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Original Article

Shu Fu Pai® Protein Short Peptides Beverage for the treatment of hypoalbuminemia in liver cirrhosis

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Abstract: Objective: To investigate the clinical efficacy of Shu Fu Pai® Protein Short Peptides Beverage in the treatment of hypoalbuminemia in liver cirrhosis. Methods: A retrospective analysis was conducted on 289 patients with liver cirrhosis and hypoalbuminemia who were admitted to Deyang People's Hospital between April 2021 and April 2023. Among them, 148 patients treated with Shu Fu Pai® Protein Short Peptides Beverage were assigned as an observation group and 141 patients treated with intravenous human albumin were the control group. Liver function, coagulation function before and after treatment, and complications after treatment were compared between the two groups. The patients whose albumin levels did not increase after treatment were counted, and the influencing factors were analyzed using univariate and multivariate analyses. Results: After treatment, there was a significant improvement in liver function, serum albumin level, Child-Pugh score, inflammatory markers, and coagulation function in both groups (all P=0.001). However, no significant difference was found in the peripheral blood indicators between the two groups (P>0.05). Also, there was no significant difference in complications between the two groups (P=0.194). Logistic regression analysis showed that age, pre-treatment serum albumin level, disease type, and abnormal liver function markers were independent factors affecting the treatment outcome of hypoalbuminemia, and treatment regimen was not an influencing factor. Conclusion: Shu Fu Pai® Protein Short Peptides Beverage for hypoalbuminemia in liver cirrhosis is not inferior to intravenous human albumin for improving liver function, inflammatory markers, and coagulation function. The therapeutic effect on hypoproteinemia is independent of type of treatment regimen, which suggests that Shu Fu Pai® Protein Short Peptides Beverage is an effective treatment for hypoalbuminemia in liver cirrhosis, without an increased risk of complications.

Keywords: Hypoalbuminemia, liver cirrhosis, Shu Fu Pai® Protein Short Peptides Beverage, human albumin, clinical efficacy

Introduction

The liver serves as the initial site for storing and metabolizing nutrients, such as carbohydrates, fats, and proteins, after their absorption in the intestine. Liver function is intricately associated with a number of liver diseases and nutritional deficiencies [1, 2]. It is reported that over 10,000 people die from liver diseases globally each year, and malnutrition is prevalent in 75%-90% of patients with cirrhosis [3, 4]. Consequently, the *European Society for Clinical Nutrition and Metabolism Guidelines* emphasize the importance of early identification of malnutrition in cirrhosis patients and the implementation of early nutritional support and treatment as pivotal measures to reduce the incidence and mortality [5].

Currently, the primary treatment for hypoalbuminemia in cirrhosis relies on intravenous infusion of human albumin and immunoglobulin at varying concentrations. However, human albumin is expensive, and its production is susceptible to multiple factors, often resulting in disruptions to the supply chain. Therefore, it is not a feasible and widespread treatment solution for hypoalbuminemia. Patients with cirrhosis are encouraged to consume nutritional supplements to mitigate the condition [6, 7]. Recent studies have shown that oral small molecule protein peptides, which are gradually applied to disease intervention and treatment, can deliver substantial clinical benefit [8]. Peptides, a type of protein hydrolysate with a small molecular weight, can be quickly absorbed by the body and transported into the digestive system

through the small intestine. The prolonged presence of peptides in the stomach in contrast to larger protein molecules can lessen symptoms such as bloating and gastric prolapse [9, 10]. Furthermore, studies have demonstrated that Shu Fu Pai® Protein Short Peptides Beverage is effective as nutritional supplements following surgeries for digestive system diseases [11, 12]. However, their use in addressing hypoalbuminemia in cirrhosis is not yet extensively studied [11, 12]. In light of this, this study explored the clinical efficacy of Shu Fu Pai® Protein Short Peptides Beverage for patients with cirrhosis and hypoalbuminemia, in order to investigate its efficacy.

Materials and methods

General data

The study subjects were clinically diagnosed with liver cirrhosis at the Deyang People's Hospital, either as outpatients or inpatients, from April 2021 to April 2023. A total of 300 cases were diagnosed. However, 11 cases were excluded due to missing information, resulting in a final sample of 289 patients.

According to different treatment methods, 148 patients treated with Shu Fu Pai® Protein Short Peptides Beverage were divided into an observation group and 141 patients treated with intravenous human albumin into a control group. This study was approved by the ethics committee of Deyang People's Hospital (approval no. 2023-06-244).

Inclusion criteria: (1) patients who met the clinical diagnostic criteria for liver cirrhosis [13]; (2) patients who aged between 18 and 80 years old; (3) patients who had hypoalbuminemia (with peripheral blood albumin content below 30 g/L) and were unable to obtain sufficient nutrition through oral intake; (4) patients who were conscious and could engage in normal communication; (5) patients who underwent the entire course of treatment and had complete data.

Exclusion criteria: (1) patients who have consumed protein, amino acid or other nutritional supplements either orally or intravenously within the past month; (2) patients whose clinical data were missing; (3) patients who were incapable of cooperating with the medical workers due to severe mental illness or impaired consciousness.

Treatment methods

The observation group underwent daily oral administration of Shu Fu Pai® Protein Short Peptides Beverage (taken as a dissolved drink, one sachet each time, three times a day; produced by Shenzhen Jianan Pharmaceutical Co., Ltd., China) for nutritional intervention. The Shu Fu Pai® Protein Short Peptide Beverage primarily utilizes the latest bio-targeting and precision enzyme cutting technology to break down, concentrate, and extract functional, highly nutritious small molecule protein peptides from high-quality non-GMO soybeans. It meets the food quality management standards (Q/QRYY0001S-2021).

The control group received daily intravenous infusion of human albumin (20%, 50 mL, produced by Chengdu Rongsheng Pharmaceutical Co., Ltd., China) for nutritional intervention. Both groups underwent treatment for two weeks.

Outcome measures

Main outcome measures covered liver function indicators (serum total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels), serum albumin levels and Child-Pugh scores.

Secondary outcome measures comprised inflammation level, coagulation function, and incidence of complications. The inflammation level and coagulation function were evaluated by hemoglobin (HB), white blood cell (WBC) count, percentage of neutrophils, percentage of lymphocytes, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), and thrombin time (TT). The incidence of complications, such as hepaticencephalopathy, nausea, vomiting, and allergies, were compared in both groups after intervention.

Statistical analysis

All data were analyzed using the SPSS22.0 statistical software. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ±

Table 1. Comparison of baseline data

Group	Observation group (n=150)	Control group (n=150)	χ^2/t/F	P
Sex			0.033	0.857
Male	74	72		
Female	74	69		
Age (years)	65.4±12.8	64.9±11.2	0.775	0.613
Duration of disease (years)	11.3±2.9	12.1±2.4	0.834	0.530
Type of disease			0.864	0.774
Viral diseases	46	42		
Tumor diseases	64	52		
Other	38	47		
Body mass index (kg/m^2)	20.3±1.2	20.1±1.1	0.446	0.311
Complications				
Diabetes	11	14	0.123	0.725
Hypertension	9	10	0.531	0.466

Note: χ^2: data from Chi-square test; t: data from t-test; F: data from ANOVA.

sd). The paired-sample t-test was used for before-and-after comparisons within the group and independent sample t-tests were used to compare data between the groups. For multi-group comparisons, one-way ANOVA was employed. The Bonferroni correction was applied for post-hoc analysis. Counted data were represented as number and percentage, and the chi-square test was used for comparisons between groups. Logistic regression was used to analyze the factors influencing the treatment efficacy of hypoproteinemia. α=0.05 was set as the significance level, and a difference was considered significant if P<0.05.

Results

Comparison of baseline data

The baseline data of two groups were comparable. Namely, there was no significant difference in terms of gender, age, course of disease, disease type, body mass index, and comorbidities between the two groups (all P>0.05). See **Table 1**.

Comparison of the changes in liver function indicators before and after treatment

There were no significant differences observed in TBIL, ALT, and AST levels between the two groups before treatment (all P>0.05). However, after one week of intervention, the levels of these three liver function indicators significantly decreased in both groups (all P<0.05), but there was no significant difference between the two groups (all P>0.05). See **Table 2**.

Comparison of the changes in serum albumin level and Child-Pugh scores before and after treatment

No significant differences were observed in the serum albumin levels, Child-Pugh scores, and HB between the two groups before treatment (all P>0.05). However, after intervention, these indicators significantly increased in both groups, but without a significant difference between groups (all P>0.05). See **Table 3**.

Comparison of the changes in coagulation function before and after treatment

Before treatment, no significant differences were found in the levels of PT, APTT, INR, and TT between the two groups (all P>0.05). Nevertheless, after intervention, both groups showed a significant decrease in coagulation function indicators (all P<0.05), but without a difference between groups (all P>0.05). See **Table 4**.

Comparison of the changes in inflammatory levels before and after treatment

Before treatment, there were no significant differences in WBC count, percentage of neutrophils, and percentage of lymphocytes between the two groups (all P>0.05). However, after one week of treatment, the inflammatory levels of both groups decreased significantly (all P< 0.05), but without a significant difference between groups (all P>0.05). See **Table 5**.

Univariate analysis of factors affecting the efficacy in hypoproteinemia in liver cirrhosis

The follow-up results of this study revealed that in 89 patients, the serum albumin levels did not increase to 30 g/L after treatment. Univariate analysis indicated that factors influencing the treatment outcomes of hypoalbuminemia included age, pre-treatment albumin level, type of disease, and abnormal liver func-

Table 2. Comparison of the changes in liver function indicators before and after treatment ($\bar{x}$ ± sd)

Group	Time	TBIL (μmol/L)	AST (U/L)	ALT (U/L)
Observation group (n=148)	Before treatment	26.54±3.27	44.54±3.57	36.55±4.07
	After treatment	17.30±1.64#	35.60±3.61#	25.43±0.32#
Control group (n=141)	Before treatment	25.90±3.85	43.98±3.64	35.91±3.87
	After treatment	18.01±1.53#	36.43±3.78#	25.00±0.32#

Note: TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase. Compared to before treatment, #P<0.05.

Table 3. Comparison of the changes in serum albumin levels and Child-Pugh scores before and after treatment ($\bar{x}$ ± sd)

Group	Time	ALB (g/L)	Child-Pugh scores (scores)	HB (g/L)
Observation group (n=148)	Before treatment	24.52±2.40	7.3±0.9	8.0±0.4
	After treatment	30.53±2.45#	5.4±0.8#	9.0±0.3
Control group (n=141)	Before treatment	24.53±2.34	7.4±1.0	7.9±0.5
	After treatment	31.64±2.60#	5.4±0.9#	8.9±0.4

Note: ALB: albumin; HB: hemoglobin. Compared to before treatment, #P<0.05.

Table 4. Comparison of the changes in coagulation function indicators before and after treatment ($\bar{x}$ ± sd)

Group	Time	PT (s)	APTT (s)	INR	TT (s)
Observation group (n=148)	Before treatment	19.65±2.52	44.54±4.57	2.91±0.41	15.67±3.54
	After treatment	12.37±1.64#	26.07±5.63#	2.05±0.17#	12.87±2.10#
Control group (n=141)	Before treatment	18.58±2.85	43.86±4.46	2.97±0.39	16.01±4.01
	After treatment	13.46±1.53#	25.93±5.52#	2.11±0.18#	13.00±2.09#

Note: PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; TT: thrombin time. Compared to before treatment, #P<0.05.

Table 5. Comparison of the changes in inflammatory levels before and after treatment ($\bar{x}$ ± sd)

Group	Time	WBC count (10^9/L)	Neutrophils (%)	Lymphocytes (%)
Observation group (n=148)	Before treatment	11.77±2.14	83.04±4.57	0.35±0.11
	After treatment	6.31±1.92#	67.92±4.83#	0.91±0.09#
Control group (n=141)	Before treatment	11.63±2.05	83.62±4.64	0.37±0.10
	After treatment	6.40±1.87#	68.01±4.91#	0.89±0.10#

Note: WBC: white blood cell. Compared to before treatment, #P<0.05.

tion, while gender, body mass index, comorbidities, and treatment methods were not related. These factors were then subjected to logistic regression analysis, which identified age, pre-treatment albumin levels, type of disease, and abnormal liver function as independent risk factors. Treatment regimen was not an influencing factor. See **Tables 6** and **7**.

Comparison of incidence of complications

There were no significant differences between the two groups in terms of the incidence of hepatic encephalopathy, nausea, vomiting, or allergy (12/148 vs. 18/141; χ^2=1.684, P= 0.194). See **Table 8**.

Discussion

Liver cirrhosis represents the terminal stage of multiple chronic liver diseases, including obesity, alcoholism, viral infections, and autoimmune conditions [14-16]. Hypoproteinemia is a major complication of liver cirrhosis, and it serves as the initial catalyst that degrades the patient's biochemical environment. Moreover,

Table 6. Univariate analysis of factors affecting the therapeutic effect

	Unelevated serum albumin levels (n=89)	Elevated serum albumin levels (n=200)	t/χ^2	P
Age				
≤65 years	57	82	13.103	<0.001
>65 years	32	118		
Gender				
Male	45	124	3.319	0.0685
Female	44	76		
Treatment methods				
Shu Fu Pai® Protein Short Peptides Beverage	43	94	0.423	0.836
Intravenous human albumin	46	106		
Body mass index	22.5±1.4	22.8±1.6	0.678	0.754
Comorbidities				
Hypertension	10	22	0.335	0.772
Diabetes	8	12	0.442	0.663
Type of disease				
Tumors	50	66	13.773	<0.001
Abnormal liver function indicators	68	115	6.771	0.010
Pre-treatment albumin levels				
<20 g/L	67	110	10.673	<0.001
>20 g/L	22	90		

Note: χ^2: data from Chi-square test; t: data from t-test.

Table 7. Results of logistic regression analysis on factors affecting the treatment outcome

Indicator	Standardized β	OR	95% CI	P
Age	0.547	1436	1.202-2.735	0.032
Type of diseases (Tumors)	1.357	2.664	1.036-4.533	0.004
Abnormal liver function indicators	0.529	1.683	1.211-6.484	0.031
Pre-treatment albumin levels	0.311	1.583	1.411-5.117	0.003

Table 8. Comparison of incidence of complications (n, %)

Group	Complications				Total
	Hepatic encephalopathy	Nausea	Vomiting	Allergies	
Observation group (n=148)	5 (3.38)	3 (2.03)	2 (1.35)	2 (1.35)	12/148 (8.11)
Control group (n=141)	8 (5.66)	4 (2.83)	3 (2.13)	3 (2.13)	18/141 (12.75)
χ^2	0.886	0.200	0.784	0.256	1.684
P	0.347	0.654	0.376	0.613	0.194

Note: χ^2: data from Chi-square test.

albumin plays an important role in immune function. Hypoproteinemia can trigger immune dysfunction, which in turn leads to secondary infections. Consequently, interventions and treatments for liver cirrhosis with hypoproteinemia are of considerable significance. The mechanism of nutrition deficiency, such as hypoproteinemia, in liver cirrhosis are intricate and multifaceted. They arise due to an imbalance between protein catabolism and synthesis, stemming from reduced intake, heightened breakdown, or increased energy expenditure. This imbalance might also be caused by a diminished appetite or delayed intestinal motility, which also leads to decreased oral intake [17]. Thus, enteral or parenteral methods can

be used to administer nutritional supplements. Enteral nutrition is generally preferred because of its simplicity, cost-effectiveness, and low risk of complications. Patients with liver cirrhosis are advised to consider oral nutritional supplements [18-20].

In recent years, a growing amount of clinical research has focused on the use of short peptide enteral nutrition powders for the intervention of nutritional deficiency diseases. A retrospective cohort study demonstrated that compared with the group receiving complete proteins, patients on a low protein diet who consumed oral short peptide proteins experienced a significant reduction in gastrointestinal adverse events, including gastric retention and diarrhea [21-24]. This highlights the importance of short peptides as a valuable source of nutritional supplementation.

In this study, a comparison was made between the patients who administered traditional human serum albumin and those who received Shu Fu Pai® Protein Short Peptide Beverage. The findings revealed that Shu Fu Pai® Protein Short Peptide Beverage exhibited comparable effects to human serum albumin in improving liver function, inflammation markers, coagulation function, and nutritional parameters. These preliminary observations suggested that orally administering small molecule protein peptides can achieve a clinical efficacy comparable to that of human serum albumin. This may be attributed to the following mechanisms. Small molecule peptide formulations have a protective effect on the regulation of gut microbiota and can be directly absorbed and utilized by intestinal epithelial cells without requiring digestive enzymes, thereby accelerating intestinal digestion and protein absorption [25, 26]. In addition, as submolecular substances of proteins, short peptides reduce gastric digestion time, and accelerate the uptake of nutrients into the blood. Similar findings were also reported in previous research [21].

It has been shown that high protein consumption may exacerbate hepatic encephalopathy in cirrhosis patients [27]. Accordingly, this study compared the incidence of complications and found no significant difference in terms of hepatic encephalopathy nausea, vomiting, or allergies between the two groups. This further supports the safety of orally administered Shu Fu Pai® Protein Short Peptide Beverage, aligning with previous findings [28]. However, this study was conducted at a single center and involved a limited sample size. Therefore, further studies, with larger sample size from multiple centers, are needed to validate the clinical outcomes. Additionally, the follow-up period in this study was short, necessitating additional research for more comprehensive evaluations.

In summary, orally administered Shu Fu Pai® Protein Short Peptide Beverage for the treatment of hypoalbuminemia in liver cirrhosis patients presented comparable effects as intravenous administration of human serum albumin in improving liver function, inflammation markers, or coagulation function. The therapeutic outcome is independent from the treatment regimen, which suggests that Shu Fu Pai® Protein Short Peptides Beverage is an effective treatment for hypoalbuminemia in liver cirrhosis, without an increased risk of complications. Furthermore, small molecule protein peptides are less expensive than human serum albumin and are in a sufficient supply, making it a viable and attractive option for clinical application.

Disclosure of conflict of interest

None.

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