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VASOCONSTRICTIVE AND VASODILATATIVE IMBALANCE AT EXPERIMENTAL FECAL PERITONITIS

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Annotation

Peritonitis problem today one of the most urgent issues in the field of clinical pathological physiology and abdominal surgery. According to various data, mortality in peritonitis is 18.3 - 62.8%. Endothelial dysfunction is the main cause of cardiovascular diseases and death in patients after postponed peritonitis.

The aim of the study – investigation of vasoconstrictive and vasodilatative potential in the pathogenesis of experimental peritonitis and its correction.

It has been proved that experimental fecal peritonitis development pathologically affects the vessels functional state at each of the research stages. It's established weakening of the vasodilatative process on the background of peritonitis development, as evidenced by a decrease in the content of S-nitrosothiols. Result of this work has been proved that in peritonitis pathogenesis the vasoconstrictor potential of the vessels is significantly increased, as evidenced by a significant increase in endothelin-1 in animals that have been modeled by fecal peritonitis. Nitric oxide donor efficiency has been proved as part of complex correction of peritonitis and endothelial dysfunction as its complication. The most pronounced positive

effect was detected at the 21st day, which indicates the expediency of long-term use of L-arginine as a remedy for correction.

Keywords: endothelial dysfunction, experimental peritonitis, correction, vasoconstrictive potential, vasodilatative potential.

Peritonitis problem today one of the most urgent issues in the field of clinical pathological physiology and abdominal surgery. According to various authors, it makes up from 18.3 to 62.8 % [1-5]. The highest mortality rate is observed during the postoperative peritonitis - from 45 to 92.3% [6, 7].

According to some authors, during the first 5 years after the peritonitis, 35% of patients have complications associated with vascular dysmetabolism, of which 65% die within 10 years [8]. The main etiopathogenetic factor of endothelial dysfunction is the development of endotoxin aggression [9].

The cause of endothelial dysfunction is chronic endotoxin aggression. Endothelial dysfunction caused by peritonitis is not limited by vascular reactions of a single organ, and as a result leads to multiple organ failure. Therefore, the increase in the concentration of endotoxin in the blood plasma should be considered as the main trigger of endothelial dysfunction and its related diseases in the remote postoperative period.

After the intraabdominal infection the patient may has the systemic endotoxinemia, which affects the liver and causes severe metabolic disorders and endothelial dysfunction[10].

Endothelial dysfunction was identified by V.S. Saveliev (2009) as the main cause of cardiovascular diseases and death in patients after postponed peritonitis [10].

The aim of the study – investigation of vasoconstrictive and vasodilatative potential in the pathogenesis of experimental peritonitis and its correction.

Materials and methods of research:

Group 1 - 20 intact animals.

Group 2 - 50 rats with simulated fecal peritonitis.

Group 3 - 50 rats with simulated fecal peritonitis with subsequent antibiotic correction and debridement by chlorhexidine solution.

Group 4 - 50 rats with simulated fecal peritonitis with subsequent antibiotic correction, chlorhexidine debridement and endothelial dysfunction correction with the use of a nitric oxide donor.

Fecal peritonitis was modeled using injection of 10% fecal suspension in a dose of 0.5 ml per 100 g of animal weight in the abdominal cavity of laboratory animals by puncture method (Lazarenko V.A., et al., 2016, patent No. 233826).

Research was conducted in accordance with the "Rules for carrying out works using experimental animals", approved by the Order of the Ministry of Health of Ukraine No. 249 of 01.03.2012 and the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel Treatment" (as amended on December 15, 2009, and 10/16/2012).

Research results:

Table 1 presents study results of S-nitrosothiols (S-NO) content, which is a marker of vasodilatative potential at all stages of the experiment.

Table 1

Vasodilatative potential dynamics in animals that was simulated by fecal peritonitis and analysis of its correction methods effectiveness on the 1st, 3rd and 21st day of the experiment

Group /Day	1st day beginning	1st day ending	3rd day	21st day
1st group	0,381±0,008	0,380±0,007	0,382±0,009	0,381±0,007
2nd group	0,340±0,008	0,160±0,012	0,121±0,011	animals do not survive
3rd group	0,341±0,007	0,243±0,009	0,261±0,004	0,292±0,007
4th group	0,342±0,006	0,290±0,007	0,324±0,009	0,393±0,008

At the 1st day beginning were found significant differences between the S-NO content in intact animals and in all groups where fecal peritonitis was modeled in rats. At the same time, comparing the groups with the experimental pathology among themselves, the absence of statistical differences, which indicates their homogeneity and suitability for further analysis. At the end of the first day in 2nd group, in which peritonitis was modeled without correction, an even more pronounced reduction of vasodilatative potential was established in comparison with the beginning of the first day, indicating a negative dynamics of the

pathological process development (differences at the significance level were detected p <0.001).

Also, confirmation of the negative peritonitis influence on the vessels state is that at the beginning of the first day, the content of S-NO in comparison with the data of intact animals was reduced by 10.8%, and by the end of the same day - by 57.9% (p <0.001). In analyzing the groups in which the adjusted peritonitis was corrected to the rats by the end of the first day, the following was established: comparing with the data obtained at the beginning of the first day, the statistical difference remains significant at the level of p <0,001, the gap is lower than in group № 2 Compared with intact animals data at this stage in 3rd group, which receiving antibiotic therapy and debridement with chlorhexidine solution, the level of the studied index was lower by 36.1% (p <0.001), and in the group receiving the specified correction in combination with the addition of the solution L-arginine, there was a better dynamics - less pronounced decrease was observed - by 23.7% (p <0.001). Also, the advantage of a three-component correction is evidenced by the fact that in comparison with the data of rats with FP without correction, the level of S-NO in the third group is higher by 51,9% (p <0,001), and in the fourth - by 81,3% (p < 0.001). Comparing the data of groups №3 and №4 with each other, a more pronounced performance in group 4 was revealed (p <0.001).

On the third day in the S-NO study, the following trend was observed. Statistically significant differences were revealed by comparing the data obtained at the 3rd and the end of the 1st day in group 2 at the level of significance p <0,05. Comparing with intact animals, it was found that at this stage, the level of S-NO decreased by 68.3% (p <0.001). Aforementioned reaffirms that the peritonitis development negatively affects on vessels state. And the deterioration of vasodilatation worsens the disease pathogenesis. In the third group at this stage, positive dynamics was found at the level of significance p <0.01 compared to the previous stage. The level of S-NO in this group was 31.7% lower compared to intact (p <0.001), and compared to 2nd group (peritonitis without correction), the level of the indicator was higher by 115.7% (p <0.001). In the fourth group, which received a three-component correction - in comparison with the previous stage, dynamics at the same level of statistical significance as in the third group. Value of the investigated indicator at this stage is more pronounced approaching the intact animals values - it is lower by 15.2% (p <0.001) compared with the intact group. Comparing with the data of group number 2 is established effectiveness of the proposed correction - the level of S-NO at 167.8% (p <0.001) exceeds the value of this indicator in the group without correction. Also, it was revealed more pronounced efficiency of the three-component correction in comparison with the two-component at the level of

statistical significance p <0.01, which testifies to the correctness of the chosen tactics of the pathological process correction.

We also investigated changes in vasodilation potential at a more distant stage - at the 21st day after fecal peritonitis modeling. Animals, which have not been corrected by the simulated pathological process, have not survived to this stage. In the group in which the pathological process was corrected by antibiotic therapy and remediation of the chlorhexidine solution, positive dynamics was established in comparison with the results obtained for the third day (p <0.001). Also, less pronounced differences between the data of this group and intact animals - if third day the difference was 31.7% (p <0.001), then at this stage - already 23, 4%. (p <0,001) However, it should be noted that differences (at the level of significance p <0,001) of the level of S-NO from intact animals still remain at the 21st day of the study, which indicates the need for correction of pathological changes of the endothelium in peritonitis. In 4th group was held correction of endothelial dysfunction with antibiotic therapy and chlorhexidine debridement was found better results than that of the group that did not receive L-arginine (identified differences at significance level p <0.001). There is also a positive dynamics compared with the data of the third day (p <0.001), which indicates the cumulative effect of using a solution of arginine. Attention is drawn to the fact that the results of the S-NO reserch in this group (group № 4) at the 21st day indicate a recovery of its level to the values of the norm (the differences between the groups of №1 - intact and the group number 4 is only 3, 1%).

Table 2 presents the results of an endothelin-1 research, which is one of the commonly accepted markers of endothelial dysfunction. An increase in the concentration of this indicator indicates the involvement of pathological mechanisms for increasing vasoconstriction.

At the beginning of the first day, in the endothelin-1 level, was marked increase (on average 65.4%) of this indicator in all groups in which animals were modeled by fecal peritonitis (comparing with the data of intact animals, statistical differences were established at the significance level p <0.001). Comparing the data of the groups with the experimental pathology, no differences were found between them, which is a positive point, indicating their homogeneity and suitability for further study.

Table 2

Vasodilatative potential dynamics in animals that was simulated by fecal peritonitis and analysis of its correction methods effectiveness on the 1st, 3rd and 21st day of the experiment

Group /day	1st day beginning	1st day ending	3rd day	21st day
1st group	3,01±0,08	3,03±0,10	3,02±0,11	3,02±0,08
2nd group	4,99±0,07	6,34±0,07	7,04±0,07	animals do not survive
3rd group	4,97±0,06	6,00±0,07	5,61±0,09	4,01±0,12
4th group	4,98±0,05	5,24±0,09	4,35±0,08	3,31±0,08

At the end of the first day, the picture of the pathological process has changed somewhat. In the group in which the pathological process was modeled without further correction (Group №2) was detected an even more pronounced increase in endothelin-1 in comparison with the data obtained at the beginning of the first day ($p < 0.001$). The increase of the pathological vasoconstriction against the background of uncontrolled peritonitis development also suggests that at this stage, compared with the results of intact animals, the level of the studied indicator increased by 109.2%. In the third group, in which the pathological process was modified by means of antibiotic therapy and debridement with a chlorhexidine solution, was observed significant increase in the marker of vasoconstriction in comparison with the previous stage ($p < 0.001$), but its level was 5.4% lower in this group in compared with group number 2 ($p < 0.001$). Comparing with the data of intact animals, the level of endothelin-1 at the end of the first day increased by 98%. In the group in which the pathological process was corrected by antibiotic therapy and the debridement of chlorhexidine in the complex with the use of a nitric oxide donor solution, the increase in endothelin-1 levels was less pronounced: compared with the data obtained at the beginning of the first day, an increase was found only by 5.2% ($p < 0.05$). In comparison with intact animals, an increase was set at 72.9% ($p < 0.001$). But it should be noted that the three-component correction is more effective compared with the data of the group without the involvement of L-arginine (p

<0,001). It was also found that in group №4 the level of the studied indicator by 17,4% (p <0,001) is lower compared with the data of group №2.

For the third day the following results are obtained. In the group without correction at this stage, was observed pronounced deterioration in vasodilation-vasoconstrictor potential balance - pathological vasoconstriction prevalence (p <0.01). Compared with intact animals, the level of endothelin-1 increased by 133.1%. In the group receiving two-component correction, the reduction of pathological vasoconstriction was detected by 20.3% (p <0.01) compared with the previous stage. It was found that the level of this indicator at this stage was higher by 85.8% (p <0.001) than in intact animals (98% difference at the preceding stage). Differences in comparison with group results without correction are also very significant (p <0.001). In the fourth group was detected marked decrease in endothelin-1 by 17% (p <0.001) compared with the previous stage. Level of this indicator by 44% exceeds the value of group № 1. Comparing with the data of the group without correction, it was found that the index of vasoconstriction is lower by 38.2%. It was also found that the three-component correction is more effective than the two-component (p <0.001).

Animals of the second group, which did not correct the pathological process, did not survive until the 21st day. In the third group, positive dynamics were detected in comparison with the previous stage: reduction of endothelin-1 level was established at the level of significance p <0.001. But comparing with the data of the control group, differences were also found at the level of significance p <0,001 - the level of the studied indicator increased by 32,8%. In the fourth group, improvement was detected by 23.9% compared with the previous stage (p <0.001). Attention is drawn to the fact that at the 21st day endothelin-1 level as close as possible to the values of the norm - its level is only 9.6% higher than the value of intact animals (p <0.05). This indicates the need to attract a nitric oxide donor to the means of correction of peritonitis and its consequences.

Conclusions:

1. It has been proved that the development of experimental fecal peritonitis pathologically affects the functional vessels state at each of the stages of the study.

2. We established the weakening of the vasodilatative process against the background of peritonitis development, as evidenced by a decrease in the content of S-nitrosothiols.

3. As a result of the research, it has been proved that in the peritonitis pathogenesis vasoconstrictor vessels potential is significantly increased, as evidenced by a significant increase in endothelin-1 in animals that have been modeled by fecal peritonitis.

4. Nitric oxide donor efficiency has been proved as part of complex peritonitis correction and endothelial dysfunction as its complication.

5. The most pronounced positive effect was detected at the 21st day, which indicates the expediency of long-term use of L-arginine as a remedy for correction.

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