The evidence base for the use of drugs in the treatment of chronic pancreatitis

M. F. Osipenko, D. S. Bordin, E. A. Bikbulatova

Novosibirsk State Medical University, Novosibirsk, Russia

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Chronic pancreatitis (CP) treatment is a difficult task. Despite the fact that this is serious, progressive disease, approaches to therapy are still far from perfection. The main goals in the treatment of CP is the relief of chronic pain, correction of malabsorption as a result of exocrine insufficiency, endocrine insufficiency correction (pancreatogenic diabetes — DM), and attempts to reduce the risk of malignancy in the organ (ductal adenocarcinoma).

The main causes of pain in pancreatitis are the rise of pressure in the duct system, inflammation of the parenchyma, ischemia, progressive fibrosis, intra- and outpancreatic obstruction. Most pancreatic pain is permanent, as a rule, quite intense, localized in the epigastrium, radiating to the back, increasing after a heavy fatty meal (type B). A number of patients may have episodic pain (type A) [21, 31].

It has been suggested that with the development of fibrosis, there is the phenomenon of "burnout", accompanied by a decrease in pain intensity and its relief. However, two prospective studies have demonstrated the association between the duration of the course and severity of CP pain. The theory of "burnout" is completely denied, but the spontaneous disappearance of pain is possible [5, 24].

Perhaps one of the basic approaches to a reduction in the severity of pain is to correct lifestyle, primarily including quitting smoking and alcohol consumption. A number of studies over the years recommend patients to avoid harmful habits, although the level of evidence and recommendations, for example, according to the Italian consensus management of patients with CP, respectively, is

2B and B in respect of non-alcohol and 4 and C in relation to smoking cessation [2, 6, 7, 16, 26, 30].

Medical pain relief is based on the WHO recommendations on the three-step approach. In the first stage, non-opioid analgesics (paracetamol), nonsteroidal anti-inflammatory drugs, including inhibitors cyclooxygenase 2 (COX2) are applied. In the second stage, tramadol, naloksen, codeine preparations are added, and the third includes opioids and considers the possibility of surgery. Additional therapy which can be applied at all stages of pain management includes tricyclic antidepressants, anticonvulsants, steroids, and certain physiotherapy therapy approaches [15, 18, 20].

Cochrane review in 2013 assessed opioids for the relief of acute pancreatic pain, analyzing five randomized clinical trials involving a total of 227 patients aged 23-76 with a predominance of males. Different opioids *(buprenorphine, pethidine, pentazocine, fentanyl*, *morphine*) were evaluated with different form of prescription: intravenous, intramuscular, hypodermic, transdermic. It has been shown that opioids have a real opportunity to stop the pain. Their use reduces the need for other analgesic and other drugs and don’t increase the risk of complications [4].

Today it is absolutely clear that the cause of pain in CP is multicomponent, and one of the pathogenic mechanisms is inflammation. It is natural to assume a positive effect in the application of antioxidants. Cochrane review included 12 trials with a total of 585 patients, 6 double-blind, placebo-controlled trials. 11 out of 12 were dedicated to evaluating antioxidant effect on pain. Pain was assessed on a visual analog scale (VAS) ranging from 0 to 10 points. Study duration ranged from 1 to 6 months. In general, pain decreased in patients who used anti-oxidants (MD) at 0.33, (95% CI 0.64-0.02, p 0.04 — reasonable proof). However, the number of pain-free patients at the end of treatment was not significantly different between the groups receiving and not receiving antioxidants (RR 1,73, 95% CI 0.95-3.15, p 0.07). The best effect was obtained with the combination of

allopurinol with dimethylsulfoxide and combinations of selenium, beta-carotene, vitamins C and E (LE 1B, C) [14].

The number of adverse effects was higher in the group receiving anti-oxidants (RR 4.43, 95% CI 1.60-12.29, p 0.0004 — moderate proof), and similarly in crossover studies (RR 5.80, 95% CI 1.56-21.53, p 0.0009). The occurrence of such side effects as headache, nausea, constipation, 16% forced to stop taking antioxidants [3, 8, 25, 32].

Only one study assessing the antioxidants for the relief of acute pain during exacerbation of CP showed a good effect, but the study was conducted in 1991. It is interesting that in patients treated with anti-oxidants, changed indicators of fibrosis markers: platelet growth factor AA, transforming growth factor β1, which is associated with a reduction in pain [12]. The results of the Cochrane review suggest the impossibility to make an unambiguous conclusion about the effectiveness of antioxidants in relieving pain in CP.

A double-blind randomized study of 64 patients showed the effectiveness of a derivative of gamma-aminobutyric acid pregabalin in relieving pain in CP: pregabalin for 3 weeks compared with placebo is more effective in reducing pain (36% vs 24%; mean difference, 12%; 95% CI, 22-2%; p 0.02). Quality of life, the number of adverse effects did not differ between the groups. Antinociceptive effect was probably realized through subcortical mechanisms, blocking calcium channels [28].

Clinical trial of phase 2 demonstrated that intravenous administration of synthetic secretin reduced the need for opioids, particularly in women with refractory B-type embodiment pain (basal VAS 5.42 vs. VAS in 30th day of treatment 3.67, p 0.07) [1].

Refractory pain requires endoscopic and surgical approaches for decompression, the blockade of the celiac trunk, extracorporeal lithotripsy. Surgery allows to gain prolonged pain relief in patients with CP (LE 1A, A). Two randomized clinical trials showed the best effect when applying pancreatojejunal anastomosis compared with endoscopic treatment (34% vs 15%). Despite this, the

frequency of endoscopic surgical procedures remains higher, probably because of the greater technical complexity [13, 27].

Summarizing the research in the treatment of pancreatic pain, we recommend the following approach: analgesics, anti-oxidants in hereditary CP, loksiglumid — cholecystokinin receptor antagonist. In case of failure — endoscopic and surgical intervention, up to pancreatectomy with islet autotransplantation in cases of severe inflammation and non-relief of pain (autotransplantation of islets, possible at some of the larger reference centers, is also carried out in order to slow down the formation of diabetes) [22].

Indications for use of pancreatic enzymes in pancreatitis are a malabsorption syndrome and malassimilation (weight loss, effects of malabsorption, maldigestion, nutrient deficiency). Preference is given in the form of enteric enzymes minimicrospheres, pH-sensitive high-lipase (LE 1B, A). At each meal it is recommended to take 25000-40000 U at the beginning of treatment; with a small amount of food when snacking enzyme dosage is 10000-20000 U. The enzymes should be taken during or immediately after a meal [11, 17].

Double-blind, placebo-controlled, randomized clinical trial evaluated the efficacy and safety of pancreatic enzymes in patients with exocrine pancreatic insufficiency. 62 patients were randomized into 2 groups (34 taking 80000 U of pancreatic enzymes at the main meal, and additional 40000, 28 — placebo). The absorption of fat in the main group increased by 18.5% (15.8-21.2) compared with the control group — 4.1% (1.0-7.2), difference of 14.4% (10.3-18.5); p 0.001.

In general, in the treatment of patients with CP with exocrine insufficiency by minimicrospheric enteric enzyme preparations was well tolerated, improved absorption of fat and nitrogen, eliminated clinical symptoms, improved nutritional status [29]. On the other hand, 10 trials, in which 361 persons were included, demonstrated that administration of enzymes reduced the amount of fecal fat, but had no effect on body weight, intensity of pain and quality of life. Adding proton pump inhibitors advisable only if steatorrhea is not controlled by enzyme preparations (LE 2a, C) [10, 19].

Limitation of fat in the diet is prescribed only in the case of intractable steatorrhea. Triglycerides of medium chain length (milk fat, palm oil and coconut oil) are not recommended for this group of patients (LE 1B, B). In severe exocrine insufficiency, parenteral administration of fat-soluble vitamins is prescribed (LE 1C, B).

SD 3 type (pancreatogenic) occurs at CP and after pancreatectomy. SD 3 type is associated with a 10-20-fold increase in the risk of pancreatic cancer. Treatment of pancreatogenic diabetes is not fundamentally different from the treatment of type 1 and type 2 (LE 4, C), but it has some peculiarities. Appointment of insulin even more increases the risk of pancreatic cancer due to overexpression of insulin receptors in the pancreas. Metformin is the first-line therapy, it in 50-70% reduces the risk of pancreatic cancer through anti-diabetic and anti-neoplastic effect. Insulin synthesizers should be avoided [9].

For patients with pancreatic-type pain, along with highly effective analgesics, antispasmodic therapy is often effective. Antispasmodics are prescribed for spasm of Oddi's sphincter, or papillitis, which impairs the flow of bile and pancreatic enzymes. Papillitis occurs in 21% of patients with chronic and 67% of patients with acute pancreatitis. The theoretical justification for the application of spasmolytics in CP is an attempt to reduce a pressure in the main pancreatic duct, common bile duct, duodenum by leveling smooth muscle spasm, especially Oddi's sphincter [1].

CP treatment is not an easy task, that can be seen from current research and treatment standards. Approaches to treatment continue to be constantly updated, expanded, improved.

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Novosibirsk State Medical University, Novosibirsk, Russia

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The present article discusses the level of evidence of different approaches to the treatment of pancreatic pain syndrome and substantiates the necessity of a rational choice of the most optimal therapy by medical preparations for relief of chronic pain in view of their possible side effects and complications.