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Characteristics of Adverse Effects in Patients with Chronic Alcoholic Pancreatitis and Concomitant Alcoholic Liver Cirrhosis Child-Pugh Class A and B

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Keywords:
alcoholic liver cirrhosis; chronic alcoholic pancreatitis; pentoxifylline; Hepasol-Neo

Abstract.

Alcohol intoxication is the third leading cause of death, and among alcohol-dependent patients alcohol-related pathology (alcoholic liver disease, acute and chronic pancreatitis, cardiomyopathy, polyneuro-encephalopathy) accounts for 42.6% of fatal cases. In many cases prominent feature of liver damage can be detected in people who consume alcohol in moderation and they can hardly be called alcoholics.

The objective of the research was to study the long-term results of the effectiveness of treating patients with chronic alcoholic pancreatitis and concomitant alcoholic liver cirrhosis Child-Pugh Class A and B as well as to establish prognostically unfavorable parameters of the clinical course of the comorbidity.

Materials and methods. The study included 89 patients with alcohol-related pathology who were observed prospectively for 1 year. 50 patients suffered from chronic alcoholic pancreatitis and concomitant liver cirrhosis Child-Pugh Class A and B; 20 patients were diagnosed with alcoholic liver cirrhosis without damage to the pancreas; 19 patients developed chronic alcoholic pancreatitis. Patients with liver cirrhosis received therapy according to the Order of the Ministry of Health of Ukraine of 06.11.2014, No 826 "Unified clinical protocol of primary, secondary (specialized) medical care "Alcoholic hepatitis"; patients with chronic alcoholic pancreatitis received therapy according to the Order of the Ministry of Health of Ukraine of 10.09.2014, No 638 "On approval and implementation of medical and technical documents on standardization of medical care in chronic pancreatitis". Patients with chronic alcoholic pancreatitis and concomitant liver cirrhosis Child-Pugh Class A and B were divided into 2 subgroups. Subgroup I (20 patients) received combination therapy according to the Orders of the Ministry of Health of Ukraine mentioned above. Subgroup II (30 patients) received pentoxifylline (Pentoxifylline-Darnitsa) at a dose of 5 ml of 2% solution per 200 ml of 0.9% sodium chloride solution intravenously for 5 days with further transition to oral medications at a dose of 200 mg up to two months including the mixture of essential, conditionally essential and non-essential amino acids (Hepasol-Neo) at a dose of 500 ml of 8% solution intravenously on alternate days 5 times in addition to basic therapy.

Conclusions. Concurrent alcohol-induced injury of the pancreas and liver increases the risk of developing more severe clinical course of this comorbidity with transition of cirrhosis to the decompensated stage, bleeding varicose veins in the esophagus occurring more often, increased pancreatic fibrosis with widening of the ductal system and further development of cysts and pancreatic exocrine insufficiency. The addition of pentoxifylline and mixture of essential, conditionally essential and non-essential amino acids to basic therapy reduces the number of patients developing complications.

Problem statement and analysis of the recent research

Alcohol abuse often results in systemic multiple organ lesions involving the liver and pancreatic gland (PG) manifested themselves as acute and chronic conditions [5]. According to the author, alcohol intoxication is the third leading cause of death, and among alcohol-dependent patients alcohol-related pathology (alcoholic liver disease, acute and chronic pancreatitis, cardiomyopathy, polyneuro-encephalopathy) accounts for 42.6% of fatal cases. According to other authors, alcoholism is killing 2.5 million people every year worldwide accounting for 4% of overall mortality and the main cause of this phenomenon is alcoholic hepatitis and liver cirrhosis of different severity degrees [18]. Both the liver and PG is the primary target of the toxic effect of alcohol in its excessive consumption that is explained by systemic nature of its metabolism, common mechanisms of neuroregulation of the digestive system functions, uniformity of the influence, the interdependence of the liver and PG in the process of digestion [2, 3]. This problem is also relevant due to the fact that in many cases prominent feature of liver damage can be detected in people who consume alcohol in moderation and they can hardly be called alcoholics [8]. The medical and social significance of digestive problems caused by alcohol abuse is also evidenced by the fact that they rank second among causes of liver transplantation in Europe [15].

In its early stages chronic alcoholic pancreatitis (CAP) may be accompanied by complications similar to those in acute alcoholic pancreatitis including necrotizing pancreatitis, pseudocyst formation, exocrine and endocrine insufficiency, visceral artery aneurysms and pseudoaneurysms, etc. [20]. Alcohol also plays a significant role in the development of calcifying pancreatitis [4].

The prognosis for patients with CAP under conditions of further abstinence depends on their adherence to the doctor's recommendations as well as keeping to a strict diet, and adequacy of maintenance treatment. 70-80% of patients who adhere to the instructions mentioned above live for about 10 years and in case of noncompliance 50% of patients die sooner [11].

Due to the improvement of therapy for alcoholic liver disease (ALD), cirrhosis and its complications in particular, the prognosis for the disease has improved recently. It depends under condition of total abstinence on the functional state of the liver, complications. In decompensated liver cirrhosis (LC) (Child-Pugh Class C) only 11-14% of patients are alive 3 years after diagnosis and in case of developing complications such as ascites life expectancy does not exceed 2–3 years. According to the data of Shipulin VP, et al [10] 12 out of 59 patients with Child-Pugh Class B and C cirrhosis being under observation died 1 year after therapy including essential phospholipids and lipoic acid; two years after the beginning of the observation 71% out of 59 patients were alive.

Taking into consideration the above-mentioned data the problem of predicting the effectiveness of therapy for alcohol-related injuries of the liver remains relevant. Particularly, Rachkovskyi MI [6] suggested several models of predicting survival in patients with alcoholic LC after treatment: the first model determines aspartate aminotransferase activity and serum creatinine levels and second one is based on estimating the time for maximum accumulation of ^{99}Tc-bromide in the liver according to the data of dynamic hepatobiliary scintigraphy which is not readily available in clinical practice. Abrahamovych OO, et al [11] recommend to use the parameters of ultrasound Doppler flowmetry of the portal venous system in order to predict the effectiveness of therapy for LC. More available and simpler criteria based on the overall estimation of changes in parameters such as the level of bilirubin, ALAT, ASAT, thymol sample, superoxide dismutase activity, malonic aldehyde level, tumor necrosis factor, interleukin-4, type IV collagen, leptin, medium molecular peptides were proposed by Samohalska OE, et al [7]. There are also other criteria, the MELD score in particular: a value of more than 32 indicates a high mortality within a relatively short period serving as an indication for the administration of glucocorticoids [18]. The GAHS, ABIC and Lille Model Score can be also used to predict the outcomes of ALD. The latter model including the patient's age, degree

of kidney failure (creatinine clearance<40), international normalized ratio>1.3, albumin level, prothrombin time (PT), bilirubin allows us to predict a 6-month survival. Therefore, as indicated by the analysis of the above-mentioned data, the problem of predicting the effectiveness of therapy for both CAP and alcoholic LC requires further improvement.

The objective of the research was to study the long-term results of the effectiveness of treating patients with CAP and concomitant alcoholic LC Child-Pugh Class A and B as well as to establish prognostically unfavorable parameters of the clinical course of the comorbidity.

Materials and methods

The study included 89 patients with alcohol-related pathology who were observed prospectively for 1 year. Alcoholic genesis of injury of the liver and PG was confirmed by the patient's life history, past medical history, particularly observation by therapists for alcoholics or drug abusers, the MAST and the CAGE Questionnaire, the Le Go Grid method, objective stigmata of alcoholism. 50 patients suffered from chronic alcoholic pancreatitis and concomitant liver cirrhosis Child-Pugh Class A and B; 20 patients were diagnosed with alcoholic liver cirrhosis without damage to the pancreas; 19 patients developed chronic alcoholic pancreatitis. Patients with liver cirrhosis received therapy according to the Order of the Ministry of Health of Ukraine of 06.11.2014, No 826 "Unified clinical protocol of primary, secondary (specialized) medical care "Alcoholic hepatitis"; patients with chronic alcoholic pancreatitis received therapy according to the Order of the Ministry of Health of Ukraine of 10.09.2014, No 638 "On approval and implementation of medical and technical documents on standardization of medical care in chronic pancreatitis". Patients with chronic alcoholic pancreatitis and concomitant liver cirrhosis Child-Pugh Class A and B were divided into 2 subgroups. Subgroup I (20 patients) received combination therapy according to the Orders of the Ministry of Health of Ukraine mentioned above. Subgroup II (30 patients) received pentoxifylline (Pentoxifylline-Darnitsa) at a dose of 5 ml of 2% solution per 200 ml of 0.9% sodium chloride solution intravenously for 5 days with further transition to oral medications at a dose of 200 mg up to two months including the mixture of essential, conditionally essential and non-essential amino acids (Hepasol-Neo) at a dose of 500 ml of 8% solution intravenously on alternate days 5 times in addition to basic therapy.

To assess the prediction and long-term results of treatment the odds ratio (OR) and the 95% confidence interval (CI) were used. The survival in patients of the main group suffering from CAP and concomitant LC Child-Pugh Class A and B was analyzed by the Kaplan-Meier method. The cumulative proportion surviving (%) in patients was calculated during different observation periods. The transition of LC Child-Pugh Class A and B to LC Child-Pugh Class C, bleeding from varicose veins in the esophagus, development of pancreatic cysts, death served as study endpoints.

Results and discussion

The odds ratios for transition of LC Child-Pugh Class A and B to LC Child-Pugh Class C after basic therapy were analyzed. The odds ratio was the most probable in case of serum albumin level of below 35% (OR–28.50, p<0.001), higher than normal levels of total bilirubin, reduced serum cholinesterase levels, increased serum concentration of type IV collagen >300 pg/ml, acceleration of wave velocity according to the results of liver elastography >2.64 m/s with a probability of 15.5; 19.0 and 44.3 times (Table 1, Fig.1).

Table 1

Odds ratio in patients with alcoholic LC Child-Pugh Class A and B

Parameter	OR	95% CI	p	Xi2
Total bilirubin, >20.5 mmol/l	35.29	3.87-321.83	0.00027	13.30
Albumins, <35%	28.50	3.16-257.44	0.00074	11.40

PT, <60%	10.36	1.10-97.69	0.05441	3.70
Ascites	6.33	0.67-60.16	0.18404	1.76
Type IV collagen, >300 pg/ml	19.00	2.12-170.38	0.00461	8.03
Elastometry, >2.64 m/s	44.33	4.78-410.94	0.0009	15.36
Phospholipase A2 type IIA, >200 pg/ml	13.57	1.34-137.45	0.03530	4.43
Cholinesterase, <5000	15.55	1.73-139.65	0.01059	6.53

Notes: OR – odd ratio; 95% CI - confidence interval; p - probability criterion

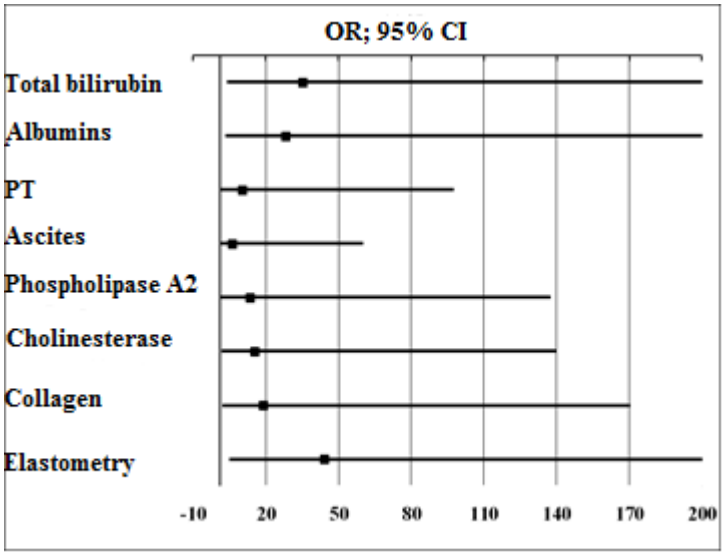


Fig. 1. Relative risk of complications in patients with LC Child-Pugh Class A and B

Correlation between increased chances of developing complications and mortality in alcoholic LC and decreased albumin level as wells as the development of hepatic encephalopathy and duration of alcohol consumption is indicated by other researches as well [12].

Unfavorable prognostic factors for alcoholic LC are known to be divided into exogenous and endogenous. Exogenous factors include the quantity and type of alcoholic beverage, duration and patterns of alcohol consumption. Endogenous factors include the gender, ethnicity as well as comorbid conditions the role of which is proven such as metabolic syndrome, iron overload, infection with hepatitis viruses and other conditions including progressive fibrosis [17]. The damage to other organs requires clarification [13].

In patients with CAP the most unfavorable prognostic indicators of developing complications included increased activity of phospholipase A2 type IIA >200 pg/ml and value of fecal chymotrypsin activity <6.0 U/g (Table 2, Fig. 2).

Table 2

Odds ratio in patients with CAP

Parameter	OR	95% CI	p	Xi2
Total bilirubin, >20.5 mmol/l	1.36	0.11-16.05	0.71536	0.13
Albumins, <35%	2.92	0.3-28.29	0.63043	0.23
PT, <60%	0.66	0.04-11.12	0.65853	0.20
Type IV collagen, >100 pg/ml	5.78	0.65-51.24	0.18069	1.79
Chymotrypsin activity, <6 U/g	38.00	3.65-395.21	0.0081	11.22
Phospholipase A2 type IIA, >200 pg/ml	57.00	5.18-627.14	0.00018	14.00
Cholinesterase, <5000	4.07	0.8-43.38	0.48177	0.49

Notes: OR – odd ratio; 95% CI - confidence interval; p - probability criterion

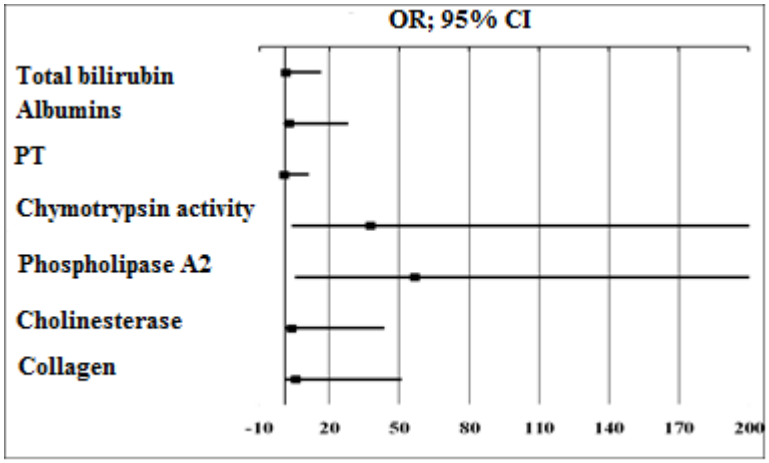


Fig. 2. Relative risk of complications in patients with CAP

In patients with CAP and concomitant LC Child-Pugh Class A and B compared to patients with CAP only the most unfavorable prognostic parameters included low serum albumin levels, reduced prothrombin time ratio, low cholinesterase levels, reduced concentration of type IV collagen (Table 3, Fig. 3).

Table 3

Odds ratio in patients with CAP and concomitant LC Child-Pugh Class A and B

Parameter	OR	95% CI	p	Xi2
Total bilirubin, >30 mmol/l	60.17	6.60-548.71	0.00001	19.90
Albumins, <35%	38.00	4.43-326.02	0.00005	16.29
PT, <60%	12.67	1.40-114.42	0.02310	5.16
Ascites	8.14	0.88-75.48	0.09601	2.77
Type IV collagen, >300 pg/ml	40.38	4.57-356.96	0.00007	15.84
Elastometry, >2.64 m/s	57.00	6.00-514.47	0.00003	17.60
Phospholipase A2 type IIA, >200 pg/ml	28.50	3.27-248.17	0.00044	12.37
Cholinesterase, <5000	35.29	3.87-321.93	0.00027	13.30

Notes: OR – odd ratio; 95% CI - confidence interval; p - probability criterion

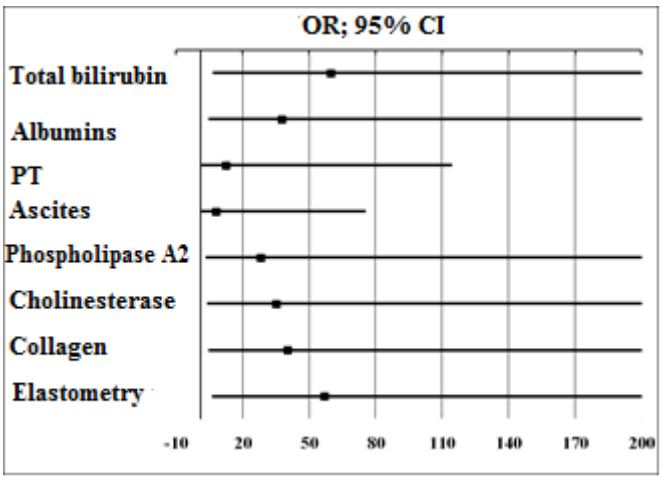
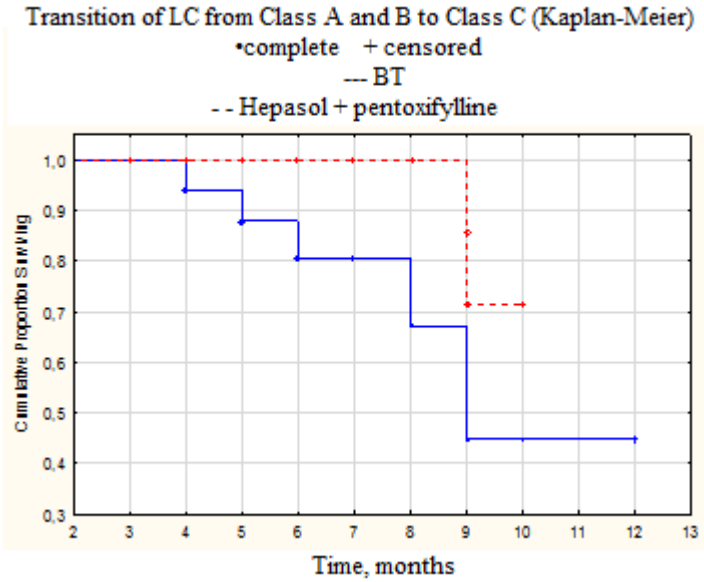


Fig. 2. Relative risk of complications in patients with CAP and concomitant LC Child-Pugh Class A and B

The chances of developing adverse events in patients with liver pathology and co-existent pancreas pathology exceeded the parameters of the odds ratio compared to patients with alcoholic LC only: total bilirubin levels increased by 1.7 times, serum albumin level of below 35% increased by 1.3 times, serum levels of type IV collagen >300 pg/ml, cholinesterase and phospholipase A2 type IIA >200 pg/ml increased by 2.1, 2.1 and 2.2 times, respectively.

To describe the long-term outcomes in patients with liver pathology and co-existent pancreas pathology depending on the method of treatment the Kaplan-Meier method was used. During the period of observation 25.0% of patients receiving basic therapy within a year developed the progression of liver pathology with the transition to Child-Pugh Class C 4, 5, 6, and 9 months after starting treatment. As indicated by Chae HB [16] according to Child-Pugh score more severe clinical course largely depends on the levels of total bilirubin and albumin. In patients who received pentoxifylline and amino acid mixtures in addition to basic therapy the transition to Child-Pugh Class C occurred in 6.7% of cases 9 month after starting treatment (Fig. 4).

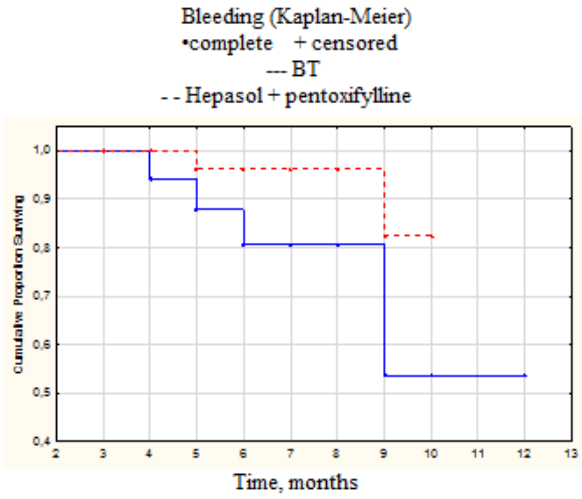


Variable: Time, months
Variable with censoring indicator: Transition of LC from Class A and B to Class C
Grouping variable: Treatment
Total number of observations: 50
uncensored: 7 (14.00%) censored: 43 (86.00%)
Z = -2.42072 p = .01549

Fig. 4. Curves of LC decompensation in patients with comorbid alcohol-related pathology depending on treatment scheme

Bleeding varicose veins in the esophagus were observed in 20.0% of patients undergoing basic therapy 4, 5, 6, and 9 months after completion of treatment. Among patients who received pentoxifylline and Hepasol-Neo in addition to basic therapy such complication was diagnosed in 6.7% of patients 5 and 9 months after treatment (Fig. 5).

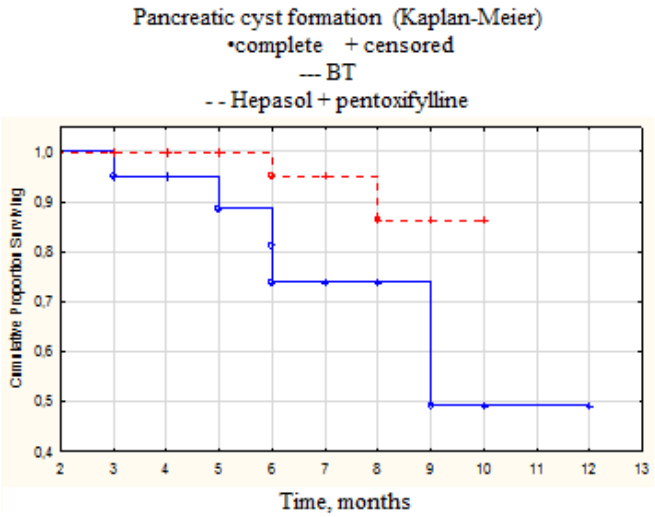
The most favorable clinical course of the comorbidity and reduction in the frequency of complications in patients receiving pentoxifylline are also indicated by other researchers who consider it as an alternative to glucocorticoid treatment [19]. Pancreatic cysts being not diagnosed after the completion of treatment were detected in 25% of patients 3, 5, 6, and 9 months after therapy.



Variable: Time, months
Variable with censoring indicator: Bleeding
Grouping variable: Treatment
Total number of observations: 50
uncensored: 6 (12.00%) censored: 44 (88.00%)
Z = -1.58740 p = .11242

Fig. 5. Curves of bleeding occurrence in patients with comorbid alcohol-related pathology depending on treatment scheme

Patients of subgroup II developed only two complications manifested themselves 6 and 8 months after completion of treatment (Fig. 6). 30% of patients with liver pathology and co-existent pancreas pathology receiving basic therapy and 10% of patients with comorbidity receiving pentoxifylline and amino acid mixtures in addition to basic therapy died within a year.



Variable: Time, months
Variable with censoring indicator: Pancreatic cysts formation
Grouping variable: Treatment
Total number of observations: 50
uncensored: 7 (14.00%) censored: 43(86.00%)
Z = -2.00731 p = .04472

Fig. 6. Curves of pancreatic cysts formation in patients with comorbid alcohol-related pathology depending on treatment scheme

Conclusions

Thus, concurrent alcohol-induced injury of the pancreas and liver increases the risk of developing more severe clinical course of this comorbidity with transition of LC to the decompensated stage, bleeding varicose veins in the esophagus occurring more often, increased pancreatic fibrosis with widening of the ductal system and further development of cysts and pancreatic exocrine insufficiency. The addition of pentoxifylline and mixture of essential, conditionally essential and non-essential amino acids to basic therapy reduces the number of patients developing complications.

Prospects for further research include the development of new available schemes to predict the effectiveness of treating patients with CAP and concomitant alcoholic LC Child-Pugh Class A and B.

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