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Effect of Antioxidant Therapy on Endogenous Intoxication Mechanism in Patients with Intestinal Obstruction and at Experiment

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ABSTRACT

The relationship between the level of indicators of lipid peroxidation (LPO), the level of middle weight molecules (MWM), and changes in the structure of the liver and the impact on them Reamberin solution in 102 patients with acute intestinal obstruction (AIO) and model of the obstruction of the small intestine (SIO) in 40 Vietnamese pigs were analyzed. During AIO we founded of increase of lipid peroxidation products in serum, MWM, and decreased ceruloplasmin securities, significant changes in the liver (destruction of grained and smooth endoplasmic reticulum, mitochondria, nuclei of hepatocytes). Surgical resolution of AIO leads to further deterioration of the temporary structure of the liver, increasing MWM, and indices of lipid peroxidation and decrease of ceruloplasmin levels. Use of antioxidant therapy in the postoperative period promotes reparative processes in hepatocytes and leads to normalization of serum parameters of endogenous intoxication and helps reduce of postoperative mortality.

Keywords: Intestinal obstruction, liver, endogeneous intoxication, lipid peroxidation, Reamberin.

1. Introduction

The problem of the treatment of acute intestinal obstruction (AIO) remains one of the most vital in emergency surgery, as evidenced by high rates of postoperative complications and mortality that ranged according 38,6-80% 25-46,1%^[1]. Leading role in the formation of a critical state in AIO plays an intense increase of endogenous intoxication (EI), which involves a variety of components of metabolic disorders and is a major cause of organ failure with inhibition of homeostasis' autoregulation to a level not compatible with life^[1]. AIO accompanied of a delay in the passage of intestinal contents, increase the number of microorganisms and changing their nature, causing the formation and admission of highly toxic substances in the blood, disorders of metabolic homeostasis in the background of intensifying endotoxemia.

Metabolic mechanisms that neutralize toxic substances include several groups of reactions, each of which is represented by the liver at a high level. Among them, attaches great importance to the conjugation of reactive metabolites and hydrophilic compounds and antioxidant protection^[1, 2].

The aim of study was study the effect of Reamberin solution who has antioxidant and hepatoprotective effect on indirect signs of EI and morphofunctional state of the liver in patients with AIO and during dynamic of experimental model of acute small intestine obstruction.

2. Material and Methods. We analyzed of 232 patients, including 202 patients with AIO aged 30 to 80 years who were hospitalized in Central City Hospital of Ivano-Frankivsk, Ukraine. Among the patients were 98 men (48.5%), 104 women (51.5%) and 30 healthy individuals. Reasons of AIO were: strangulated hernia - 56 (27.7%) patients, including postoperative hernia - 22 (10.8%) patients; strangulating ileus - 44 (21.7%) patients, adhesive ileus-63 (31.1%) patients, obstructive ileus - 17 (8.4%) patients.

We investigated of clinical, biochemical and morphological parameters of the functional state of resected section of the small intestine in the preoperative period and on the 1-st, 5-th and 14-th postoperative day. The material for the study (small intestine of 13 patients) was taken during the resection of the small intestine. As a control, we used of the small intestine fragments, which were taken at autopsy in 9 patients after 3-9 hours of death from diseases not associated with disorders of the gastrointestinal tract.

The patients were divided into two groups: basic – 102 persons, and control - 100 patients. With the aim to correct of metabolic disorders in the basic group patients we used of Reamberin

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("POLISAN") solution 400-800 ml (depending on severity), 2 times a day, i/v with the speed of 90 dr /Min. prior to surgery and during the first 5 days of the postoperative period. Reamberin has antioxidant action, causing a positive effect on aerobic processes in the cell, reducing the production of free radicals and restoring the energy potential of cells [2]. The drug is licensed for use by State Pharmacology Center of MPH of Ukraine.

The experimental studies were conducted in the vivarium of Ternopil State Medical University named after I. Gorbachevsky during 2011-2012 years on 40 Vietnamese breed pigs weighing 15-25 kg. All interventions, care and euthanasia of animals was carried out in compliance with the substantive provisions of the Convention on the protection of vertebrate animals used in experiments and other scientific purposes from 18.03.1986; the EU Directive № 609 from 24.11.1986, the order of Ministry of Health of Ukraine No 690 from 23.09.2009.

Surgical restoration of patency of the intestine was carried out at 12, 24, 36, 48 and 72 hours after modeling disease by resection of the affected area overlapping interintestinal anastomosis side-to-side. Anesthesia and surgical procedures performed euthanasia by i.v. administration of thiopental sodium at a dose calculated on body weight of the animal

after preliminary sedation. In the postoperative period, the animals of II group additionally accepted of treatment by Reamberin solution i.v. administered for 5 days twice a day, at a rate of 10 ml per kg body weight. To assess the state of the liver in the dynamics of the flow and treatment of diseases studied morphological and ultrathin body structure, the degree of endogenous intoxication and the balance of pro-and antioxidant systems by identifying securities. As a control serum were ones from healthy and intact animals.

Statistical analysis of the results was performed using mathematical program-complex for computer based on Microsoft Windows 1985-2005, as well as programs for statistical analysis Anlys + Soft, 2007. Verification of the distribution of samples for normality was performed using criterion Shapiro-Wilk. To test the hypothesis of equality of averages using Student's t-test, Fisher normally distributed samples and criteria Wilcoxon-Mann-Whitney for samples whose distribution is different from the normal.

3. Results and Discussion

It was established that intensive growth of endotoxemia in the body of patients and animals on the background of a violation of the intestinal passage depends on the length AOI (see Table 1).

Table 1: The values of oxidative-antioxidative balance and EI in patients with AIO and in experimental animals

Groups	Stages of Investig.	Values			
		CP, IU	MWM, IU	DC, IU	MDA, mcmol/l
A) Patients with AIO					
Norma (control n=8)		29,12±1,04	0,24±0,04	0,38±0,04	3,69±0,16
AIO before treatment		*25,47±0,85	**0,46±0,05	**0,53±0,04	***5,22±0,39
After treatment without Reamberin	1-2 days	***23,33±1,02	***0,54±0,06	***0,68±0,07	***5,72±0,61
	5-6 days	26,68±2,05	***0,50±0,02	***0,78±0,03	**101±0,52
	11-12 days	***22,29±1,33	***0,54±0,04	**0,57±0,05	***4,86±0,23
After treatment with Reamberin	1-2 days	23,96±0,95	0,69±0,03	0,64±0,10	5,51±0,64
	5-6 days	°34,45±1,15	°0,44±0,03	°0,60±0,04	°5,12±0,25
	11-12 days	°28,13±1,77	°0,45±0,03	°0,40±0,02	°3,75±0,30
B) Experimental animals					
Hopma (n=10)		36,34±1,19	0,20±0,01	0,33±0,02	2,46±0,14
II (n=20) without Reamberin	12	*89,74±2,31	**0,29±0,02	0,40±0,06	**4,320,62
	24	***47,86±1,91	***0,27±0,03	*0,52±0,06	*3,45±0,41
	36	34,26±1,37	***0,33±0,03	***0,75±0,10	***4,56±0,40
	48	***25,28±1,01	***0,33±0,03	**0,81±0,12	***5,76±0,47
	72	***21,09±1,24	0,46±0,06	***0,52±0,04	*3,05±0,15
IV (n=20) with Reamberin	12	34,97±2,31	0,29±0,04	0,40±0,06	3,64±0,43
	24	°54,70±1,56	0,24±0,07	0,50±0,06	3,20±0,52
	36	°°40,52±1,14	°°0,26±0,01	°°°0,47±0,03	3,56±0,33
	48	°°33,51±1,46	0,24±0,04	°0,50±0,05	°4,51±0,28
	72	°°26,75±0,72	°0,34±0,01	0,56±0,08	°3,59±0,18

Remarks: *P<0,05; **P<0,01; ***P<0,001 – difference compared norma
 °P<0,05; °°P<0,01, °°°P<0,001– difference compared type of treatment

In the clinic of AOI and experimental model of AOI we revealed the same trend of changes of oxidation-antioxidant balance, EI, depending on which observations were carried out against the background.

The table shows that the activity of CP in the serum of patients with AIO before treatment, and especially in the experiment (II group) compared with control decreases with further increase and subsequent decrease to a critical level at 11-12 days after treatment patients and 72 hours of observations in experiment (III group). It is believed that this dynamic of CP is the result of increased using of this enzyme due to the increase in the substrate of its action with further increase in synthesis in the liver "acute phase proteins". Progressive reduction of the CP level, which occurred in the course of AIO (II group) without the use of Reamberin is a bad prognostic sign. After surgery of AIO the CP level had a slight tendency to normalization.

The CP level in animals of III group in some periods exceeding for 6-7 IU compared to the second group of animals, and its possible decline lower than control was observed only after 72 hours of AIO. After surgery of AIO on background of Reamberin its activity in the serum goes to the normal range.

The research of primary (DC) and secondary products of lipid peroxidation (MDA) in serum indicates of lipid peroxidation process intensification during the course of AIO surgery. Toxicity of blood serum correlated with the level of lipid peroxidation products, a manifestation of which is the initiation of free radical oxidation in target organs, especially in the liver^[3]. The levels of DC and MDA at period of clinical recovery were at a level higher than normal in patients and in experiment.

Apply for therapeutic purposes of Reamberin caused to reduce of lipid peroxidation intensity in AIO.

We observed the typical changes in the liver in cases of AIO patients as in the experiment and are approximately the same direction. In 13 persons autopsy who died after surgery for AIO, was noted enlargement of the central veins and capillaries, tissue swelling, dyscomplectation of beams of hepatocytes, which are observed in the cytoplasm of all kinds of degenerative changes and focal necrosis surrounded by histio-lymphocytic infiltrates.

In 5 patients with AIO we studied of ultra-structure of the liver. Established that profound changes in the liver parenchyma correlated with disease stage and duration of ileus and suggest of necrobiotic changes development in all components of the body. During electronic microscopy we saw the large spaces in the cytoplasm of hepatocytes, which occasionally there remains organelles and thin-granular substance and NES are missing. ZES as short tubules often extended, scattered in locations organelles remaining. The nuclei of hepatocytes are in a state of picnosis with density of parietal component. Mitochondria are with loss of structure and space Disse are full destroyed. Necrosis also touched of endothelial cells and Kupfer' sinusoids.

In experimental animals the morphological changes and ultra-structure of the liver have a lot in common with those of AIO patients. At laparotomy the liver of animals responded flushing central venous and capillar-stasis, and dyscomplectation of hepatic beams, degenerative changes in the hepatocytes, which are stabilized by 4-5 days of the experiment. Within 24 hours of the experiment, mitochondria tend to swell with partial lysis of cristae. ZES most disorganized cells and by single small tubules, reducing available until the disappearance of the NES, Golgi apparatus obsolete, Disse space narrowed sharply with symptoms of gyalinosis. Liver sinusoids filled with blood elements. After 48 hours the degenerative changes in hepatocytes were grow. The nuclei of cells are with different intussusception, others - swollen, almost empty. Most of mitochondria in cells dramatically increased in size from almost absent of cristae, and part cell they look almost empty. ZES presented be degraded small tubules. Most of the cytoplasm is empty or filled with fragments of some organelles. NES and Golgi apparatus so atrophied and detection of their structure were not possible. Much of the hepatocytes in a state of necrobiosis and some are necrotic. Duting additional use of Reamberin solution described changes were expressed in a somewhat lesser degree.

Thru 72 hours after restoration of patency of the intestine without prescription solution Reamberin ultrathin structure elements liver compared with data for surgical treatment worsened and only in isolated groups of parenchymal cells is part of their recovery. In the case of inclusion of Reamberin for the complex treatment during the same period a normalization of the fine structure of the majority of hepatocytes were observed.

The data of morpho-dynamics and ultra-structure of the liver in patients with AIO corresponded to the so-called nonspecific reactive hepatitis, the extent of which increases with increasing levels of EI products.

4. Conclusions

1. We established the correlation between stages of pathological morphological changes of liver at AIO and intensification of EI in human body and during animal experiment.
2. Additional use of antioxidant and hepatoprotective therapy caused of intensive decrease of pathological morphology and functional changes in liver and level of endogenous intoxication.

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