CLINICAL EFFICIENCY AND TOLERABILITY OF THE NEW DETOXIFYING AGENT"NEOREODEZ" IN PATIENTS WITH ACUTE PERITONITIS

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Annotation. *In a clinical study, it has been shown that the use of drug "Neoreodez", a solution for infusion of 200 ml and 400 ml as a component of basic therapy significantly increases the effectiveness of treatment in patients with acute peritonitis compared with the administration of basic therapy only. Registered efficacy in the main group of patients receiving Neoreodez was 94.2%, that is significantly higher than the control group - 52.0%. Thus, the hypothesis regarding the excess of treatment efficacy in the main group of patients as compared to the control group has been confirmed.*

Key words: *clinical efficacy, acute peritonitis, detoxifying therapy, "Neoreodez".*

Peritonitis is one of the most severe complications of diseases and damages of the abdominal cavity and it is steadily occupying a leading place in the structure of surgical lethality, which varies from 1.3% at local to 80% with disseminated purulent peritonitis (DP), with the toxic and terminal stage of DP - 25-30%, in case of progression of multiple organ failure syndrome - 60-87% of cases [1, 2, 3]. The use of modern achievements of intensive care, aggressive surgical tactics, introduction of minimally invasive interventional diagnostic and therapeutic technologies for the treatment of patients with hypertension did not significantly improve the results, that supports the interest of scientists in the development of innovative principles for treatment of patients with DP [4, 5].

For today, a new innovative solution "Neoreodez" has been synthesized, which represents a 0.06% solution of sodium hypochlorite stabilized with taurine (2-aminomethansulfonic acid) with the reproduction of N-chlorateurin (N-chloro-2-aminomethansulfonic acid), stable in vitro but unstable (disassociated with sodium hypochlorite and taurine) in vivo [6].

The presented medicinal product contributes to reducing the toxic and metabolic load on the organs of excretion and detoxification, and also corrects metabolic processes, which can significantly reduce the severity of endotoxicosis and avoid its chronicity and related complications. Also, the drug exhibits a moderate antimicrobial action in vitro, stimulates reparative processes in the body, while not exposing the irritant to the skin and mucous membranes. In addition, the solution "Neoreodez" shows an expressive anti-aggregate activity, while not causing changes in the gas transport function and shifts of acid-alkaline state in the blood [7].

The mechanism of therapeutic action of the drug is due to the reproduction of taurine

chloramine, namely, taurine captures chlorine from hypochloric acid, thus becoming non-aggressive antioxidant, which does not damage the white blood cells and endothelium. In addition, it is believed that taurine chloramine suppresses inflammatory signals through the nucleic factor (NFkappa b), which contributes to a clear cytoprotective effect [9].

The purpose of this work was to establish the clinical efficacy of the preparation "Neoreodez", which is used on the background of basic therapy in patients with acute peritonitis compared with the group of patients receiving baseline therapy only.

Materials and methods of research. Research design - opened, randomized comparative, parallel.

104 patients with acute peritonitis were included in the clinical trial. Patients were divided into main (52 patients) and control group (52 patients) on the basis of the randomization method in the 1: 1 ratio. All patients received detoxification therapy solutions of crystalloid, reamberin, and lotrene on the background of specific treatment (laparotomy, sanation, drainage of the abdominal cavity, antibiotic therapy). In addition, the patients of the main group assigned a test solution "Neoreodez" within 3 days.

The efficacy of treatment was evaluated by changing of the average weight molecules level after 3 days of therapy compared to the original state. The treatment was determined to be effective if the level of the average mass molecules declined by 35% from the original level and more.

The safety of the drug was assessed on the basis of monitoring data on the patient's condition, frequency and nature of adverse reactions, laboratory data, assessment of the subjective state of the patient [8].

In the course of the study, known clinical and statistical methods were used: quantitative analysis, variation statistics, and comparison of the effectiveness between groups [10].

Research results. Patients aged 19 to 65 years were included in the clinical trial. Distribution of patients by age categories is presented in Table 1.

Table 1

Distribution of patients by age

Age,	Main group		Control group	
	n	%	n	%
18-30	5	9,6	4	7,7
31-40	9	17,3	10	19,2
41-50	13	25,0	15	28,8
51-65	25	48,1	23	44,2
Total	52	100,0	52	100,0

To assess the homogeneity of groups by age, a hypothesis was checked regarding the normal distribution of the relevant data in each group using the Shapiro-Wilk criterion. According to the results of this test, the data for the "Age" indicator were normally

distributed in both groups, therefore, for comparison of groups by age the Student criterion was used according to the significance level of 0.05. Consequently, according to the results of the groups comparison by age, one can conclude that the experimental groups were statistically homogeneous.

There were 64 men and 40 women among the patients included in the clinical trial. Distribution of patients by sex is presented in Table. 2. For the evaluation of gender homogeneity, the Chi-squared Person criterion was used, taking into account the correction for continuity.

Table 2

Distribution of patients by sex

Sex	Main group		Control group		Total	
	n	%	n	%	n	%
Male	31	59,6	33	63,5	64	61,5
Female	21	40,4	19	36,5	40	38,5
Total	52	100,0	52	100,0	104	100,0

Clinical trials included patients urgently taken to a clinic with manifestations of acute abdomen, and also operated earlier in the planned order, which subsequently developed peritonitis.

Distribution of patients by the nature of acute peritonitis main cause by methods of descriptive statistics (frequency and fraction in %) are presented in Table. 3

Table 3

Distribution of patients by the nature of the underlying disease

Disease	Main group		Control group		Total	
	n	%	n	%	n	%
Destructive appendicitis	24	46,2	25	48,1	49	47,1
Destructive cholecystitis	9	17,3	10	19,2	19	18,3
Perforation of the stomach and duodenum	6	11,5	7	13,5	13	12,5
Perforation of the small intestine	2	3,8	-	-	2	1,9
Postoperative peritonitis	5	9,6	4	7,7	9	8,7
Penetrating abdominal wounds	2	3,8	3	5,8	5	4,8
Purulent-inflammatory diseases of the uterus and appendages	1	1,9	2	3,8	3	2,9
Purulent-inflammatory complications of pancreatic necrosis	2	3,8	1	1,9	3	2,9
Perforation of the large intestine	1	1,0	-	-	1	1,0
Total	52	100,0	52	100,0	104	100,0

The duration of peritonitis symptoms before the patient was admitted to the clinic was from 3 to 35 hours. Postoperative peritonitis (general causes of anastomosis failure, inadequate rehabilitation of the abdominal cavity, inadequate hemostasis, intraoperative tissue injury) developed from 24 to 72 hours after surgical intervention.

Also, an assessment of the peritonitis clinical signs severity (namely, symptoms of peritoneum irritation, signs of intestine paresis and the amount of fluid from the peritoneal cavity) was evaluated. The degree of expressiveness for these signs was evaluated on the following scale: 0 - absence of signs, 1 - insignificant degree of expressiveness, 2 - moderate degree of expressiveness, 3 - significant degree of expressiveness (also the volume of fluid was taken into account: 0 is absence, 1 - up to 100 ml, 2 - 100-1000 ml, 3 - more than 1000 ml and 0 - no separation, 1 - serous separation, 2 - serous purulent, 3 - purulent).

The method of the average mass molecule (AMM) determination was used to evaluate the degree of endogenous intoxication. The estimation was carried out with spectrometry in different modes of X = 254 nm and X = 280 nm. Output data for the estimation of MSM by descriptive statistics are presented in Table. 4.

Table 4

Analysis of the initial homogeneity of the groups according to the estimation of the medium-molecular peptides level by the methods of descriptive statistics

Index	Group	N	Arithmetic mean	Median	Standard deviation	Min	Max
AMM when X = 254 nm	Main	52	0,635	0,629	0,019	0,600	0,670
	Control	52	0,651	0,633	0,022	0,610	0,680
AMM when X = 280 nm	Main	52	0,879	0,867	0,019	0,840	0,910
	Control	52	0,890	0,892	0,026	0,830	0,920

Of the patients included in the study, 52 patients in the main group and 50 patients in the control group completed all procedures according to the protocol. 2 patients in the control group were eliminated from the study (1 patient was transferred to the emergency ward with the increasing polyorganic insufficiency phenomena and a relaparotomy was performed due to purulent complications in 1 patient).

In all other cases, the postoperative process proceeded steadily. As a baseline therapy, all patient were taking parenteral antibiotics, taking into account the sensitivity of the microflora, analgesics, anticoagulants and prokinetics if necessary. As a detoxification therapy patients were given crystalloids, reamberine 400 ml / per 1 time per day, DEK 400 ml / per 1 time a day, Lotr - 200 ml 1 time a day. In addition, the test patients included in the main group received the study drug Neoreodez, a solution for infusion of 400 ml at a concentration of NaCl 600 mg / l in glass bottles produced by the state enterprise "Cherkasy-Pharma". The drug was administered intravenously, drip, slowly at a rate of 20-40 dpi / min (approximately 3-3.5 ml / min) per 400 ml twice daily in 12

hours for 3 days.

As a result of treatment, at the end of 3 days of therapy a re-assessment of the of the average mass molecules level was conducted according to the protocol of the clinical study (Table 5).

Table 5

Estimation of the relative change of the AMM level in dynamics (in relation to the baseline), %

Index	Group	Degree of relative changes
AMM when X = 254 nm	Main	-44,25 %
	Control	-29,11 %
AMM when X = 280 nm	Main	- 46,08 %
	Control	-32,25 %

Thus, at the end of the treatment course, 49 (94.2%) patients in the main group and 26 (52.0%) patients in the control group managed to reduce the level of AMM at X = 254 nm and the AMM level at X = 280 nm by 35% and compared to the original rate.

During the clinical study, definition of the drugs effectiveness was studied simultaneously with their tolerability examination. For this purpose, the data of the objective and laboratory examination of patients were analyzed in the dynamics, taking into account the appearance of subjective complaints of patients during the treatment.

Daily control of the general well-being of the patients was carried out during the study. In all patients of both groups, gradual decrease in the severity of endogenous intoxication indicators - tachycardia, hyperthermia, tachypnea was determined from 1-2 days of treatment. Initially reduced blood pressure gradually normalized. The positive dynamics of the estimated indicators was somewhat better in the main group of subjects. Thus, the phenomenon of hyperthermia was determined after 3 days of treatment in 13 subjects of the main group and in 22 patients of the control group. The heart rate decreased significantly without achieving normal values.

There were no adverse reactions that could be associated with the administration of the investigated drugs during the course of the clinical study. There were no local and general reactions immediately after the introduction of the drug "Neoreodez" and in the subsequent period at every-day skin examination. The skin and visible mucous membranes remained clean, allergic manifestations were not observed. No cases of postinfusional phlebitis have been observed. No cases of peripheral edema appearance were observed. In some cases, hyperthermia was determined. All cases of hyperthermia were due to post-traumatic inflammatory reaction, in no single case, the temperature response to the administration of the studied drug was noted. Vesicular breathing was determined in the auscultation of the lungs in all patients included in the study, initially accelerated and superficial breathing 2-3 days after beginning of therapy normalized. Auscultation of the heart revealed no significant changes in comparison with the baseline

data; in some cases, extrasystole and respiratory arrhythmia were observed.

During the study, there was no adverse effect on blood pressure, heart rate and respiratory rate, and these rates gradually normalized. In several cases, episodes of arterial hypertension associated with concomitant hypertension were determined. Laboratory indices have not undergone any negative changes in any one case.

Conclusions. Thus, the use of the drug "Neoreodez", a solution for infusion of 200 ml and 400 ml in glass bottles produced by the State Enterprise "Cherkasy-Pharma" as part of basic therapy significantly increases the effectiveness of treatment in patients with acute peritonitis compared with the use of basic therapy alone. Thereby, the effectiveness in the main group of subjects receiving the drug Neoreodez was 94.2%, which is significantly higher than the indicator of effectiveness in the control group - 52.0%. So, the hypothesis about the superiority of treatment in the main group of subjects compared to the control one is confirmed.

Prospects for further research. The next stage of our study is investigation of the clinical and economic rationale for the treatment of acute peritonitis with the innovative detoxifying agent "Neoreodez".

References:

1. Polianskyi. I.Iu. The choice of therapeutic tactics for various forms of acute peritonitis depending on genetically determined disorders of immunological reactivity / I.Iu. Polianskyi , P.V. Moroz // Arkhiv klinichnoi medytsyny. – 2014. - №2 (20). – P.96 – 97

2. Polovyi V.P. Estimation and prediction of severity of the course of the early postoperative period in patients with acute surgical diseases of the abdominal cavity, complicated by peritonitis / V.P. Polovyi, R.I.Sydorchuk, S.M. Vozniuk, A.S.Palianytsia // Ukrainskyi Zhurnal Khirurhii. – 2013. - № 2 (21). – P. 80 – 84

3. Ruttinger D. Acute prognosis of critically ill patients with secondary peritonitis: the impact of the number of surgical revisions and of the duration of surgical therapy / D. Ruttinger, D. Kuppinger, M. Holzwimmer, S. Zander et al. // Am. J. Surg. – 2012. – N 204 (1). – P. 28 – 36.

4. Muntian S.O., Kryshen V.P., Liashchenko P.V. Transmembrane dialysis in the complex treatment of surgical patients with peritonitis // Medychni perspektyvy. – 2012. – Tom 17, № 1, chastyna 2. – P. 131 – 135.

5. Bereznytskyi Ya.S. Organization standards and professionally oriented protocols for the provision of medical care to patients with urgent surgical abdominal pathology / Ya.S. Bereznytskyi, P.D. Fomin. – Kyiv : Doktor – media, 2010. – 470 p.

6. Patent №2488382, RU, MPK A61K. Detoxification infusion solution "Neoreodez" / Yvanov V.K., Bylenkyi H.Z., Snezhko Z.Y.; - patentoobladatel Yvanov V.K., Belenkyi H.Z., Snezhko Z.Y. – zaiavl. 07.02.12; opubl. 27.07.13.

7. Das J., Vasan V., Sil P.C. Taurine exerts hypoglycemic effect in alloxan-induced diabetic rats, improves insulin-mediated glucose transport signaling pathway in heart

and ameliorates cardiac oxidative stress and apoptosis// Toxicol. Appl. Pharmacol. – 2012. - №258 (2). - P. 296 – 308.

8. Unified clinical protocol for secondary (specialized) and tertiary (highly specialized) medical care. Prevention, diagnosis and treatment of infections associated with peritoneal dialysis / Nakaz № 89 vid 11 liutoho 2016 r.

9. Bilenkyi H.Z. Effect of Intravenous Administration of the "Neorezoleum" solution on the course of Experimental Endotoxicosis and Evaluation of the Regenerative Properties of the Agent under Applied Applications / V.I. Mamchur, S.M. Dronov, H.Z. Bilenkyi // Medychni perspektyvy. – 2016. - №3. – P. 13-17.

10. Lapach S.N., Chubenko A.V., Babych P.N. Statistical methods in biomedical research using EXCEL. – K.: «Moryon», 2001. – 408 p.