The effectiveness of local cryotherapy in the treatment of pancreatic necrosis

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Introduction

Among the urgent diseases of the abdominal organs pancreatic necrosis is reported to be one of the most challenging issues due to 40-fold increase of frequency over the last 20 years. The disease is often accompanied by life-threatening complications such as purulent necrotic parapancreatitis, multiple organ failure, sepsis and mortality up to 82%.

Promising opportunities for the treatment of this disease are connected with the use of local cryotherapy (LCT). It was proved that LCT has a multifactorial therapeutic effect - antiinflammatory, cytostatic, anti-cytokinetic, antienzyme, antibacterial, hemostatic, analgetic, immunomodulating and regenerative. These factors substantiate the use of LCT in pancreonecrosis treatment.
The range of low temperatures effects on biological tissues is extremely wide: from destruction to organotypic regeneration. The injuries in cryotherapy are classified in: primary, associated directly with the destruction of cells under the influence of low temperatures, and secondary - as a result of hemodynamic disorders and aseptic inflammation.

Biological tissues are dense, resilient and energy-rich system. There are $10^{10} - 10^{12}$ cells in one cubic centimeter, and one gram of the human body emits energy 10 thousand times more than one gram of the sun.
LCT application and factors influencing it

There is still no sound concept of the mechanism of primary tissue damage. One should take into account:
1) the thermophysical properties of the tissues (metabolic and microcirculatory characteristics);
2) both extensive thermodynamic variables (mass, volume, entropy, energy) and intensive (pressure, temperature, density, concentration, electric potential);
3) the state of water in the tissues;
4) layering of tissues;
5) natural cryoprotection of living tissues associated with a complex system of interstitial and intraorganic regulatory interactions.

All the mentioned above determines the characteristics of the alternative, disculatory and regenerative processes in cryotherapy.
**LCT application and factors influencing it**

The focus of cryoapplication consists of three zones: the zone of freezing to -20°C, the cooling zone is from -20°C to +5°C and the zone of hypothermia, from +5°C to +37°C. This focus possesses biological inertness, causing only minimal perifocal reaction.

Healing effect of LCT can influence all the mechanisms and clinical symptoms of pancreonecrosis pathogenesis, improving the diseases management. It favorably differs LCT from application of other physical factors.
The pathogenesis of pancreonecrosis involves four main processes:

1) lipolysis;
2) proteolysis;
3) demarcation inflammation;
4) pancreatogenic toxemia.

The production of proinflammatory mediators, vasoactive substances, cytokines, activation of lipid peroxidation and immunodeficiency are of great importance.
Treatment options and strategy are specified by classification of a disease. In pancreonecrosis, it includes clinical and morphological form, stage and severity of the disease.

The inherent features of the pancreas as an organ, especially its possible pathology should be taken into account for effective use of LCT in pancreatic necrosis.
LCT application and factors influencing it

The pancreas is a complex three-dimensional structure in configuration, having a variety of geometric shapes in different parts (head, body, tail). It has a complicated topographic-anatomical location and close relationship with a number of important structures in the retroperitoneal region and the abdominal cavity (retroperitoneal tissue, duodenum, stomach, large blood vessels). This can lead to simultaneous damage to the abdominal cavity and retroperitoneal space in case of pancreas pathology.
In functional terms, pancreas is a gland of both exocrine and endocrine secretion. Due to the features of the pathogenesis of pancreatic necrosis, the main objective of LCT is the reduction of exocrine functions and the creation of "physiological extirpation" of the pancreas. The LCT technique should be applied in a way to preserve the endocrine function, represented by the cells of the Langerhans islets, which are unequally distributed throughout the pancreas.
When using LCT, it is necessary to take into account thermodynamics and thermophysics of the pancreas tissue, stage of the disease, degree of damage, the bioplasticity of the tissue, the coefficient of heat capacity and thermal conductivity, their alterations due to inflammation and colliquative necrosis, the amount of hemoperfusion and its changes due to alterations of hemodynamics and local microcirculation, development of local and general complications.
LCT application and factors influencing it

A necessary condition for LCT application is the determination of the area and depth of pancreatic lesions by instrumental methods. When performing LCT it should be noted that various pathomorphological changes can occur simultaneously in different parts of the pancreas. Response of different parts of pancreas to LCT differs. Response of the proximal part parenchyma to LCT of the tail was not reported. Response of the distal part parenchyma to LCT of the head is due to the anatomical structure of the excretory system and significant alteration of carbohydrate metabolism.
Indication of LCT and the choice of this technique are caused by the frequency of severe complications which are also typical for pancreonecrosis. At the present stage, it is necessary to develop clear indications for LCT application as an alternative method in the treatment of pancreatic necrosis. This generally refers to the main, and the most difficult problem of surgical treatment of pancreatic necrosis, still far from objectification.

Calculations using biophysical constants and experimental studies were performed to develop the LCT protocol for pancreonecrosis treatment.
LCT application and factors influencing it

To develop the temperature and duration regime of LCT, an experimental study of LCT thermodynamics in the pancreas of dogs was performed. Cryoapplicator with temperature of 140-160°C was applied by contact method for 90-120 seconds on the front surface of the pancreas in 3-4 points, resulting in decrease of the back surface temperature to 20-23°C, rarely to 15-18°C. This fact demonstrates the ability of LCT to freeze the whole thickness of the pancreas to reduce its exocrine function.
Clinically, 97 patients with infected pancreatic necrosis (IPN) were subjected to LCT by primarily the contact method. The comparison group consisted of 116 patients. The groups were identical in age, severity and duration of the disease. During the operation, after the dissection of the gastrocolic ligament, the anterior surface of the pancreas was exposed. Titanium nickelide cryoapplicator with a diameter of up to 1 cm and the tip temperature of 140-160°C was applied in 3-4 points of the most altered tissue for 20-30 seconds with the cycle repeated 2-3 times. Parenchymal bleeding in hard to reach places was stopped using cryoapplicator for 5-10 seconds, which is 4 times faster compared to other hemostatic methods.
One of the most frequent and threatening complications as parapancreatitis (PP) develops in 100% of cases. So, the pancreonecrosis and parapancreatitis can be regarded as a single pathological process. If necessary, surgical interventions on the biliary tract were performed. The operation was completed with bursoomentostomy accompanied by lumbotom in advanced process.

A more prompt normalization of clinical and laboratory data (by 3-4 days), a 12% decrease in purulent-septic complications and a 3.1% decrease of bleeding frequency were reported in the experimental group. Postoperative mortality in the experimental group was 12.2% lower compared to the comparison group.
Conclusions

The presented results demonstrate a significant clinical effect of LCT in the surgical treatment of pancreonecrosis. Development of fundamental sciences, further improvement of thermodynamic, kinetic, morphological and histoimmunological factors as well as engineering technology improvement will contribute to wider implementation of the pathogenically substantiated LCT method into clinical practice.
THANKS FOR YOUR ATTENTION !!!

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