ORIGINAL ARTICLE

PAIN SYNDROM IN CASES OF PATIENTS WITH A COMBINATION OF CHRONIC PANCREATITIS AND HYPERTENSION: RELATIONSHIPS, INTERACTIONS, CORRECTION

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ABSTRACT

The aim: To identify the relationships and interactions of the pain development in cases of patients with a combination of Chronic Pancreatits and Arterial Hypertension, with the next correction

Materials and methods: We have conducted a comprehensive examination of 102 patients with a diagnosis of Chronic Pancreatitis in combination with stage II Arterial Hypertension during 2018-2020. The investigative contingent was divided by two study groups which depended from the treatment regimen. The first (I) group (n = 53) received basic therapy (BT) in accordance with the requirements of the relevant clinical protocols; the treatment of the second (II) group (n = 49) included the basic therapy with optimization (OT) by mineralocorrection (Zinc, Selenium, which have antioxidant properties), ω-3 polyunsaturated fatty acids and Folic Acid. The therapy duration was 8 weeks.

Results: The performed regression analysis was mathematically substantiated the influence of the studied laboratory parameters of the inflammatory response and antioxidant system on the formation, dynamics of abdominal pain (the main clinical sign of CP) and the value of PAP (hypertensive vascular remodeling marker and risk predictor of cardiovascular events). The severity of abdominal pain is significantly influenced by leukocytes, ESR, α1-AT, cortisol, CRP, Bilirubin and Urea, and the value of PAP – CRP and selenium, from laboratory parameters of the inflammatory response and AOS,

Conclusions: The effectiveness of the assigned optimized treatment scheme has been proven, which is indicated by the appearance of a reliable regression coefficient on the parameter of glutathione peroxidase after completion of treatment in comparison with patients used basic therapy

KEY WORDS: patients, pain syndrom, Chronic Pancreatitis with Arterial Hypertension, correction

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INTRODUCTION

Chronic Pancreatitis (CP) is a chronic inflammatory disease of the pancreas, which is characterized by the gradual destruction of the exocrine parenchyma of the parenchymal organ with its subsequent atrophy and progressive fibrosis. The prevalence of CP confirms the relevance of the studied problem. Thus, the prevalence of CP ranges from 42 to 73 per 100,000 adults in the United States [1], and in European countries there are 25 cases per 100,000 population [2]. The epidemiological rates of CP In Ukraine are 3-4 times more than in Europe, while the morbidity have tendency to the steady growth (Stepanov Yu. M., 2018; Filippov Yu. O., 2016) [3].

The main signs of CP are pain, exocrine and endocrine pancreatic insufficiency. In current situation, we are able to partially correct the Pancreas function inadequacies with using of replacement therapy. However, abdominal pain, which has a chronic duration, is not always fully treatable by pharmacological standart scheme. These, of course, are significantly impairs for the improving the quality of CP patients life. The pain pathogenesis include the following components: inflammatory mechanisms, disorders of the prooxsidant-antioxidant system [4], structural problems (obstruction of the ducts by strictures and micro-macroliths, leading to ductal and parenchymal hypertension), visceral hypersensitivity (neuropathic pain) and centralization of pain. All of the above leads to chronic pain syndrome [5].

Our attention was drawn to the insufficiency of the antioxidant system (AOS) and the persistence of the inflammatory response in patients with CP., we obtained quite contradictory data on the effectiveness of antioxidant therapy in cases of patients with CP, according to the literature data. Thus, Singh N. et al. conducted a double-blind, randomized, placebo-controlled study of 107 patients and did not find significant reduction in pain in CP patients who used antioxidant therapy in comparison with the placebo group [6]. Instead, P. Bhardwaj et al., Who prescribed combination antioxidant therapy, which included selenium, β-carotene, vitamin C, vitamin E and methionine in 86 patients with CP (35 – with alcohol and 92 – with idiopathic) indicate a significant effectiveness of the proposed scheme therapy. The study of prooxidant status with usage of combination antioxidant therapy showed a regression of lipid peroxidation markers and an increase in the non-enzymatic AOC concentration. The antioxidant therapy is effective in relieving pain and reducing oxidative stress levels in patients with CP, according to the authors [7].

Most scientific studies convincingly prove that the vast majority of people who were diagnosed with non-infectious chronic disease have more than one disease [8]. This fact requires taking into account all the risks, factors of interaction and modification of a comprehensive treatment regimen. Our attention was drawn to the presence of Arterial Hypertension (AH) in patients with CP. More than 1 billion people have high blood pressure (BP), up to 45% of all adults have this disease, according to the worldwide data. In 2016, the "Lancet» published a report on a global health study of patients from 67 countries. The conclusion of this study establishes AH as the leading death cause of disability worldwide since 1990 [9].

The Oxidative stress and chronic inflammatory reactions certainly play an important role in the hypertension formation and worsen of the disease course. AH accompanied of an increasing in the reactive oxygen species production. There is a decreasing in antioxidant protection of enzymatic and non-enzymatic origin, at the same time, which caused endothelial dysfunction, vascular remodeling and tissue damage [10-13].

We considered to study the modification therapy possibility in patients with a combination of CP and AH, given the abovementioned information.

THE AIM

The aim was to identify the relationships and interactions of the pain development in patients with a combination of CP and AH, with the next correction

MATERIALS AND METHODS

We conducted a comprehensive examination of 102 patients who were hospitalized in the therapeutic department of Khust Central District Hospital with a diagnosis of CP in combination with stage II AH during 2018-2020.

Diagnosis and treatment tactics of CP and AH were carried out in accordance with the requirements of the "Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation approved by the order of the Ministry of Health of Ukraine.

The investigative contingent was divided into two study groups which depended from the treatment regimen. The first (I) group (n = 53) received basic therapy (BT) in accordance with the requirements of the relevant clinical protocols; the treatment of the second (II) group (n = 49) included the basic therapy with optimization (OT) by mineralocorrection (Zinc, Selenium, which have antioxidant properties), ω-3 polyunsaturated fatty acids and Folic Acid. The therapy duration was 8 weeks.

There was not significant difference between the studied groups by age: the average age of patients in group I – 49.7 ± 9.6 years, group II – 52.1 ± 9.5 years. The analysis of the gender distribution indicated a slight predominance of females in both groups (54.7% and 57.1%, respectively). The duration of CP was 7.00 ± 3.00 years, and AH – was 5.00 ± 2.00 years.

All patients underwent a clinical laboratory-instrumental study. Pain intensity was determined with using a 10-point visual analog scale (J. J. Bonica, 1990). Measurements were made in the serum of the following indicators: glutathione peroxidase (GPO), selenium (Se), zinc (Zn), albumin, transferrin, bilirubin, urea. For the antioxidant status evaluation. We determined the level of interleukins in the serum: proinflammatory IL-6 and anti-inflammatory IL-4, leukocytes, C-reactive protein (CRP), fibrinogen, α1-antitrypsin (α1-AT)), cortisol and erythrocyte sedimentation rate (ESR). These analyses presented the body's response on the activation of chronic inflammation in studied groups patients. Informative agreement was btained from all patients for the participate in the necessary research, in accordance with the requirements of the Declaration of Helsinki (1975) and its revision (1983). Statistical analysis of the results was performed using the computer program "Statistica for Windows" version 10.0.

RESULTS

Since the initial examination of patients was carried out in the stage of CP exacerbation, all patients were diagnosed with pain (n = 102; 100%). The epigastric region was the center of localization of pain (in 31 (30.4%) persons in the left hypochondrium) in the majority of patients (n = 71; 69.6%). The intensity of abdominal pain is shown on Figure 1.

The measurement of blood pressure indicated its increase within 1-2 degrees of hypertension. The obtained results of blood pressure and heart rate (HR) are given in table I.

We performed regression analysis of dynamic patients data of the formation and development of pain, modeling the level of PUP to determine the effect and interdependence of inflammatory markers and indicators of the antioxidant system The patients had the different treatment scheme, according the groups.

The main significant laboratory components of pain development were leukocytes, ESR, α1-AT, cortisol and CRP ($p < 0.05$), from the inflammatory response indicators,

Table I. Blood pressure level and heart rate in groups of patients with comorbid pathology

Parameters	SAP (mm.Hg.)	DAP (mm.Hg	PAP (mm.Hg	Heart Rate (beats/min)
I grope (n=53)	154,15 ± 9,24	94,53 ± 9,05	59,62 ± 11,52	80,26 ± 10,73
II grope(n=49)	153,27 ± 9,71	93,98 ± 8,84	59,29 ± 11,77	83,53 ± 8,46
Statistical significance of differences (p)	0,64	0,76	0,88	0,09

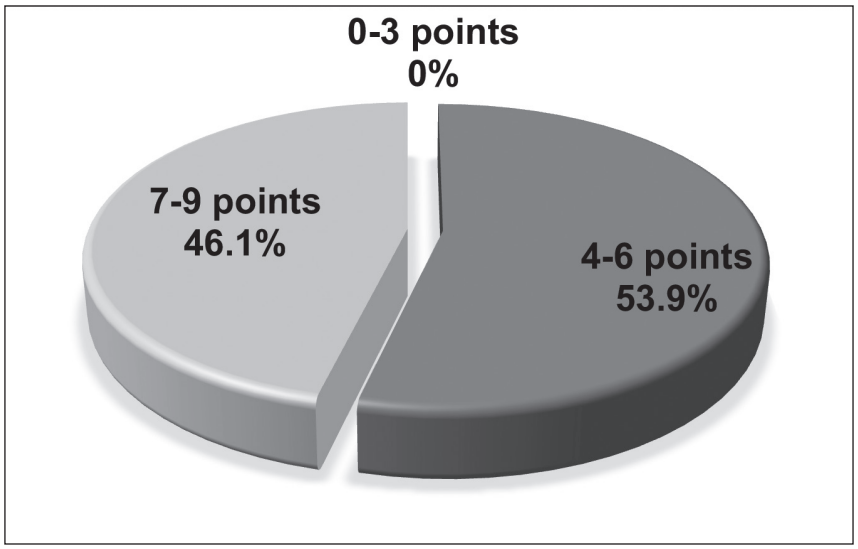

Fig. 1. The intensity of abdominal pain

Table II. The Influence of inflammatory indicators on pain syndrome

	Parameters	Before treatment	After treatment	
			BT	OT
Pain	Leukocytes	B=0,09 p=0,000005	B=-0,01 p=0,89	B=0,01 p=0,40
	ESR	B=0,06 p=0,000002	B=0,005 p=0,81	B=-0,01 p=0,59
	α1 – AT	B=0,78 p=0,0003	B=0,18 p=0,66	B=-0,02 p=0,91
	IL-4	B=0,004 p=0,99	B=0,14 p=0,53	B=0,19 p=0,1
	IL-6	B=0,02 p=0,53	B=0,01 p=0,84	B=0,002 p=0,93
	Cortisol	B=0,0005 p=0,03	B=0,00003 p=0,95	B=0,0003 p=0,06
	Fibrinogen	B=0,16 p=0,08	B=0,12 p=0,46	B=0,08 p=0,35
	CRP	B=0,11 p=0,04	B=-0,04 p=0,85	B=0,13 p=0,48

Table III. The influence of antioxidants on pain syndrome

	parameters	Before treatment	After treatment	
			BT	OT
Pain	Bilirubin	B=0,02 p=0,00004	B=0,01 p=0,72	B=0,0006 p=0,95
	Urea	B=0,11 p=0,0002	B=0,04 p=0,55	B=-0,01 p=0,78
	Folic acid	B=-0,02 p=0,36	B=-0,02 p=0,42	B=-0,01 p=0,43
	Zn	B=-0,0007 p=0,08	B=-0,0003 p=0,53	B=0,0001 p=0,61
	Se	B=0,002 p=0,69	B=0,01 p=0,25	B=-0,002 p=0,48
	Glutathione peroxidase	B=-0,008 p=0,31	B=-0,02 p=0,05	B=0,01 p=0,18
	Transferrin	B=-0,2 p=0,43	B=-0,18 p=0,54	B=0,04 p=0,67

Table IV. The Influence of inflammatory markers on the level of pulse arterial pressure

	Parameters	Before treatment	After treatment	
			BT	OT
PAP	Leukocytes	B=-0,52 p=0,23	B=0,61 p=0,49	B=0,03 p=0,97
	ESR	B=-0.15 p=0,49	B=-0,13 p=0,72	B=-0,39 p=0,35
	α1 - AT	B=-5,41 p=0,28	B=-1,37 p=0,84	B=2,55 p=0,74
	IL-4	B=1,37 p=0,79	B=2,39 p=0,53	B=5,84 p=0,19
	IL-6	B=-1,02 p=0,16	B=-1,31 p=0,17	B=0,03 p=0,97
	Cortizol	B=-0,001 p=0,82	B=0,01 p=0,36	B=0,0002 p=0,97
	Fibrinogen	B=1,82 p=0,39	B=0,7 p=0,8	B=0,06 p=0,98
	CRP	B=3,53 p=0,008	B=-1,04 p=0,74	B=6,41 p=0,38

Table V. The role of antioxidants in the formation of pulse arterial pressure

	Paramenrs	Before treatment	After treatment	
			BT	OT
PAP	Bilirubin	B=-0,06 p=0,59	B=-0,63 p=0,27	B=-0,3 p=0,44
	Urea	B=0,78 p=0,13	B=-0,17 p=0,87	B=0,44 p=0,62
	Folic acid	B=-0,26 p=0,51	B=-0,07 p=0,88	B=-0,1 p=0,7
	Zn	B=0,009 p=0,22	B=0,004 p=0,6	B=0,002 p=0,79
	Se	B=-0,29 p=0,007	B=0,02 p=0,89	B=-0,014 p=0,14
	Glutathione peroxidase	B=0,14 p=0,37	B=-0,02 p=0,89	B=0,1 p=0,5
	Transferrin	B=0,74 p=0,88	B=6,94 p=0,19	B=-1,55 p=0,68

according to our data (Table II). The regression analysis (before treatment) was performed for the whole patients contingent without distribution into groups, because the primary data did not have significant difference between the study groups

The influence of the studied inflammation markers on the pain severity is undeniable, because in the inflammatory reaction cascade, cytokines synthesized by macrophages in the inflammatory focus are the first to react (table II).

The values of regression coefficients (B) varied in both groups after treatment, but no reliable indicators were recorded in either of them. However, it was important, that more significant value reduce of the coefficient B in the group of patients who received OT, when studying the effect of the following parameters at the end of drug correction:

- ESR – reduction of the regression coefficient in patients of group II on 0.07 units (from 0.06 to -0.01). In cases of patients of the group I – on 0,05 units (from 0,06 to 0,005);
- α1-AT – dynamic index decreased on 0.8 units (from 0.78 to -0.02), and in patients receiving BT – on 0.6 units (from 0.78 to 0.18).

An important pathogenetic link in the combined pathology of CP and AH is the level of antioxidant activity of the organism and its dynamic indicators of the influence on the abdominal pain severity (Table III).

The data obtained indicate that the formation of abdominal pain was significantly influenced by the following parameters of AOS: bilirubin and urea (low molecular weight non-enzymatic antioxidants).

The pathogenetic effect of bilirubin on the intensity of abdominal pain includes the following points. The main pancreatic duct is anatomically connected to the common bile duct, which opens at the level of the large duodenal papilla, controlled by the sphincter of Oddi. Oddi's sphincter dysfunction is a fairly common combination, since 35 (34.3%) patients showed the signs of chronic cholecystitis. It is known that the dysfunction of the sphincter of Oddi disrupts the outflow of both pancreatic and bile secretion, which is accompanied by an increase in intraductal pressure, both in the Virsung duct and in the biliary tract. The pressure in the biliary ducts is higher, which causes bile reflux in the duct of the pancreas. The consequence is the activation of proenzymes with subsequent autolysis of pancreatic tissue, and clinical manifestations of pancreatic abdominal pain. This whole pathogenetic chain is accompanied by the appearance of laboratory markers that indicate the appearance or exacerbation of CP, and the obligatory, at least a slight increase in bilirubin, which is consistent with the of pancreatology scientists opinion [14].

Since the results of our analysis indicate that urea also affects the formation of pain in CP, we need to determine its pathogenetic potential. The assumption about the effect of urea on the development of pain is that, in some patients, in addition to the visceral component of pain caused by inflammation of the pancreatic tissue. There is a component of parietal pain due to a pathological process in the urinary system. vessels with high blood pressure, with increasing urea levels as a marker of elimination of low molecular weight uremic toxins. Another explanation may be the presence of oxidative stress, which also forms a pain syndrome that requires immediate activation of the AOS protection, which includes urea. The antioxidant properties of the latter have been shown to be associated with chelation of free iron and inhibition of L-arginine resynthesis to L-citrulline [15].

However, the consideration of the mechanisms of influence of urea and bilirubin on the development of abdomenalgia, there is a tendency to reduce the impact of the following indicators, with a more pronounced group of patients with OT. Thus, the coefficient B (bilirubin effect) in patients of group II decreased 33 times (from 0.02 to 0.0006) against 2 times in patients of group I (from 0.02 to 0.01). The subjects of group II decreased by 0.12 units (from 0.11 to -0.01), and patients of group I by 0.07 units (from 0.11 to 0.04), according to the parameters of urea exposure. Although, credible results have not been achieved, the dynamic indicators are significant and have tendency to decrease.

The next step was to study the effect of the investigated laboratory parameters on blood pressure. Because PAP abnormalities are an early marker of hypertensive vascular remodeling and an increased risk of cardiovascular events, consideration and analysis of levels of this parameter is appropriate and scientifically sound. Markers of the inflammatory reaction affected the PAP dynamics as follows (Table IV).

Therefore, the obtained results indicate the dominant role of CRP in the formation of the level of PAP ($B = 3.53$; $p = 0.008$). Since the value of PAP is statistically significantly correlated with SAP ($r = 0.66$; $p < 0.01$) and DAP ($r = -0.60$; $p < 0.01$), then, accordingly, CRP will have a significant effect on SAP and DAP. In addition to actively participating in the dynamics of the inflammatory response, CRP actively increases the production of endothelin-1, which is a powerful vasoconstrictor. Thus, vascular spasm and elevated blood pressure are as results of endothelial dysfunction. Therefore, the role of CRP, both for the development and progression of systemic inflammatory response, and GC is quite significant.

Regarding the influence of other studied parameters of inflammation on the development of AH, no reliable values were recorded.

We conducted a regression analysis of AOS, in order to study the participation of antioxidants in the formation of the level of PAP. The results present in table V.

After treatment (table V*)*, no significant regression coefficients were found in any of the study groups. However, it should be noted that in the group of patients with OT there is a more significant tendency to reduce the effect of the studied trace element on the level of PAP ($B = 0.02$ and $B = -0.014$, respectively, by groups).

DISCUSSION

Cytokines synthesized by macrophages in the inflammatory focus are the first to react in the inflammatory reaction cascade and have the influence of the studied inflammation markers on the pain severity. The latter increase the production of Glucocorticoids, promote the appearance of leukocytosis, ESR growth. The next step is the intensification of CRP production, the synthesis of which is activated by the influence of Cytokines, Glucocorticoids. So, these given laboratory parameters (CRP, leukocytes, ESR, cortisol) are basic mechanism in the inflammation and pain pathogenesis. The Interleukin levels had a less important role in the pathogenesis of pain, according to regression analysis. This phenomenon is a specific feature, due to the fact that life cycle of Cytokines is short.

Another inflammation indicator (α1-AT) had significant affects on the pain formation. Its involvement in the inflammatory response which initiated pain caused by the specific neutralization of Lysosomal proteases, which appear as a result of inflammatory-activated macrophages and leukocytes actions[4].

Although there are no reliable indicators of the Cortisol exposure on the pain formation after treatment, but the results show a tendency to regression coefficient decrease in both groups. Therefore, we can assume, that both treatment regimens are close to the regulatory value of the studied hormone, but the determining effect of therapeutic measures to reduce the Cortisol level of ("stress hormone") to the reference values was not observed in either group.

The dynamics of fibrinogen levels in the group of patients with OT is indicative, despite the absence of regression

coefficient probable values, which confirms a more inflammatory response intense attenuation of the compared with the group of patients receiving BT.

The prescribing OT expediency is confirmed by the appearance of a reliable regression coefficient on the parameter of GPO after treatment in the group of patients who received BT. GPO is a selenium-containing metalloprotein, and in the conditions of Se deficiency, which was found in both groups. The further synthesis of GPO will not be regulated, without the additional introduction of this factor. In patients of group II by additional introduction of Se, as a structural component of the synthesis of GPO, was possible to eliminate the negative effects of the detected deficiency and achieve a positive trend of the intensity abdominal pain reducing[2]. This is primarily due to the ability of this metal to accumulate in the focus of ischemia, which occurs under conditions of oxidative stress and to carry out a direct membrane-stabilizing effect. Although the regression coefficient, which reproduces the effect of Se on the severity of abdominal pain, in none of the groups did not reach a probable value, but in the examined group I its level increased compared to the initial value (from 0.002 to 0.01), and in patients group II – on the contrary, decreased from 0.002 to -0.002. In group I, metalloenzyme deficiency maintained the persistence of abdominal pain after treatment, indicating an insufficient level of AOS protection and continued pathological effects of free radicals on tissues and cells.

The obtained results show the dominant role of Se in the formation of the PAP indicator. Since the value of blood pressure directly depends on the balance between vasodilation and vasoconstriction factors, under conditions of oxidative stress there is an imbalance of endothelium-producing factors. These cause the appearance and progression of vasospasm. Due to the presence of Se deficiency (as an element of antioxidant protection) at the beginning of treatment in the entire contingent of patients, it is natural to have endothelial dysfunction due to damage of the vascular wall by free radicals.

CONCLUSIONS

1. The performed regression analysis was mathematically substantiated the influence of the studied laboratory parameters of the inflammatory response and antioxidant system on the formation, dynamics of abdominal pain (the main clinical sign of CP) and the value of PAP (hypertensive vascular remodeling marker and risk predictor of cardiovascular events).
2. The severity of abdominal pain is significantly influenced by leukocytes, ESR, α1-AT, cortisol, CRP, Bilirubin and Urea, and the value of PAP – CRP and selenium, from laboratory parameters of the inflammatory response and AOS.
3. The effectiveness of the assigned optimized treatment scheme is proved, which is indicated by the appearance of a reliable regression coefficient on the parameter of glutathione peroxidase after completion of treatment in comparison with patients used basic therapy.

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The Authors declare no conflict of interest.

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