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CHOICE OF PHARMACOTHERAPY FOR ACUTE DESTRUCTIVE PANCREATITIS (REVIEW)

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ВЫБОР ФАРМАКОТЕРАПИИ ПРИ ОСТРОМ ДЕСТРУКТИВНОМ ПАНКРЕАТИТЕ (ОБЗОР)

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Abstract. This paper is devoted to a modern, promising, minimally invasive endovascular method for treating acute pancreatitis: prolonged regional arterial pharmacotherapy. The main methodological and technical issues are discussed, on which there is no consensus in the literature. This primarily concerns the purpose and indications of the method in question, the timing of its initiation and duration, the drugs used, and evidence of its effectiveness using modern methods of statistical analysis.

Аннотация. Работа посвящена современному, перспективному, малоинвазивному эндоваскулярному методу лечения острого панкреатита: длительной региональной артериальной фармакотерапии. Обсуждаются основные методологические и технические

вопросы, по которым в литературе нет единого мнения. В первую очередь это касается цели и показаний к применению рассматриваемого метода, сроков его начала и продолжительности, используемых препаратов, а также доказательств его эффективности с помощью современных методов статистического анализа.

Keywords: acute pancreatitis, pancreatic necrosis, prolonged regional intra-arterial therapy, infectious complications, mortality.

Ключевые слова: острый панкреатит, панкреатический некроз, длительная региональная внутриартериальная терапия, инфекционные осложнения, смертность.

In the literature, the method of conservative treatment of acute pancreatitis discussed here is referred to by various names, but its essence is the same: prolonged regional arterial pharmacotherapy (hereinafter referred to as PRAP) in the complex treatment of patients with acute pancreatitis (hereinafter referred to as AP). This method should not be considered purely conservative, since it is essentially microinvasive endovascular pharmacotherapy. First and foremost, this concerns the indications for the use of this technique, certain methodological aspects, the optimal timing of its implementation, the composition of perfusion solutions, the assessment of its effectiveness, etc. Naturally, when discussing pharmacotherapy, it is impossible not to briefly touch upon the individual mechanisms of AP pathogenesis [1, 2].

There is no doubt that the prognosis for AP is based on the timely administration of emergency pathogenetic conservative and minimally invasive treatment, which in some cases can abort the development of pancreatic necrosis (hereinafter referred to as PN) and prevent the development of infectious complications [3].

An increase in the area of gland necrosis to 40–70% sharply increases the risk of bacterial infection with the spread of the infectious-necrotic process not only in the PG, but also in the peritoneal cavity and throughout the retroperitoneal tissue, which can initiate the development of massive severe endotoxemia with clinical signs of abdominal sepsis, leading to the formation of multiple organ failure syndrome and/or infectious-toxic shock [4-6].

One of the main causes of death in patients with necrotic forms of OP is systemic organ dysfunction with impaired blood flow [7, 8].

In the early stages of OP, the main pathogenetic role belongs to acute hypovolaemia, as a consequence of impaired metabolic, resorptive, and perfusion processes. As a result, the bioavailability of drugs administered directly to the affected area, primarily the liver itself, is reduced. Moreover, drugs entering the general bloodstream are partially bound to blood plasma proteins (albumins, globulins) and, as a result, become pharmacologically inactive. In OP, a significant disadvantage of intravenous administration of drugs is their inefficiency and low delivery to the liver tissue [9–12].

As a result, endogenous intoxication progresses, necrotic foci become infected, which requires repeated surgical interventions and is accompanied by high mortality – up to 85% [13].

In this regard, the development of methods for the selective regional delivery of drugs directly to the affected organ with an increase in their local concentration in the tissues of the pancreas is of particular relevance [14, 15].

Since the beginning of this century, we are aware of five candidate dissertations and two doctoral dissertations in Russia alone devoted to this method in the complex surgical treatment of acute pancreatitis [6-21].

A number of researchers have proven the advantages of regional intra-arterial administration of antibiotics and protease inhibitors (hereinafter referred to as PI) compared to intravenous infusion in pancreatitis and pancreatic surgery [22, 23].

Compared to intramuscular and intravenous administration, intra-arterial infusion increases the concentration of drugs in the organs and tissues of the abdominal cavity several 6–8 times, the concentration of 5-fluorouracil with this method of administration increases in pancreatic tissues by 12–18 times compared to intravenous administration. The concentration of nafamostat mesylate (a short-acting anticoagulant) administered by prolonged regional arterial infusion (PRAI) to dogs with experimental OP was 5 times higher than with intravenous administration [7, 24–28].

In another experimental study conducted on rats, a 10-fold increase in the concentration of this drug was found with prolonged regional arterial infusion (PRAI) compared to intravenous administration [25].

Purely theoretically, that prolonged intra-arterial therapy not only reduces the load on the pulmonary circulation in patients with severe pancreatitis, but also increases the concentration of drugs in the focus of pancreatic destruction several times over by "bypassing" the natural biological filters – the liver and lungs [18].

Many authors believe that, with the same safety as intravenous infusion, this technique is significantly more effective in terms of correcting metabolic disorders in the blood, lungs, cardiovascular system, and renal and hepatic dysfunction [6, 16]. The total number of registered complications of intravenous and intra-aortic catheterisation and therapy did not differ, which allows us to conclude that they are comparable in terms of safety [19].

In this review, we consider it necessary to discuss a number of important practical aspects of prolonged regional arterial pharmacotherapy in the complex treatment of OP. Indications: for which category of patients with OP is the drug therapy method in question necessary? One of the tasks of DRAI is to prevent the development of pancreatic necrosis in OP at the stage of microcirculation disturbance (ischaemia) and to prevent infection, i.e., to be proactive before infection occurs. The indication for DRAI is OP when CT with contrast agent administration reveals uneven contrast of the PS, which is not yet necrosis, but a manifestation of microcirculation disorders that can be observed in the early days of the disease. Early initiation of treatment can improve its results. When comparing the effect of treatment using intravenous infusion of protease inhibitors (hereinafter PI) and antibacterial drugs with IAT of the same drugs, the mortality rate in the latter was significantly lower [29].

Performed intra-arterial drug therapy in combination with prolonged regional blockade of the organ nerves of the celiac plexus in all patients with sterile pancreonecrosis (hereinafter PN): hemorrhagic, fatty, used it in combination with selective intestinal decontamination in the treatment of patients with moderate and severe AP, patients with severe acute pancreatitis, used it to treat patients with PN. Used it to treat complicated acute destructive pancreatitis (ADP). Nevertheless, most authors point to high clinical efficacy with improved survival when using prolonged regional intra-arterial infusion in the treatment of severe and complicated acute pancreatitis [17–37].

The method of transfemoral catheterisation of the celiac trunk and its branches (a. gastroduodenalis, a. lienalis) according to Seldinger-Edman with various modifications is used. Taking into account the location of the pathological focus in the pancreas, anatomically correctly determined the arterial vessel: in cases of damage to the body and tail of the pancreas, the splenic artery was catheterised; in cases of damage to the head, the common hepatic artery was catheterised; and in cases of damage to the entire gland, the celiac trunk was catheterised [14, 15, 38, 39].

Angiography of the celiac trunk and superior mesenteric artery is performed first. An artery from the area of inflammation is selected for the administration of drugs. If this area is located in the

head of the pancreas, the catheter (4–5 Fr) should be placed in the common hepatic, gastro-duodenal, or superior mesenteric artery. If the inflammation is located in the body and tail of the pancreas, the catheter is inserted into the splenic artery or dorsal pancreatic artery. In cases of total pancreatic involvement, the catheter is placed in the celiac trunk [40].

In our opinion, the most optimal vessel for prolonged regional arterial perfusion in the treatment of OP is the celiac trunk. Firstly, it is easier than catheterisation of its first- and second-order branches. Secondly, it covers the entire upper part of the abdominal cavity, which is quite acceptable in terms of the prevention and treatment of liver dysfunction/insufficiency, which is observed in AP in 47.4% of cases [14, 15].

In the oedematous form of AP, hepatic insufficiency (HI) is present in only 4.8% of cases [41], whereas in pancreonecrosis it is present in every fourth patient, and in infected pancreonecrosis in 41.5% [42].

In 40% of cases, it is the cause of death, and in destructive forms, in 90–95.2% of cases [41, 43, 44].

In addition, targeted delivery of antiseptory agents (proton pump inhibitors, H₂ histamine receptor blockers) is carried out, since all arteries of the stomach are branches of the celiac trunk. Additional catheterisation of the superior mesenteric artery is justified when the destruction is localised in the head of the pancreas. To establish the state of extra- and intra-organ arterial blood supply to the pancreas and the extent of organ damage, an angiographic examination is mandatory before perfusion drug therapy, which, incidentally, should also be performed before removing the intra-arterial catheter.

The assessment of intraorgan haemodynamic disorders, as well as the extent of pancreatic destruction, is most informative based on the results of multislice spiral computed tomography celiacography with contrast administration [20].

The basis for this is the well-known fact that in destructive pancreatitis (hereinafter referred to as DP), as a rule, there is a so-called "perfusion block," i.e., pathological changes in the vascular bed of the pancreas due to external compression and thrombosis of large arteries supplying blood to the organ, as well as spasm and microthrombosis of extra- and intra-organ arteries, which leads to the progression of hypoxia, necrosis, and prevents the access of drugs to the sites of damage [14-19].

The main pathogenetic role in the disruption of the microcirculatory bed of the pancreas belongs to the activation of the kallikrein-kinin system, as well as the transition of pancreatic cells to anaerobic oxidation, contributing to acidosis and endothelial dysfunction with microthrombus formation [3].

Intestinal paresis and increased intra-abdominal pressure – intra-abdominal hypertension syndrome – also impair microcirculation in the abdominal organs, including the pancreas [20, 45].

Preserved PA perfusion in patients with PN occurred in only 31.4% of patients. Whereas in 68.6% of cases, the blood vessels of the PA were partially or completely non-contrasted. Signs of extravasal compression of arteries and veins were present in 21.6% of cases, and occlusion of the gastroduodenal artery was present in 13% of cases. These are the morphological signs of vascular disorders. There were also functional signs. In 45.1% of cases, redistribution of contrast medium from the common hepatic artery to the splenic artery was observed. Spasm of the common hepatic artery was observed in 41.2% of cases. Impoverishment of the intraorgan arterial bed was observed in 54.9% of cases. Absence of the venous phase of blood circulation in the pancreas was observed in 25.5% of cases. Proximal perfusion block was present in 39.2% of patients with PN, distal block in 29.4%. Moreover, distal circulatory disorders were at the level of small intraorgan arteries, and proximal disorders were associated with occlusion of large extraorgan arteries, up to the celiac trunk [16].

According to S.B. Zergetaev, in 46.7% of patients with severe OP, the parenchyma of the pancreas was not contrasted partially (57.1%) or completely (42.9%) during angiography. Moreover,

distal perfusion block was usually observed in large-focal PN, and proximal perfusion block was observed in widespread PN [18].

The most complete picture of changes in the arteries supplying the pancreas in patients with acute destructive pancreatitis (ADP) before and after long-term regional intra-arterial drug therapy is presented [19].

The morphological features observed were: occlusion and stenosis of the celiac trunk (9.8%), thrombosis of the splenic artery (2%), occlusion of the superior mesenteric artery (2%), occlusion of the gastroduodenal artery (13.7%), and occlusion of the pancreaticoduodenal artery (17.6%). In 68.6% of cases, there was no contrast enhancement of the pancreatic parenchyma (35.3% - large-focal, 23.5% — subtotal, 9.8% — total). Signs of extravasal compression of arteries and veins were found in 21.6% of patients. There were also functional angiological signs: redistribution of contrast medium from the common hepatic artery to the splenic artery (45.1%), spasm of the common hepatic artery (42.1%), impoverishment of the intraorgan arterial pattern (54.9%), intensification of the intraorgan arterial pattern (23.5%), enlargement of the splenic vein (3.9%), earlier onset of the venous phase — up to 7 seconds (11.8%), late onset of the venous phase — after 11 seconds (11.8%), absence of the venous phase (25.5%), contrast depot in the LV projection (7.8%), avascular formations in the LV projection (2%).

Proximal pancreatic perfusion block was established in 39.2% of cases, distal – in 29.4%. In addition to regional drug therapy, selective catheterisation of the pancreatic arteries can sometimes be performed urgently in cases of AP in order to stop arterial bleeding from pseudoaneurysms [35].

Endovascular embolisation is considered the optimal method of prevention in destructive pancreatitis [46].

Results of prolonged intra-arterial drug therapy, according to a control angiographic study. After a course of regional intra-arterial drug therapy, none of the patients with destructive pancreatitis (DP) showed progression of pathological changes in the vascular bed. In 47.1% of patients, there was a complete restoration of pancreatic tissue perfusion, characterised by recanalisation of the vessels supplying it. Partial restoration of pancreatic tissue perfusion was observed in 9.8% of patients. In 9.8% of cases, the effect was absent on repeat angiography. In all patients with distal perfusion block, it was possible to achieve complete restoration of blood flow with good contrast of the gland parenchyma. In 39.2% of patients with proximal perfusion block, it was possible to completely restore blood supply to the pancreas in only 17.6% of patients. In 11.8% of the patients examined, almost all of whom had recanalisation of large arteries, these patients had distal perfusion block instead of proximal. In 9.8% of cases, there was no positive angiographic dynamics. In 7.8% of patients, avascularised formations (non-perfused areas of necrosis, delimited at the periphery by areas of increased vascularisation) were again detected in the projection of the PV, as a rule, arising at the site of contrast deposition during the initial angiography. Among the functional signs characterising changes in PV blood circulation, the predominance of intraorgan arterial pattern enhancement was observed [19].

Based on the analysis of 51 cases of long-term intra-aortic therapy in patients with PD, complications are possible in one quarter of patients. These include: erosive bleeding (1.4%), aneurysm of the catheterised vessel (1.4%), subcutaneous haematoma (8.3%), thrombosis of the catheterised vessel (4.2%), local infectious complications (9.8%), and catheter thrombosis (1.4%). Observed bleeding from the femoral artery puncture site in 6.5% of cases and catheter thrombosis in 3.2% of cases during selective catheterisation of the celiac trunk [30].

Timing of the onset of PRA. The authors' opinions on this issue are ambiguous, which is most likely due to differences in patients' clinical diagnoses, the severity of their general condition at the time of hospitalisation, the presence of complications, and other factors that cannot be ignored. The

time factor is crucial here, as the death of the pulmonary arteries develops rapidly – by the third day of the enzymatic phase of OP [3].

For example, G.L. Kuznetsov considers it advisable to perform it after stabilising the patient's condition, performing mandatory therapeutic and diagnostic procedures, emergency operations, which were performed in 97.5% of patients, on average 6.6 ± 0.5 and 2.5 ± 0.2 days after admission to the hospital, since the usual duration of the disease at the time of hospitalisation was 6.5 ± 0.6 days. A.M. Yatsyn performed aortic catheterisation on the second day in half of the patients with OP, on the third day in one third of the patients, and later in the rest. This discrepancy in timing is most likely explained by differences in the severity of the patients' condition at the time of their admission to the hospital. Sterile PN occurred in 100% of cases. However, the vast majority of authors believe that regional intra-arterial perfusion should be started as early as possible [3, 7, 14-18, 24, 47, 48].

Began to consider this method of intra-arterial administration of drugs no later than 3 days after the establishment of acute destructive pancreatitis. According to I.P. Shlapak et al. [14, 15, 36], adequate fluid resuscitation (restoration of microcirculation and increased cardiac output – the main component of shock treatment) in the first three days contributes to the stabilisation of the pathological process and reduces the transformation of the disease into more severe forms by 21.5%, which makes it possible to avoid surgical interventions and is probably decisive in terms of patient survival in the longer term [49].

Share this opinion. Of the 41 patients with destructive pancreatitis, 29 underwent catheterisation of the celiac trunk with simultaneous perfusion on the first day, 7 on the second day, and 5 on the third day [47].

Assert that early regional intra-arterial infusion of alprostadil (angioprotector and microcirculation corrector, antiaggregant, vasodilator) into the gastro-duodenal artery restores arterial blood flow to the head of the pancreas (according to control angiography), prevents or reduces the depth of necrosis (according to CT data), reduces the possibility of peripancreatic infiltrates forming, and significantly reduces postoperative mortality. Intra-arterial administration of pentoxifylline with heparin and antibiotics is accompanied by a reduction in the foci of necrosis and prevents their infection [48].

Believe that patients with PN should undergo prolonged intra-arterial therapy in combination with differentiated surgical and minimally invasive treatment during the reactive phase of the disease in order to prevent possible early and late complications [3].

I.P. Shlapak et al. disagree with the prevailing opinion that intra-arterial infusion therapy should be most aggressive in the early stages of OP [14, 15, 50].

According to E. de-Madaria et al., the largest volume of infusion therapy (more than 4.1 litres) in the early phase of OP is significantly and independently of other factors associated with persistent heart failure, acute accumulation of fluid in the organs and throughout the body, and increasing respiratory and renal failure [51].

In this regard believe that patients with respiratory and/or cardiac dysfunction require a restrictive infusion therapy regimen, i.e., a limited volume of fluid administered to the patient's body using vasopressors, in order to maintain stable haemodynamics [14, 15].

Compared different treatment durations depending on the onset of the disease [52, 54].

The mortality rate when conducting DRAI within the first 48 hours, 48–72 hours, and after these periods from the onset of the disease was 3.2%, 9.1%, and 26.3%, respectively. Later studies reported mortality rates of 11.9% in the first 48 hours and 23.6% after 48 hours [53].

Of course, patients with the most severe forms of the disease should undergo intra-arterial regional perfusion against a background of intensive peripheral and central intravenous infusion –

endovascular therapy. In the later stages of melting and sequestration of the pancreas, the intra-arterial infusion technique under consideration is not very effective [30, 55].

Dosages of medicinal products for PRAP and its duration. The duration is primarily determined by monitoring data on the effectiveness of the treatment. The infusion is performed using an infusion pump and/or FM controller device in continuous mode for 3–10 days [3, 16, 18, 36, 47, 56–58] (more often from 4 to 6 days), or longer – 10–18 days [6, 19]. The specific recommended doses of drugs used for IAPT are described below.

Intra-arterial perfusion pharmacotherapy programme. A pathogenetically justified intra-arterial perfusion programme should be balanced in terms of the quantitative and qualitative composition of solutions and pharmacological agents. As a rule, combinations of 2–3 or more drugs are used. For long-term regional arterial perfusion, the above drugs are used in various combinations: IP+antibacterial drugs [38, 59], disaggregants + antibacterial drugs [38], anticoagulant+antibacterial agent [59], anticoagulant + trental + antispasmodic [16], alprostadiol (antiplatelet and vasodilator) + antibacterial drug [38], IP (urinastatin) + anticoagulant [60, 61], antibacterial drugs + antisecretory agents [62], IP + antibacterial drugs + antispasmodic + trental [16, 36].

Long-term regional arterial infusion (LRAI) of IP and antibacterial drugs has been proposed as a special therapy. The effectiveness of LRAI IP and/or antibacterial drugs has been demonstrated, especially in the early stages of the disease [25, 32, 52, 53, 63].

H. Imaizumi et al. recommend nafamostat mesylate (240 mg) dissolved in 500 ml of 5% glucose solution, administered continuously at a rate of 20 ml/h. Imipenem (0.5 g) is dissolved in 100 ml of saline solution and administered into the artery every 12 hours. The duration of DRAI is 5 days, followed by a 7-day course of antibacterial drugs. M.V. Lazutkin et al. [47, 64] continuously administered heparin 10–20 thousand IU/day, trental 200 mg/day, and sandostatin (octreotide) 300–900 mcg/day intra-arterially in the treatment of destructive pancreatitis.

N. P. Shiryayev et al. administered a solution of the following composition through a catheter inserted into the gastro-duodenal artery for 3–5 days: S. Dropaverini 4.0 + S. Pentoxifyllini 5.0 + S. Verapamili 2.0, S. Octridi 0.1% in 100.0 ml of saline solution at a rate of no more than 10 ml per hour. G.A. Arutyunov et al. administered pentoxifylline (disaggregant) 10 ml, heparin 10,000 units, octreotide 0.3 mcg, followed by third- and fourth-generation cephalosporins or carbapenems at a daily dose of 3–4 g [3, 65]

The most comprehensive pathogenetically targeted methods developed protected by a Ukrainian patent, are a method for treating pancreatitis and a method for preventing septic complications of necrotising pancreatitis. Later, the results of experimental clinical studies of these treatment methods were summarised. These methods are based on cytoprotective therapy administered through the celiac trunk in the treatment of pancreatitis or into the superior mesenteric artery for the prevention of septic complications of necrotising pancreatitis. In the first case, a cytokine-protective complex is administered into the celiac trunk. It includes at least one of the following: a third- or fourth-generation antibiotic, an antioxidant (emoxipine), an antihypoxant (diavitol), an anticytotoxin (emoxipine or another agent), and an antiphospholipase (emoxipine, lidocaine) drug [57, 58],

To prevent septic complications of necrotising pancreatitis, the superior mesenteric artery is catheterised. The perfusion solution contains at least one of the following: a third- or fourth-generation antibiotic, an antioxidant (emoxipine), pentoxifylline, an antihypoxant (diavitol), the anti-cytokine pentoxifylline, and an antiphospholipase (lidocaine) drug. The perfusion rate of drugs is as follows: emoxipine 1% – 5 ml/h; pentoxifylline – 3.3 ml/h; lidocaine 2% – 4 ml/h; cephalosporins 1 g – 5 ml/h. Pentoxifylline and emoxipine solutions are used ready-made at 10 ml, while lidocaine and

antibiotics are diluted in 0.9% NaCl to 10 ml. Twice a day, 5,000 units of heparin are administered to prevent thromboembolic complications and maintain catheter patency.

At our clinic, patients with acute destructive pancreatitis (hereinafter referred to as ADP) undergo perfusion into the splenic artery with a pentacomplex of drugs: 1) papaverine 2% – 2.0 in 16 ml of saline solution, 2) ulinastatin 100,000 in 200 ml of saline solution twice a day, 3) trental 5.0 per 16 ml of saline solution, 4) contrical 10,000 units per 20 ml saline solution, 5) ceftriaxone 1.0 per 200 ml of saline solution. The duration of intra-arterial perfusion is 5 days, followed by intravenous administration of these drugs for at least 7 days [Zh.A. Doskaliev et al. [36]]. In our opinion, it would be more appropriate to optimise this protocol by replacing two anti-protease drugs with one, including new main components: anticoagulants (short-acting nafamostat and sulodexide), alprostadil (disaggregant and vasodilator), replacing papaverine with droperidol, using antioxidants and antihypoxants, anti-cytokine drugs, antiphospholipase agents, as well as drugs that regulate metabolic processes in cells.

In our opinion, the doses (single) of drugs administered intra-arterially should be 1.5 times higher than the minimum or average therapeutic doses, similar to the doses used in oncology for regional intra-arterial chemotherapy [66].

Solutions and pharmacological agents used for IAC attach great importance to the following as key components: saline solutions (physiological solution, Ringer's lactate solution), multifunctional balanced solutions, hydroxyethyl starch (HES) 130/0.6 [14, 15, 18, 67].

According to B.U. Wu et al. [68], compared to traditional NaCl saline solution, Ringer's lactate solution leads to faster regression of CVA. Intra-arterial infusion of HEC solutions in OP revealed a favourable regional tissue perfusion profile combined with a prokinetic effect [14, 15, 69].

Other solutions are also prescribed: rheosorbilact, glucose-novocaine mixture [30].

Anticoagulants and disaggregants, antispasmodics. There is no doubt that the nature and severity of vascular disorders in the PV basin and surrounding tissue depend on the duration of the disease and the extent of primary necrosis. Microcirculatory disorders lead to circulatory and tissue hypoxia of the PV tissue, including in areas where there is no direct influence of aggressive factors. This, together with the activation of LPO processes, forms the background for the further impact of aggressive factors in OP. This mechanism triggers a chain reaction in biological membranes, resulting in their destruction. There are primary (enzymes), secondary (biologically active amines) and tertiary (nitric oxide, pro-inflammatory cytokines, prostaglandins, etc.) direct aggressive factors [3].

Blockage of microcirculation determines the depth and extent of necrosis and is an important factor in possible infection [11, 70, 71].

Impaired microcirculation in the liver in the early phase of OP may play a key role in the progression of the destructive-inflammatory process [9, 11, 72].

The area of damage depends on the level of intraorgan perfusion disorders [6, 10, 73].

Therefore, most researchers believe that at the initial stage, regional intra-arterial perfusion therapy should be aimed at removing the so-called "perfusion block" in the arteries of the pancreas and its microcirculatory bed [74–76].

In the treatment of PN used heparin (20,000 IU/day), pentoxifylline (trental) (200 mg), and the antispasmodic verapamil (5–10 mg). Subsequently, to prevent local thrombosis, "preserved perfusion" was prescribed: low-dose antithrombotic drugs (heparin at 5–10 thousand IU/day) [16].

In the treatment of severe OP from the first day of prolonged intra-arterial infusion, increased the dose of heparin to 1–2 thousand IU per hour (24–48 thousand IU/day) with the addition of fibrinolysin activators (complamine up to 120 mg/day) – controlled hypocoagulation according to Lee-White 18–23 min. In the absence of perfusion block, standard intra-arterial infusion therapy with forced diuresis is performed for 3–5 days [18].

Thus, anticoagulants, disaggregants, and antispasmodics should be used when indicated (in the presence of perfusion block) as early as possible in the reactive phase of OP.

Cytoprotective drugs. It should be noted that virtually all drugs used for conservative treatment of AP are direct or indirect cytoprotective agents. There are drugs with direct membrane-protective properties, primarily antioxidants and antihypoxants.

Synthetic prostacyclins (iloprost, alprostadil, PGEI) stabilise the membranes of acinar cell lysosomes, restore microcirculation and inhibit proteases [77].

This category also includes drugs with antiphospholipase (lidocaine) and anticytokine (emoxipine, pentoxifylline) properties, as well as those that regulate cellular metabolic processes [57].

Enzyme synthesis inhibitors. They are administered in parallel with cytoprotectors to relieve the inflammatory process in the pancreas [6].

Most often, these are the cytostatic drug 5-fluorouracil, sandostatin and its analogues [3, 14, 15, 17, 30, 47].

At one time, this group of drugs was considered the main medication for treating OP [25].

In clinical guidelines proposed by Japanese specialists in 2003, in accordance with the principles of evidence-based medicine, it is recommended to use them as basic methods [29].

However, the question of their effectiveness remains highly controversial. It should be noted here that, according to some reports, sandostatin drugs are not fully capable of significantly reducing exocrine secretion of the pancreas [78-80] and are effective in the treatment of OP in combination with other protease inhibitors (ulinasatin, gabexate mesylate) [81].

Moreover, they can suppress the endocrine activity of β -cells in the pancreatic islets [82].

Proteolysis inhibitors (PIs) and antienzyme drugs. Proteolysis inhibitors (PI) [14,15] and antienzyme drugs [3] are effective in the early stages of the disease [25, 32, 36, 37, 63]. S.B. Zergetaev [18] prescribed Contrycal (at least 200 KIE) or Gordox (at least 2 ml KIE) per day to patients with severe AP from the first day. However, randomised clinical trials (RCTs) have not established a noticeable effect of IP (aprotinin, gabexate mesylate) on the course of mild OP [83,84], reduction in the frequency of surgical interventions and mortality rates [85-88].

This may be due to the short half-life of IP in vivo, insufficient daily dose of the drug [86-90], and microcirculatory disorders in the liver [89, 90].

American and European clinical guidelines for the treatment of OP also do not confirm the efficacy of IP [91, 92].

Many researchers believe that the autolysis theory does not explain all the triggering mechanisms in the pathogenesis of OP [93-98].

However, double-blind controlled studies conducted at the end of the last century demonstrated the high efficacy of IP (urinastatin, gabexate mesylate) [60, 61, 99].

With prolonged intravenous administration of gabexate mesylate (2400 mg for 7 days), a significant reduction in the incidence of complications and mortality in patients with OP [56], while the use of the drug at a dose of 900–2400 mg for 4–12 days resulted in a decrease in the frequency and severity of complications. Reconfirmed that there is no convincing evidence in favour of the use of intravenous protease inhibitors to prevent death, abdominal pain, pseudocyst formation, intra-abdominal abscess, surgical intervention, intestinal obstruction, or any complications of pancreatitis, except for complications after ERCP. There is no reliable evidence of an effect on reducing mortality, where the control mortality rate (CMR) was less than 0.1, but there may have been a reduction when the CMR was greater than 1.0 [100].

Most importantly, observational studies [54, 59, 64] and a randomised controlled trial [101] indicate the effect of continuous arterial infusion of IP in OP, including PN. It should also be noted that in OP, IP, in addition to its main anti-proteolytic action, is also capable of preventing vascular

thrombosis in circulatory disorders [102, 103] and altering cytokine secretion [102]. Most likely, these effects are not the result of direct IP mechanisms, but rather a consequence of the anti-proteolytic action that stops destruction and subsequent acute inflammation. Thus, the use of IP is clinically effective in OP only with intra-arterial regional perfusion of the drug.

Antisecretory drugs. Some authors use antisecretory drugs: proton pump inhibitors, bolus administration of quamatel, H₂ histamine receptor blockers. It is believed that the latter do not improve clinical outcomes [104]. Although the effect of drugs in this functional group in the treatment of OP is questionable, their use is considered possible in the early stages of the disease [14-18, 50, 104].

Antibacterial drugs. In PN, early adequate prevention of infection is always necessary – de-escalation antibacterial therapy [6, 25, 32, 36, 37, 63, 105].

Targeted intra-arterial administration of antibiotics in OP significantly increases their concentration in the focus of destruction and inflammation [18].

As antibacterial therapy for sterile forms of PN, third- and fourth-generation cephalosporins (ceftriaxone 1.0/day, clavulanic acid or fortum 4 g/day, cefepime 2 g/day) were prescribed to prevent purulent complications. For infected PN, ciprofloxacin 400 mg/day + metronidazole 1,000 mg/day were used [16].

Used empirical combination therapy for severe OP from the second day onwards: third- and fourth-generation cephalosporins or fluoroquinolones were prescribed in combination with clindamycin and metronidazole. For fungal superinfection, fluconazole 150 mg/day was used. Imipenem is most effective for combating infection in the pancreas in acute pancreatitis, as established by a randomised clinical trial [18, 106].

In acute necrotising pancreatitis, high concentrations of imipenem have been found in the tissue surrounding necrotic areas. Antibiotic therapy is usually continued until the symptoms of SSI regress, which corresponds to a score of less than 4 on the APACHE-II scale [30, 107].

The most effective antibiotics are third- and fourth-generation cephalosporins [3, 57]. Thienam is also used [3].

Antioxidants and antihypoxants. The activation of lipid peroxidation (LPO) processes plays a major role in the onset and development of functional and structural disorders of the pancreas and the body as a whole, along with circulatory and tissue hypoxia. Lipoperoxidation products are the main factors in the fragmentation and destruction of pancreatic cell membranes. Free radicals cause endothelial dysfunction, increasing permeability to active proteases that affect intracellular homeostasis, followed by leukocyte activation. They have chemotactic activity towards phagocytes and other immunocompetent cells [108].

In addition, under the action of free radicals, molecules involved in adhesion during microvascular thrombus formation are expressed [109].

That is, in this case, POL and hypoxia (circulatory tissue) can have a synergistic effect, leading to cytodestruction in areas of the PV tissue that are not directly exposed to aggressive factors. Therefore, the activation and direct use of antioxidants in the complex treatment of OP is of fundamental importance, especially since the antioxidant level of liver tissue is one of the lowest in the body. The degree of clinical manifestation of endotoxic syndrome directly correlates with a decrease in the function of the antioxidant system (AOS) and an increased content of under-oxidised products of POL. The lower the AOS indicators, the more pronounced the volumetric and haemodynamic disorders, and the more significant the hepatic insufficiency [15].

The antioxidant mexidol slows down destructive processes in the liver, more quickly limits inflammation, more rapidly relieves enzymatic toxemia and hyperglycaemia, and has a hepatoprotective effect. It has been used in the complex conservative treatment of the oedematous

form of OP and necrotic pancreatitis. However, they do not significantly alter the course of the disease in cases of irreversible decompensated systemic disorders [16].

In addition to mexidol, emoxipine and halovit are recommended for the treatment of patients with AP. Experimental studies have shown the effectiveness of other antioxidant drugs: etoxidol, cytochrome C in combination with sandostatin. Information on the use of antioxidants and antihypoxants for intra-arterial regional pharmacotherapy in the treatment of AP [57, 58].

Thus, the main pathogenetic mechanism of intra-arterial therapy for acute destructive pancreatitis (ADP) is the maintenance of compensatory reactions that contribute to the correction of endotoxemia (ET) and organ dysfunction. It is aimed at restoring microcirculation in the pancreas, reducing its enzymatic activity, preventing the development of purulent-septic complications, and treating them.

The effectiveness of long-term intra-arterial therapy for AP. The effectiveness of OP treatment is assessed by the primary criterion – mortality. There are also secondary criteria: 1) reduction of pain syndrome, 2) formation of pseudocysts, 3) intra-abdominal abscesses, 4) surgical interventions, 5) paralytic small bowel obstruction, 6) other serious complications, including multiple organ failure (MODS). In addition, general clinical indicators such as the length of stay in the intensive care unit, the duration of hospitalisation, etc., are used.

Monitoring of prolonged regional intra-arterial drug therapy for AP is assessed based on the dynamics of the clinical course, laboratory test data, and instrumental examination methods. The main criterion for uninfected pancreonecrosis is the "break" in the progression of the disease in the phase of enzymatic toxemia and the absence of purulent-septic complications [47].

It should be noted that in almost all studies known to us, the monitoring of the effectiveness of intra-arterial drug administration was carried out without using established severity criteria (the APACHE-II scoring system), which is a serious omission. Nowhere is the controlled mortality rate (CMR) in the control group indicated. With prolonged intravenous administration of IP – gabexate mesylate (2400 mg for 7 days), a significant reduction in the frequency of complications and mortality in patients with OP was noted. There is evidence of the effectiveness of IP DRAI and/or antibacterial drugs, especially in the early stages of the disease [25, 29, 32, 52, 63].

When comparing the effect of treatment with intravenous infusion of IP and antibacterial drugs with DRAI, combining both protease inhibitors and antibacterial drugs, the mortality rate in the latter was significantly lower [29].

Based on data obtained from the treatment of 53 patients with acute necrotising pancreatitis, DRAI nafamostat (a short-acting anticoagulant) in combination with antibacterial drugs reduced mortality by 6.5 times and completely eliminated the likelihood of infection, compared with intravenous administration of the same drugs [59].

Moreover, when these drugs are administered separately (nafamostat – DRAI, antibiotic – intravenously), mortality is reduced by at least 3 times, and the infection rate by 2 times. Intra-arterial administration of drugs to patients with acute PN significantly reduced the frequency of surgical interventions by more than 1.5 times (from 28.6% to 16.7%) and postoperative mortality (from 18.3% to 11.1%) [39].

The clinical and laboratory effectiveness of administering drugs into the "intra-arterial regional infusion tract" is present in uninfected (aseptic) pancreonecrosis. As for patients with infected pancreonecrosis, no significant advantages of this method over traditional treatment have been established. In cases of pancreonecrosis, prolonged arterial infusion of disaggregants in combination with an antibacterial drug in the early stages resulted in no fatalities and a more than 2.5-fold decrease in the percentage of surgical interventions, but the duration of hospital treatment did not change. In

other words, DRAI is most effective in the early stages of the disease, even in cases of pancreonecrosis [20, 48].

Describe a conservative treatment strategy that was used in 156 patients with uninfected OP over a period of 4–8 weeks. The limitation technique included local intra-arterial rheological therapy, which was performed on 98 patients. In 46 cases, video laparoscopic drainage was performed; in 12 cases, decompression retroperitoneal drainage (transabdominal, transgastric) was performed. Open surgery was mainly performed in cases of progression of the purulent-necrotic process. These conservative measures reduced mortality to 19.9%, whereas in cases of early extensive surgery for infected retroperitoneal necrosis with the formation of retroperitoneal phlegmon, mortality was 55.4%. In any case, the authors indicate that local rheological drug therapy reduces mortality to 21.4%, and video-laparoscopic drainage to 10.9% [21].

There are several retrospective case series whose results suggest that continuous regional arterial infusion may reduce mortality associated with acute necrotising pancreatitis [7, 64, 101].

According in cases of AP, the use of this method with five pathogenetically justified drugs (papaverine, ulinastatin, trental, contrycal, ceftriaxone) resulted in a significant reduction in the number of urgent surgical interventions, the duration of hospitalisation and, most importantly, mortality (from 11.1% to 5.6%); however, the percentage of septic complications decreased insignificantly [36].

As mentioned earlier, most authors note the highest clinical efficacy and reduced mortality when using prolonged regional intra-arterial infusion in the treatment of severe forms of acute pancreatitis. It is extremely difficult to perform a qualified meta-analysis of the effectiveness of the results of the methods of prolonged intra-arterial drug therapy proposed by the authors (both individually and in combination with other methods of surgical treatment). The main reason for this is the incomparability of patients in terms of age, sex, time of admission to hospital, nature and extent of pancreatic necrosis, clinical diagnoses and severity of the disease. Another reason is the virtual absence of full-fledged randomised controlled trials with sufficient evidence. The advisability of using a number of modulators of the course of OP (proteolysis inhibitors, somatostatin and its analogues, H(2) histamine receptor antagonists, etc.) has also not been confirmed by randomised studies and meta-analysis [22, 23].

S. B. Zergetaev concludes that in patients with severe OP, long-term (7–10 days) regional intra-arterial therapy reduces the frequency of purulent complications from 52.5% to 26.7%. And with the development of purulent-destructive complications, in combination with closed (mainly percutaneous) interventions, the overall mortality rate decreases from 22.5% to 10%, and postoperative mortality from 22.2% to 11.1% [18].

The reduction in postoperative complications and hospital mortality was 1.35 times (from 35% to 26%). Where sterile PN was present in all cases, the number of infectious complications decreased from 26.6% to 11.5%. With OP, it decreased from 23.5% to 7.6% [6, 17, 53].

Use of regional intra-arterial drug therapy in the complex treatment of pancreonecrosis reduced the number of purulent complications and infected forms from 78.6% to 58.8%, and mortality from 35.7% to 9.8%. Points to a decrease in infectious complications in patients with moderate and severe AP from 64.3% to 23.2% with the use of selective intestinal decontamination and regional intra-arterial drug therapy. Accurate prediction, early detection, effective prevention, and differentiated surgical tactics have made it possible to reduce the incidence of infectious complications from 62% to 38.5% and mortality from 29.8% to 18.2%. A similar percentage reduction in mortality — from 28% to 17.5%.[19, 21, 33].

In patients with complicated ODP, the method under consideration reduced mortality by 2 times (4% versus 8% in the control group). Further listing of treatment results from other researchers does not change the overall picture [30].

That is, we once again emphasize the lack of randomized controlled studies evaluating the clinical and prognostic effectiveness of prolonged regional intra-arterial drug therapy in the complex surgical treatment of patients with acute pancreatitis, as well as data obtained from a meta-analysis of several randomized controlled clinical trials. The majority of scientific works on this issue are based on small randomised controlled trials involving a limited number of patients or on non-randomised clinical trials. Most likely, this explains the absence of regional intra-arterial infusion therapy in the clinical guidelines of the Russian Federation and the Republic of Kazakhstan.

Based on the results of Cox's regression model, found a significant effect on improving the outcome of the early phase of OP – the earliest possible administration of intra-arterial infusion therapy using antisecretory drugs: somatostatin analogues – octreotide and gastric secretion blockers, as well as limiting the volume of infusion therapy in severe cases of OP. However, some researchers have reported the opposite, namely an increase in the frequency of surgical interventions due to infectious complications, which increases the length of hospitalisation [14, 15, 90].

In all the studies we reviewed, statistical processing of results and the evidence base are based on standard methods: Student's t-test, relative values (%). The difference in risk is not indicated – risk in the main group minus risk in the control group (RD). Positive values of intervention risk (RD) indicate an increased risk, while "-" indicates a reduced risk. For binary data, it is customary to calculate a weighted pooled estimate. To pool RD, a fixed-effect model weighted by the Mantel-Haenszel (M-H) method is used, followed by homogeneity testing. The homogeneity of studies is assessed using the I^2 test: $I^2 \leq 25\%$ – low, I^2 from 25% to 50% – moderate, $I^2 \geq 50\%$ – high heterogeneity. If the hypothesis of homogeneity is not confirmed, a random effects model is used with the Dersimonian-Laird (D-L) method. The possibility of systematic error is checked using the funnel method with the Begg criterion or the Egger criterion.

The number of patients needed to treat (NNT, i/RD) to prevent one undesirable event can be used as an indicator of treatment effectiveness. The number of patients who need to be treated to benefit (NNTB, the number of patients who need to be treated to benefit from the treatment of one additional patient) and the number of patients who need to be treated to harm (NNTD, the number of patients who need to be treated to harm from the treatment of one additional patient) are used for negative NNT. If the upper or lower limit of the 95% confidence interval (CI) was infinite, the NNT scale including infinity is used. The severity of OP is usually assessed using the Ranson score and health status assessment (APACHE-II) [107-109].

Statistical analysis should be performed using appropriate statistical software. We are aware that the above methods of statistical analysis are not yet widely used in Kazakhstan and the CIS countries, but their widespread implementation is only a matter of time. In concluding this analytical review, it should be noted that regional drug therapy is not recognised by all researchers as the most effective method in the complex treatment of OP. The use of this method of conservative treatment is inferior to the method of video laparoscopic drainage in terms of the frequency of fatal outcomes by almost 2 times (21.4% and 10.9%, respectively). The study involved 470 patients, of whom 314 (67%) had infected cases (retroperitoneal abscesses, phlegmons).

Mortality rates for patients with PN undergoing laparoscopic sanitation and drainage are more than twice lower than for those undergoing laparotomy (17.2% and 37.5%, respectively). With the aim of stabilising the general condition of patients with OP, performed laparoscopic drainage of the abdominal cavity prior to intra-arterial administration of drugs in 16.8% of cases. [3, 65].

In conclusion, we can make several important generalisations, in our opinion. The high clinical, laboratory, and prognostic effectiveness of prolonged regional intra-arterial perfusion in the complex surgical treatment of patients with acute pancreatitis is beyond doubt. This method is most clinically and laboratory effective in the treatment of patients with uninfected (aseptic) pancreonecrosis in terms of preventing the progression of destruction and necrosis in the pancreatic tissues and the development of infectious complications. In cases of infected PN, as well as in the late stages of the disease with total autolysis and sequestration of the pancreas, this method is not very effective. Not all methodological aspects of the implementation of this method have been definitively resolved to date. Prolonged regional arterial pharmacotherapy for patients with acute pancreatitis should begin as early as possible and be differentiated depending on the nature and extent of pancreatic damage, as well as taking into account the severity of the patient's condition. The duration and doses of continuous regional intra-arterial perfusion pharmacotherapy should be determined by monitoring the effectiveness of the treatment. There are no fundamental differences in the opinions of various authors regarding the medicinal determinants (drugs) necessary for intra-arterial regional perfusion. However, the pharmacotherapy of this method needs to be constantly optimised. Prolonged regional arterial pharmacotherapy is most effective in the treatment of severe forms of acute destructive pancreatitis in combination with laparoscopic drainage of the omental bursa and/or percutaneous drainage of the retroperitoneal space, as well as selective decontamination of the intestine. The method under consideration has great prospects in terms of both improving purely technical aspects and developing new protocols and regimens as more effective pathogenetic drugs with targeted action or polypotent properties become available. It may be necessary to develop the use of membrane-stabilising and anti-lipase drugs, antioxidants, immunomodulators, new anti-proteolytic drugs, more effective modern antibiotics, etc., in complex therapy.

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