

The Effectiveness of Albumin Combined with Diuretics in Treating Ascites in Cirrhosis

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Abstract: Cirrhosis often leads to various complications during its progression, with ascites being one of the most common. Among these cases, 5% to 10% are classified as refractory ascites. In recent years, clinical research on the treatment of cirrhotic ascites has yielded increasingly enriched results. In this paper, a large number of clinical data on the treatment of ascites using albumin combined with diuretics were collected, and it was found that there were more results in group control studies. It was believed that albumin combined with diuretic therapy could effectively improve symptoms, reduce the occurrence of adverse reactions, ensure the safety of patients, and have a good clinical application prospect. This paper reviews the efficacy of albumin combined with diuretics in the treatment of ascites in cirrhosis.

Keywords: Albumin; Diuretics; Cirrhotic ascites; Curative effect

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1. Introduction

The liver is the main organ of metabolic function, which plays an important role in oxidation, storage of liver sugar, and synthesis and secretion of protein. When liver dysfunction occurs, many non-nutrients such as various drugs, poisons, and some metabolites *in vivo* and *in vitro* cannot be broken down and transformed, resulting in reduced body resistance, dysfunction of liver synthetic proteins, and serious symptoms, such as reduced plasma protein synthesis^[1]. Cirrhosis often leads to various complications during its progression, with ascites being one of the most common, among which 5% to 10% are refractory ascites. Especially in elderly patients, ascites are more difficult to treat due to multi-organ dysfunction, low immunity, poor body regulation ability, etc.^[2]. Ascites in cirrhosis are the result of increased portal vein pressure, lymphocytosis, secondary clinical hyperaldosterone, increased vasopressin secretion, and insufficient effective circulating blood volume. The main pathogenesis of cirrhosis is progressive fibrosis. Normal interstitial collagen (types I and III) is mainly distributed around the portal and central veins. In cirrhosis, type I and type III collagens are significantly increased and deposited in lobules, leading to obstruction of material exchange between blood and liver cells^[3]. Traditional treatment methods usually involve the use of diuretics. While diuretics can help reduce ascitic fluid, their prolonged use often leads to adverse reactions such as bloating, nausea, and vomiting. Over time, patients

may also develop diuretic resistance, which gradually diminishes the therapeutic effect. Some scholars have pointed out that the combined application of human serum albumin can reduce diuretic resistance and improve the therapeutic effect. However, in clinical practice, there are still different views on the combination of drugs. This paper aims to clarify the efficacy and safety of the combination of drugs.

2. Overview of cirrhotic ascites

For patients with cirrhosis, ascites can be graded according to the amount of fluid accumulated in the abdominal cavity into grade 1 (small amount), grade 2 (medium amount), and grade 3 (large amount). Grade 1 or a small amount of ascites can only be found by ultrasound examination. Patients generally have no abdominal distension, and negative shifting dullness during physical examination. Ultrasound examination shows ascites located in various spaces with a depth < 3 cm. Patients with grade 2 or moderate ascites often had moderate abdominal distension and symmetrical abdominal eminence, and shifting dullness was negative/positive during physical examination. Ultrasound examination showed ascites flooding the bowel, but not yet across the mid-abdomen, with a depth of 3–10 cm. Patients with grade 3 or a large amount of ascites showed obvious abdominal distension, positive shifting dullness during physical examination, and even umbilical hernia formation. Ultrasound examination showed that ascites occupied the entire abdominal cavity, and the mid-abdomen was filled with ascites with a depth of > 10 cm. Ascites can also be divided into simple ascites, recurrent ascites, and refractory ascites (RA) according to treatment response. Recurrent ascites refers to the recurrence of ascites at least 3 times within 1 year despite dietary sodium restriction and diuretic treatment, which may be a precursor of RA. RA refers to ascites that cannot be reduced or recur after large-volume paracentesis (LVP) despite dietary sodium restriction and diuretic therapy.

3. Methods of administration of albumin combined with diuretics

A number of studies believe that the basic treatment of patients with ascites of cirrhosis is also critical, including fluid replenishment, anti-inflammatory, liver protection, and so on. At the same time, patients were told to stay in bed and control their diet, mainly low-fat foods. It has been suggested that diuretics should be given at the same time as basic treatment, 75 mg of captopril tablets (Huazhong Pharmaceutical Co., LTD.; H42020384) and 120 mg of spironolactone tablets (Hangzhou Minsheng Pharmaceutical Co., LTD.; H33020070) given orally every day, and ascites were assessed after 2 weeks. Weight loss of 0.7–1 kg is the standard for continued drug treatment. If this standard is not met, 20–40 mg of dopamine (Guangzhou Baiyunshan Mingye Pharmaceutical Co., LTD.; H44022388) and 40–80 mg of furosemide (Henan Runhong Pharmaceutical Co., LTD.; H41020310) should be injected once a day. After 3 weeks, if the ascites still did not meet the standards, intravenous mannitol (Anhui Fengyuan Pharmaceutical Co., LTD.; H34021793) was injected 100–150 mL each time, once a day. The treatment lasted for 1 month. There are studies on the basis of routine treatment of cirrhotic ascites patients, adding human serum albumin (Boya Biotherapy Group Co., LTD.; S10940011), 10 g dissolved into 50 mL 50% glucose injection, once a day, for intravenous injection. The treatment lasted for 1 month^[4].

4. Study on drug efficacy

4.1. Effect of albumin combined with diuretics

Some studies have suggested that human serum albumin plays an important role in the treatment of ascites in cirrhosis. Firstly, it can enhance the plasma colloid osmotic pressure, increase the binding with sodium and

potassium ions, and expel ascites through the kidneys. Secondly, it can supplement the effective circulating blood volume, improve kidney function, and achieve the effects of protecting the vascular endothelium, anti-oxidation, and dilation, thus increasing urine volume. Thirdly, human serum albumin can also activate diuretic sensitivity, inhibit resistance phenomenon, and enhance diuretic effect. Lastly, it can correct hypoproteinemia, increase plasma albumin content, accelerate liver cell repair, slow down liver fibrosis, reduce portal hypertension, accelerate ascites regression, improve body immunity, and reduce patient mortality. In addition, human serum albumin has no effect on hemodynamics, will not be decomposed and utilized by tissues, and has a low incidence of adverse reactions ^[5]. In a group control study, it was found that the effective rate of treatment in the observation group was 95.00% (38/40), which was significantly higher than that in the control group [75.00% (30/80)]. Compared with the control group, the changes in body weight, 24-hour urine volume, and abdominal circumference in the observation group were significantly improved before and after treatment. The incidence of adverse reactions in the observation group was 10% (4/40), which was significantly lower than that in the control group [40.00% (16/40)] ^[6]. Treatment with human serum albumin combined with diuretics can reduce lower limb edema and abdominal swelling, improve dyspnea symptoms, increase urine volume, and is not prone to adverse reactions such as abdominal distension, vomiting, and nausea. This is because the two drugs have different pharmacological actions and can achieve a synergistic effect, so they can prevent adverse reactions while improving diuretic effects. In one study, the observation group received human serum albumin combined with diuretic treatment, the overall efficacy and recovery effect of related clinical indicators were better than the control group, and the incidence of adverse reactions such as nausea and vomiting during treatment was significantly reduced. It is suggested that diuretics combined with human serum albumin can achieve satisfactory results in the treatment of ascites in elderly cirrhosis. It is of great significance to further improve the treatment effect and reduce the amount of abdominal ascites as soon as possible, so as to optimize the relevant clinical indicators of patients and improve the treatment safety. In cirrhotic ascites patients, albumin index and liver function decreased significantly, accompanied by metabolic disorders. In addition, the formation of refractory ascites in patients leads to a large amount of albumin loss and a significant reduction in effective circulating blood volume and urine volume, further increasing the retention of water and sodium in patients. Ascite symptoms in cirrhotic patients continue to worsen, and diuretics alone cannot fundamentally reduce the formation of ascites in patients. However, intravenous administration of human serum albumin can increase plasma colloid osmotic pressure and block the vicious cycle in the body, improve the effective circulating blood volume, restore the patient's urine volume, and accelerate the regression of ascites. The causes of cirrhosis vary in different countries, more than 50% of liver cirrhosis patients in Europe and the United States are alcoholic liver disease patients, 60% of liver cirrhosis patients in Japan are highly correlated with hepatitis C virus infection, and 80% of liver cirrhosis patients in China are highly correlated with hepatitis B virus infection ^[7]. Differences in genes, ethnicity, and pathogenesis of cirrhosis may lead to differences in the efficacy of human serum albumin combined with diuretics in the treatment of ascites in senile cirrhosis. Future studies are required to provide more solid proof.

4.2. Controversy over the use of albumin for ascites in cirrhosis

The ANSWER study is the first prospective, multicenter, randomized, parallel-controlled, open study to demonstrate the long-term benefit of human serum albumin therapy in patients with decompensated cirrhosis. The study enrolled 431 patients with cirrhotic ascites who received standard therapy (SMT) and SMT combined with human serum albumin therapy respectively. The results suggest that compared with patients in the SMT group, patients in the SMT combined with human serum albumin group had a 38% lower risk of death, and

the incidence of spontaneous bacterial peritonitis (SBP), non-SBP bacterial infection, renal insufficiency, and hepatorenal syndrome were also significantly reduced [8]. However, the MACHT study showed that in patients with decompensated cirrhosis who had met the indications for liver transplantation, treatment with midodrine and human serum albumin decreased plasma renin activity and aldosterone and norepinephrine levels, but there was no significant difference in cirrhosis complications or survival compared with placebo.

An in-depth analysis of the ANSWER and MACHT studies revealed several differences in sample size, design, and follow-up time, so the conflicting results of the two studies do not imply that long-term use of human albumin does not benefit patients. A post-operative analysis of the ANSWER study showed that serum albumin concentration 1 month after treatment was associated with 18-month overall survival, with mortality 80% lower in patients with ≥ 4.0 g/dl than in patients without this level of albumin (HR = 0.20 [95% CI 0.08–0.52], $P < 0.001$). In addition, baseline serum albumin and model of end-stage liver disease (MELD) levels independently predict survival after human albumin treatment, and patients may benefit from long-term human albumin treatment even if their serum albumin level does not reach the normal range (35 g/L) after 1 month of treatment [3].

According to the ANSWER, after 1–2 months of treatment, Kaplan-Meier curves of survival and other secondary endpoints began to deviate once the increase in albumin concentration occurred and stabilized. In the ATTIRE trial, the mean duration of albumin treatment was only 8 days, which did not correct hypoproteinemia (slightly more than 3 g/dL), and short-term human albumin infusion brought the risk of volume overload. As a result, long-term human albumin represents an entirely different mode of treatment compared to acute or short-term use, where treatment often lasts for months or even years with the goal of controlling ascites and preventing other complications, thereby altering the course of the disease [3]. A single dose of long-term human albumin is low, and with intermittent long-term administration and a low risk of volume overload, the treatment is safe. In current clinical trials, no treatment-related adverse reactions have been reported.

Therefore, when the infusion dose of human serum albumin is sufficient to increase the serum albumin concentration in the body, human serum albumin can play its therapeutic role. The long-term therapeutic effect of human serum albumin is related to dose selection and treatment time, and the serum albumin concentration during treatment can be used as a monitoring index of therapeutic effect and guide the adjustment of dose and time, which is helpful to optimize the treatment plan of human serum albumin.

4.3. Exploration of human serum albumin combined with diuretics in the treatment of cirrhosis

About 16% of liver disease patients in China have cirrhosis, and all patients have varying degrees of high lymphatic fluid secretion and portal vein pressure, which increases aldosterone levels and stimulates more vasopressin secretion. In addition, the absorption rate of interstitial fluid is reduced and the effective circulation capacity is insufficient, resulting in the reduction of urine and sodium output and the retention of water and sodium, thus forming ascites. Especially in elderly patients, the incidence is higher. If the ascites do not subside for a long time or there are repeated attacks, it will cause complications such as ascites infection and hepatic encephalopathy, and increase the mortality of patients [7].

Elevated portal vein pressure and secondary clinical aldosterone elevation after cirrhosis are typically due to excess ascitic fluid production. The main cause of ascites is a decrease in effective circulating blood volume, and antidiuretic hormones often increase, leading to hypoproteinemia. In particular, the reduction of liver cells in elderly patients leads to a decreased regenerative capacity, resulting in the significant proliferation of fibrous tissue. The characteristics of poor liver synthesis and decreased liver function in elderly patients with cirrhosis

make refractory ascites more likely to occur.

Clinical use of diuretics can achieve the effect of sodium discharge, potassium preservation, and diuresis, but elderly patients often experience serious pressure on the kidney due to ascites, affecting the renal artery blood circulation, increasing water and sodium retention and circulation disorders, and aggravating the symptoms of ascites. In addition, diuretic resistance will develop as the drug dosage gradually increases, easily leading to water and electrolyte imbalance, so the effect of diuretic treatment alone is limited^[9]. A large amount of ascites will put pressure on the kidney, resulting in serious insufficiency of renal artery blood supply, further affecting blood circulation, aggravating water and sodium retention, and affecting the effect of diuretic treatment. Human serum albumin helps to improve the osmotic pressure of plasma colloid in cirrhotic ascites patients and binds with corresponding ions to help relieve clinical symptoms of patients. At the same time, the application of human serum albumin can help improve the body resistance of patients, promote the rapid recovery of liver cell function, and exert a significant effect in the treatment of hypoproteinemia.

A systematic review of eight randomized controlled trials showed that infusion of human albumin combined with diuretics significantly improved treatment response rates compared with diuretics alone or liquid resuscitators in patients with grade 2 ascites in cirrhosis (RR = 3.43, 95% CI: 1.84–6.38) showed statistical significance in shortening the time of ascites resolution, increasing urinary sodium excretion, and decreasing serum creatinine concentration, but no statistical difference was found in the incidence of adverse reactions and 24-hour urine volume^[10]. Another study on the clinical efficacy of terlipressin combined with human serum albumin in the treatment of cirrhotic refractory ascites showed significant improvement in clinical symptoms, decreased body mass, abdominal circumference, ascites depth, creatinine, and prothrombin, and increased serum albumin than before treatment^[11]. The inner diameter of the portal vein and splenic vein were both shortened, and no serious adverse reactions occurred during treatment^[12].

5. Conclusion

In summary, the combined application of human serum albumin and diuretics in the treatment of cirrhotic ascites patients can improve the therapeutic effect and accelerate the improvement of symptoms, with high safety. However, due to the lack of standard application of human serum albumin in our country, coupled with the cognitive errors of many patients, the abuse and misuse of human serum albumin are serious, resulting in the shortage of human serum albumin, increasing the treatment cost, and limiting the clinical promotion to a certain extent.

Disclosure statement

The author declares no conflict of interest.

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