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Research Article

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Prevention of Infectious Complications in Acute Pancreatitis

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AIM OF STUDY The study was aimed to evaluate the effectiveness of treating acute pancreatitis by early enteral nutrition and selective introduction of nutritional mixtures directly into the initial sections of the jejunum, bypassing the duodenum.

MATERIAL AND METHODS A comprehensive treatment method for acute pancreatitis was developed based on the use of a pancreatoduodenal catheter. The method focuses on preventing intestinal failure syndrome by isolating the duodenum and preventing any liquid from entering it while ensuring the selective introduction of glucose-saline solutions and/or enteral nutritional mixtures directly into the initial sections of the jejunum. Several Russian clinics are currently conducting the research approved by local ethics committees. This article presents preliminary results from the data analysis. The study included moderate to severe forms (according to the 2012 Atlanta classification) of acute biliary pancreatitis without indications for endoscopic retrograde cholangiopancreatography, as well as alimentary-alcoholic pancreatitis. The first group of patients received standard therapy according to the 2020 clinical guidelines of the Russian Society of Surgeons. The second group received standard therapy combined with the new selective enteral nutrition method. The observation period lasted until the end of the hospital treatment, including five mandatory visits and a final visit to the physician. A follow-up survey was conducted three months or more after discharge to identify delayed episodes of acute pancreatitis complications, focusing on the incidence of infectious complications and surgical interventions.

RESULTS A total of 148 patients were treated. Patients were evenly distributed by etiology, gender, age, and body mass index. The analysis revealed that the number of patients with infectious complications decreased from 19.3% in the comparison group to 6.67% in the study group (p=0.041). The number of patients requiring surgical interventions was 5.0% in the study group compared to 19.3% in the comparison group (p=0.017).

CONCLUSIONS The study demonstrated that the use of the new method in the comprehensive treatment of acute pancreatitis, including early enteral feeding at the onset of the disease, may improve the course of the disease by reducing the incidence of infectious complications and the number of necessary surgical interventions.

Keywords: acute pancreatitis, infectious complications, enteral feeding

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Conflict of interest Authors declare lack of the conflicts of interests

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AP — acute pancreatitis
BMI — body mass index
COVID-19 — novel coronavirus disease
ERCP — endoscopic retrograde cholangiopancreatography
EPST — endoscopic papillosphincterotomy
MODS — multiple organ dysfunction syndrome
SIRS — systemic inflammatory response syndrome

INTRODUCTION

Acute pancreatitis (AP) is a serious disease, the treatment costs of which in the United States alone amount to 2.6 billion dollars per year. The incidence of AP tends to increase, and the outcomes of treatment of this pathology have not changed fundamentally over the past decade [1–4]. The annual prevalence of AP is, according to various sources, from 23 to 50 per 100 thousand of the population; it is believed that by 2050 this figure may reach 105-125 per 100 thousand [4]. According to existing estimates, mortality in AP ranges from 11% to 15.6%; but in severe forms of AP it is more than 30%, and according to some data it increases to 57% [5–8]. At the same time, the mean age of those suffering from AP has decreased to 30–54 years, and the current mortality rates indicate that this pathology is socially significant [4, 5].

Among the factors negatively affecting the treatment outcomes of AP, multiple organ dysfunction syndrome (MODS) due to systemic inflammatory response syndrome (SIRS) and infectious complications leading to severe purulent lesions mainly of the retroperitoneal space, which are often accompanied by sepsis, are usually distinguished [8, 9]. The source of infection is considered to be the intestinal microflora; the question of the prevalence of the small or large intestine in the process of translocation of bacterial flora through abdominal effusion, lymph or blood, remains debated [10, 11]. High demand for energy, microelements and nutrients, both for ongoing autolytic inflammation and for combating purulent complications, have led in the last 10 years to the abolition of the “starvation” doctrine in favor of mandatory use of nutritional preparations, which has reduced mortality in severe forms of AP by almost 2 times [12]. At the same time, the data of a meta-analysis demonstrated that the enteral method of nutrient media delivery is better than the parenteral one [13, 14]. The main reason for the positive effect is considered to be the fact that the supply of nutrients to the intestinal cavity leads to protection of the mucous

membrane epithelium from necrosis and improves its barrier function, and thus prevents the translocation of bacterial flora from the intestinal lumen to the retroperitoneal tissue, leading to its infection [11, 15]. Most data indicate a positive effect of early enteral feeding, reducing the risk of various complications and mortality [16]. The method of introducing nutritional mixtures remains debatable: through the mouth or using a nasogastric or nasointestinal tube [13]. The literature notes the advantage of nasointestinal administration of nutrient media, since this allows avoiding neurohumoral stimulation of the excretory function of the pancreas, and thus achieving its rest. However, the complexity and cost of the manipulation itself negatively affects the use of this technique. The ease of placement and low cost of a nasogastric tube are leveled by pathophysiological aspects; and the risk of regurgitation of gastric contents with the development of pneumonia cannot be excluded [17, 18].

In the clinical study of patients with moderate to severe forms of AP, we proposed a variant of early enteral nutrition. The developed method combined a number of conditions, such as disconnecting the duodenum from the flow of both gastric and small intestinal contents, and creation of controlled low pressure in this segment with active drainage of the lumen. In this way we achieved the prevention of acidification of the environment and prevented the activation of enzymes, reduced the production of both cholecystokinin and secretin, preventing neurohumoral stimulation of the exocrine function of the gland. Reduction of intraluminal pressure due to active aspiration stimulated the outflow of both bile and pancreatic juice into the intestinal lumen [19, 20]. On the other hand, separation with the help of catheter balloons, drainage of the stomach and jejunum prevented the reflux of intestinal contents, mixing of bacterial flora. Thus, the selective feeding method recreated all those physiological parameters that were disrupted in the first phase of AP, provided topical administration of nutritional mixtures and prevented reflux.

The aim of the study was to evaluate the effectiveness of the early selective enteral nutrition method in the treatment of patients with moderate and severe forms of AP.

MATERIAL AND METHODS

We are conducting an open, prospective, randomized trial in 6 cities of the Russian Federation and 7 clinical centers. The clinical trial protocol was developed in accordance with GCP (2006) and ISO 14155:2020 standards. Before the work began, the plan was agreed upon with each institution, and approval was obtained from the local ethical committee of the clinics. This article presents the interim results of the analysis of the data obtained.

Participants in the research are patients with moderate to severe AP, according to 2012 revision of the Atlanta classification of acute pancreatitis [21] (Fig. 1).

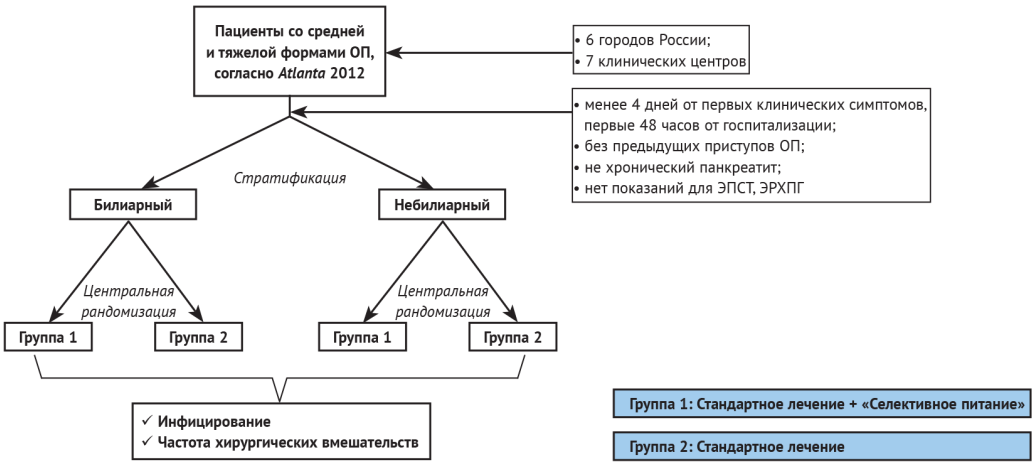

Fig. 1. Scheme of randomization trial of patients with acute pancreatitis
Notes: ОП — acute pancreatitis; ЭПСТ — endoscopic papillosphincterotomy; ЭРХПГ — endoscopic retrograde cholangiopancreatography

The study included patients with AP within the first 4 days from the onset of the disease and no more than 48 hours from the beginning of hospitalization. To determine the severity, generally accepted prognostic scales (BISAP, RANSON, CTSI, SOFA) were used. If at the time of inclusion there were insufficient data to establish the severity, a combined criterion was used, which included the presence of SIRS and the presence of local complications according to the results of computed tomography. The research included patients with AP of non-biliary and biliary etiology without indications for endoscopic retrograde cholangio-pancreatography (ERCP). Before randomization, non-inclusion criteria were assessed, including the presence of previous AP attacks, malignant neoplasms of the hepatopancreatoduodenal region, duration of pain syndrome more than 4 days, duration of hospitalization more than 48 hours, presence of purulent septic inflammation, novel coronavirus infection (COVID-19), age of patients less than 18 or more than 80 years, pregnancy, Child-Pugh class B and C cirrhosis, peptic ulcer in the acute stage, concomitant severe comorbid background.

The exclusion criteria were as follows: withdrawal of consent by the patient; violation of the trial protocol; development of adverse and serious adverse events associated with the use of the selective enteral nutrition method, development of complications and (or) diseases not associated with the underlying disease, but capable of influencing its course. Both groups received standard infusion and antisecretory therapy, according to the recommendations of the Russian Society of Surgeons [22]. Additionally, all the patients had a nasogastric or nasointestinal tube inserted to provide fluid and enteral formula. In the study group (Group 1), nutrition was carried out bypassing the duodenum, while in the comparison group (Group 2) it was performed orally or through a gastric tube. The Isycath® catheter was developed to perform selective enteral nutrition and active aspiration from the lumen of an isolated section of the duodenum (Fig. 2). Both Russian and international patents (RU 2761080 C1, WO 2021/137739 A1) have been obtained, as well as a registration certificate for the

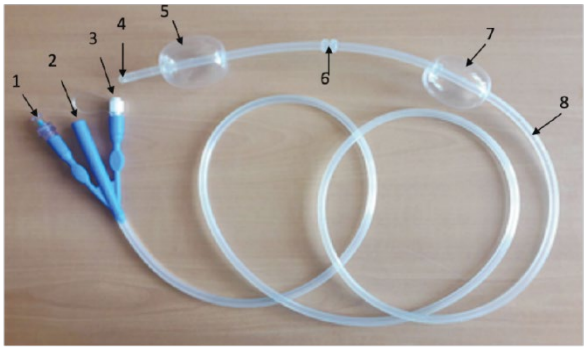

Fig. 2. Catheter "Isycath". 1 – channel for inflating balloons 7, 5; 2 — General channel for providing selective enteral nutrition; 3 — manipulative channel, connecting with pump for VAC-therapy, 4 — distal part of the catheter placed in proximal part of jejunum; 5, 7 — inflatable balloons isolating part of the duodenum around the papilla; 6 — openings of manipulative channel 3; 8 — openings in channel 2 for draining of the stomach

medical device (RZN 2022/19981). The function of the catheter is to isolate a section of a hollow organ, in this case the duodenum, around the large duodenal papilla, using inflatable balloons. Moreover, the design ensures communication between the sections of the hollow organ above and below the isolated area, bypassing this area. To prevent stagnation of the contents in the isolated area, a separate manipulation channel is opened in it, which is connected to a controlled negative pressure pump. To perform active aspiration, we set the parameters to 20–60 mm Hg.

The procedure for inserting the original catheter in Group 1 patients was always performed with endoscopic assistance and medical intravenous sedation. The manipulation of catheter placement was standard and similar to that used for insertion of nasointestinal feeding catheters for prolonged nutrition. The difference being that it was not necessary to insert the endoscope to the Treitz ligament together with the catheter, the whole manipulation consisted of its direction from the lumen of the stomach towards the duodenum; for this purpose, several guide threads were fixed and passed into the jejunum using a clamp. The guidewire technique for catheter placement was not widely used, since this requires additional specialized X-ray equipment which was not always available in emergency care. A mandatory condition was the location of the upper balloon immediately

behind the pyloric sphincter. The correct positioning of the probe was controlled both endoscopically during insertion and radiographically. After the physician had verified the correct positioning of the Isycath catheter, the balloons were inflated (Fig. 3). As can be seen from the presented radiograph, the design of the probe allows for isolation of the duodenum from other parts of the gastrointestinal tract, aspirate duodenal contents from this area, and also makes possible early selective administration of nutritional formula, bypassing this area.

Fig. 3. X-ray examination of contrast selective dispersion in stomach and in proximal part of jejunum marked by arrows, without spreading in duodenum

Early feeding was started 48 hours after the medical history was established. To assess the patient's tolerance to enteral nutrition, 1 liter of glucose-salt mixture was administered. For the next 24 hours, we started to introduce a high-calorie mixture; given that there are no recommended elemental or semi-elemental enteral nutrition media, we focused on the daily energy requirement based on the established values of 30–35 kcal/kg/day. Enteral nutrition was initiated with a trial administration of 100–150 ml, followed by an hour-long break to assess patient perception (absence of nausea and vomiting, presence of peristaltic waves during auscultation of the intestine), followed by drip administration into the main channel of the catheter (Fig. 2). To assess its effectiveness, parameters such as the number of patients with infectious complications and the number of patients who underwent surgical operations were analyzed. If inclusion and/or non-inclusion criteria were violated after randomization, the patient was excluded from the analysis.

All patients recruited into the research, according with compliance with inclusion and non-inclusion criteria, were initially stratified based on the etiology of severe AP: biliary, non-biliary. Central randomization was performed using pre-prepared block randomization tables.

Data analysis was performed using the standard t-test for quantitative parameters such as age, body mass index (BMI), etc. To analyze non-quantitative parameters such as etiology, gender, presence of multiple organ dysfunction syndrome (MODS) and SIRS, infectious complications, frequency of surgical manipulations, mortality, a comparison of proportions was performed using the online calculator: https://www.socscistatistics.com/tests/ztest/default2.aspx. In all cases, two-sided tests were used. A p-value of 0.05 was used to assess statistical significance.

All the patients who underwent treatment according to the protocol were interviewed after 3 months or more to identify delayed infectious complications.

RESULTS

A total of 148 patients were studied, of which 31 patients (20.9%) were excluded from the data analysis due to non-compliance with the inclusion and/or non-inclusion criteria. The reasons for exclusion from the data analysis are presented in Table 1.

Table 1

Analysis of patient's exclusion due to violation of protocol

Reason for excluding these patients from the analysis	Number of exclusion cases, n (%)
Discrepancy in diagnosis	9 (29.0)
COVID-19	4 (12.9)
Presence of non-inclusion criteria*	14 (45.2)
Serious violations of protocol **	4 (12.9)
Total	31 (100)

Notes: * — presence of infectious complications at the time of inclusion, choledocholithiasis, sepsis, serious comorbid background; ** — failure to place the tube, failure to ensure control and non-functioning of the tube. НКВИ 19 — novel coronavirus infection detected within the first 10 days from the onset of acute pancreatitis

Thus, 117 patients were included in the analysis of the research results. The patients' condition was analyzed according to how they were randomized in the study. 60 patients were randomized to Group 1 with standard therapy and selective enteral nutrition bypassing the duodenum; 57 - in Group 2 with standard therapy and enteral nutrition (Table 2).

Table 2

Characterization of patient's cohorts randomized in trial

Indicators	Group 1, *n*=60				Group 2, *n*=57				*p*
Gender	Male		Female		Male		Female		0.977
	37	61.67%	23	38.33%	35	61.40%	22	38.60%	
Etiology	Biliary		Non-biliary		Biliary		Non-biliary		0.767
	14	23.33%	46	76.67%	12	21.05%	44	77.19%	
Mean age	46.69				48.16				0.599
Mean body mass index	27.35				28.46				0.263

As can be seen from Table 2, the groups are fairly well balanced in terms of gender, age, etiology, weight and height indicators; no statistically significant difference was observed between the groups for any of them (p>0.05).

The patients were evenly distributed in terms of disease severity at the time of inclusion in the study, as SIRS and/or multiple organ dysfunction syndrome (MODS) were observed with approximately the same incidence in both groups. At the same time, the presence of these complications was more often observed among patients in Group 1 (Table 3).

Table 3

Presence of systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) during the 24 h after randomization

	Group 1	Group 2	*p*
MODS in the first 24 hours	27.45%	18.75%	0.306
Patients with SIRS in the first 24 hours	74.55%	70.00%	0.603

Notes: MODS - multiple organ dysfunction syndrome; SIRS - systemic inflammatory response syndrome

To assess AP severity, a number of prognostic scales, as well as the volume of infusion therapy were used (Table 4).

Table 4

Comparison of acute pancreatitis severity in groups by usage of prognostic scales and volume of resuscitation therapy

		Group 1	Group 2	*p*
BISAP		3.08	2.75	0.806
Ranson		4.01	3.96	0.703
CTSI		4.92	4.11	0.211
SOFA		3.98	3.21	0.621
Volume of infusion therapy (L)	First 48 hours	6.64	6.47	0.364
	Second 48 hours	5.28	5.26	0.959

Notes: BISAP — bedside index of severity in acute pancreatitis; Ranson — the oldest prognostic score indicating the probability of a fatal outcome; CTSI — computer tomography severity index; SOFA — sequential organ failure assessment

As can be seen from the data obtained, the severity of pancreatitis was no less than moderate, while there was no statistically significant difference between the study group and the comparison group. The volume of infusion therapy administered in the intensive care unit also indirectly confirmed the severity of the patients' condition, and corresponded to national recommendations; no deviation was observed between the groups.

When analyzing the complication rate data in Group 2, the obtained results were consistent with the data of domestic and foreign literature [16, 17]. Comparative analysis of the data showed a significant decrease in the infection rate: from 19.30% of patients in Group 2 who developed infectious complications to 6.67% in Group 1 (p=0.041). An indirect indicator of treatment effectiveness was the persistence of MODS for 96 hours or more after hospitalization. Such cases were less common in Group 1 (Table 5), despite the fact that the opposite situation was observed at the beginning of hospitalization (Table 3). According to the recommendations, in the presence or suspicion of purulent-necrotic parapancreatitis, the treatment tactics were determined collegially and, as a rule, it started with minimally invasive ultrasound-guided drainage procedures followed by laparo-lumbotomy in case of sequestrum formation. Overall, there was a significant reduction in the number of patients undergoing surgery and the total number of surgeries performed in Group 1: 3 patients (5%) in Group 1 versus 11 patients (19.3%) in Group 2 (p=0.017), a total of 5 and 23 surgeries, respectively.

Table 5

Comparison of treatment results of patients with acute pancreatitis

	Group 1, n=60		Group 2, *n*=57		*p*
	n	%	*n*	%	
Infection	4	6.67	11	19.30	0.041
Multiple organ dysfunction syndrome ⩾ 96 hours from inclusion in the study	10	16.67	15	26.32	0.203
Number of patients who underwent surgical procedures	3	5.00	11	19.30	0.017
Number of surgeries performed	5		23		–

When interviewing patients 3 months or more after discharge from the hospital, 1 case of rehospitalization was identified in Group 2 due to staged sanitation of purulent complications of AP.

DISCUSSION

Early enteral nutrition has proven its effectiveness in preventing the development of infectious complications of acute pancreatitis [13, 14]. All the taken therapeutic measures are aimed at restoring the peristalsis of the gastrointestinal tract. Nevertheless, the incidence of complications remains at a fairly high level, which indicates the presence of a number of unresolved problems. In particular, with the existing approaches to the introduction of nutritional mixtures, the passage of the stomach contents through the duodenum is maintained. Recommended drainage of the upper gastrointestinal tract at the onset of the disease mainly consists of placing a nasogastric tube. Tubes inserted endoscopically behind the Treitz ligament are suitable for feeding due to their diameter, but are not suitable for the outflow of contents; thus, the contents of the small intestine in the presence of paresis are retrogradely thrown through the duodenum into the stomach and from there are drained out [5, 6, 22, 24]. These unresolved issues play a significant role in the development of intestinal failure syndrome, especially in the first 48 hours from the start of hospitalization [22, 24]. Therefore, the development of new methods is of great importance.

CONCLUSION

During the study, it was possible to achieve a uniform distribution of patients. One of the important points was the fact that the included patients were comparable in the time of onset, etiology and severity of the disease, as evidenced by the absence of statistically significant differences between the groups (p> 0.05 in all cases). It is important that all the patients were observed in the intensive care unit when included in the research, and there was no statistically significant difference in the volume of infusion therapy (p> 0.05). At the same time, the failure to achieve a statistically significant difference for such indicators as mortality and length of stay is quite natural, based on the

sample size, as well as the experience of similar international multicenter trials. However, a positive trend and pattern that is strictly observed at all stages of the study are extremely important. The article presents a new method of early selective nutrition, combining a number of functions: passaging drainage of the stomach and initial sections of the jejunum, active decompression of the duodenum, and selective delivery of enteral nutritional mixtures. The developed method may be of great importance in the treatment of phase 1 of acute pancreatitis, as it is aimed at restoring peristalsis of the gastrointestinal tract, preventing intestinal insufficiency syndrome and infectious complications.

FINDINGS

Statistical data showed that the use of our method of early selective enteral nutrition in the treatment of patients with moderate and severe forms of acute pancreatitis reduced the number of infectious complications by 4 times (p=0.041), and the number of surgeries – by almost 5 times (p=0.017).

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