

PATHOPHYSIOLOGY OF PAIN AND TREATMENT APPROACHES WITH CHRONIC PANCREATITIS

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Abstract. *This article will focus on some peculiarities of pancreatitis concerning pain and treatment processes.*

Keywords: *chronic pancreatitis, pancreatology, abdominal pain, precordial region.*

Clinical manifestations of chronic pancreatitis (CP) are very variable, they are different during remission and exacerbation of the disease, depend on the clinical form, course, stage of CP and a number of other factors. The dominant symptom of CP, especially at the onset of the disease and in the first years after diagnosis, is pain. Pain syndrome occurs in most patients with CP and serves as the most striking manifestation of the disease. There is no pain in patients with CP, which is partly observed against the background of a progressive decrease in the exocrine function of the pancreas (pancreas) [1]. Most experts in the field of pancreatology tend to believe that the abdominal pain syndrome in CP is not very specific, since it has a multifactorial nature and changes over time, however, a thorough analysis of the literature still allows us to identify the main clinical features of pancreatic pain. The origin of pain in patients with CP is not fully understood and is most likely due to multifactorial effects, including inflammation, ischemia, obstruction of the pancreatic ducts with the development of pancreatic hypertension with the continued secretion of pan pancreatic enzymes. This opinion is confirmed by observations of patients with external pancreatic fistulas, in which the introduction of fluid (isotonic sodium chloride solution or contrast agent) through the fistula into the ducts of the pancreas immediately causes typical pains that disappear after evacuation of the injected fluid from the ducts [2]. The mechanism of pain is explained by their intensification after ingestion food and other stimulators of pancreatic secretion that increase pressure in the ductal system, partially or completely blocked due to cicatricial and inflammatory strictures, concretions. The use of drainage operations in the treatment of CP is based on the recognition of this mechanism. According to R. Ammann, the genesis of abdominal pain syndrome in CP is due to 2 mechanisms [3]:

The first mechanism is associated with inflammation, while the pain syndrome may be pronounced, resembling that of acute pancreatitis, but more often it is less significant, periodically recurs and is accompanied by pain-free periods of varying duration. The pain syndrome is more pronounced in the first 6 years from the onset of the disease, with time the pain decreases, after 10 years this syndrome persists in less than 50% of patients. According to G. Cavallini et al., after 15 years since the diagnosis, more than 25% of patients with CP continue to suffer from recurrent pain abdominal syndrome, however, the frequency of pancreatitis attacks on average, as a rule, does not exceed 1 episode of exacerbation of CP per year [4].

The second mechanism of abdominal pain syndrome, according to R. Ammann, is due to the development of complications, in particular pseudocysts, capable of having a compression effect on the duodenum (duodenum), virsung duct, biliary tract and other organs at certain locations and sizes [3]. It is assumed that progressive fibrosis in the areas of sensory nerves leads

to their compression and the development of neuropathy, increasing the tropicity of pancreatic sensory nerves to various exogenous influences (alcohol, drugs and other factors). In addition, there are other factors – peripancreatic inflammation involving the duodenum and retroperitoneal space, stenosis of the distal choledochus, irritation of the peritoneal leaf covering the anterior surface of the pancreas, the presence of pseudocysts and pathology of neighboring organs. Concomitant pathology of the stomach and duodenum, the component, together with CP, 40% of cases and more, also plays a significant role in the severity of abdominal pain syndrome [1]. There is an opinion that mechanical allodynia of central origin (perception of pain with non-painful irritation) is one of the mechanisms for the formation of abdominal pain syndrome in patients with CP. With the simultaneous implementation of 2 or more mechanisms, a persistent pain syndrome develops; it is expressed even after the acute exacerbation of CP has subsided [1]. Pain disappears with the appearance of calcifications in the pancreatic parenchyma, steatorrhea and diabetes mellitus, i.e. on average, 5-18 years after the clinical manifestation of CP. These data are confirmed by A. Girdwood [5], who found that 31% of patients with pain-free forms of CP had pronounced external secretory pancreatic insufficiency. The number of patients with CP with severe external secretory insufficiency and persistent abdominal pain syndrome is significantly less – only 3%. With CP, the pain does not have a clear localization; arising in the upper or middle abdomen on the left or in the middle, it radiates into the back, sometimes assuming a shingling character. In some cases, the pain is initially localized in the back. Such a most common symptom as shingles in the upper abdomen (considered, perhaps, an "unavoidable" sign of an exacerbation of CP) is a consequence of paresis of the transverse colon or an independent pathology of the colon [1]. Sometimes patients complain of "high" pains, interpreting them as pain in the ribs, in the lower parts of the left half of the chest. With the progression of extracorporeal pancreatic insufficiency in patients with CP, secondary enteritis is associated with excessive bacterial growth in the intestine, especially pronounced in alcoholic and biliary variants of the disease. At the same time, the pain in the epigastrium, the left hypochondrium subside somewhat; cramping pains in the umbilical region begin to dominate. Patients with alcoholic pancreatitis often experience pain in the right hypochondrium due to concomitant cholecystitis, hepatitis, cirrhosis of the liver, duodenitis [1]. The most characteristic is the irradiation of pain in the left half of the chest cap from behind, in the left half of the waist (according to the type of "left half-belt" or according to the type of "full belt"). Irradiation is also possible in the left arm, under the left shoulder blade, behind the sternum, in the precordial region, the left half of the lower jaw. At the same time, patients are often hospitalized in cardiology departments with suspected acute coronary syndrome.

More than half of the patients have a painful abdominal syndrome of high intensity and (or) persists for a long time, often leading to the development of secondary mental disorders. As a rule, the pain increases against the background of eating, usually after 30-0 minutes (especially with stenosis of the pancreatic ducts), which is associated with the beginning of evacuation of food from the stomach to the duodenum, when the pancreas experiences secretory tension. Relapse of pain is provoked by abundant, fatty, fried, smoked (to a lesser extent – spicy) food, alcohol and carbonated drinks, i.e. increased stimulating effects on the pancreas.

Most often, patients report an exacerbation CP with the combined effect of the above factors and smoking. In some patients, the appearance of pain is not associated with food. The pain can be paroxysmal, the duration of attacks – from several hours to 2 days; constant monotonous or constant with paroxysmal intensification. With the development of pancreatic necrosis, pain

decreases due to the death of the endings of sensitive nerves. Pain relief is the most important task in the treatment of patients with CP. At the same time, the following fundamental measures are necessary (in the absence of a part of these, treatment may be unsuccessful): the elimination of alcohol and tobacco smoking, therapeutic nutrition, drug therapy (analgesics, antispasmodics, enzyme preparations that do not contain bile acids, antisecretory drugs, neuroleptics, etc.), surgical and endoscopic treatment. First of all, with a relapse of abdominal pain syndrome in a patient with CP, especially with its atypicality and lack of effect from standard therapy, it is necessary to evaluate "fresh" structural changes of the pancreas (inflammation, pseudocyst, papillitis, stricture or stone, volumetric formation), which in general and it will determine the further tactics of the patient's management: continuation and (or) modification of pharmacotherapy, endoscopic or surgical treatment. In the complex therapy of abdominal pain syndrome in CP, strict adherence to a diet, the elimination of alcohol and tobacco smoking are necessary. With the cessation of alcohol intake, the frequency and severity of abdominal pain syndrome decrease in 75% of patients with alcoholic CP [1]. Patients with painful forms of CP who continue to smoke react worse to therapy aimed at correcting pain, which also needs to be taken into account when selecting therapy. The use of analgesics remains one of the main methods of pain relief in patients with CP. In many patients without edematous changes in the pancreatic parenchyma, without the phenomena of pancreatic obstruction and complications of pancreatitis (large pseudocysts, fistulas, duodenal obstruction, etc.) often persist pronounced abdominal pain caused by ischemia and progressive fibrosis in the areas of sensory nerves. In such cases, even outpatient analgesic therapy may be required. The analgesics of the 1st choice are paracetamol and metamizole, which must be taken before meals to prevent postprandial pain enhancement. Doses of analgesics are selected individually, and the lowest effective dose should be used.

If non-narcotic analgesics are ineffective, their use in the maximum permissible daily therapeutic doses, a change in the regimen and route of administration, or an attempt to replace the drug with another of the same group is possible. The additional inclusion of psychotropic drugs (neuroleptics, antidepressants, tranquilizers), which have both direct analgesic and potentiating effects against non-narcotic analgesics, also allows to increase the effectiveness of analgesic therapy. In addition, the own effects of these drugs are also important, since many patients have borderline mental disorders, anxiety-depressive and other neurotic disorders. In case of resistance to non-narcotic analgesics, opiates and their synthetic analogues can be used. The main limitation to the widespread use of narcotic analgesics is the development of drug dependence. When working out the tactics of treating abdominal pain syndrome in patients with CP, it is necessary to take into account the presence of hypermotor disorders of the motility of the gallbladder and duodenum, modification of which by prescribing antispasmodics will ensure normal passage of pancreatic secretions. The outflow of bile and pancreatic secretions may be hindered due to inflammation in the area of the large duodenal nipple, which requires the appointment of anti-inflammatory and (or) antibacterial therapy (semi-synthetic penicillins, tetracycline preparations, cephalosporins released in sufficient concentrations with bile). With dysfunction of the Oddi sphincter after cholecystectomy, which, as is known, plays a significant role in the genesis of abdominal pain syndrome in patients with biliary CP, the administration of analgesics in combination with myotropic antispasmodics (mebeverin, etc.) gives a good effect [1]. Thus, it is quite logical in patients with CP to use combined drugs containing analgesic and antispasmodic components (Spasmalgon), which will provide a pronounced direct (analgesic effect of

metamizole) and indirect analgesic effect due to the anti-inflammatory effect of metamizole and the antispasmodic effects of pitofenone hydrochloride and fempiverinium bromide (papaverine-like and m-holinoblocking action). Thus, the combination of components. Spasmalgon leads to a mutual enhancement of their pharmacological action. The release form is also convenient, containing 1 and 5 ml of the drug solution (500 and 2500 mg metamizole), which allows individual dosing of the drug. The maximum daily dose for adults is 10 ml / day (5000 mg of metamizole). Usually, 3-5 days of administration of the drug in a hospital are enough to reduce or relieve pain, which allows you to switch to oral administration in the future or limit yourself to other approaches (pancreatic enzymes, antisecretory drugs). Almost 40 years ago, experimental studies showed that intramuscular administration of trypsin or chymotrypsin inhibits the secretion of pancreatic enzymes [6]. Thus, it seems logical that in patients with CP, decreased secretion of pancreatic enzymes with external secretory insufficiency can lead to hyperstimulation of the pancreas with high levels of cholecystikinin in blood plasma and, consequently, to abdominal pain syndrome.

These facts allowed G. Isakson and I. The authors, based on the results of a double-blind cross-sectional study, reported that the severity of abdominal pain in CP decreases by 30% against the background of taking poly-enzyme preparations. At the same time, the number of pain attacks decreased in 15 out of 19 patients [7]. However, it should be noted that this approach proved to be effective only with moderate pancreatic insufficiency. 2 subsequent double-blind placebo-controlled studies [8, 9], it was possible to talk about a good overall result when using poly-enzyme preparations in patients with a painful form of CP - pain relief in 73% of cases (in 36 out of 49 patients) [7-9]. herefore, in the future, the opinion was strengthened that in order to relieve pain in patients with CP, it is necessary to use tablet preparations of pancreatin that do not have an acid-proof shell begin to activate in the stomach and upper parts of the duodenum. Somatostatin is a natural hormone, one of the effects of which is inhibition of pancreatic secretion. The effects of somatostatin include cytoprotective effect and beneficial effect on the reticuloendothelial system, which theoretically can be useful in the treatment of CP. In addition, the antinociceptive activity of somatostatin in humans and animals has been shown. However, to protect pancreatin from hydrochloric acid, these drugs must be taken with gastric secretion blockers. Somatostatin is a natural hormone, one of the effects of which is inhibition of pancreatic secretion. The effects of somatostatin include cytoprotective effect and beneficial effect on the reticuloendothelial system, which theoretically can be useful in the treatment of CP. In addition, the antinociceptive activity of somatostatin in humans and animals has been shown. Short 3-day studies using 100 and 150 mcg of octreotide 3 times a day did not demonstrate any effect in relieving pain in patients with CP [11]. In a randomized multicenter 4-week placebo-controlled study, octreotide was used at a dose of 40-100 mg 3 times a day to evaluate its effectiveness in CP with severe abdominal pain syndrome.

Although no statistically reliable results were obtained in this study, octreotide at a daily dose of 600 mg was the most effective for pain relief (65% compared to 35% in the placebo group). In addition, the authors noted that octreotide is more effective in patients with persistent pain syndrome than in patients with periodic pain [12]. Despite the optimistic results of studies on the use of octreotide in patients with painful forms of CP, the prospects of such studies are limited by a significant increase in side effects the effects of the drug with prolonged use. It is known that with prolonged treatment with octreotide, maldigestion is aggravated due to a sharp decrease in the secretion of pancreatic enzymes in the duodenum, the development of intestinal paresis and

deterioration of blood supply in the pancreas is possible. Octreotide is used especially cautiously in cholelithiasis due to an increase in the likelihood of stone formation when hypotension of the gallbladder is created against the background of treatment. Since in a number of patients abdominal pain syndrome is caused by secretory tension in the pancreas with an increase in the volume of pancreatic juice and the concentration of enzymes in it, a decrease in the exocrine function of the pancreas should lead to the creation of a "functional rest" of the gland, a decrease in ductal and tissue pressure and, consequently, a reduction in pain. This can be achieved indirectly, by inhibiting the synthesis of hydrochloric acid, which would lead to a decrease in the formation of secretin and, to a certain extent, cholecystokinin. The presented pathogenetic mechanism and the effectiveness of the addition of antisecretory drugs to the complex treatment of CP led to the inclusion of CP in the number of acid-dependent diseases. In other words, the attribution of CP to the group of acid-dependent diseases is due to the fact that effective treatment of CP is possible only with a fairly long decrease in the acidity of gastric juice. Among the blockers of histamine H₂receptors, the drugs of the III generation are of the greatest interest (famotidine belongs to them), since they have fewer side effects than their predecessors and a more pronounced antisecretory effect. Although the question of the expediency of introducing histamine H₂receptor blockers into basic therapy CP has been repeatedly discussed, controlled studies have not yet been conducted either in Russia or abroad.

Nevertheless, the available individual uncontrolled studies on the use of drugs of this group indicate their effectiveness. The use of these drugs is limited not only by their low effectiveness compared to proton pump inhibitors (PPIs), but also by a number of other disadvantages: reversible connection with receptors, the presence of a "ricochet flash" of secretion after withdrawal; the dependence of the effect on the maximum concentration of the drug in the blood. According to pilot studies, the most effective secretion inhibitors are currently considered to be PPIs that inhibit the operation of the system that directly secrete hydrochloric acid [13]. For the treatment of chronic abdominal pain In recent years, minimally invasive and endoscopic techniques have been increasingly used in patients with CP. Indications for endoscopic treatment are mainly obstructive forms of CP, which arose against the background of strictures of the main pancreatic passage, ductal and ampullary concretions, stenosis of the large duodenal nipple and other causes. It is believed that an alternative to narcotic analgesics is the neurolysis of the abdominal plexus (percutaneous injection under the control of imaging techniques) of ethanol and other substances into the zone of the abdominal plexus. Only if all possible conservative methods used for pain relief have been exhausted, including minimally invasive interventions, and surgical treatment options should be considered. The variant of the operative manual is chosen depending on the etiology of pancreatitis, the clinical and instrumental picture of the disease and the alleged pathomechanism of pain.

REFERENCES

1. Sarkisova V., Xegay R., Numonova A. ENDOCRINE CONTROL OF THE DIGESTION PROCESS. GASTROINTESTINAL ENDOCRINE CELLS //Science and innovation. – 2022. – T. 1. – №. D8. – C. 582-586.
2. Sarkisova, V. "ASPECTS OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM IN HYPOXIA." *Science and innovation* 1.D8 (2022): 977-982.

3. Sarkisova, V., et al. "ESSENTIAL ROLE OF BRADIKININ IN THE COURSE OF BASIC LIFE PROCESSES." *Science and innovation* 1.D8 (2022): 576-581.
4. Vladimirovna, Sarkisova Viktoriya. "About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia." *Global Scientific Review* 12 (2023): 25-32.
5. Vladimirovna, Sarkisova Viktoriya. "Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis." *The Peerian Journal* 15 (2023): 84-93.
6. Саркисова В., Абдурахманова К. Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке //Журнал вестник врача. – 2014. – Т. 1. – №. 1. – С. 163-166.
7. Sarkisova V., Xegay R. Causes, Diagnosis, Conservative And Operative Treatment Of Uterine Myoma //Science and innovation. – 2022. – Т. 1. – №. D8. – С. 198-203.
8. Саркисова В. В. Патогенетические отношения артериальной гипертензии и сопротивления инсулина //IQRO. – 2023. – Т. 2. – №. 1. – С. 727-731.
9. Vladimirovna S. V. PATHOGENETIC RELATIONSHIPS OF ARTERIAL HYPERTENSION AND INSULIN RESISTANCE //IQRO. – 2023. – Т. 2. – №. 1. – С. 685-691.
10. Sarkisova V., Regina X. РОЛЬ БРАДИКИНИНА В ПРОТЕКАНИИ ОСНОВНЫХ ЖИЗНЕННЫХ ПРОЦЕССОВ //Science and innovation. – 2022. – Т. 1. – №. D8. – С. 587-593.
11. Sarkisova, V., A. Numonova, and R. Xegay. "АНТИБИОТИКОРЕЗИСТЕНТНОСТЬ ИЛИ БОРЬБА С ГЛОБАЛЬНОЙ УГРОЗОЙ XXI ВЕКА." *Science and innovation* 1.D8 (2022): 232-241.
12. Sarkisova V., Numonova A., Xegay R. Аспекты Состояния Вегетативной Нервной Системы При Гипоксии //Science and innovation. – 2022. – Т. 1. – №. D8. – С. 228-231.
13. Джуманов Б. и др. Применение инструментальных методов исследование в диагностике острого аппендицита у беременных //Журнал проблемы биологии и медицины. – 2014. – №. 1 (77). – С. 9-12.
14. Саркисова В., Джуманов Б., Исроилова Г. Анализ репродуктивного и соматического здоровья женщин, госпитализированных по поводу гиперплазии эндометрия и маточных кровотечений //Журнал вестник врача. – 2014. – Т. 1. – №. 1. – С. 169-170.
15. Саркисова В., Абдурахманова К. Роль гормональных препаратов в терапии гиперпластических процессов эндометрия и в частности при миоме матки //Журнал вестник врача. – 2014. – Т. 1. – №. 1. – С. 167-168.
16. Vladimirovna S. V. et al. PREGNANCY WITH CONGENITAL HEART DISEASE //Science and innovation. – 2023. – Т. 2. – №. D4. – С. 127-136.
17. Sarkisova V., Alvi I. THE PROBLEM OF COMORBIDITY OF AFFECTIVE DISORDERS AND PERSONALITY DISORDERS //Science and innovation. – 2023. – Т. 2. – №. D5. – С. 170-177.
18. Vladimirovna S. V. et al. TORCH-Complex //Scholastic: Journal of Natural and Medical Education. – 2023. – Т. 2. – №. 6. – С. 183-187.
19. Vladimirovna S. V. et al. Ovarian Apoplexy and its Impact on Reproductive Health //Central Asian Journal of Medical and Natural Science. – 2023. – Т. 4. – №. 2. – С. 381-388.

20. Vladimirovna S. V., Anvarovna S. L., Vladimirovna M. E. Menorrhagia-One of the Formidable Complications in Gynecology //Scholastic: Journal of Natural and Medical Education. – 2023. – T. 2. – №. 4. – C. 72-79.
21. Vladimirovna S. V. et al. TORCH-Complex //Scholastic: Journal of Natural and Medical Education. – 2023. – T. 2. – №. 6. – C. 183-187.