Efficiency of cytokines, glutargin and vortex pulse magnetic field in the treatment of patients with chronic pancreatitis

O. O. Krylova, V. M. Ratchik, V. E. Kudryavtseva, A. I. Rudenko, V. A. Makarchuk

Institute of Gastroenterology of the NAMS of Ukraine, Dnepropetrovsk, Ukraine

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Chronic pancreatitis (CP) is a serious disease that is not only widespread, but has a long course, serious complications, significantly affects the quality of life of large segments of the population, has a high social value [1, 7, 8, 10].

Until now there is no drug for specific treatment of CP, and the aim of conservative impact is a treatment of acute disease, chronic pain, exocrine/endocrine pancreatic insufficiency, correction of metabolic disorders and complications [5, 6, 9, 15].

Central code and the object the use of drugs is a pain syndrome, which is characteristic of the disease [2, 4, 11]. Treatment of CP includes non-pharmacological (lifestyle modification, diet), medical, endoscopic and surgical. According to some scientists, the basic components of CP treatment, including the elimination of harmful factors, pain relief through the use of analgesics, narcotic and drug in combination with antidepressants, reducing of intrapancreatic pressure, the appointment of enzyme preparations, ductal decompression (endoscopic or surgical), nervous blockade transmission (solar plexus blockade, thoracoscopic splanhectomy), surgery after failure of conservative treatment (resection of the pancreas, pancreatectomy) [3, 12, 13, 14].

Materials of the research. The observation included 210 patients with CP who underwent a comprehensive survey followed a conservative choice, and in some cases — surgical treatment in the clinic SI "Institute of Gastroenterology of the NAMS of Ukraine" for the period from 2006 to 2012.

Among surveyed were 169 men and 41 women, age of the patients ranged from 26 to 72 years, the average age was (47,3±0,7) years. Ratio of women and men — 1:4.1.

According to the Marseille-Roman Classification 1998, patients (210 people) were divided into four clinical groups: 26 patients (12.4%) for obstructive form of CP, 56 patients (26.7%) of calcific CP, 78 patients (34.1%) of parenchymal fibrous form, 50 patients (23.8%) of CP complicated with pseudocyst. All patients were studied risk factors for the different morphological forms of CP and quality of life; evaluated the possibilities of modern methods of diagnostics of different morphological forms of CP; by morphological features of the pancreas, role of lipid peroxidation and antioxidant protection (POL-AOP) in the progression of morphological forms and features CP lipid spectrum of the blood of patients; studied the diagnostic possibilities of markers of inflammation, fibrosis, stone, apoptosis in morphological forms of CP; developed diagnostic and therapeutic algorithm CP considering factors of disease progression and assessed its effectiveness in improving the clinical course of disease and quality of life of patients.

To study the effectiveness of the proposed treatment, the patients were divided into two groups: I — 34 patients of the main group, and II — 25 patients of the comparison group.

Therapeutic strategy in CP was taking into account the complexity and pathogenetic features of the disease. Therapeutic tactics in these patients included a set of tools and the basic principles to achieve the main goal — to halt or slow the progression of CP, improvement of patients achieving remission and its extension. It was used in the treatment methods that directly affect the regulatory system, promoting braking fibrotic process.

Baseline CP treatment was conducted according to the standards [6]. Medical complex designed to solve several problems: exclusion provoking factors (alcohol, drugs, obstruction); pain relief; correction of exo- and endocrine insufficiency;

treatment of related disorders. Depending on the severity of abdominal pain syndrome, used stepwise treatment of CP, which includes the following components: diet, split meals, fats less than 60 g/day; pancreatic enzymes (25-40,000 lipase units for the main meal and 10,000 lipase units — for lunch), H2-blockers of histamine receptors or proton pump inhibitors; narcotic analgesics (aspirin, diclofenac, ibuprofen, piroxicam); octreotide (sandostatin); endoscopic drainage; Narcotic analgesics (butorphanol, antakson, fortal, tramadol, sedalhin-neo); solar plexus blockade; inefficiency — surgery. To correct nutritional deficiency prescribed mid-chain triglycerides (trisorbon) and fat-soluble vitamins A, D, E, K.

The therapeutic approach to CP in its early stages should include a mechanism to interrupt molecular-cellular level activation of fibroblasts and their transformation to myofibroblasts, and progressive accumulation of collagen in the extracellular matrix, which expression indicates the irreversible formation of sclerotic changes in cancer. Therefore, for the normalization of proinflammatory and profibrotic cytokines and correction of immune system we used autocytokines therapy as a 3-dial-up subcutaneous administration of the autocytokines created by peripheral blood mononuclear cells of patients who received stimulation cascade. Course of autocytokines therapy was administered on the 14-16 day stay of the patient in the clinic (in subacute period of the disease), sessions conducted at intervals of 3-5 days, autocytokines dose — 100 mg/ml.

To limit oxidative stress and reduce lipid peroxidation products, improve the AOP system and normalize the metabolism of collagen administered to patients with CP glutargin 3 tablets (0.75 g) three times a day for 15-21 days.

For relief of chronic pain used vortex pulse magnetic field (VPMF) with influence on the projection of the pancreas and biologically active points on 5 — 15 minutes rate 10 — 15 sessions. VPMF activates defense mechanisms of the body by improving microcirculation, normalization of blood rheology, biochemical parameters and disturbances of the immune system, changes the speed of transmission of nerve

impulses. VPMF used in 8-10 days of treatment (during subsiding exacerbation). Duration of treatment — 3-4 weeks to complete normalization of clinical data, the decline in indicators of inflammation, loss of neutral fat, starch and the muscle fibers in the feces.

Research methods — general clinical, instrumental (endoscopy, ERCP, X-ray, CT, ultrasound), functional (gastric and duodenal intubation), morphological (determining the degree of pancreatic fibrosis, apoptotic nucleases, morphometry), biochemical (determination of POL and AOP, middle molecules (MM), collagen synthesis products — oxyproline protein-binding (OP_{pb} and CC), immunological (enzyme to determine blood levels of interleukins TNF-α, TGF-β1, REG-1α, lactoferrin, fecal elastase-1, methods of analysis of immune status and nonspecific resistance of the organism), microbiological (microbial definition contamination of gastric contents and ducts of the pancreas), experimental. We used the method of statistical analysis.

The results of the study. As a result of work we determined that activity of fibrotic processes (TGF-β1) is higher in patients with a longer history of the disease on the background of reduction of apoptosis protein receptor — CD95. The level of proinflammatory cytokines (TNF-α) is higher in patients with impaired outflow of pancreatic secretion and pseudocyst of the pancreas. Found that for patients with parenchymal fibrous CP and complicated pseudocyst characterized by dysfunction of cellular immunity (by formula of immune disorders), and for patients with calcific CP — humoral. In patients with different clinical and morphological forms of CP installed unidirectional changes in markers of stone — a significant increase in content litostatine (REG-1α) and lactoferrin. It was established that the probability of stone formation is high — at a value of 0.5-1.0 coefficient of calcification (REG-1α/lactoferrin), low — at 1.5 and above.

It is shown that there are different mechanisms of apoptosis in exo- and endocrine parts of the pancreas — proapoptotic protease DNAse I expressed in the

cytoplasm of acinar cells, and endonuclease-G — in insular cells in the epithelium of the ducts. Early marker of apoptosis is DNAse-I translocation from the cytoplasm to the basics acinar cells in the nucleus.

The identified markers of progression CP: value ratio calcification (REG 1α/lactoferrin) 0.5-1.0, translocation of DNAse-I from the cytoplasm to the nucleus of acinar cells, activation of collagen (reduced ratio of OP_{pb}/CC below 0.5), growth activator of fibrosis (TGF-β1, TNF-a), intensification of LPO (malonic dialdehyde — MDA).

In experimental studies as a result of long-term (12 days) administration to rats intraperitoneally in submaximal doses of non-selective NO-synthase inhibitor NG-nitro-L-arginine in rats with CP developed stasis of blood cells in blood vessels, focal accumulation of leukocytes in the pancreatic parenchyma. Some pieces developed acinar cell degeneration. In some cases, after a 6-day administration of the inhibitor in the area of developing tissue atrophy acinar delicate fibrosis caused by inflammation, and after the 12-day — pronounced signs of pancreatic fibrosis. Prolonged administration inhibitor NOs — L-NNA caused activation of lipid peroxidation, increase the concentration of toxic products, violation of excretory function of the pancreas that changes manifested phase enzyme protein and carbohydrate metabolism, a gradual increase in the concentration of the marker of fibrosis of the pancreatic parenchyma — $OP_{mixing.}$ Thus, by using a rat nonspecific NO-synthase inhibitor NG-nitro-L-arginine in the tissue of rats pancreas generated morphological changes that are characteristic of chronic inflammation of the pathological process, pancreatic parenchymal fibrosis in the areas of atrophy and marked activation exocrine function of the pancreas.

Studied in the experiment that the introduction glutargin leads to normalization of MDA in blood and returning to the limits of physiological norm content of collagen metabolism markers (OP_{pb} and oxyproline free — OP_f). Therefore glutargin can be used in treatment of patients with CP as the drug which reduces the level of

lipid peroxidation products, improves the AOP system and helps to normalize the metabolism of collagen.

On the basis of these studies and factor analysis improved diagnostic and treatment algorithms for patients with CP of the main ways of determining therapeutic strategy of patients considering forms of CP. Treatment included: non-pharmacological (lifestyle modification, rejection of alcohol and tobacco, diet), medical, endoscopic and surgical.

After the diagnostic methods we defined group of patients who underwent surgical treatment. Most patients require surgical treatment when other therapeutic and endoscopic procedures are not able to relieve abdominal pain. Surgical methods are also used in the strictures, bleeding and suspected neoplasia of the pancreas. Indications for surgery were: continuous and intermittent pain due to obstruction at different levels ductal system of the pancreas, development of complications that can not be eliminated by conservative methods. Surgical treatment of patients with CP was generally aimed at improving the outflow of pancreatic juice duct or to resect affected body.

In obstructive CP treatment aimed at eliminating the causes of obstruction, which is achieved only by surgical methods. Require treatment in the surgical department as patients with CP, complicated pseudocyst formation, which in the first stage of treatment carried gastro-/duodenotcystomy or percutaneous puncture of the pseudocyst, and further surgery was performed.

At present widely used in the treatment of pancreatic diseases minimally invasive surgery techniques. In patients with CP, complicated with pseudocyst, used mini-invasive intervention that performed in 5.5% of cases — endoscopic papillosphincterotomy, stenting of the main pancreatic duct (MPD) followed by percutaneous drainage of cysts of the head of the pancreas that supressed supraduodenal part of choledoch, accompanied by jaundice. Used plastic stents CLSO-SF-10-5 with a side lock (firm Cook, United States).

In violation of the outflow of pancreatic juice at the Oddi's sphincter of with MPD expansion to 4 mm in 10.9% of endoscopic isolated papillosphincterotomy carried out, which is 5.5% of cases was supplemented Wirsungtomy. Restoring adequate outflow of pancreatic juice into the duodenum contributed to pain relief.

In large pseudocyst that accompanied by gastric or duodenal deformity of walls, or when combined MPD with abdominal cyst, we examined endoscopic approaches: endoscopic transmural drainage and transpapillary drainage.

Transmural drainage is used in 12.7% of cases (7 patients). In 4 cases, drainage was carried out through duodenum, 3 — in the stomach. Under ultrasound guidance through the stomach or duodenal cyst puncture was performed with the maximum aspiration of its contents, followed by Seldinger Fogarty catheter was performed with blow hydrobalonu. After 5 — 7 days when bonding occurred between the cyst and the stomach, the catheter was removed under control of gastroscope and in the hole hydroballoons of different diameters were performed, by which created anastomosis also extended to 20 mm.

Upon communication of pseudocyst with MPD one option endoscopic internal drainage is transpapillary drainage, 2 patients (3.6%) was used combined with X-ray equipment — MPD contrast through the catheter and puncture the cyst followed cyst wall and holding stent, proximal part of which published in the lumen of the duodenum. Stent maintained a cyst within 7-10 days. The second stage of treatment in these patients was surgery.

Results of conservative treatment of patients with CP were studied in terms of 6 to 12 months. The analysis of treatment of 34 patients of the main group and 25 patients of the comparison group was conducted. The patients performed sonographic and general clinical examination evaluated biochemical, immunological parameters. In assessing the patient's condition the dynamics of body weight, diet, attitude to alcohol were taken into account.

Evaluation of clinical and laboratory parameters allowed to distribute the results of treatment:

1) good — a high degree of effectiveness of treatment, characterized by the fact that patients there are no symptoms is related to the pathology Pancreas: improving the general condition of the patient; disappearance of pain; normalization of laboratory indices; weight gain> 8kg;

2) satisfactory — average degree of efficiency of treatment, characterized in that there are mild symptoms who are treated conservatively, do not require invasive methods of diagnosis and treatment, improving the general condition of the patient; episodic increase performance enzymatic functions; rare, weak intensity pain in the projection of the pncreas; a slight increase in body weight (2-3 kg);

3) bad — low degree of effectiveness of treatment (requiring invasive methods of diagnosis and treatment): slight improvement of the patient; persistent pain; progression of exogenous disturbances and pancreatic endocrine insufficiency; effects of portal hypertension.

After treatment in the study group found good results in 25 patients (73.5%), satisfactory — in 7 (20.6%), bad results — in 2 patients (5.8%). In the comparison group outcomes significantly ($p<0.05$) differed in the direction of deterioration from the main group. Thus, good results occurred in 12 patients (48.0%), satisfactory — in 7 patients (28.0%), bad results that showed a low degree of effectiveness of treatment, noted in 6 patients (24.0%). So, good and satisfactory results in the main group patients were 94.1% and 1.2 times higher than in the comparison group. Bad results in this group exceeded this figure in the main group 4.1 times.

Under the influence of treatment in most patients of the main group we observed the positive dynamics of the clinical picture. Thus, in the main group of patients pain disappeared an average of 4-6 days earlier than in the control group. Dyspeptic syndrome in patients of the group decreased an average of 8 days in the control group — in 10-12 days. After 11-13 days of treatment (the main group) and

17-19 days (the control group) stool frequency was normalized. Good clinical outcome contributed to the improvement of the immune system biochemical parameters and quality of life of patients.

The analysis of the changes in immune parameters studied groups of patients after treatment showed positive changes in the level of cytokines, activation of relevant stellate cells of the pancreas, fibrosis regulation and stone formation (Table 1).

Table 1

Changes in performance of triggers of the pathology upon CP in the examined patients after treatment

Indicator	Before treatment (N = 12)	After treatment (N = 12)	Norm
IL -10, pg/ml	30.57 ± 1.47	29.36 ± 0.87	28.6 ± 1.83
TNF- α, pg/ml	302.43 ± 117.64	177.89 ± 110.51	2.20 ± 0.81
lactoferrin, ng/ml	17,458.35 ± 846.91	7,167.68 ± 1599.15 **	653.57 ± 11.89
litostatyn (REG-1 α , pg/ml)	2,143.17 ± 87.29	1,179.83 ± 99.51 **	185.0 ± 23.0
TGF- β 1 ng/ml	39.34 ± 8,05	22.12 ± 3.37 *	3.46 ± 0.07
elastase, mg/g stool	156.5 ± 12.73	198.6 ± 11.39 *	200

Note: * — p <0.05, ** — p <0.001 — significant changes before and after treatment.

Thus, in patients in one year after treatment we determined a significant reduction of lactoferrin from serum (17458.35±846.91) ng/ml to (7,167.68±1599.15) ng/ml ($p<0.001$); litostatyn (REG-1 α) — from (2,143.17±87.29) pg/ml to (1179.83±99.51) pg/ml ($p<0.001$); activator fibrosis TGF-1β — from (39.34±8.05) ng/ml to (22.12±3.37) ng/ml ($p<0.05$). Level of fecal elastase rate, pancreatic exocrine insufficiency increased significantly ($p<0.05$), and 75% of patients were in the normal range.

These changes occurred against the background of improving all parts of immunity in patients of groups: humoral, cellular, regulatory (Table 2). Thus, after treatment the absolute number of T cells in 100.0% of patients of the main group normalized ($p<0.05$). Significantly increased the relative number of T-helper cells ($p<0.05$). Significant decrease in the relative number of T-suppressor ($p <0.05$) was

after treatment so that their levels did not differ from the control group. The above changes led to the restoration of immunoregulatory index CD4+/CD8+, which after treatment did not differ from the control group ($p>0,05$). In 41.6% of cases, elevated levels of B cells after treatment decreased in the study group ($p<0.05$), which led to the normalization of this index in the whole group. The main group of patients after treatment normalization observed NST and CIC ($p<0.05$), indicating that the normalization of the functional activity of neutrophils and phagocytic immunity.

In the comparison group were noted such positive changes in all parts of the immune system (humoral, cellular, regulatory) in patients of the main group. There was a normalization of relative numbers of B cells (SD19+) and CEC level ($p<0.05$). Other indicators did not change significantly after treatment, and most importantly — positive changes were observed in the restoration immunoregulation. On the positive treatment effect as evidenced by changes in serum biochemical parameters in patients. In the analysis of post-treatment processes characterized by fibrosis, cholestasis, lipid metabolism, endotoxemia, analyzed the contents of Ca and Cu (Table 3).

Index of endotoxemia (MM), which was significantly elevated in both groups of patients compared with controls, after treatment decreased to 1.54 times (493,18±30,87) mg/l in group I ($p<0.001$) and did not change significantly in group II. The content of total lipids and cholesterol following treatment remained almost at the same level. This points to a violation of splitting lipids and their subsequent absorption in the intestine by pancreatic type. Total TG and β-LP in patients after treatment were not significantly different from controls.

After treatment, there was a decline OP_{pb} in patients of the groups I in 1.15 times (159, 74±6,51) mmol/l ($p <0.01$) and to GA (6,63±0,42) mg/l ($p<0.05$) with no significant changes in these parameters in patients in group II when comparing the period before and after treatment. The phenomena of cholestasis were confirmed by increase in patients of both groups in H-LP 1.63 and 1.3 times, respectively, with substantially unmodified LCD. GGT activity in patients of both groups before

treatment tended to increase, and in remote period after treatment was observed a gradual decrease in activity this enzyme compared to previous rates (p>0.05).

Table 2

Indicators of immune status in patients after treatment

Indicator	Control group (N = 20)	Group I (n = 34)		Group II (n = 25)	
		for treatment	after treatment	for treatment	after treatment
1	2	3	4	5	6
leukocytes, 10^9/l	5,35±0,21	6.98 ± 0.68 *	5.89 ± 0.39	6,87 ± 0.72 *	6,63 ± 0.81
lymphocytes, %	28,71±0,81	33.73 ± 1.73 *	29.58 ± 2.65	34.2 ± 1.76 *	34.7 ± 2.03 *
lymphocytes, 10^9/l	1,61±0,07	2.32 ± 0.29 *	2.17 ± 0.22 *	2.34 ± 0.31 *	2.19 ± 0.27 *
CD3 +, %	50,88±0,68	41.07 ± 1.46 **	49.25 ± 1,51+	40.84 ± 1.51 **	39.87 ± 1.74 **
CD3 +, 10^9/l	0,76±0,04	0.95 ± 0.08 *	0.84 ± 0.09	0.96 ± 0.09 *	0.87 ± 0.08
CD19 +, %	14,78±0,48	21.34 ± 1.64 *	15.67 ± 1,70+	21.09 ± 1.72 *	16.3 ± 1,49+
CD19 +, 10^9/l	0,25±0,01	0.36 ± 0.04 *	0.33 ± 0.05	0.39 ± 0.03 **	0.34 ± 0.06
CD4 +, %	38,71±0,52	28.38 ± 1.73 **	36.08 ± 0,87+	29.14 ± 1.81 **	27.3 ± 1.07 #
CD4 +, 10^9/l	0,53±0,03	0.53 ± 0.09	0.52 ± 0.05	0.54 ± 0.09	0.56 ± 0.08
CD8 +, %	18,39±0,57	26.46 ± 1.75 **	18.05 ± 1,32+	27.07 ± 1.64 **	24.94 ± 1.72 **
CD8 +, 10^9/l	0,30±0,02	0.42 ± 0.06	0.32 ± 0.08	0.43 ± 0.07	0.39 ± 0.08
CD16 +, %	19,07±0,90	19.08 ± 1.81	18.83 ± 1.33	19.11 ± 1.76	21.42 ± 1.36
CD16 +, 10^9/l	0,31±0,02	0.43 ± 0.07	0.35 ± 0.08	0.44 ± 0.07	0.41 ± 0.08
CD95 +, %	17,24±0,57	15,08±0,83 *	16,94±0,67	14.97 ± 0.93 *	15.01 ± 0.97
CD95 +, 10^9/l	0,24±0,02	0,27±0,03	0,24±0,04	0.28 ± 0.04	0.27 ± 0.03
T/A	2,78±0,15	2.75 ± 0.18	2.77 ± 0.28	2.67 ± 0.23	2.48 ± 0.94
CD4 +/CD8 +	1,97±0,07	1.56 ± 0.12 *	1.89 ± 0.23	1.54 ± 0.21	1.52 ± 0.87
CIC, units of opt. dens.	3,42±0,23	6,94 ± 0.28 #	2.99 ± 0,31+	6,76 ± 0.3 # 1	4.02 ± 1,08+
NST	12,03±0,74	19.82 ± 3.26 *	12.56 ± 2.35	20.01 ± 2.94 *	16.27 ± 1.56 *
CPA	0,20±0,01	0.34 ± 0.08	0.18 ± 0.05	0.36 ± 0.09	0.29 ± 0.09

Notes:

1. * — p<0.05, ** — p<0.01, # — p<0.001 — significant changes compared with the control group.
2. + — p<0.05 — significant changes before and after treatment.

Table 3

Biochemical parameters of blood serum of the patients after treatment (M±m)

Indicator	Control group (N = 20)	Group I (n = 34)		Group II (n = 25)	
		for treatment	after treatment	for treatment	after treatment
lipids, g/l	6,00±0,70	3,55±0,15 ***	3,5±0,26 ***	3,61±0,16 ***	3,69±0,001 ***
Cholesterol, mmol/L	5,20±0,60	4,76±0,21	5,01±0,34	4,63±0,19	4,41±0,76
β-LP, units	45,00±2,25	47,20±2,81	44,85±4,02 *	46,14±2,47	48,33±7,69
H-LP, units/ml	2,75±0,28	4,56±0,38 ***	4,5±0,67	4,81±0,93 *	3,5±0,87
TG, mmol/l	1,16±0,06	1,33±0,09	1,18±0,14	1,29±0,14	1,30±0,17
LCD, mmol/l	0,144±0,027	0,194±0,007	0,19±0,01	0,195±0,008	0,16±0,03
GGT, mkkat/l	0,82±0,025	1,20±0,27	1,15±0,60	1,45±0,36	1,40±0,7
Cu, mmol/l	17,70±0,57	24,73±0,93 ***	24,21±1,09 ***	24,96±1,02 ***	23,34±3,33
OPp_b, mmol/l	136,04±4,30	184,97±7,84 ***	159,74±6,51 **	189,41±7,39 ***	196,6±29,4 *
GA, mmol/l	5,61±0,22	6,73±0,24 ***	6,63±0,42 *	6,94±0,29 ***	7,63±1,07
MM, mg/l	445.60 ± 18.20	760,44±46,31 ***	493.18±30.87●●●	617,47±35,15 ***	643,75±129,15
Ca, mmol/l	2,50±0,09	2,17±0,04 ***	2,11±0,12	2,23±0,06 *	2,19±0,12 *

Notes:
1 * — $p<0.05$, ** — $p<0.01$, *** — $p<0.001$ — the probability of changes between indicators of patients compared with the control group.
2. ●●● — $p<0.05$ — the likelihood of performance changes between patients before and after treatment.

Analysis of changes in the system of POL-AOP patients in both groups before and after treatment (Table 4) showed that in patients in group I after treatment there was a significant decrease in the concentration of substrates of lipid peroxidation in α-phase, compared with the period before treatment ($p<0.05$). JDC in heptanes fraction in both groups of patients after treatment were not detected, unlike groups of patients before treatment. Characteristic was a lack of SO in both phases. There was a tendency to reduce the concentration of POL-MDA products — in both groups of patients after treatment, compared with similar groups to treatment.

When considering the AOP system after treatment in group I patients SOD activity was reduced ($p<0.05$), and in II group — increased to 53.0%, in contrast to the same group before treatment, while in group I CA activity reached the limits of physiological norm, and in II group — increased by 32.2%.

In analyzing the enzymatic activity of pancreas in patients after treatment, probable decrease in activity α-amylase ($p<0.05$) in group I was found, group II in the activity of the enzymes also tended to decrease (Table 5). Trypsin and lipase activity

decreased in both groups of patients. In group II patients 1.4 times decreased activity of phospholipase A. The accumulation of glucose in the blood was more typical of patients in group I, where GHb level rose from (6,52±0,84) to (7,17±1,41) Fru uM/g Hb, group II concentration of this index tended to decrease.

In the analysis of sonographic data found that after treatment in group I decreased the size of the pancreas by the size of the head ($p < 0.002$), while the body and tail were not changed (Table 6). MPD diameter was not significantly changed and remained moderately advanced. Contours of the pancreas were in most cases irregular and in almost half of the patients unclear because of fibrotic changes, as evidenced by the increase of the index relative parenchymal density of the pancreas.

In group II in patients after treatment size of the pancreas virtually unchanged and remained close to the upper limit of normal (Table 7). Pancreas had uneven and clear contours, indicating that the absence of fibrosis and organ inflammation at the time of the study.

MPD lumen significantly decreased, indicating a decrease in intraductal pressure: (5,27±1,23) mm in 3-6 months after treatment and (4,38±0,87) mm in 6 months or more ($p<0.01$). Local expansion of the duct was defined only in isolated cases and its size was significantly decreased to (5.01±1.20) mm after 3 — 6 months, and (4.56±2.05) mm after 6 months or more after treatment against (8.36±1.7) mm before treatment ($p<0.001$).

Table 4

Dynamics of changes in the system of POL-AOP in patients of the groups I and II (M±m)

Indicator	Phases	Control group (n = 20)	Group I (n = 34)		Group II (n = 25)	
			before treatment	after treatment	before treatment	after treatment
IPZ, U/ml	α	0,99±0,04	1,10±0,04 *	0,89±0,08 •	0,99±0,06	0,97±0,03
	β	3,12±0,12	3,22±0,10	3,59±0,38	3,06±0,08	3,22±0,14
DC, U/ml	α	0,67±0,03	0,71±0,03	0,6±0,09	0,65±0,04	0,68±0,05
	β	1,53±0,08	1,85±0,07 **	1,87±0,25	1,65±0,07	1,53±0,07
JDC, U/ml	α	0	0,06±0,01	0	0,03±0,01	0
	β	0,80±0,03	0,99±0,07 *	0,93±0,19	0,73±0,05	0,6±0,08 *

SO, U/ml	α	0	0	0	0,01±0,01	0
	β	0	0,40±0,03	0	0,36±0,04	0
MDA, nmol/ml		2,07±0,13	3,04±0,15 ***	3,0±0,20 ***	2,66±0,23 *	3,0±0,20 ***
LDS, standard units		30,3±1,22	32,62±2,8	29,35±2,98	21,63±3,57 * •	29,35±2,98
CA, mcM/min x mgNv		1149,6±49,3	1035,65±24,61 *	1050,18±32,28	1101,8±67,94	1050,18±32,28
CPU, mg/ml		308,08±8,79	447,37±11,18***	434,70±17,5***	455,69±22,36***	434,70±17,5***
K/f, CPU/MDA		1,71±0,11	1,58±0,08	1,58±0,09	1,95±0,28	1,58±0,09

Notes:

1. α — heptane phase; β — izopropanol phase.
2. * — $p<0.05$, ** — $p<0.01$, *** — $p<0.001$ — the probability of changes between indicators of patients before and after treatment compared with the control group.
3. • — $p<0.05$ — probability of changes between indicators of patients before and after treatment.

Table 5

Dynamics of changes in enzyme activity and content of GHb in patients (M±m)

Indicator	Control group (n = 20)	Group I (n = 34)		Group II (n = 25)	
		before treatment	after treatment	before treatment	after treatment
α-amylase, mg/s · l	6,10±0,37	15,56±1,81 ***	8,74±2,16 •	16,44±2,76 ***	11,90±3,97
lipase, nmol/s · l	1,07±0,05	1,44±0,11 ***	1,36±0,11 *	1,38±0,08 ***	1,30±0,09 *
trypsin, uM/ml · min	2,50±0,27	8,60±0,66 ***	7,08±0,88 ***	8,81±0,71 ***	7,87±1,31 ***
GHb, Fru m/g Hb	5,25±0,28	6,52±0,84	7,17±1,41	6,30±0,74	5,49±2,06
phospholipase A, units F/l A in 1 ml of serum	0,98±0,07	1,91±0,13 ***	1,82±0,30 **	2,07±0,20 ***	1,47±0,14 **

Notes:

1. * — $p<0.05$, ** — $p<0.01$, *** — $p<0.001$ — the probability of changes between indicators of patients before and after treatment compared with the control group.
2. • — $p<0.05$ — probability of changes between indicators of patients before and after treatment.

Table 6

State of the pancreas in patients of the group I after treatment

Indicator	Before treatment (n = 34)	After treatment	
		to 6 months (N = 23)	>6 months (N = 11)
Pancreatic head, mm	35,97±2,07	28,00±1,00 *	30,45±2,42 *
Pancreatic body, mm	17,30±0,81	16,08±0,79	15,36±1,11
Pancreatic tail, mm	25,46±1,79	24,87±0,83	28,70±0,42
MPD, mm	4,78±0,74	5,30±1,19	4,90±0,87
Contours:			
smooth, abs. k. (%)	5 (16.6)	2 (8.0)	-
uneven, abs. k. (%)	25 (83.4)	23 (92.0)	12 (100.0)
clear, abs. k. (%)	17 (56.6)	11 (44.0)	5 (41.6)
fuzzy, abs. k. (%)	13 (43.4)	14 (56.0)	7 (58.3)
structural unit, U	3,66±0,15	3,55±0,18	3,46±0,19
echo density, U	6,31±0,67	5,95±0,71 *	7,64±1,16 *

Note: * — p <0.05 — significant difference index before and after treatment.

Concretions of MPD were located only in 3 (23.1%) of patients within 3-6 months and in 2 (6.7%) patients after 6 months, compared with 15 (55.6%) before treatment.

Table 7

Indicators of the state of the pancreas in patients of the group II

Indicator	Before treatment (N = 25)	After treatment	
		to 6 months (N = 13)	>6 months (N = 12)
Pancreatic head, mm	32,78±1,29	27,54±1,08	32,33±1,55
Pancreatic body, mm	16,81±0,61	15,92±0,61	16,25±1,21
Pancreatic tail, mm	25,19±0,64	24,77±0,62	24,50±1,06
MPD, mm	7,19±0,57	5,27±1,23 *	4,38±0,87 *
Contours:			
smooth, abs. k. (%)	2 (7.4)	-	-
uneven, abs. k. (%)	25 (92.6)	13 (100.0)	12 (100.0)
clear, abs. k. (%)	15 (55.5)	4 (30.8)	9 (75.0)
fuzzy, abs. k. (%)	12 (44.5)	9 (69.2)	3 (25.0)
structural unit, U	3 (11.1)	8 (61.5)	1 (8.3)

Note: * — p<0.05 — significant difference index before and after treatment.

After treatment, quality of life (QOL) of patients, that we studied using a questionnaire and SF-36 questionnaire developed by us, has undergone positive changes.

QOL indicators of patients with CP before and after treatment are shown in Fig. 1.

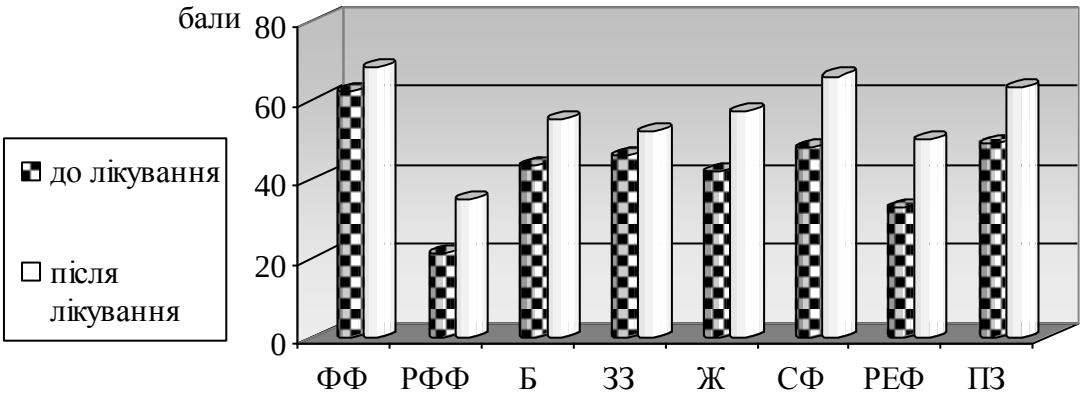

Fig. 1. Quality of life in patients with CP in the dynamics of treatment.

After treatment, QOL parameters significantly improved. Thus, as a result of treatment significantly raised performance physical component of health — (52,3±6,7) points against (43,2±8,4) before treatment ($p<0.05$). Improving physical component of QOL was due to significant improving overall health: (52,9±3,5) points against (46,2±2,1) before treatment ($p<0.05$). According to other scales (RFF, FF, B), there was tendency to improve QOL of patients, but significant differences of indicators were not found.

Index of psychological component of health also significantly increased: (57,5±4,9) points against (43,0±3,7) before treatment ($p<0.05$). Improving QOL for psychological component was due to significant improvement in viability, social functioning, mental health: (57,0±4,0) points against (42,1±2,6) before treatment ($p<0.05$); (66,1±4,5) points against (48,0±3,3) before treatment ($p<0.05$); (63,2±3,5) points against (49,2±2,8) before treatment ($p<0.05$), respectively.

According to a scale of role-emotional functioning (REF), QOL of patients tended to improve, but significant differences in performance were not found.

We also analyzed the subjects' assessment of their own health as compared to last year. Thus, if the treatment level health compared to last year was estimated on average by patients in (34,6±3,9) points, after treatment it increased 2.1 times and amounted to (74,1±5,1) ($p<0.0001$).

We have developed and applied a specific questionnaire for QOL research, which is due to the presence of CP. It could accommodate a question about the

impact of the disease on the patient's QOL in general and the question of complaints (pain in the left hypochondrium, shingles pain, bloating, etc.) due to the presence of CP. Patients also independently evaluated in a developed specific questionnaire how complaints related to CP interfere in everyday life, how emotionally they perceive their disease (answers varied from "quiet" attitude to "significantly emotionally concerned").

As shown in Fig. 2, according to the survey, we observed a positive trend. So much pronounced pain before treatment was in 27.5% surveyed patients, moderate — in 55.0%, slightly pronounced — 12.5%. After treatment, patients reported only moderately expressed pain in 32.5% of patients and in 42.5% — insufficient, the rest — the pain bothered.

Similarly, swelling in the abdomen disturbed much less.

All these facts were reflected in the complaint as patients with CP interfere with their daily lifestyle and worsen QOL (Fig. 3).

As shown in Fig. 3, after treatment, only 5.0% of patients indicated a significant negative impact of the disease on QOL against 37.5% before treatment. The percentage of patients whose disease did not worsenand worsen a bit QOL increased slightly — from 7.5% to 15.0% and from 30.0% to 42.5%, respectively.

Unexpressed complaints, which can be ignored, 32.5% surveyed noted before treatment vs. 52.4% after treatment. Moderate complaints and manifestations of CP, which can't be marked, but do not break the habitual rhythm of life, were noted by 35.0% of patients with CP vs. 42.5% of patients after treatment.

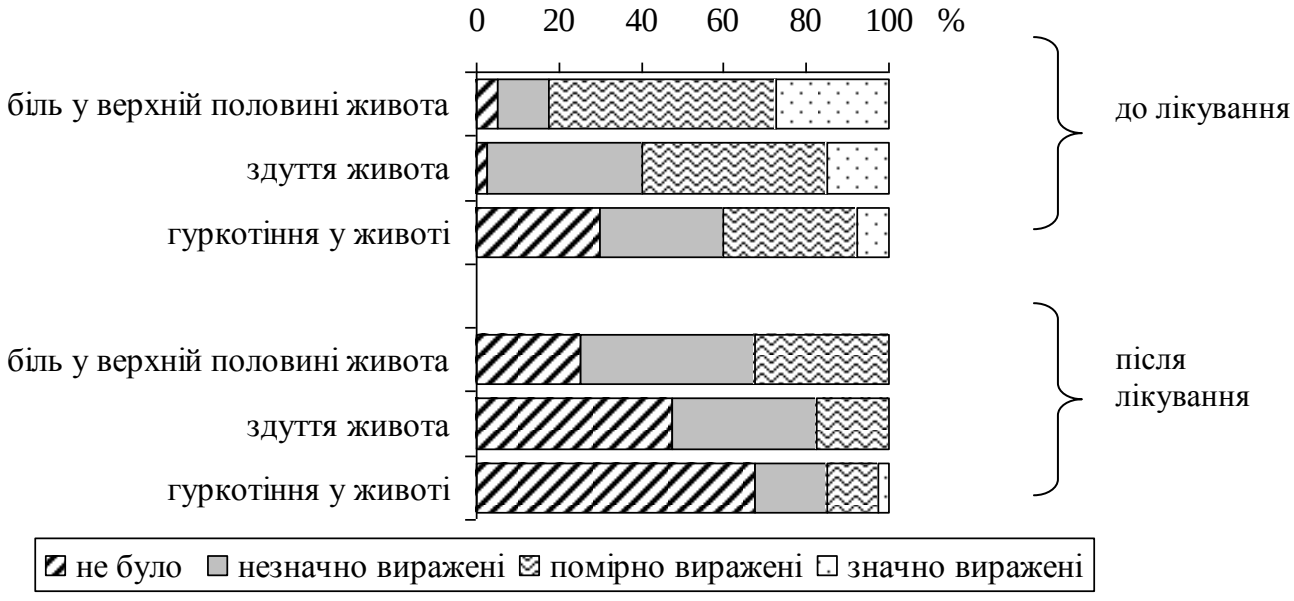

Fig. 2. Changes in the frequency and severity of complaints of patients with CP in the dynamics of treatment.

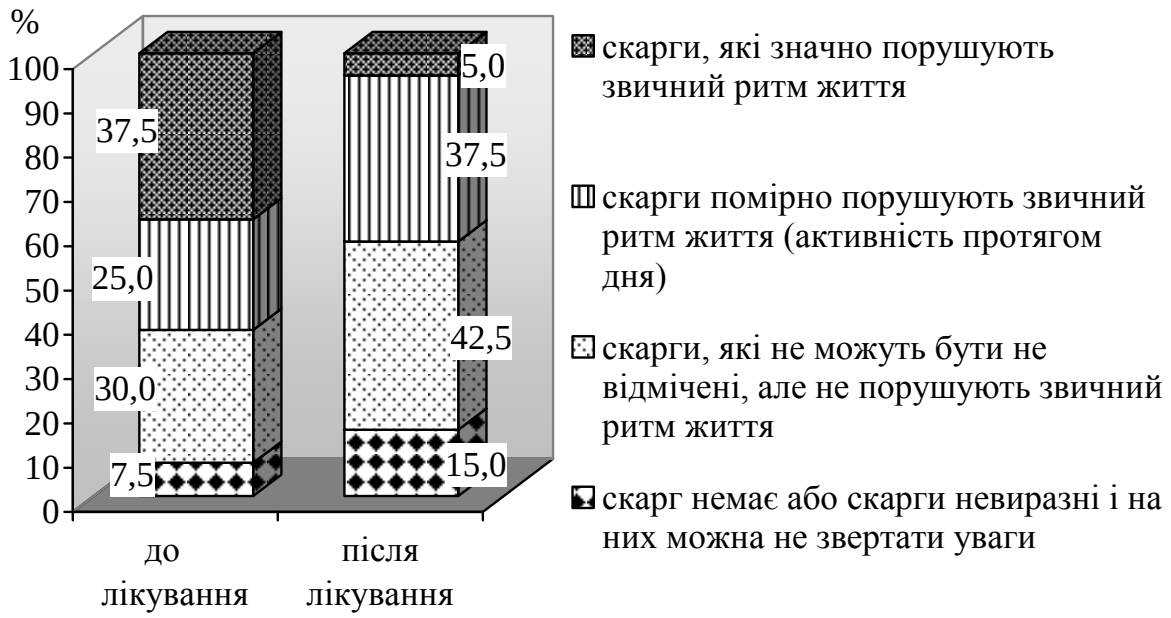

Fig. 3. The impact of the disease on quality of life of patients.

However, 32.5% of the surveyed before treatment and 5.0% after treatment noted significant problems and complaints that significantly violate activity and rhythm of life of the patient during the day.

Thus, the positive trend set in the complaints of patients, as well as self-esteem and their impact on everyday lifestyle. However, as for the emotional perception of patients of their disease, situation improved, but not significantly (Fig. 4).

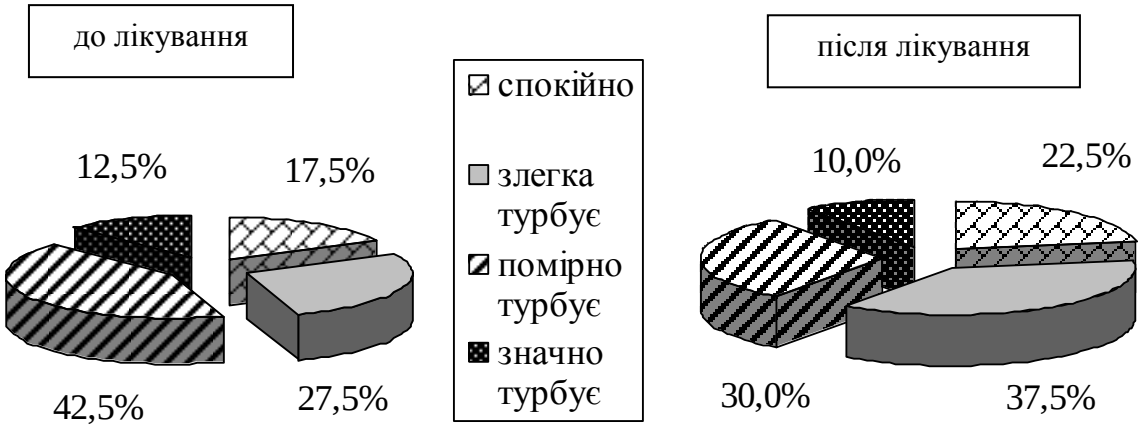

Fig. 4. Emotional perception of the disease by patients.

Indeed, CP emotionally severely disturbed 12.5% of patients before treatment versus 10.0% after treatment, moderately — 42.5% and 30.0%, slightly — 27.5% and 37.5%, and 17.5% patients before treatment related to their disease emotionally calm, after treatment this figure rose to 22.5%.

Thus, in patients of the group I after treatment with the use of complex autocytokines, glutargin, VPMF it is found that after treatment there is no full recovery of the immune system, which explains the importance of its chronicity and progression to CP. At the same time, the rate of TGF-β1, which shows the development of fibrotic processes, activates stellate cells of the pancreas, that produce extracellular matrix and are responsible for fibrosis of the pancreatic parenchyma, was significantly decreased ($p<0.05$), and the level of cytokines, which indirectly related processes fibrosis — IL-10, TNF-α — tended to decrease ($p>0.05$). The positive effect of treatment on calcification processes — significantly reduced the level of REG-1α (litostatyn), which is the main component of pancreatic stones ($p<0.001$).

In addition, there was a normalization of amylase, lipase, trypsin and phospholipase A in comparison with similar indicators to treatment. The decrease in the severity of endotoxemia, fibrosis (CA and OP_{pb}), but these figures remained higher after treatment from that of the control group. Evidence of cholestasis (H-LP) has decreased significantly as compared to the control group ($p<0.05$) and remained pronounced lipid metabolism disorder (decrease in total lipids) ($p<0.05$), showed an increase in the amount of copper and decrease in serum calcium.

There was a significant decrease in the concentration of substrates LPO (IPZ in heptane phase) and lipid peroxidation products (JDC in heptane phase), and lack of SO in both fractions ($p<0.05$). There was a decrease of MDA concentration, while the AOP system activity after treatment tended to increase.

It is established that almost all indicators of physical and mental health patients after treatment were statistically higher as compared to those before treatment, indicating the effectiveness of the proposed complex. Good and satisfactory results in

patients of the group I accounted for 94.1% and were 1.2 times higher than in the comparison group.

Thus, the treatment allowed to obtain a positive effect in most patients. Therefore, treatment strategies of CP should be comprehensive and able to influence the pathogenesis of major diseases in order to inhibit the development of fibrous and other structural changes in the pancreas.

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Efficiency of cytokines, glutargin and vortex pulse magnetic field in the treatment of patients with chronic pancreatitis

O. O. Krylova, V. M. Ratchik, V. E. Kudryavtseva, A. I. Rudenko, V. A. Makarchuk

Institute of Gastroenterology of the NAMS of Ukraine, Dnepropetrovsk, Ukraine

Key words: chronic pancreatitis, treatment, cytokines, pain, oxidative stress

The authors conducted the analysis of conservative treatment of 34 patients of the main group with chronic pancreatitis and 25 patients of the comparison group. Autocytokine therapy, glutargin and vortex pulsed magnetic field were used in the main group in addition to basic therapy. Results of treatment of patients were studied in terms of 6–12 months. Analysis of the results showed that the proposed method allowed to increase the effectiveness of treatment due to the correction of cytokine profile, indices of peroxidation and endogenous intoxication, optimization of the antioxidant protection, and improvement of the overall quality of patients' life.