
Segmented cores,%	Segmented cores,%56,8±1,7	62,3±2,1*	62,5±1,9*	62,4±2,0*
Eosinophils, %	1,30±0,10	0,50±0,09*	0,30±0,07*	0,41±0,08*
Lymphocytes, %	35,4±0,2	24,6±1,1*	23,6±0,9*	23.9±1.1 *
Monocytes, %	5,3±0,1	3,2±0,8*	1,1±0,9*	2,1±0,9*
LII	0,66±0,1	2,26±0,5*	3,13±0,8*	2,69±0,7*
ESR, mm / h	7,8±0,2	16,4±1,1*	17,8±1,6*	17,1±1,2*

Note: * - reliable relative to the control, P<0.05.

Taking into account the statistically unreliable nature of differences in the level of leukocytosis and morphological types of leukocytes in groups with diffuse and diffuse peritonitis, for further analysis, we identified a general group of children with RAP.It is noteworthy that, despite the fact that the average values of the total number of leukocytes and the number of rod neutrophils were higher in the group of children with diffuse peritonitis, these differences were statistically unreliable. Changes in the leukocyte formula in RAP were characterized by the neutrophil-eosinopenic type, when a decrease in eosinophils, lymphocytes, and monocytes occurred against the background of leukocytosis and neutrophilosis, which is characteristic of purulent-septic processes.

The relative content of lymphocytes in children with diffuse and diffuse peritonitis was significantly lower than the control level, however, it did not depend on the form of RAP.

The detected increase in LII over 2.0 units (в 4.1 times relative to the control) in children with RAP indicates the presence of a focus of necrobiotic altered tissues and a high risk of generalization of the process both due to bacterial exotoxicosis and due to the inflammatory and destructive process in the abdominal cavity [5, 14]. More precisely, the intensity of endogenous intoxication can be judged by the indicators of medium-molecular peptides in the blood-a classic marker of endotoxicosis, as well as a marker of membrane-destructive processes and cell membrane lipoperoxidation-MDA [9, 13].

Assessment of the level of SMP and MDA in the blood of children with RAP revealed a sharp increase in them compared to the control against the background of inhibition of the AOS enzymatic link, however, changes depending on the prevalence of peritonitis are unreliable (Table 2).

Thus, in RAP, regardless of the prevalence of peritonitis, there is a significant activation of the processes of degradation of biomolecules, which is accompanied by an almost twofold increase in the level of MDA and SMP against the background of inhibition of SOD activity by 2.5 times and catalase-by 1.8 times compared to the control.

First of all, the development of membrane-destructive processes occurs in the abdominal cavity, as well as in the blood. Accumulation of MDA and other LPO intermediates in the blood has a cytopathic effect on the formed blood elements [14], which is reflected in changes in the properties of leukocyte membranes.

Table 2

Content of SMP, MDA and activity of antioxidant system enzymes in the blood of children with RAP

Indicator	Control group, n=40	Diffuse peritonitis, n=38	Diffuse peritonitis, n=34	Total group-RAP n=72
MDA, nmol / l	7,1±0,1	12,8±0,4*	13,6±0,1*	13,2±0,3*
SMP, UE	0,250±0,025	0,501±0,026*	0,581±0,090*	0,539±0,035*
SOD, E/mg of protein	4,20±0,04	1,71±0,05*	1,68±0,01*	1,70±0,03*
CT, mcat / l	23,5±1,6	12,9±0,7*	13,9±0,2*	13,3±0,5*

So, we found that in RAP there is an increase in spontaneous agglomeration of neutrophils around lymphocytes, the number of such" agglomerates " reaches 15-25 per thousand counted white blood cells.

An indicator that characterizes the increased agglomeration of white blood cells around lymphocytes due to changes in the properties of their plasma membrane-an indicator of spontaneous agglomeration of white blood cells-PSAL is normally 3-4. In children with RAP before surgery in the phase of the height of clinical manifestations, there is a significant increase in PSAL relative to the control. We believe that the increase in the PSAL index is due to changes in the structural and functional characteristics of leukocyte membranes, which leads to an increase in their adhesive properties and agglomeration of neutrophils around lymphocytes. It is possible that an excessive antigenic load of bacterial toxins, as well as products of macromolecule degradation, triggers a cascade of pathological processes leading to increased sensitization of immune system cells, and affects the state of their membranes, resulting in increased spontaneous agglomeration of white blood cells.

In addition, we detected changes in the morphology of neutrophils in children with RAP, which was manifested by a decrease in the segmentation of their nuclei. If the neutrophil normally contains 3-4 segments, then in RAP the number of segments decreased to 2-3. This may reflect the level of granulocytopoiesis intensity with the release of immature forms, so we proposed an integral indicator that reflects the number of immature forms of neutrophils - the neutrophil nuclear segmentation index. Changes in PSAL and IASN in RAD are reflected in Table 2, which shows that changes in PSAL were significant, and IASN-unreliable relative to the control in children with RAD; differences between the groups of diffuse and diffuse peritonitis were statistically insignificant(Table 3).

Table 3
PSAL and IASN parameters in children with RAP

Indicator	Control group, n=40	Diffuse peritonitis, n=134	Diffuse peritonitis, n=130	Total group-RAP n=264
PSAL	3,7±0,1	18,5±0,6*	17,8±0,7*	18,1±0,7*
IASN	2,6±0,3	2,3±0,1	2,4±0,2	2,3±0,2

Note: * significantly different from the control group $p<0.05$

The IASN indicator in children with RAP was not informative enough, because its changes were statistically unreliable, indicating only a tendency to disorders in the processes of neutrophil maturation.

The proposed indicators of spontaneous agglomeration of leukocytes and the neutrophil nuclear segmentation index are objects of intellectual property (patent no. IDP 05125, 2001).

With the development of RAP, changes occur in the hemostatic system, which are characterized by a significant decrease in the number of platelets relative to the control, an elongation of APTT and PV, which can be interpreted as a prerequisite for the development of acute DIC syndrome in RAP in children (Table 4).

Table 4
Indicators of screening tests of the hemostatic system in children with RAP

Indicator	Control group, n=40	Diffuse Diffuseperitonitis, n=207	Diffuse peritonitis, n=195
Platelet count, $\times^{109}$/l	230,0±3,1	193,1±16,3*	162,2±12,7 *
APTT, s	31,0±0,3	34,2±0,5	35,7±0,6*
PV, with	18.0±0.2	22.1±0.5	23.7±0.8 *
Fibrinogen concentration, g / l	2,8±0,06	4,40±0,10*	4,60±0,04*

Note: * - significantly different from the control group, p<0.05; * * - significantly relative to

An increase in the content of fibrinogen by 1.5-1.6 times relative to the control can also be considered as a component of the systemic inflammatory response, since fibrinogen is an acute phase reactant. There were no significant differences in APTT, PV and fibrinogen between the groups of diffuse and diffuse peritonitis, as well as the number of platelets.

Thus, the pronounced inflammatory process and endotoxicosis that inevitably accompanies RAP have a direct effect on the platelet link of hemostasis, which can be a prerequisite for disorders in the microcirculation system, aggravating both peritoneal damage and increasing the risk of intra - and postoperative complications.

Based on the results obtained, it can be stated that children with RAP have signs of systemic inflammatory response syndrome, endogenous intoxication and oxidative stress, which are equally pronounced in both diffuse and widespread peritonitis, indicating the presence of membrane-destructive processes. This requires additional corrective measures.

Progressive multiple accumulation of LPO products in the body of children with peritonitis was manifested by an almost twofold decrease in the concentration of SOD (superoxide dismutase) and catalase (CT), as well as an increase in the concentration of MDA and SMP (medium molecular weight peptide) by more than 2 times compared with healthy children.

Children with RAP are classified as severe surgical patients, which undoubtedly requires adequate preoperative preparation in terms of volume and duration. Immediate surgical intervention without correction of central and peripheral hemodynamics, hypovolemia, and monitoring of the state of water-electrolyte and acid-base balance in conditions of significant violations of the child's body homeostasis, in our opinion, is a serious tactical mistake.

Conclusions:

1.It was found that in RAP, regardless of the prevalence of the process, there is a significant activation of the processes of degradation of biomolecules, which is accompanied by an almost twofold increase in the level of MDA and SMP against the background of inhibition of the enzymatic link of the antioxidant system - a decrease in the activity of SOD by 2.5, and catalase - by 1.8 times relative to the control.

2.There were no significant differences in hemostasis parameters (APTT, PV, and fibrinogen) between the groups of diffuse and diffuse peritonitis, and the platelet count was significantly lower in children with diffuse peritonitis, which may be a prerequisite for disorders in the microcirculation system, exacerbating both peritoneal damage and increasing the risk of intra-and postoperative complications

3.In children with RAP, the intensity of endogenous intoxication and oxidative stress are equally pronounced in both diffuse and widespread peritonitis, indicating the presence of membrane-destructive processes.

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