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GENETIC TRIGGERS AND NEUROHUMORAL MESSENGERS OF POSTOPERATIVE INTESTINAL PARESIS, ITS VALUE IN PREDICTION, PREVENTION AND TREATMENT

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Abstract

The aim of research: to study the causes and mechanisms of postoperative intestinal paresis on the base of assessment of genetic determinism of neurohormonal processes which regulate the contractile ability of the intestines, to determine their role for the choice of treatment tactics.

The study presents data about connection between variants of SERT gene, which regulates the reuptake of serotonin, and its concentration in blood plasma and the probability of occurrence of postoperative intestinal paresis. This made it possible not only to predict the occurrence of postoperative disorders of motor-evacuation function of the intestines, but also to improve the algorithms of prevention and pathogenetic based treatment.

Keywords: postoperative paresis, trigger, serotonin, SERT.

1. Introduction

Disorders of contractile ability of the intestine after surgery on the hollow digestive organs are one of the most severe complications in planned and emergency surgery. The occurrence of postoperative intestinal paresis leads to development of different complications that reduce efficiency of patient treatment and require surgical interventions repeating and complex of measures which are directed at restoring the contractile ability of the intestines.

However, the diagnosis of postoperative intestinal paresis has low informative value and existing ways of its prevention are not effective enough. Therefore, the study of the new development mechanisms of postoperative intestinal motility disorders, including genetic and neurohormonal, is one of the important tasks of modern surgery, which will improve the results of planned and urgent surgical interventions [1–7].

2. Material and Methods

The study involved 112 patients who were operated on the hollow digestive organs. They formed 2 groups. The first group included 54 patients whose motor-evacuation function of the intestines was restored during the three days after surgical interventions. The second group included 58 patients with signs of postoperative paretic intestinal obstruction. Patients during pre- and postoperative period were examined by means of clinical, laboratory, genetic, instrumental methods and phonoenterographic study by developed technique. Statistical analysis of the results was conducted by the definition of Student and Fisher criteria and the coefficient of probability.

3. Results

The diagnosis of the postoperative intestinal paresis was confirmed on the base of absence of defecation and gases elimination after third day of postoperative period and by means of interpretation of phonoenterographic parameters.

Phonoenterographic study (**Fig. 1**) registered clinically significant differences between peristaltic parameters in patients of both groups during the three days after surgery.

Phonoenterographic peristaltic parameters of the first group patients during postoperative period were lower than normal, especially the amount of peristaltic waves, its average value of time, maximum amplitude and increasing time, but its dynamics had tendency to increasing.

Phonoenterographic peristaltic parameters of the second group patients in the postoperative period were significantly lower than in patients of first group, particularly the power index of peristaltic waves the root mean square of contractions in peristaltic period.

For evaluating of the neuroendocrine mechanisms which regulate the intestinal motility we studied the level of serotonin in the blood plasma in patients of both groups. It is known that serotonin acts on receptors in the postsynaptic membrane causing the contraction of the bowel muscular layer [8–11] and causes the peristalsis [12–14].

The results of our research showed (**Fig. 2**) that patients with postoperative

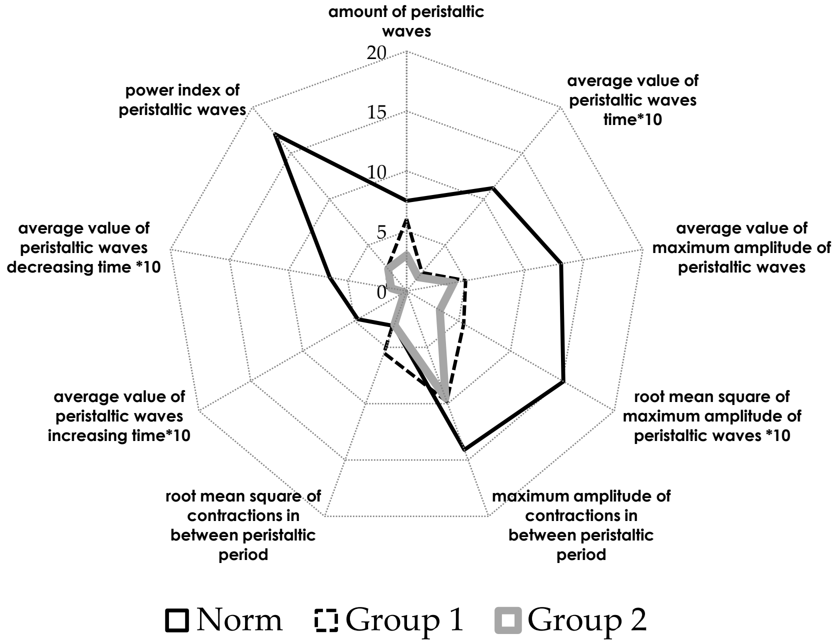

Fig. 1. The comparison of phonoenterographic parameters in examined patients

This suggests that the low plasma concentration of serotonin is one of the leading causes and the trigger of contractile ability disorders of the intestines in the postoperative period.

As it is known, the concentration of serotonin in the blood plasma and its distribution in tissues are regulated by transporter-protein that provides the reuptake of serotonin from the synaptic cleft into presynaptic vesicles. The synthesis of this transporter-protein is regulated by SERT gene which polymorphism determines the activity of serotonin reuptake and its concentration in blood plasma. There are three variants of genotype SERT: SS, LS, LL [15–16].

We carried out genetic research that helped to reveal that among patients whose motor-evacuation function of intestines was restored during 2–3 days in postoperative period LL-genotype was observed in 44 (81.49 %) cases, and SS variant – in 4 (7.40 %) and LS variant – 6 (11.11 %) cases (**Fig. 3**).

Among the patients with postoperative intestinal paresis SS-genotype have met in 45 cases (77.6 %), LS-genotype have revealed in 7 cases (12.06 %) and LL-genotype – in 6 cases (10,34 %).

Such distribution of SERT gene variants in patients of studied groups indicates that the most favorable for adequate restoration of intestinal contractile ability after surgery on intestines is LL-genotype, which is characterized by a high concentration of serotonin in the vesicles of presynaptic membrane. It provides adequate muscle contraction of intestinal wall. Than LS- and especially SS-genotype of SERT gene due to disorder of the reuptake of serotonin and its low concentration in the presynaptic vesicles reduces contractile ability of the intestines. This became the basis for the development of prediction algorithms of different variants of postoperative period course in patients operated on hollow organs of the digestive system. When LS and especially SS variant of SERT gene are present in patients we predict unfavorable course of postoperative period with probability of development of postoperative ileus.

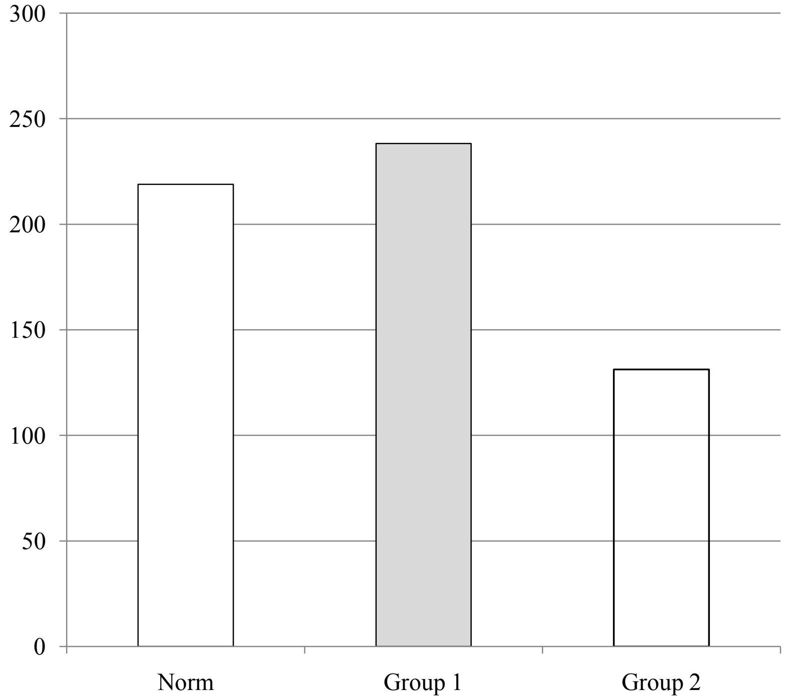

Fig. 2. The serotonin concentration in blood plasma of examined patients (ng/ml) intestinal paresis had significantly lower serotonin level in blood plasma (131,24±16,36 ng/ml) than patients without postoperative disorders of motor-evacuation function of the intestines (238,18±20,36 ng/ml (p<0.001)

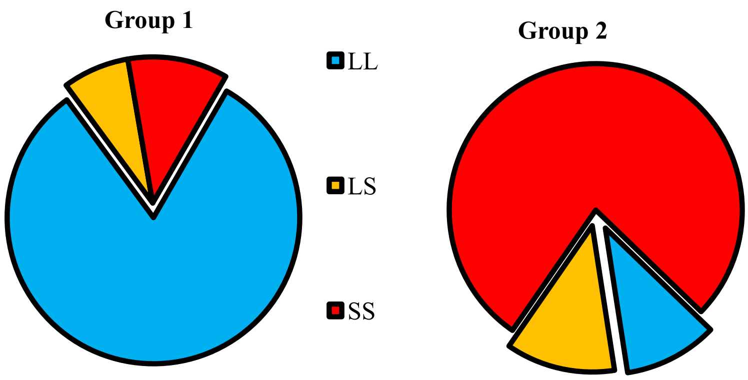

Fig. 3. The structure of SERT gene polymorphism in examined patients

Proteolytic activity of the blood plasma plays an important role in the pathogenesis of the intestinal dysfunction and significantly affects on the neurotransmitters metabolism. Proteolytic activity to low molecular weight peptides (azoalbumin) of the examined patients also differed significantly. In the first group of patients proteolytic activity almost did not differ from controls but in patients of the second group it was significantly higher in comparison with controls (1,88±0,171 vs. 1,47±0,172 E440/mL/h, p<0,05) and higher than in patients of first group (1,88±0,171 vs. 1,48±0,131, p<0,05 E440/mL/h).

The analysis of blood biochemical parameters revealed that proteolytic activity to medial molecular weight peptides (azokasein) in patients of the first group did not differ from the controls but in the patients of the second group parameters of proteolytic activity were significantly higher in comparison with controls (1,74±0,242 vs. 1,131±0,211 E440/ml/h; p<0,05) and higher in comparison with patients of first group (1,74±0,242 vs. 1,08±0,113 E440/ml/h; p<0,01) (**Fig. 4**).

Proteolytic activity by azokolagen in examined patients was also different. In the first group of patients it was significantly higher than in controls (0,68±0,071 vs. 0,46±0,031 E440/mL/h, p<0,05). In the second group of patients this indicator did not differ from controls.

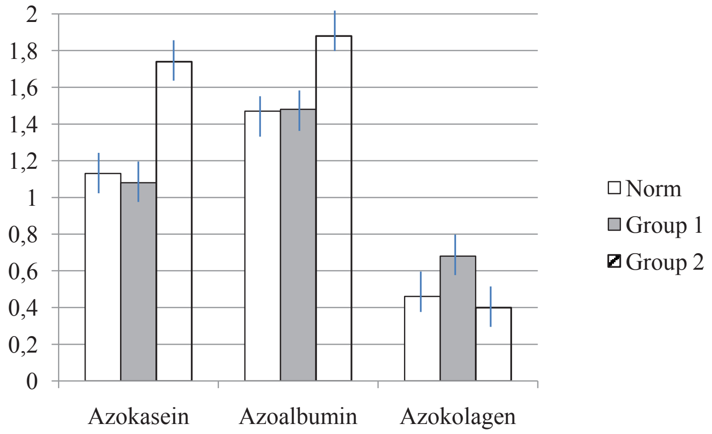

Fig. 4. The comparison of PA parameters in examined patients (E440/ml/h)

Fibrinolytic system plays an important role in the energy supply of the intestines and regulates the aggregate state of blood. The research showed (**Fig. 5**) that the total fibrinolytic activity in patients of the first group did not differ from the controls. In patients of the second group it was significantly lower than in controls (1,02±0,125 vs. 1,46±0,072 E440/mL/h in control, $p<0,01$) and lower in comparison with the patients of first group (1,02±0,125 vs. 1,62±0,391 E440/mL/h; $p<0,01$). This activity was lower mainly due to non-enzymatic fibrinolysis.

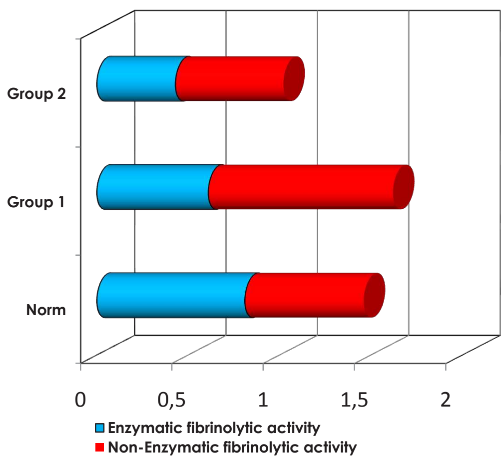

Fig. 5. The comparison of Total fibrinolytic activity (EFA+NFA) parameters in examined patients (E440/ml/h)

4. Discussion

Thus this study suggests that the disorders of motor-evacuation function of intestines in postoperative period occur more often in SS-genotype of SERT.

This causes the change in the treatment tactics of such patients. We consider it advisable to extend the indications for intestinal intubation even without intraoperative signs of intestinal paresis. It is important to use nasointestinal intubation more often with conducting of tube to the transverse colon. Mandatory addition for such intubation is divulsion of anal sphincter. In four cases we performed retrograde intestinal intubation through the stoma.

We proposed a technique which includes the performing of nasointestinal intubation of the small intestine and forming which is indicated in conditions of presence of unfavorable SERT genotypes. After that the nasointestinal tube is being output in retrograde direction where it is being cut off near the first hole which after that is being placed in the stomach and the opposite end of tube is being output in antegrade direction through existing stoma. This greatly simplifies the technique of intestinal intubation and allows avoid various complications which are associated with retrograde intubation.

We have developed the method of long-term local supply of serotonergic drugs in bowel mesentery which positively affect on the contractility of the intestines. In addition in the early postoperative period we are introducing these drugs in the cavity of intestines through the intestinal tube ensuring their local effect.

The use of this complex made it possible in all patients with postoperative intestinal paresis to restore contractile ability of intestines and to avoid the development of postoperative ileus.

5. Conclusions

Studies show a high risk of postoperative intestinal paresis in patients with SS variant of SERT gene which is associated (correlated) with disorders of proteolytic and fibrinolytic activity of blood plasma in surgical patients who had expressed disorders of motor-evacuation function of the intestine after surgical interventions on the digestive organs. Improved algorithms of treatment of such patients allow reduce the risk of postoperative ileus and to conduct the effective complex treatment in case of its occurrence.

Perspectives of scientific research: due to the certain genetic determinism of pathogenesis of postoperative intestinal paresis and its role in triggering the mechanisms of postoperative ileus we may affirm the feasibility of further genetic research for predicting these complications even in preoperative stage.

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