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Prednisolone and Pentoxifylline Combination in Patients with Severe Acute Alcoholic Hepatitis.

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ABSTRACT

Clinical manifestation of alcoholic hepatitis is a serious and adverse sign of progression of alcoholic liver disease. Therapy of acute alcoholic hepatitis is currently limited to symptomatic therapy and prednisolone. The aim of our study was to analyze pentoxifylline and prednisolone combination in patients with severe acute alcoholic hepatitis. 136 patients with severe acute alcoholic hepatitis (Maddrey discriminant function > 32) were included. Patients in the control group (73 patients) received symptomatic therapy, the patients in the first study group (41 patients) additionally received 400-600 mg pentoxifylline intravenously. The second study group (22 patients) additionally treated by combination of pentoxifylline and prednisolone. In the group of patients treated with pentoxifylline significant reduction in creatinine was determined ($p < 0.05$). Short-term mortality in pentoxifylline group of was lower (15 %) than in the control group (25%). In prednisolone and pentoxifylline combination groups was the maximum mortality rate - 45%. Pentoxifylline improves short-term survival in patients with severe acute alcoholic hepatitis, significantly reduces the incidence and mortality from hepatorenal syndrome. The combined use of prednisolone and pentoxifylline probably negates the positive effect of pentoxifylline against hepatorenal syndrome.

Keywords: alcoholic hepatitis, hepatorenal syndrome, pentoxifylline, prednisolone.

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INTRODUCTION

Acute alcoholic hepatitis

In 1961, Beckett, Livingstone and Hill first used the phrase "acute alcoholic hepatitis" (AAH) to describe the syndrome identified in 7 patients with alcohol abuse, which appeared after prolonged alcoholic excess [1]. The syndrome included jaundice, abdominal pain, fever, loss of appetite, and leukocytosis. Histological examination of the liver tissue of these patients revealed the characteristic, but not necessarily manifestations - fibrosis or cirrhosis, acute inflammatory infiltration of the lobules, alcoholic hyaline – Mallory bodies, degeneration or necrosis of hepatocytes. Since then, the syndrome of acute alcoholic hepatitis was seen as a stage of alcoholic liver disease.

Clinical manifestation of alcoholic hepatitis is a serious and adverse sign of progression of alcoholic liver disease. To evaluate the prognosis and severity of alcoholic hepatitis account for changes in prothrombin time and serum bilirubin. As key indicators are used in the calculation of the modified discriminant function (Maddrey index) (DF), which is calculated as $4.6 \times (\text{patient's prothrombin time} - \text{prothrombin time in the control (sec)}) + \text{serum bilirubin (mmol / L)} / 17$.

It has been calculated that if the value of DF more than 32, the risk of death is more than 50 % in the short term (within 30 days) [2]. Patients with AAH usually have hepatomegaly, jaundice, anorexia, low-grade fever, coagulopathy and encephalopathy. Approximately half of the patients develop ascites. Life-threatening clinical signs of acute alcoholic hepatitis are the development of hepatorenal syndrome (HRS) and bleeding (the frequency of occurrence of each of up to 10 % -16 %) [3]. Mortality during the development of complications up to 80-90 % [4].

The underlying mechanism of cell damage in alcoholic hepatitis is considered activation of cellular and humoral immune responses. AAH accompanied by a pronounced cytokine response to overproduction of proinflammatory cytokines [5,6,7]. One of the first cytokines enhancement products, which have been shown in AAH in vitro, was the tumor necrosis factor (TNF) [6]. Studies found that in patients with AAH serum TNF levels increased and correlated with mortality [8,9]. Besides TNF in alcoholic hepatitis also other cytokines such as IL- 6 and IL- 8 had elevated levels and their levels correlated with the acute phase response markers, liver function and clinical outcomes [6,10,11] .

AAH therapy remains controversial. The only proven method that improves the outcome of the AAH, is abstinence and good nutrition. Because the pathogenesis of liver inflammation assumed the leading role of the immune system the usefulness of corticosteroids has been widely discussed. Some researchers believe that steroids reduce mortality and slow the progression of fibrosis [12,13]. However, the largest meta-analysis on the corticosteroids effect on short-term survival have been conflicting [13-15].

In recent years, the role of the "universal" means to the AAH became eligible pentoxifylline. It is assumed that pentoxifylline inhibits TNF synthesis by increasing the intracellular concentration of cyclic AMP and cyclic GMP. In vitro study revealed that pentoxifylline reduces TNF gene transcription [16]. Later it was shown that pentoxifylline suppresses the synthesis of cytokines (protein-1, IL- 6, IL- 8 , an inflammatory protein 1a and 1b macrophages) reduces neutrophil activation, and suppresses the proliferation of lymphocytes and monocytes [6,10,11]. In animals, pentoxifylline inhibited the development of cirrhosis [17].

The first randomized trial of pentoxifylline was conducted in the United States from 1992 to 1997 [18]. It turned out that the use of pentoxifylline improves 28 -day survival in patients with severe alcoholic hepatitis by reducing the risk of hepatorenal syndrome (50 % vs 91,7%, $p = 0.009$). TNF - α levels correlated with serum creatinine at randomization and during the course of a hospitalization, which suggested a role of TNF - α in the pathogenesis of renal function, however, in patients treated with pentoxifylline, showed no significant reduction of TNF - α as compared with the control.

Pentoxifylline, in addition to vasodilatory properties, improves rheological properties of the blood, blocking phosphodiesterases reduces the adhesion of platelets and red blood cells, inhibition of the synthesis of TNF - α , potentiates the efficacy of conventional immunosuppressive drugs [19].

A number of studies with the combined use of pentoxifylline and prednisolone therapy for sarcoidosis and glomerulonephritis revealed promising results significantly improved the course of the disease, however, in all studies, some patients had to cancel pentoxifylline in connection with the development of side effects (nausea, heartburn, dizziness) [19,20].

Based on this approach, the goal of our study was to evaluate the efficacy of a combination of pentoxifylline and prednisolone compared with pentoxifylline alone and symptomatic therapy in patients with severe alcoholic hepatitis.

MATERIALS AND METHODS

The study included patients with a severe AAH, as defined by a Maddrey discriminant function of at least 32 who were hospitalized at clinical department PFUR (hospital № 64, Moscow) between September 2003 and December 2007.

The diagnosis of acute alcoholic hepatitis was based on:

- Data history (alcohol abuse, rapid increase in symptoms after alcohol excess)
- Clinical picture (objective and laboratory signs of chronic alcohol intoxication)
- Any of the following symptoms: fever, hepatomegaly, leukocytosis, an increase of CRP, jaundice, anorexia, ascites.

We excluded the following patients:

- Drug users
- Non-alcoholic liver disease
- With decompensated heart disease

Inclusion in the study was within 4-6 days of admission. Laboratory parameters were analyzed at intervals of 1 and 2 weeks from the time of inclusion. The average duration of follow up was 20 ± 9 days. HRS development criteria considered doubling of creatinine during hospitalization.

Therapy

All patients adhered to a strict abstinence received symptomatic therapy including adequate food gross caloric 35-50kcal/kg, salt restriction, as well as total protein restriction in the presence of severe encephalopathy (grade 3-4). In the case of ascites and edema patients received a Spironolactone (200 mg daily), Furosemide (40-80 mg intravenously every other day) with the control of diuresis and electrolytes. In hypocoagulopathy patients received a Vit K (15-30 mg per day). Patients received Ciprofloxacin for secondary infections preventing as well as for suppressing the intestinal microflora. In order to reduce encephalopathy patients received Lactulose (15-45 ml), for the prevention of bleeding from esophageal varices Propranolol (60 mg daily). In the case of persistent hypotension, oligo or anuria, increased level of creatinine, patients received continuous infusion of dopamine (3-5 mg/kg/min). Vitamin B was prescribed for polyneuropathy correction. Also, most patients with edema and ascites in case of low level of serum albumin received infusion of 10% albumin solution and fresh frozen plasma.

RESULTS

The study was conducted on a case-control. The study included 136 patients. 41 patients (12 women and 29 men) received pentoxifylline at a dose of 400-600 mg intravenously over 14-16 days, maximally of 22 days. In 3 patients the drug had to be canceled due to continuing headaches and nausea. Prednisolone was used intravenously at a dose of 60-120 mg during 7-14 days.

Statistically significant differences in disease severity index Maddrey, age, duration of hospitalization was not revealed. Low-grade fever occurred at an average of 28%. 41% had ascites. The main clinical and demographic characteristics of the comparison groups are presented in Table № 1. All patients had an enlarged liver and encephalopathy.

Comparison groups did not differ significantly in the level of white blood cells, hemoglobin, creatinine, glucose, total protein, albumin, and cholinesterase. However, in the group of pentoxifylline laboratory parameters of cholestasis and cytolysis were statistically significantly higher than in the control group. Synthetic function indicators were lower in the control group, statistically significantly different prothrombin index, albumin and cholinesterase difference was not significant.

The analysis of laboratory parameters showed no significant changes in the dynamics of leukocytes and bilirubin. In the second week of therapy in both groups of patients there was a decrease of leukocytes. In the dynamics of AST and GGT was a significant difference in the groups. AST and GGT decreased in both groups. Under pentoxifylline average 88.4 U / L and 558.2 U / l in the control group of 36.9 U / L and 286.8 U / L, respectively ($p = 0.04$ and 0.01 respectively).

No significant differences in the level of dynamics or bilirubin were observed in the control group, neither group pentoxifylline, both the first and the second week of therapy. Interesting was the creatinine dynamic. If at the end of the first week of therapy in pentoxifylline group was an increase of creatinine in an average of 2.7 mmol / l and in the control group decreased by 1.4 mmol / l, but changes in the groups were not statistically significant ($p = 0, 84$), then on the 14th day in pentoxifylline group a statistically significant decrease in average creatinine was showed, compared with the control group, where there was an increase in average creatinine ($p = 0.0007$).

Thus, long-term use of pentoxifylline (more than 10 days) significantly reduced the level of creatinine. Also in the group of patients treated with pentoxifylline, best observed decrease in AST and GGT.

For further analysis of the effectiveness of pentoxifylline, all patients were divided into 2 subgroups according to creatinine level: patients with normal creatinine levels (up to 110 mmol / l), and patients with serum creatinine more than 110 mmol / l on admission.

In pentoxifylline group number of patients with normal baseline creatinine level was 29 (71%), in the control group - 51 (70%). On therapy in pentoxifylline group 1 patient had doubling and further normalization of serum creatinine; all others patients had no changes in creatinine level. In the control group, 12 (24 %) patients had an increase in creatinine level more than twice. In 2 patients creatinine level became normal.

Initially elevated serum creatinine was observed in 22 (30%) and 12 (29%) patients in the control and pentoxifylline groups, respectively. In the control group, in 4 (18 %) patients creatinine level continued to increase, in 10 (45 %) patients level became normal, in 8 (36 %) patients creatinine level remained unchanged. In pentoxifylline group creatinine increase was in 2 (16.5 %) patients, in 8 (67%) patients creatinine level became normal, in 2 (16.5 %) remained unchanged.

Thus, in patients with initially normal creatinine levels the development of hepatorenal syndrome was significantly less frequent ($p < 0.05$) during pentoxifylline therapy. In the presence of renal functional disorders on pentoxifylline therapy normalization of creatinine was observed significantly more often ($p = 0.0001$).

19 (24.7 %) patients of the control group, and 3 (7 %) patients of pentoxifylline group hepatorenal syndrome developed ($p = 0.037$). Mortality in the pentoxifylline group was 6 (15%), that was lower than in the control group 18 (25%), however, differences are not statistically significant ($p = 0.21$). The hepatorenal syndrome was death cause in 1 (2 %) patients in a group of pentoxifylline and in 3 (4 %) patients in the control group. 4 (5 %) of the control group died from gastrointestinal bleeding. In other cases, the cause of death was hepatocellular insufficiency.

Analysis of laboratory parameters revealed that persons who died during hospitalization, had significantly higher creatinine levels, CRP, DF and lower the level of albumin ($p < 0.05$).

Pentoxifylline and prednisolone combination

22 patients received prednisolone and pentoxifylline, 17 of them (77 %) males and 5 (23%) women. The average age of patients was 50.1 +13.3 years. Mortality in this group of patients was 10 (45 %), that was

not statistically significant differ from the mortality in the control group ($p = 0.06$). Severity of the disease in two drugs group did not differ from the control group ($DF 62.6 \pm 2.9$) ($p = 0.76$).

Analysis of laboratory parameters revealed no significant differences in the dynamics of leukocytes in the first week of therapy between groups.

On second week of therapy in drugs combination group was a significant decrease in white blood cell count, in contrast to other groups, where there was an increase of leukocytes. Significant differences were found in the GGT dynamics between the drugs combination group and pentoxifylline group. In the pentoxifylline group there was a statistically significantly greater GGT reduction. Between the other groups no significant differences were detected.

Creatinine dynamics didn't difference significant between the groups of drugs combination and of pentoxifylline.

Changes in the bilirubin level were significantly different in both groups.

During the first week of therapy in drugs combination group was bilirubin increase ($- 35.5 \text{ mmol / l}$), while in the pentoxifylline group was decrease ($+70.7 \text{ mmol / l}$) ($p = 0.027$). In the second week of treatment in both groups bilirubin levels decreased - in drugs combination group by 21.6 mmol / L , in pentoxifylline group by 116.9 mmol / l ($p = 0.038$).

Comparison of study group and control depending on the level of creatinine showed no statistically significant difference in the results of clinical outcome.

Improvement of biochemical parameters or survival wasn't found on pentoxifylline and prednisolone combination compared with the pentoxifylline therapy.

DISCUSSION

All patients included in our study had a severe acute alcoholic hepatitis with the development of hepatic encephalopathy. In addition, all patients had evidence of alcoholic encephalopathy with obvious signs of intellectual-mental decline. This fact and the routine practice when installing venous catheters in our hospital led to the choice of parenteral administration. Absence of the recommended doses for intravenous administration of pentoxifylline and prednisolone for acute alcoholic hepatitis led to the use of the drug at a dose for intravenous administration the maximum recommended by the manufacturer for pentoxifylline and empiric dose for prednisolone. Official statement admits the introduction of pentoxifylline up to 600 mg / day . However, years of experience with pentoxifylline prior to this study shows that the majority of patients with AAH can not achieve the recommended dose due to poor tolerability, manifested by dizziness, intense headache, nausea, vomiting. Thus, the intravenous dose pentoxifylline of $400\text{-}600 \text{ mg/day}$ was chosen empirically adjusted in this range for portability.

HRS development predetermines extremely poor prognosis on AAH. Short-term mortality in the development of type I HRS is $80\text{-}90\%$ [4]. Only a liver transplant provides life expectancy increase in patients with HRS. Therefore it is very important to search approaches for HRS prevention. HRS less developed in the pentoxifylline group compared to control group (0% vs 20%). Pentoxifylline not only prevented the development of HRS, but also contributed to its regression - 66% vs 45% .

Confirmation of mutual induction, we found in the literature for the treatment of sarcoidosis and glomerulonephritis [4, 20]. However, in prednisolone and pentoxifylline combination groups was the maximum mortality rate - 45% , in excess of mortality in the control groups and pentoxifylline group. In this group was a trend towards more frequent rate of gastrointestinal bleeding - 14% compared to 3% in the control group and 0% in the pentoxifylline group.

A definitive conclusion about the risk of gastrointestinal bleeding on use of pentoxifylline and prednisolone combination is not possible, due to the small group.

Analysis of laboratory data cannot identify the cause of the mortality in the group drugs combination. It may be noted that creatinine in pentoxifylline group was significantly decreased by the end of the second week, but in the group of drugs combination remained relatively stable. On drugs combination in patients with initially elevated levels of creatinine mortality was 100%. Thus, the combined use of prednisolone and pentoxifylline probably negates the positive effect of pentoxifylline against HRS.

Table 1: The main clinical and demographic characteristics of the comparison group.

	Pentoxifylline group (41 patients)	Prednisolone and pentoxifylline group (22 patients)	Control group (71 patients)
Возраст (years)	47,3±1,6	50,1±2,8	49,1±1,5
Hospitalization (days)	21,6±1,5	24,2±1,8	19,7±0,9
DF	61,4±3,8	64,4±4,1	62,6±2,9
leukocytes (x10 ⁹ /l)	13,3±1,1	13,9±1,1	12,9±0,9
Hb (g/l)	116,4±3,4	111,4±4,4	106,5±3,5
AsT (U/L)	221,4±25,4	134,8±19,3	138,6±10,0
AlT (U/L)	130,3±21,8	86,9±14,0	60,7±6,9
AIP (U/L)	1472,5±265,5	1303,9±184,4	694,2±69,0
GGT (U/L)	1062,9±143,7	680,5±108,9	523,1±83,2
Creatinine (mmol/l)	97,5±13,4	94,2±12,7	95,3±6,5
Bilirubin (mmol/l)	307,4±39,7	394,2±47,4	166,4±17,9
Cholesterol (mmol/l)	7,3±0,9	8,6±1,1	4,2±0,4
Glucose (mmol/l)	5,8±0,2	6,1±0,5	6,3±0,2
Total protein (g/l)	70,8±1,4	66,6±1,3	70,9±1,1
Albumin (g/l)	28,6±1,4	31,4±2,0	25,7±1,2
Cholinesterase (U/l)	3639,3±317,8	3570,8±408,0	3101,9±273,0

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