ORIGINAL ARTICLE

METABOLIC THERAPY IN THE COMPLEX TREATMENT OF CHRONIC PANCREATITIS WITH STABLE CORONARY ARTERY DISEASE

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ABSTRACT

The aim: To study the effectiveness of using medicine meldonium in standard therapy to the correction of prooxidant-antioxidant and kallikrein-kinin disorders in patients with chronic pancreatitis andstable coronary artery disease.

Materials and methods: The study included 90 patients with chronic pancreatitis andstable coronary artery disease.They were divided into two groups: I group (45 patients) received standard treatment; II group (45 patients) along with basic therapy received medication meldonium (Vazonat) for 2 capsules (500 mg) once daily for two months. Indicators prooxidant-antioxidant system in blood plasma was determined by biochemical method, indicators of kallikrein-kinin system– by chromatographic method.

Results: The better status of the prooxidant-antioxidant system and kallikrein-kinin system was observed in patients who received in addition to standard protocol treatment with meldonium.

Conclusions: Adding to the complex therapy of patients with chronic pancreatitis and stable coronary artery disease of the medicine meldonium helps to improve the prooxidation-antioxidant status and disorders in the kallikrein-kinin system more significantly compared with standard basic therapy.

KEY WORDS: chronic pancreatitis, stable coronary artery disease, treatment, metabolic therapy, meldonium

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INTRODUCTION

Chronic pancreatitis (CP) is one of the most common, rapidly progressing disease of pancreas with a high incidence of temporary disability and primary disability. It is known about the negative effect of CP on the cardiovascular system. It is established that in 15.5 % of patients with gastroenterological pathologies, including pancreatitis, there is stable coronary artery disease (SCAD). To date, the mechanisms for realizing the impact of the inflammatory process in the software on the development and progression of CP have not yet been fully understood [1]. The combination of CP and SCAD is characterized by a progressive course with increasing of the functional insufficiency of pancreas and the development of disorders in the kallikrein-kinin (KKS) system and prooxidant-antioxidant system [2, 3]. The uncertainty of these mechanisms leaves open the question of drug therapy for such a contingent of patients, which generally reduces the effectiveness of the treatment of patients with SCAD. Therefore, the search for effective treatment regimens in this direction is relevant for modern medicine [4, 5].

Standard basic therapy for comorbidity of CP and SCAD does not include the correction of prooxidant-antioxidant disorders and imbalances in the KKS [6, 7]. In recent years, the use of metabolic drugs has become common in medical practice. Meldonium, as a representative of metabolic therapy, refers to partial inhibitors of fatty acid oxidation. Its mechanism of action is related to the inverse limitation of the rate of biosynthesis of carnitine from its predecessor, gamma-butyrobetaine. As a result, carnitine-mediated transport of long-chain fatty acids through the mitochondrial membranes is inhibited without affecting the metabolism of short-chain fatty acids, thereby making meldonium capable of altering the prooxidant-antioxidant status and KKS [8].

The use of meldonium in combination with conventional therapy for CP combined with SCAD (nitrates, beta-blockers, angiotensin-converting enzyme inhibitors, statins, antiplatelet agents, antispasmodics, prokinetics, proton pump inhibitors, enzymes) allows to improve parameters of prooxidant-antioxidant status and imbalance in KKS.

Therefore, the use of meldonium in standard basic therapy for comorbidity of CP and SCAD is appropriate.

THE AIM

To investigate the effectiveness of course treatment meldonium (Vazonat) in standard therapy for the correction of prooxidant-antioxidant and kallicrein-kinin disorders in patients with CP and SCAD.

MATERIALS AND METHODS

The study was conducted at the Department of General Practice – Family Medicine, I. Horbachevsky Ternopil State Medical University (within 2016-2017).

To achieve this goal, 90 patients were selected from the CP in the stage of remission with MS. They were comparable to the etiological factor, socio-economic conditions and nutrition. Also, the influence of the alcohol factor was excluded. Among patients, there were 47 (52.22 %) male age (49.7±7.6) years and 43 female (47.78 %) age (51.15±6.4) years. The average duration of CP was (12.6±4.4) years, SCAD– (4.6±1.2) years. Patient examination was carried out with their consent. The study did not include patients with moderate to severe DM requiring insulin, severe arterial hypertension, myocardial infarction, cancer and somatic illness in the stage of decompensation. The studies meet the requirements of the Helsinki Declaration of the World Medical Association «Ethical principles for medical research involving human subjects as the object of study» opinion of the Committee on bioethics SHEI «Ternopil State Medical University by I. Horbachevsky of MPH of Ukraine»№ 41/2017.

Depending on the treatment program, the patients were divided into two groups: I group (45 patients)received standard protocol treatment (SPT) (creon 25.000 IU during meals, pantoprazole 40 mg once a day and/or domperidone 10 mg 3 times daily, atorvastatin 10 mg in the evening, in the presence of arterial hypertension – ramipril 5 mg in the morning, aspirin 75 mg in the evening, nebivolol 5 mg in the morning (with pulse control), nitrates as needed); II group (45 patients), in addition to SPT additionally received a medication of meldonium (Vazonat) for 2 capsules (500 mg) once daily for two months. The control group consisted of 20 practically healthy persons aged 19 to 46 years, the average age – (32.2±1.8) years. Among them there were 11 (55 %) men and 9 (45 %) women.

The diagnosis of CP was verified on the basis of the generally accepted classification in Ukraine proposed by the Scientific Research Institute of Medical Sciences of Ukraine, which corresponds to the Marseilles-Roman classification according to the «Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation of patients with chronic pancreatitis» approved by Order of the Ministry of Health of Ukraine № 638 dated 10.09.2014 [9]. The diagnosis of SCAD was established according to guidelines from the Health-National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA) [10, 11]. The state of prooxidant-antioxidant system was established by levels of malonic aldehyde (MA), superoxide dismutase (SOD), SH-groups, catalase and ceruloplasmin (CP) of blood, which were determined by biochemical methods. Indicators of KKS in blood plasma were determined by chromatographic method [12].Specific proteolysis was evaluated by the content of KK, PKK (prekallikrein), α_2-MG (α_2-macroglobulin), and kininase-II. Non-specific proteolysis was evaluated by the level of PAP (proteolytic activity of plasma) and α_1-IP (α_1-proteaseinhibitor) in blood plasma. All studied parameters were determined twice before and after treatment.

Statistical processing of the received data was performed on a personal computer using standard software packages of Microsoft Excel and with help of the computer program Statistica for Windowsversion6.0 (Stat Soft inc., USA).

RESULTS

By analyzing the prooxidant-antioxidant indices before and after treatment in patients of the two study groups, we determined a statistically significant improvement in the entire spectrum of this system ($p<0.05$).In the study of the state of the indicators of the prooxidant-antioxidant system for the treatment of patients with CP and SCAD, it was found that the level of MA was significantly higher in the I and II group compared with the control and was accordingly (6.35±0.07) μmol/L and (6.39±0.09) μmol/L. After the treatment, the level of MA in I group significantly decreased by 1.40 μmol/l (22.05 %), whereas in II group, this indicator significantly decreased by 2.22 μmol/l (34.75 %) (Fig. 1).

Also, prior to treatment, there was a significant decrease in the activity of antioxidant system enzymes at the level of SOD (I group – (39.22±0.47) units, II group – (39.52±0.45) units) and SH-groups (I group – (38.55±0.47) mmol/l; II group – (38.52±0.45) mmol/L) in both groups compared to control. After the treatment, a more significant increase in

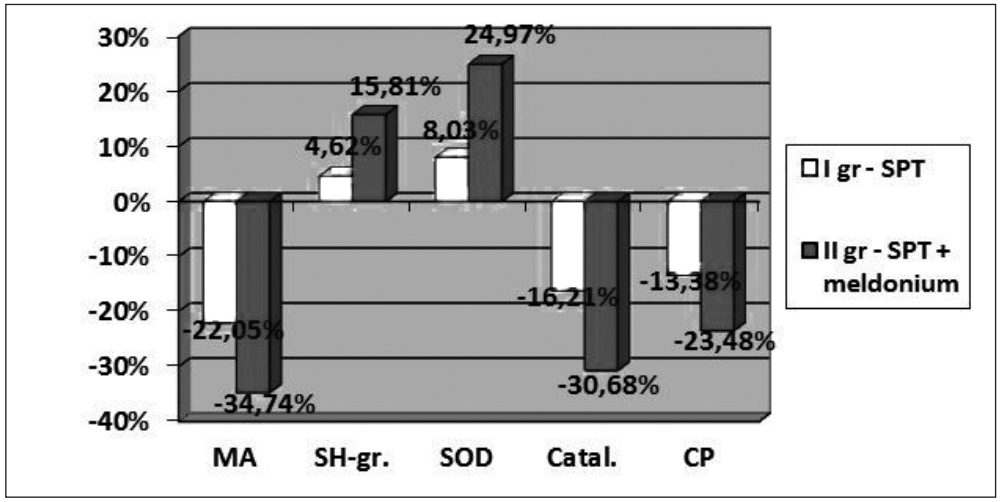

Figure 1. Dynamics of indicators of the prooxidant-antioxidant system after treatment in patients with CP and SCAD in comparison groups

Table 1. Dynamics of KKS under the influence of SPT with the in clusion of meldonium

Indicator	Control group (n=20)	I group (n=45)		II group (n=45)	
		before treatment	after treatment	before treatment	after treatment
PAP, mmol / (h·L)	31.83±0.71	55.68± 0.93* p2-3<0.05	49.03± 0.63#	55.52± 0.76** p4-5<0,05	45.73± 0,48## p3-5<0.05
KK, μmol / (min·L)	52.15±1.43	177.51± 1.62* p2-3<0.05	164.16± 1.63#	177.26± 1.59** p4-5<0.05	154.31± 0.84## p3-5<0.05
PKK, μmol / (min·L)	72.57±1.21	36.91± 0.67* p2-3<0.05	40.44± 0.73#	36.94± 0.67** p4-5<0.05	43.08± 0.80## p3-5<0.05
α1-IP, g/L	1.41±0.02	1.98± 0.06* p2-3<0.05	1.82± 0.01#	1.98± 0.02** p4-5<0.05	1.71± 0.01## p3-5<0.05
α2-MG, g/L	1.50±0.03	0,45±0,02* p2-3<0.05	0.56±0.01#	0,45±0,02** p4-5<0,05	0,67±0,01## p3-5<0.05
The activity of kininase-II, μmol / (min·L)	269.84±1.74	152.97± 2.50* p2-3<0.05	165,44± 1.16#	152.84± 2.00** p4-5<0.05	176.10± 2.12## p3-5<0.05

Note 1. * – (p1-2<0.05); Note 2. # – (p1-3<0.05);
Note 3. ** – (p1-4<0.05); Note 4. ## – (p1-5<0.05).

the activity of SOD (by 24.98 %) and an increase in the level of SH-groups (by 15.81 %) in II group was observed, while in the I group, these indices increased slightly and unreliable.

The level of catalase in blood plasma before treatment in I and II groups of patients was significantly higher compared to control ((55.72±1.12) % and (55.77±1.03) % respectively). After treatment, this indicator decreased significantly by 16.22 % in I group and 30.68 % in II group (Fig. 1).

Table 1 shows the results of the obtained indicators of general and specific proteolysis in the comparison groups that characterize the state of KKS before and after treatment.

While analyzing indicators of general and specific proteolysis, a positive effect of the treatment in I group and II group was observed, but in II group the therapeutic effect was more significant: the level of PAP decreased by 11.94 % in I group and by 17.63 % – in II group, the level of KK decreased by 7.52 % in I group and by 12.95% – in II group, the level of PKK increased by 9.56% in I group and by 16.62 % in II group. The levels of these indicators after treatment in two groups were statistically significantly higher than those before treatment (p<0.05). The level of α_1-IP decreased significantly and statistically significantly in II group compared to I group by 6.04 % (p<0.05). With regarding to α_2-MG and kininase-II levels, ther values in the SPT + meldonium group increased statistically significantly by 19.64% and 6.44 %, respectively relative to the SPT group (p <0.05).

DISCUSSIONS

Assessing the state of the prooxidant-antioxidant system in patients with CP in combination with SCAD after treatment, we found a statistically significant decrease in the level of MA. From this we can conclude that the addition of meldonium to SPT led to a decrease in the intensity of lipoperoxidation processes. After treatment, there was also an increase in SOD and SH-groups in the two comparis on groups, but this in crease was more statistically significant in patients with CP in combination with SCAD who, in addition to SPT, received the drug meldonium. With regard to the CP level and the catalase in the blood of the patients under study, their levels after treatment alsodecreasedsignificantlymorestatistically inpatientswithadditionaluse of meldoniumin SPT. This demonstrates the regulatory ability of the metabolic agents in terms of antioxidant protection [13].

Therefore, the use of meldonium in the complex treatment of patients with CP in combination with SCAD leads to an improvement in antioxidant protection and to reduce the processes of lipidperoxidation [14].

Analyzing KKS rates in patients with CP with SCAD, we noted a more significant improvement in the group of patients with additional admission of meldoniumto SPT. Indicators of specific proteolysis after treatment were statistically significantly lower in patients of II group compared with patients of I group. From this we canconclude about the regulatory effect of meldonium on the imbalance in the specific proteolysis system. Regarding the in dices of nonspecific proteolysis, we observed the same positive effect of meldonium in patients of II group [15].

Therefore, on the basis of the above, it is advisable to use meldonium in SPT in patients with CP in combination with SCAD in the following scheme: 2 capsules (500 mg) once a day for 2 months to improve the prooxidant-antioxidant status and imbalance in KKS.

CONCLUSIONS

1. Use in the complex treatment of patients with chronic pancreatitis and stable coronary artery disease medication of meldonium contributed to a more reliable regression of prooxidant-antioxidant disorders in comparison with standard conventional therapy($p<0.05$).
2. Adding to the basic therapy of patients with chronic pancreatitis and stable coronary artery disease medication of meldoniumled to a more significant improvement in balance of kallikrein-kinin system ($p<0.05$) than with standard protocol treatment.

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Conflict of interest:
The Authors declare no conflict of interest.

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