

Combined human growth hormone and lactulose for prevention and treatment of multiple organ dysfunction in patients with severe chronic hepatitis B

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Abstract

AIM: To evaluate the efficiency and safety of combined recombinant human growth hormone (rhGH) and lactulose for treatment and/or prevention of multiple organ dysfunction in patients with chronic severe hepatitis B.

METHODS: Forty-eight inpatients with chronic severe hepatitis B were randomly divided into rhGH group ($n = 28$) and control group ($n = 20$). In rhGH group, 4-4.5 IU of rhGH was injected intramuscularly once daily for 2-4 wk, and 100 mL of enema containing 30 mL of lactulose, 2 g of metronidazole and 0.9% saline was administered every 2 d for 2-4 wk. Their symptoms and complications were noted. Liver and kidney functions were analyzed by an Olympus analyzer. Serum GH, IGF-1, IGFBP1 and IGFBP3 were measured by ELISA.

RESULTS: Clinical symptoms of 90% of these patients in rhGH group were obviously improved. The total effectiveness in rhGH group was better than that in control group (75% vs 40%, $P < 0.05$). After 2- and 4-wk treatment of rhGH respectively, serum albumin (26.1 ± 4.1 vs 30.2 ± 5.3 , 31.9 ± 5.1 g/L), prealbumin (79.6 ± 28.0 vs 106.6 ± 54.4 , 108.4 ± 55.0 g/L), cholesterol (76.3 ± 16.7 vs 85.6 ± 32.3 , 96.1 ± 38.7 mg/dL), and IGFBP1 (56.8 ± 47.2 vs 89.7 ± 50.3 ng/mL after 2 wk) were significantly increased compared to control group ($P < 0.05$). However, serum GH was decreased. The increase of serum IGF1 and IGFBP3 after rhGH treatment was also observed.

CONCLUSION: rhGH in combination with lactulose may be beneficial to the prevention and treatment of multiple organ dysfunction in patients with chronic severe hepatitis.

INTRODUCTION

Severe viral hepatitis, namely severe acute or chronic liver failure, develops quickly with an extremely dangerous prognosis. Its mortality rate is between 60% and 90%^[1] and there is still no breakthrough in medical treatment. It has been proved that multiple organ dysfunction is the main cause of death of these patients^[2,3]. Therefore, it is very important to treat effectively severe hepatitis patients with multiple organ dysfunction. The mortality would fall significantly if patients with multiple organ dysfunction are properly treated. The aim of our study was to evaluate the efficacy and safety of recombinant human growth hormone (rhGH) in combination with lactulose for treatment and/or prevention of chronic severe hepatitis B with multiple organ dysfunction. The mechanism of these drugs was also studied.

MATERIALS AND METHODS

Patients and controls

Forty-eight patients with chronic severe hepatitis B from January 1999 to February 2002 were enrolled. Chronic severe hepatitis was previously defined during the National Conference of Xi'an in 2002. In brief, inclusion criteria were as follows: a history of chronic hepatitis or liver cirrhosis; severe asthenia, serum total bilirubin more than 171 μ mol/L; prothrombin time activity (PTA) less than 40%. Of those patients, 28 were in treatment group (23 males and 5 females, average age of 42.6 years), 20 were in control group (17 males and 3 females, average age of 41.5 years). Their clinical data, such as liver and kidney biochemical parameters, were comparable.

Protocol of study

Treatment methods All patients in treatment group received standard treatment: rhGH 4-4.5 IU im injection once daily

for 2-4 wk, enema containing 0.9% normal saline 100 mL plus lactulose 30 mL and metronidazole 2.0 g once every 2 d for 2-4 wk. Patients in control group only received standard treatment.

Sample collection Venous blood 3 mL was collected at 6:00-7:00 a.m., and centrifuged at 4 °C, stored at -20 °C. Clinical symptoms and complications were recorded and the patients were followed-up for at least 6 mo according to CRF.

Biochemical tests Serum growth hormone (GH), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding proteins 1, 3 (IGFBP1, IGFBP3) were respectively measured by ELISA. All the test kits were purchased from DSL Corporation, and used according to their manufacturer's instructions.

Efficacy endpoints Clinical symptoms were completely improved and complications were controlled in 4 wk, and no new complications occurred. Liver functions were markedly improved in 3 mo, the total bilirubin decreased by 30-60%. PTA value was increased. All patients were followed-up for 6 mo.

Statistical analysis

Statistical evaluations were performed using SPSS 10.0 statistical software. Clinical effects of the two groups were compared by χ^2 test, quantitative data were expressed as mean \pm SD and analyzed with two-way variance test. *P* less than 0.05 was considered statistically significant.

RESULTS

The results of this study indicated that the clinical symptoms of 90% of the patients were markedly improved. The total effective rate was 75% in treatment group and 40% in control group. There was a significant difference between the two groups (*P*<0.05).

In treatment group, serum prealbumin, cholesterol and total protein in 60% of the patients were significantly increased (*P*<0.05, Table 1). The albumin level could maintain for 2-4 wk after rhGH was stopped. In contrast, prealbumin, cholesterol and albumin in 60% of the patients in control group were consistently decreased.

Table 1 Effects of rhGH on liver function of patients with severe chronic hepatitis B (mean \pm SD)

Marker of liver function	Pretreatment <i>n</i> = 28	2-wk treatment <i>n</i> = 28	4-wk treatment <i>n</i> = 16
Total protein (g/L)	51.6 \pm 4.3	67.8 \pm 8.4 ^a	69.2 \pm 7.8
Prealbumin (g/L)	80 \pm 28	107 \pm 54 ^a	108 \pm 55
Albumin (g/L)	26.1 \pm 4.1	30.2 \pm 5.3 ^a	31.9 \pm 5.1 ^b
Cholesterol (mg/dL)	76 \pm 17	86 \pm 32 ^a	96 \pm 39
Total bilirubin (mg/dL)	15 \pm 14	20 \pm 16	12 \pm 13
PTA (%)	21.3 \pm 5.5	24.7 \pm 12.2	36.8 \pm 7.9
ALT (IU/L)	117 \pm 210	83 \pm 77	59 \pm 43
AST (IU/L)	171 \pm 243	104 \pm 79	76 \pm 56

^a*P*<0.05, ^b*P*<0.01 vs pretreatment.

The level of serum GH in chronic severe hepatitis patients was relatively higher than that in normal subjects. But it decreased after rhGH was used for 2-4 wk. The level

of IGF-1 and IGFBP3 had a trend increase, but there was no statistical difference. The serum IGFBP1 level was markedly increased (Table 2). The mortality rate of the patients with high serum GH level after treatment was nearly 100%.

Table 2 Effects of rhGH on GH-IGF axis in patients with severe chronic hepatitis B (mean \pm SD)

Marker of GH-IGF axis	Pretreatment (<i>n</i> = 15)	2-wk treatment (<i>n</i> = 15)
GH (ng/mL)	10.4 \pm 7.6	6.2 \pm 8.1 ^a
IGF-1 (μ g/mL)	6.3 \pm 4.5	8.8 \pm 6.7
IGFBP1 (ng/mL)	56.8 \pm 47.2	89.7 \pm 50.3 ^a
IGFBP3 (μ g/mL)	3.5 \pm 1.7	5.1 \pm 3.4

^a*P*<0.05 vs pretreatment.

DISCUSSION

Up to now, there has been no ideal treatment for severe hepatitis. It was reported that the mortality rate of severe hepatitis was more than 80% if liver transplantation was not performed^[4]. Liver transplantation is the optimal choice for treatment of liver failure. Therefore, the fundamental purpose of internal medical treatment is to make the state of illness stable and to wait for appropriate liver donor for liver transplantation^[4]. Many complications in severe hepatitis patients had a close relation to the prognosis^[1,2]. It was found in our previous study that the mortality rate of severe hepatitis patients with more than two complications was 72.8% and nearly 100% of those with more than four complications. The pathophysiological mechanism of multiple organ dysfunction in severe hepatitis patients is still not clear^[1,3]. At present, it is considered that infection and severe endotoxemia could play an important role in severe hepatitis with multiple organ dysfunction^[1-3]. Malnutrition of severe hepatitis patients, especially chronic severe hepatitis patients, was the leading cause of accompanying infections^[1,5]. Therefore, if infection is controlled effectively and endotoxin is removed, malnutrition may improve, and the multiple organ dysfunction of severe hepatitis patients may be prevented and cured effectively. According to this hypothesis, we designed a new therapy method for chronic severe hepatitis: human GH combined with lactulose enema.

GH, composed of 191 amino acids, is a sort of single chain polypeptide secreted by adenohipophyseal acidophils. It is well known that GH not only promote growth and development but also has comprehensive biological functions, concerning cell multiplication and differentiation. GH could also regulate immunity and metabolism^[6]. Furthermore, liver is the main target organ of GH *in vivo*, and the center of GH-IGF axis^[7,8]. It has been found that decreased serum IGF-1, IGFBP3 and ALS had a close relation to liver reserve function and the prognoses of liver cirrhosis patients^[9]. It was also found^[10] that serum IGF-1 and IGFBP3 were decreased in severe viral hepatitis patients while IGFBP1 was increased. The decrease of IGF-1 also had a close relation to the prognosis of severe hepatitis patients. Assy *et al*^[9], performed hypodermic injection in liver cirrhosis patients with rhGH 0.4 U/kg, and measured serum IGF-1 24 h later with RIA. If IGF-1 <10 nmol/L, the prognosis was bad, the 1-year survival rate was only 15%; if IGF-1

>10 nmol/L, the 1- and 2-year survival rates of liver cirrhosis patients were both 100%; indicating that IGF-1 could be used to forecast the prognosis of liver cirrhosis patients^[11,12]. Our study showed that the GH level of chronic severe hepatitis patients was high, exogenous human GH could increase IGFBP1, IGF-1 and IGFBP3, while serum GH level was decreased. These results indicated that exogenous GH might improve GH resistance state of chronic severe hepatitis^[10-12]. GH resistance is related to metabolic disturbances, such as malnutrition, energy metabolism abnormality, both of which play an important part in secondary hepatocyte damage and multiple organ dysfunction of severe hepatitis. On the other hand, the prognoses of severe hepatitis patients depend on the balance between necrosis and regeneration of liver. Many cell factors (such as HGF, HSGF) can stimulate the proliferation of hepatic cells, but the clinical curative effect is not satisfactory. It has been found that epidermal growth factor could significantly alleviate the multiple organ failure due to thioacetamide. Our study also showed that the use of human GH for 2-4 wk in treating chronic severe hepatitis patients could reduce the occurrence and development of complications, prolong the survival and improve the life-quality of patients. Serum prealbumin, albumin level increased and the overall effective rate was 75% without any obvious side effect^[13].

It has been proved that toxic substances (such as endotoxin, NH₃, γ -GABA, *etc.*) and high level of inflammatory cell factors in the serum of severe hepatitis patients could lead to fever, hypotension, ARDS, and eventually multiple organ dysfunction^[1]. Besides, these substances may affect the regeneration capacity of liver. Therefore, it is important to look for an effective method to reduce endotoxin and inflammatory cell factors. Biological and non-biological artificial livers could be used to treat severe hepatitis, through reducing the toxic substances in serum, such as endotoxin and bilirubin. However, most of the toxic substances could combine with proteins into large molecules and could not be filtered through, so treatment should be conducted repeatedly. Some useful cell factors were also filtered. Meanwhile there were some complications, such as secondary bacterial or virus infections. For this reason, the long-term treatment of severe hepatitis with artificial liver should be further explored, and at present it has been only used as the transient therapy before liver transplantation^[3]. Professor Fan (Hong Kong University) *et al.*, used selective filtration to remove toxic substances, and retained some liver growth factors meanwhile. They achieved perfect results in animal experiments, but there has been no clinical experiment^[3]. Some scholars utilized tumor necrosis factor antibody to treat experimental hepatic failure animals, and also obtained good results, but there is no clinical experiment report, either.

Lactulose can be decomposed into lactic acid and acetic acid by enteric bacteria. Both of them can acidify the intestinal tract, and restrain the production and absorption of toxic substances, such as endotoxin, NH₃, *etc.*, so that they can remove endotoxin perfectly without severe side effects. It has been proved by clinical researches that

lactulose can remove endotoxin and decrease the generation of endotoxin. In this study, we preliminarily observed the curative effects of human GH associated with lactulose in treating chronic severe hepatitis, and achieved satisfactory results. In treatment group, the clinical symptoms of most of the patients were improved evidently. According to the modified criteria of therapeutical effect, the markedly effective rate was 21.4% (6/28), the effective rate was 53.5% (15/28), the overall effective rate was 75%, and there was a significant difference compared to the control group. This result indicated that human GH combined with lactulose could effectively prevent exacerbation of severe hepatitis, and prevent and cure its complications. Its mechanisms may lie in the following factors: preventing the generation and absorption of intestinal endotoxin, curing endotoxemia; improving GH resistance of chronic severe hepatitis patients and abnormal metabolic status, and increasing serum prealbumin, albumin and cholesterol level. It is preliminarily concluded that human GH combined with lactulose could prevent and cure severe hepatitis complicated by multiple organ dysfunction.

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