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Effectiveness of pentoxifylline in treatment of alcohol-induced combined lesion of liver and pancreas

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Abstract

The article presents the results of the use of pentoxifylline in the treatment of patients with a combination of chronic pancreatitis and cirrhosis of alcoholic etiology. The use of this scheme leads to more frequent decrease of pain and astheno-vegetative syndrome in patients with chronic pancreatitis, signs of portal hypertension in examined with cirrhosis, helps to reduce the activity of phospholipase A2, especially in case of combined lesion of both organs, increases chymotrypsin activity in the stool, it also decreases the levels of indirect indicators of fibrosis and collagen IV, and slows the progression of fibrosis in the liver according elastography.

Keywords: *liver cirrhosis, chronic alcoholic pancreatitis, elastography, pentoxifylline.*

1. Introduction

Alcohol liver disease, especially cirrhosis, and diseases of the pancreas are one of the most frequent pathologies of internal organs associated with the alcohol consumption [16]. There is no consensus regarding the dose of alcohol, which causes damage to both organs do not exist, although its growth to 12-14 grams per day increases the risk of death from liver cirrhosis (LC) [13]. The frequency of hospitalization of patients with alcoholic liver disease increases with increasing annual dose of alcohol per capita in patients with cirrhosis and not always keeps this trend in patients with chronic pancreatitis [17].

The data on the frequency of lesions of both organs (liver cirrhosis and chronic alcoholic pancreatitis) is also heterogeneous and sometimes contradictory, due to the different methods of statistical evaluation. Thus, Y. Nakamura *et al.* [10] believe that despite the fact that chronic alcoholic pancreatitis and alcoholic liver cirrhosis are major alcohol-induced diseases, there is no parallel connection between these two disorders and other factors affect the frequency of their combined injury, in addition to the daily dose of alcohol (genetic, family history, smoking). As a result of comparative history of two groups of patients, one of whom diagnosed with liver cirrhosis, and the second were examined with disorders of the cardiovascular and respiratory systems, pathological changes of the pancreas, specific to chronic alcoholic pancreatitis were found in 20% of patients in 1st group and 2.6% in 2nd group [15]. According to data of endoscopic ultrasonography and retrograde cholangiopancreatography chronic pancreatitis was diagnosed in 19% of patients with alcoholic cirrhosis [5]. Epidemiological studies on the combination of chronic pancreatitis and alcoholic liver cirrhosis show that their simultaneous development under the influence of alcohol recorded at 0.32 cases per 100,000 population, and with this combination had the highest mortality [21]. The frequency of simultaneous injury of both organs depends on the activity of glutathione-S-transferase, apolipoprotein E, genetic predisposition [5, 9], and severity of oxidative stress [20]. Combined lesion of the pancreas (chronic pancreatitis alcoholic) and alcoholic liver disease, characterized by mutually aggravating influence, requires selecting individual tactics and finding ways to treat effectively [12].

According to the guideline of the European Association for the Study of Liver [3] for the treatment of alcoholic liver disease, along with corticosteroids, the use of which in this condition leads to an increase in terms of survival, it is appropriate as the use of S-adenozyl-L-methionine, silymarin, propiluratsyl. Although the results of the effectiveness of these drugs are heterogeneous and not fully understood. Currently to treat alcoholic liver disease are more often involved in the medicines possessing anti-cytokine activity. In particular, it appears that pentoxifylline inhibits the production of a number of cytokines (FNPA, IL-1, IL-2, IL-6, IL-8) [14] and it was a higher 6-month survival in patients it received thanks to the antioxidant, immunosuppressive properties [3]. Other positive effects of pentoxifylline in patients with

alcoholic liver lesion include inhibition of hepatic fibrogenesis, providing its effectiveness on the stage of fibrosis and cirrhosis. Prescription of pentoxifylline also contributed the reduction of growth factor B and vascular endothelial cell proliferation in animals with experimental cholestasis and reduction of IL-6 in blood and collagen formation [8]. As a phosphodiesterase inhibitor, pentoxifylline decreases the level of kinases FNP α in acinar cells in acute pancreatitis. It also reduces the effects of fibrosis of the pancreas in case of experimental pancreatitis as around ducts so in acinar tissue.

These data indicate the possibility of using pentoxifylline for the treatment of combined alcoholic liver disease and pancreas, although its effectiveness in chronic alcoholic pancreatitis and liver cirrhosis class A, B by Child Pugh not been studied.

Purpose - to increase the effectiveness of treatment of alcoholic combined injury of the pancreas (chronic alcoholic pancreatitis) and liver (cirrhosis class A, B by Child Pugh) by adding pentoxifylline to the treatment.

2. Material and Methods

The study involved 46 patients with alcoholic liver cirrhosis class A, B by Child Pugh and 50 patients with concomitant lesions of the pancreas (chronic alcoholic pancreatitis), which were hospitalized in the clinic of medical university, gastroenterological department of City Clinical Hospital №1 of Ivano-Frankivsk, therapeutic department of Central Regional Hospital Lisets. Males dominated among surveyed (94.79%).

Alcoholic etiology of lesions of the liver and pancreas was confirmed by a history of life, disease, analysis of previous medical records and monitoring the number of patients by narcologist, indicators of questionnaires CAGE, MAST, assessment scales LeGo, stigmas of alcohol intake.

The diagnosis of liver cirrhosis established by order of the Ministry of Health of Ukraine № 826 from 06.11.2014, the "Unified clinical protocols of primary, secondary (specialized) medical care to patients with alcoholic hepatitis", and chronic alcoholic pancreatitis - according to criteria recommended by the Ministry of Health of Ukraine from 09.10.2014 № 638 "On approval and introduction of medical and technological documents for standardization of care for chronic pancreatitis".

Patients in both groups were divided into subgroups depending on the mode of treatment. Patients with cirrhosis of the control subgroup (26 patients) received ADE-methionine (Geptral) 400 mg intravenously twice a day the first 5 days, and then 400 mg orally 2 weeks, Duphalac 30 ml orally, 2 times a day, Veroshpiron 100 mg 2 weeks, and saw this therapy as a baseline. Patients (30 pers.) with combined liver and pancreas lesion: to such therapy added proton pump inhibitor by 40 mg daily, two weeks replacement enzyme therapy (Creon or Pangrol 25,000 U twice daily during or after meals), pyridoxine 2 ml per day for 2 weeks. Research subgroups included - 20 patients with cirrhosis and 20 patients with liver cirrhosis + chronic alcoholic pancreatitis. Pentoxifylline (Pentoxifylline-Darnitsya) was added to the basic treatment for these patients - 5 mL of 2% solution in 100mL of 0.9% sodium chloride intravenous infusion for 5 days, transition to ingestion by 200 mg, 1 time per day to 3 months.

The effectiveness of the therapy in the main and control groups evaluated the results of the dynamics of basic clinical syndromes (pain, asthenic vegetative, external secretory failure, cytolytic, mesenchymal-inflammatory, hepatomegaly),

the results of non-invasive methods survey (elastometry - based on acoustic mode generate shear waves using technology ARFI - Acoustic Radiation Force Impulse, made by the foundation of a diagnostic system S2000 Siemens (Germany) to determine the speed of shear waves severe numerical value in m/s using the apparatus Siemens ACUSON S2000). Among minimally invasive methods for assessing the degree of fibrosis, we investigated levels of collagen type IV in serum by the IFA method using kits Argutus Collagen IV (Germany) for its quantitative evaluation. Patients with alcoholic combined lesions of both organs conducted repeated ultrasound diagnostics of pancreas using the apparatus Siemens after 2 months and external secretory function of the pancreas was assessed by chymotrypsin activity in feces using sets Chymotrypsin Activity Immundiagnostic (Germany).

Statistical analysis of the results of research conducted with the use of the program «Statistica 12.5» calculated and Student's t-test, Pearson and Fisher criteria.

3. Results and Discussion

After hospital treatment in patients with cirrhosis class A, B by Child Pugh using basic therapy significantly reduced the size of only the left lobe of the liver, while the addition of pentoxifylline contributed to a significant decrease in the size of the right lobe at 11.9, and left at 10.9mm. In cases of combined alcoholic liver disease and pancreas, as under the influence of basic and combination therapy with the inclusion of pentoxifylline was significantly decreased both size fractions of the liver (Table 1).

Pain of dull character in the upper right abdomen disappeared in 53.85% of patients with cirrhosis who received basic therapy and in 75% of patients, who received basic therapy with pentoxifylline. In case of combined alcohol-induced pain in both of the upper umbilical zone and the and right upper quadrant decreased, 40.0% in 1st subgroup and 55.0% in 2nd subgroup taking pentoxifylline. A significant decrease of pain was spotted in patients with combined alcoholic liver cirrhosis and chronic pancreatitis, probably due to pentoxifylline's anti-inflammatory properties, as demonstrated in his experimental models [10] and clinical studies [2]. The manifestation of asthenic-vegetative syndrome upon completion of basic treatment was not detected in 42.31% of patients with cirrhosis, and in 60.0% of patients, which was administered pentoxifylline. Asthenic-vegetative syndrome was not registered after treatment of patients with two combined alcohol-induced symptoms in 29.73% of those who received basic treatment and in 45.0% of patients who used pentoxifylline.

Analyzing the effect of a basic therapy on indicators of the functional condition of the liver in patients with cirrhosis and without lesions of pancreas revealed that total bilirubin level decreased by 1.2 times (from 52.2 to 42.89mkmol / l), while in patients with the same pathology with the appointment of pentoxifylline - in 1.5 times (from 44.8 to 28.41mkmol/l). The activity of AST in patients with cirrhosis of the liver after a course of treatment significantly decreased ($p_{1,2} < 0.05$) in the patients, receiving basic therapy (from 1.17 ± 0.05 to 1.03 ± 0.04 mmol/l) and when it is combined with pentoxifylline (from 1.23 ± 0.09 to 0.94 ± 0.05 mmol/l), while the activity of ALT - only in patients who received pentoxifylline (from 0.87 ± 0.04 to 0.64 ± 0.03 mmol/l). In cases of alcohol combined lesions of both organs (liver and pancreas) AST activity was significantly reduced in patients receiving combined therapy with pentoxifylline (from 1.45 ± 0.07 to 1.23 ± 0.05 mmol/L, p

<0.05), the tendency to fall in activity under the influence of basic therapy.

Involvement of pentoxifylline to complex therapy of combined cirrhosis and chronic alcohol-induced pancreatitis also contributed to a significant decrease in the size of the pancreas (Figure 1) according to its sonography, especially the head and body. In patients with comorbidity, which were assigned a base therapy, pancreatic head size did not change after 2 weeks, and the size of a body and tail decreased in 1.8 and 1.24 times.

A more expressed effect of pentoxifylline in patients with pancreatitis according to Luis Gomez-Cambroner [6] caused by a decrease in the accumulation of fibrin in tissues of the pancreas, neutrophils and mononuclear cells and decrease vacuolization of acinar cells. Courses prescription of pentoxifylline in patients with isolated chronic alcoholic pancreatitis and its combination with cirrhosis class A, B contributed to the improvement of external secretory function of the pancreas, as indicated by the increased activity of chymotrypsin in stool, by 1.8 times (by 5.16 ± 0.31 to 9.40 ± 0.39 U/g) and 1.6 times (from 4.46 ± 0.48 to 7.21 ± 0.49 U/h), while under the influence of baseline therapy slightly less pronounced.

The effectiveness of pentoxifylline in treating alcoholic cirrhosis and its combination with chronic alcoholic pancreatitis evaluated according to the results of Acoustic Radiation Force Impulse (ARFI-elastography), since the ultrasound diagnosis, besides determining the size of organs not always detect diffuse changes in the liver parenchyma and fully evaluate the effectiveness of treatment of such conditions [19], despite the fact that between elastography and liver biopsy

revealed a strong direct correlation [1]. Repeat elastometry in patients of both groups performed 3 months after completion of the treatment course. It was found that ARFI indicator (median) increased from 2.92 ± 0.05 to 3.05 ± 0.03 m/s ($p < 0.05$), in patients with cirrhosis class A,B by Child Pugh, 3 months after completion of basic therapy, corresponding to F4 fibrosis stage. ARFI tended to decrease (from 3.10 ± 0.06 to 3.02 ± 0.08 m/s) at the surveyed patients with cirrhosis who continued to take pentoxifylline 200 mg daily for 3 months. The absence of the negative dynamics of median of fibrosis indicates stabilization of fibrogenesis in the liver. Prolonged use of pentoxifylline in patients with combined alcohol-induced liver and pancreas lesion resulted a decrease in the rate of shear waves from 2.95 ± 0.07 to 2.69 ± 0.07 m/s ($p < 0.05$), while the same indicator grew in patients who underwent only basic treatment (shear wave velocity significantly increased from 3.06 ± 0.10 to 3.56 ± 0.09 m/s, corresponding to F4 fibrosis stage).

The level of collagen type IV had only a downward trend after 2 weeks of standard treatment, and returned after 3 months to the values that were registered prior to treatment. Long-term medication of pentoxifylline leads to lowering the level of collagen type IV at the end of a 2-week course by 20.63% (from 321.78 ± 21.44 to 272.59 ± 21.14 pg/ml) in liver cirrhosis and 14.96% (396.60 ± 24.12 to 337.30 ± 15.30 pg/mL) in combination of cirrhosis with chronic alcoholic pancreatitis. Prolonged use of pentoxifylline provided slight further reduction of collagen type IV. Pentoxifylline has inhibitory effect on the processes of fibrogenesis in the liver due to its ability to inhibit the activity of stellate cells at the level of proinflammatory cytokines [22].

Table 1: Liver sizes under various treatment regimens

Indicators	Patients with alcoholic liver cirrhosis		Patients with a combination of cirrhosis and chronic alcoholic pancreatitis	
	Basic therapy	Basic therapy + pentoxifylline	Basic therapy	Basic therapy + pentoxifylline
Sizes the right lobe of the liver (mm)	$177.0 \pm 4.0^*$ 168.74.3	183.2 ± 2.8 171.3 \pm 2.9*	182.4 ± 2.0 169.1 \pm 1.9	174.6 ± 3.1 162.8 \pm 2.5*
Sizes the left lobe of the liver (mm)	80.1 ± 2.3 74.1 \pm 2.5*	78.1 ± 1.8 67.2 \pm 1.1*	72.2 ± 1.2 64.9 \pm 0.99	75.1 ± 2.0 63,8 \pm 1.3*

Remarks: * - significance compare control $p < 0,05$

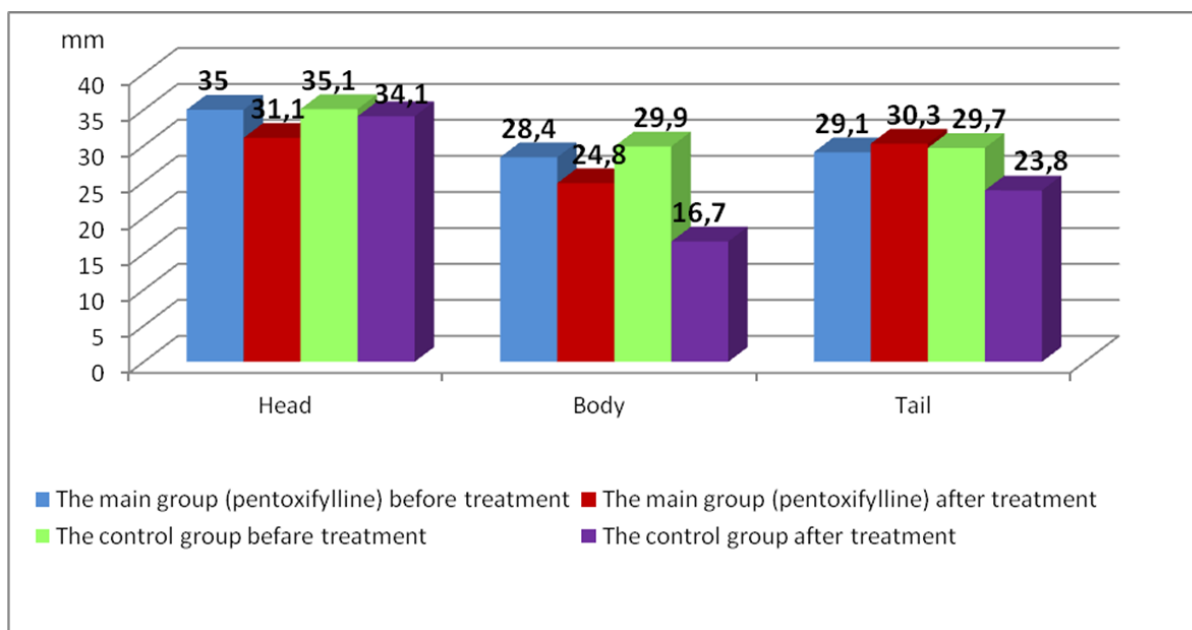


Fig 1: Sizes of the pancreas in patients with a combination of liver cirrhosis and chronic alcoholic pancreatitis

4. Conclusions

Thus, as seen from the data, involving pentoxifylline to the complex therapy of patients with alcoholic cirrhosis and its combination with chronic alcoholic pancreatitis improves the clinical course of disease, functional condition of the liver and slows the progression of fibrosis in the liver and helps to normalize the size of a pancreas.

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