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PANCREONECROSIS. BACKGROUND

Acute pancreatitis is an inflammatory disease of the pancreas which is one of the leading causes of hospitalization among patients with gastrointestinal tract diseases. Alcohol abuse and gallstone disease are long-known risk factors. However, today new causes of the disease improving understanding of the disease along with the aspects of pathophysiology are known. As the incidence and hospitalization rate of acute pancreatitis increase, consequently, the need for effective treatment is growing either.
***Keywords**: pancreatic necrosis, hypothermia*

Relevance of the study: The clinical course of acute pancreatitis is divided into mild and severe. Severe pancreatitis is usually the result of pancreatic necrosis. The morbidity and mortality from acute pancreatitis is higher when the gland is undergone with necrosis, especially when the affected area becomes infected [1]. It is important to identify patients with pancreatic necrosis in order to apply appropriate treatment. In recent years the treatment tactics for these patients have moved from early surgical intervention (necrectomy) to intensive care, with special criteria for surgical and conservative treatment of the patient [2].

Histologically, acute pancreatitis can be classified as interstitial edema or as necrosis, depending on inflammatory changes in the parenchyma of the gland. The International Symposium on Acute Pancreatitis in 1992 defined pancreatic necrosis as one or more diffuse or focal areas of non-viable pancreatic tissue [3].

Pancreatic necrosis is determined during surgery or at an autopsy. Pancreatic necrosis is diagnosed using computed tomography of the abdomen with intravenous contrast. Whereas normal pancreatic microcirculation is disordered during acute necrotizing pancreatitis, the affected areas of the gland do not show normal contrast enhancement. Lack of normal contrast enhancement can be better detected several days after the initial clinical manifestation. Computed tomography of the abdomen with contrast is the gold standard for non-invasive diagnosis of pancreatic necrosis with an accuracy of more than 90%, with necrosis of the parenchyma of the gland more than 30% [4].

The total level of lethality caused by severe acute pancreatitis is 30%. The lethality is divided into 2 stages. Early death occurs 1-2 weeks after the onset of the disease and is associated with multi-system organic insufficiency caused by the release of inflammatory mediators and cytokines. Late death is the result of a local infection or sepsis. Whereas acute necrotizing pancreatitis remains sterile, the overall mortality rate is about 10%.Infection triples the level of mortality [5].

In the process of supervision of the patient local and systemic complications of acute necrotizing pancreatitis may occur. Systemic complications include acute respiratory distress syndrome, acute renal failure, shock, coagulopathy, hyperglycemia, and hypocalcaemia. Local complications include gastrointestinal bleeding, infected necrosis and adjacent bowel necrosis. Late local complications are pancreatic abscess, pseudo-cysts.

Clinically, it is difficult to distinguish sterile pancreatitis from the infected one as in cases fever, leukocytosis and severe abdominal pain occur. Timely diagnosis of infected necrotizing pancreatitis is very important since without intervention the mortality rate reaches 100% [5].

One of the factors in the development of acute pancreatitis aggravating prognosis of treatment is smoking. A number of prospective studies report that metabolites from cigarette smoke, namely nicotine and NNK (nicotine derivative nitrosamine ketone) can cause functional and histological changes in the pancreas. Their main mechanism of action is the influence on the secretion of pancreas acinal cells and zymogens by means of nicotinic preganglionic receptors. The impact on micro vascularization of the pancreas passes through the path of nitric oxide (endothelial vasodilation factor, leading to vasodilation). There is indirect evidence that nicotine and acrolein lead to CTFR gene dysfunction thereby affecting ductal secretion. The effect of cigarette smoke metabolites on stellate cells and islets requires further scientific study [6]. Medical literature gives some data that malfunction of the stellate cells of the pancreas can lead to the development of pancreatitis and pancreatic cancer [7].

The incidence and mortality from acute pancreatitis is largely determined by the level of distant organs insufficiency in case of severe attacks. It is considered that this systemic manifestation of the disease initially located and limited to the pancreas is the result of the activation of various pro-inflammatory and anti-inflammatory mediators released from the pancreas by various other organs during the disease. Studies have shown that these mediators are produced in various tissues in a specific sequence triggered by the local release of pro-inflammatory mediators such as IL-1β, IL-6 and IL-8 which cause systemic inflammation and lead to inflammatory infiltration of distant organs with multiple organ failure and death.

The authors proved that the co-localization of digestive enzymes and lysosome hydrolase play an important role in the development of destructive process which gives a trigger for the activation of digestive enzymes in the intra-acinar cell [9].

Systemic manifestations of acute pancreatitis are the cause of death in most cases and this is due to the action of specific inflammatory cytokines. The sources that studied the information about the involvement of cytokines in clinical and experimental pancreatitis note that some cytokine and other inflammatory mediators are rapidly produced during acute pancreatitis. These mediators appear in many tissues regardless of the model of experimental pancreatitis and the etiology of the disease among people. Prevention of these mediators activity has a profound beneficial effect on experimental animals [10]. In addition, prospective clinical study observes an imbalance between IL-1β / IL-1RA in severe acute pancreatitis with pulmonary insufficiency while IL-1RA is an early marker of disease severity and IL-6 is the best prognostic indicator of pulmonary failure [8].

At the moment, flaxinellone is a natural inhibitor of inflammation and one of the newest drugs for the experimental treatment of acute pancreatitis. It is obtained from the root of perennial herbal plant of DICTAMNUS(Fraxinella) group. Its action was jointly studied by scientists from Wonkwang University, South Korea. A model of acute pancreatitis was hourly reproduced by means of intraperitoneal cerulein injections for 6 hours in rats. The scientists concluded that intraperitoneal injection of flaxinellone inhibits pancreatic activation of many inflammatory mediators such as NAGHT, LRR and PYD, NLRP3, PY-CARD,

caspase-1, IL-18 and IL-1β in case of acute pancreatitis. In addition, fluxinellone treatment reduced pancreatic damage, suppressed the activity of serum amylase and lipase, the infiltration of inflammatory cells such as neutrophils and macrophages but did not affect pancreatic edema [11].

In clinical practice, hypothermia is used to combat systemic reactions after ischemia, cell damage and it is also studied as a mechanism of inhibition of processes such as cardiogenic shock, lung damage, intestines, reperfusion injuries of the lungs, liver and endothelium. Numerous studies have shown the immunomodulation effect of hypothermia including a decrease in pro-inflammatory cytokines (TNF-α, IL-6), stimulation of anti-inflammatory cytokines (IL-10), a decrease in systemic oxidative stress and inhibition of neutrophils, monocytes and macrophages. The most notable study was conducted on the cerulein model of acute pancreatitis among rats, where it was shown that therapeutic hypothermia reduces serum IL-1, IL-6, TNF-α, increases serum IL-10, reduces serum amylase and lipase and reduces the histological degree of pancreatic damage glands in comparison with norm thermic one and significantly increases survival level. Therapeutic hypothermia is actively used to treat traumatic brain injury, neonatal asphyxia, spinal cord injury and cardiac arrest.

The first data on the use of local hypothermia as a method of treating acute pancreatitis dates back to 1966 [12]. The studies were conducted under V.V. Vinogradova with R.A. Markosyan and V.P. Burlachenko; they came to the conclusion that local trans-gastric hypothermia positively affects the course of acute pancreatitis. Further, the positive effect of cooling the pancreas was noted in the reports of scientists such as I.Z. Kozlov in 1969, [13], I.V. Babrys 1972, [14], A.G. Caravan in 1976, V.G. Vasilkiv in 1977, [15].

A big contribution in the study of hypothermia in the cases of pancreatitis was made by A.A. Shalimov and co-authors. They used the method of hardware hypothermia. The book Clinical Surgery, 1982, 11, p. 1-7 provides information: "The apparatus" Cryoelectronics -2 "equipped with a cryo-applicator is tightly pressed to the cooled surface of the organ". The temperature in the zone of exposure to cold is reduced to 0°-4 ° C within 3-8 minutes and in this mode cooling is continued to 10-20 minutes while the gland tissue is cooled to 24 ° C. After the termination of cold exposure the temperature in the gland increases independently, but it remains 0.5°-1.5 ° C below the reference value. Manipulation leads to a noticeable edema decrease of the gland. Cryogenic action on the gland is also carried out using a latex balloon which is connected with tubes to a reservoir supplying 30° ethanol. The balloon is introduced either into the cavity of the stomach or into the lesser sac. The duration of cooling is 2-4 hours every 6-8 hours for 1-2 days. The main disadvantage of the method mentioned above according to V.I. Shaposhnikov is "the need for a wide opening of the lesser sac with full exposure of the gland and the impossibility of uniform and volumetric cooling of all parts of the organ due to the roughness of its surface and the presence of dense elastic infiltration of the tissue which is observed in case of destructive forms of acute pancreatitis". Using the prototype model of A.A. Shalimova, V.I. Shaposhnikov offered his own method of hardware hypothermia. This method includes chloroethyl irrigation of the front and side surfaces of the gland with free evaporation into the atmosphere. Afterwards a layer of ice crystals forms on the surface of the gland appears and allows reducing the temperature of the gland to 0°-4 ° C while destruction exocrine apparatus with preservation of the function of islet tissue is inhibited. (RF patent, No. 2110219, publication date 05/10/1998)

At the present stage of the development of biomedicine and biotechnology a multi-disciplinary team of mechanics and bioengineers of Temple University, Philadelphia offered an innovative method to solve the problem of acute pancreatitis. They constructed a nasopancreatic stent which allows using endoscopy to cool pancreatic tissue locally. As a result of in-duct cooling cell damage is reduced and the inflammatory process slows down consequently therapeutic effect is achieved. The invention is highly estimated by the United States National Institute of Biomedicine and Biotechnology.

In 2011, Dr. Tao, Jao, and Lee conducted a study on a mouse model of myocardial ischemia at the Texas University of Health and Sciences. They studied the influence of adenosine 5'-monophosphate on the ability to reduce ischemic damage during myocardial infarction. Adenosine 5'-monophosphate is a recently discovered biomolecule that allows not hibernating mammals to achieve fast and safe hypothermia. This is the first endogenous biomolecule possessing this effect [16]. The model of myocardial ischemia was reproduced by ligation of the left anterior descending coronary artery followed by reperfusion. In comparison with the norm thermic control group mice treated with 5'-AMP induced hypothermia showed a significant decrease in neutrophil infiltration and a decrease in the expression of matrix metallopeptidase 9 (MMP-9) in the myocardium. The total area suffered from myocardial infarction was also smaller among mice treated with 5'-AMP-induced hypothermia (AIH). According to the results of the study, the scientists came to the following conclusions that mice receiving a high dose of 5'-AMP pass into a transient hypo metabolic state. At appropriate ambient temperature (Ta) the internal body temperature (Tb) of mice can be safely reduced to 15°-16° C. The decrease level of the animal Tb can be regulated by controlling Ta. Treatment with the use of 5'-AMP-induced hypothermia has a cardio protective effect after myocardial infarction. [17]

In 2012, scientists from Qingdao Universities, China conducted a study on rats confirming the therapeutic effect of AIH on lung damage model caused by lipopolysaccharides. They examined either the level of inflammatory cytokines in plasma and on fluid taken using bronchoalveolar lavage and pathological changes in the lungs. As a result the studies found that AIH can reduce the level of inflammatory cytokines such as TNF, IL-1β, IL-6 and increase the level of anti-inflammatory cytokines such as IL-10 thereby reducing lung damage [18].

There is also some data that 5'-AMP-induced hypothermia has a neuroprotective effect. In 2015, scientists from Jiao Tong University, Shanghai with scientists from the University of Texas, Houston conducted a study on a rat model of cerebral ischemia. A model of cerebral ischemia was reproduced by occlusion of the middle cerebral artery. As a result, rats treated with AIH had a significant decrease in neutrophil infiltration of neurons, matrix metalloproteinase 9. The total area of the infarction zone was significantly smaller in rats treated using AIH in comparison with the control group [19].

In 2013, scientists from Qingdao University, China published their research results by examining the effect of AIH on rat with acute pancreatitis models induced by L-arginine. They concluded that AIH is able to make a protective effect on the models of acute pancreatitis and express the following manifestations as a decrease in mortality, pancreatic edema decrease, a significant decrease either in serum amylase, IL-6, IL-1β, TNFα and in the activation of nuclear factor (NF-kB), a significant reduction in hemorrhage and necrosis of acinar cells [20].

Conclusion: Thus, the authors concluded that the cardio-protective, neuro-protective, protective effect on inflammation of the lungs and pancreas of 5'-adenosine monophosphate is based on hypothermia.

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ПАНКРЕОНЕКРОЗ. ФОН

Түйін: Клиникалық практикаға жедел панкреатиттер мен панкреонекроздар кезінде жоғары ақпаратты зерттеу әдістерін енгізуге қарамастан, протеаз тежегіштерін қамтитын дәрі-дәрмектік терапияның тиімді тәсілдерін пайдалану, панкреонекрозды емдеудің қанағаттанғысыз нәтижелерінің жиілігі мәселенің шешілмегенін көрсетеді.
Түйінді сөздер: панкреонекроз, гипотермия

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ПАНКРЕОНЕКРОЗ. ФОН

Резюме: Несмотря на внедрение в клиническую практику высокоинформативных методов исследования при острых панкреатитах и панкреонекрозах, использование эффективных способов медикаментозной терапии, включающая ингибиторы протеаз, частота неудовлетворительных результатов лечения панкреонекроза указывает на нерешенность вопроса.
Ключевые слова: панкреонекроз, гипотермия