

Clinical efficacy of octreotide acetate combined with thrombin in the treatment of liver cirrhosis complicated with gastrointestinal hemorrhage

XIAOYAN WANG, YANYAN LIU, JINGJING ZHAO and JINMEI ZHANG

Department of Hepatological Surgery, Weifang People's Hospital, Weifang, Shandong 261041, P.R. China

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Abstract. Clinical efficacy of octreotide acetate combined with thrombin in the treatment of liver cirrhosis complicated with gastrointestinal hemorrhage was investigated. A retrospective analysis of 157 patients with liver cirrhosis and gastrointestinal hemorrhage admitted to Weifang People's Hospital from March 2012 to September 2014 was performed. Among them, 74 patients treated with octreotide acetate were enrolled into the octreotide group, and 83 patients treated with octreotide acetate combined with thrombin were enrolled into the combination group. Comparison between the two groups was made in terms of the average hemostasis time, the hospitalization time, the amount of blood transfusion during hospitalization, the efficacy of hemostasis and visual analog scale (VAS) scores. The mean hemostasis time of the octreotide group was higher than that of the combination group, with a statistically significant difference between the two groups ($P < 0.05$); the hospitalization time of the octreotide group was significantly longer than that of the combination group ($P < 0.05$); the blood transfusion volume of patients in the octreotide group was significantly higher than that of the combination group ($P < 0.05$); the overall effective rate of the combination group after treatment was higher than the overall effective rate of the octreotide group (89.19%) ($P < 0.05$). The VAS scores of the combination group at 24 and 72 h after treatment were lower than those of the octreotide group ($P < 0.05$); the VAS scores of both the octreotide and the combination group at 24 and 72 h after treatment were significantly lower than those before treatment ($P < 0.05$). In conclusion, the combination of octreotide acetate and thrombin is worthy of clinical promotion as it could reduce the average hemostasis time, the bleeding volume, and the hospitalization time of

patients with liver cirrhosis combined with gastrointestinal hemorrhage, with better efficacy than the use of octreotide acetate alone.

Introduction

Liver cirrhosis, the histological development of regenerative nodules surrounded by fibrous bands after chronic liver injury, can lead to portal hypertension and liver cancer, with high incidence in developed countries (1). Liver cirrhosis in the long-term can cause increased portal pressure, and cause the rupture of blood vessels in the upper digestive tract, especially esophageal gastric varices, resulting in acute bleeding, which is fierce and has fast disease progression as well as high mortality (2,3). Therefore, early local hemostasis treatment and lower portal pressure are very important for patients. In the past, the most common method for the treatment of this disease in clinical practice was to use the three-chamber two-capsule tube to stop bleeding, but the possibility to bleed again, and the high incidence of adverse reactions and complications have limited its use in clinical practice (4). At present, the treatment of liver cirrhosis with gastrointestinal hemorrhage mainly adopts emergency endoscopic therapies and drug treatments. Due to the severity and rapid development of the disease, finding suitable and effective treatment methods is very important for patients (5).

According to the study of D'Amico *et al* (6), which compared the efficacy and safety between the emergency endoscopic therapy and the drug treatment, the drug treatment has similar efficacy as the emergency endoscopic therapy with fewer side-effects. Octreotide acetate, an octapeptide derivative of synthetic natural somatostatin, is widely used in clinical practice because of its certain control of the blood flow of portal vein and liver, its low incidence of adverse reactions, and because it is usually combined with other drugs due to its short onset time (7). Thrombin, a somatostatin analogue that directly participates in the blood coagulation and promotes the conversion of soluble fibrinogen in the plasma into insoluble fibrin for quick hemostasis, can promote the production of epithelial cells and the healing of body wound, working as a quick-acting local hemostatic (8,9). So far, only a few clinical studies have been reported on the combination of octreotide acetate and thrombin in the treatment of patients with liver cirrhosis

Correspondence to: Dr Jinmei Zhang, Department of Hepatological Surgery, Weifang People's Hospital, 151 Guangwen Road, Weifang, Shandong 261041, P.R. China
E-mail: jh98us@163.com

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and gastrointestinal hemorrhage (10,11). Therefore, this study investigated the clinical efficacy of octreotide acetate combined with thrombin.

Patients and methods

Patient data. A retrospective analysis of 157 patients with liver cirrhosis complicated with gastrointestinal hemorrhage, admitted to the Weifang People's Hospital (Weifang, China), from March 2012 to September 2014, was performed. Seventy-four patients treated with octreotide acetate were set as the octreotide group, aged from 38 to 71 years, with a mean age of 57.37 ± 3.83 years, and an average bleeding volume of 643.14 ± 40.71 ml; while 83 patients treated with octreotide acetate combined with thrombin were set as the combination group, aged from 35 to 73 years, with a mean age of 56.18 ± 4.04 years, and an average bleeding volume of 636.32 ± 41.84 ml. Inclusion criteria: patients diagnosed with liver cirrhosis with upper gastrointestinal hemorrhage; patients with a complete medical record; patients receiving no relevant treatment in other hospitals. Exclusion criteria: patients with allergic reactions and contraindications for the drugs used in this study; patients who were transferred or died during hospitalization; patients during pregnancy or lactation; patients with gastrointestinal bleeding caused by other diseases; patients with blood diseases or tumors; patients with a communication disorder or cognitive disorder. The study was approved by the Ethics Committee of Weifang People's Hospital. Patients who participated in this research had complete clinical data and cooperated with the medical staff to complete the relevant medical treatment. Signed informed consents were obtained from the patients and/or their guardians.

Methods. Patients were given blood supplement immediately after admission and were asked to follow routine fasting. Then, conventional symptomatic supportive treatments, such as, treatment for acid suppression, liver protection, anti-shock, and maintenance of water and electrolyte balance, were performed to maintain normal body consumption. Patients in the octreotide group were given 0.1 mg octreotide acetate by injection (Chengdu Shengnuo Biopharm Co., Ltd., Chengdu, China; medical product permitted by the China Food and Drug Administration: H20153159), combined with 20 ml of 0.9% sodium chloride, continuously pumped intravenously at the speed of 0.025-0.05 mg/h (the injection was continuously pumped until 48-72 h after the hemostasis); in the combination group, patients were injected with a mixture of 0.1 mg octreotide acetate and 2,000 units of thrombin (Penglai Nuokang Pharmaceutical Co., Ltd., Penglai, China; medical product permitted by the China Food and Drug Administration: H20051840) and 20 ml saline through gastric tube bolus or oral administration once every 4-6 h. The treatment for both groups continued for 3 days.

Regular basic nursing was performed and the fasting time and bedtime of patients were carefully guided to prevent hemorrhoids. Vital signs, such as, the patient's blood pressure, pulse, and breathing were closely observed and recorded. Conditions, such as, nausea, color-change of vomit from brown to bright red, and increased incidence of black and thin stool, it was required to be reported to the nurse immediately,

in order to get adjusted treatment and nursing measures. Patients and their family members were informed in detail about the drug name, drug function, dosage, time and method of administration, and effective communication with the patient was required to reduce patients' anxiety and depression and to improve patients' satisfaction toward nursing. All patients were directed to avoid irritating food and to attend follow-up regularly.

Observation indicators and standards

Observation indicators. Factors, including the average hemostasis time (the time from the start of medication to successful hemostasis), the hospitalization time, the amount of blood transfusion during hospitalization, the efficacy of hemostasis at 24 h after treatment, the visual analog scale (VAS) score before treatment, and at 24 and 72 h after treatment, were compared between the octreotide and the combination group.

Evaluation of the treatment efficacy (12), and the VAS scoring standard (13). Significant efficacy: no hematemesis, black stools, or abnormal blood routine examination results within 24 h after treatment was considered as successful hemostasis; certain efficacy: relieved hematemesis, black stools, and not-obviously-abnormal blood routine examination results within 24 h after treatment was considered as effective hemostasis; no efficacy: aggravated or not-relieved hematemesis, black stools, and abnormal blood routine examination results within 24 h after treatment was considered as ineffective hemostasis. Overall effective rate = (number of patients with significant efficacy + number of patients with certain efficacy)/total patient number of the group $\times 100\%$. VAS score: the score ranges from 0 to 10 points, and the higher the score, the higher the patient's pain index is.

Statistical methods. Statistical analysis was carried out using SPSS 17.1 software (Shanghai Yuchuang Network Technology Co., Ltd., Shanghai, China). Count data were expressed as a percentage [n (%)], and their difference between the two groups was measured by Chi-square test. Measurement data were expressed as the mean \pm standard deviation and their difference between the two groups was compared by t-test. Analysis of variance of repeated measures, with Least Significant Difference test, was used to compare the differences between different time-points. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of clinical data of patients. Considering the accuracy and credibility of the experimental results, factors such as, sex, age, weight, anemia, hematemesis, alcohol abuse, and bleeding location, were compared between the two groups. The difference between the two groups was not found to be statistically significant ($P > 0.05$), indicating that the two groups are comparable to each other. Table I shows the basic information of the patients.

Comparison of mean hemostasis time and hospitalization time between the octreotide and the combination group. The hemostasis time of patients in the octreotide group was

Table I. Basic information of patients in the octreotide and the combination group.

Characteristics	Octreotide group (n=74)	Combination group (n=83)	Chi-square test	P-value
Sex			0.083	0.773
Male	48 (64.86)	52 (62.65)		
Female	26 (35.14)	31 (37.35)		
Age (years)			2.412	0.120
≤45	33 (44.59)	27 (32.53)		
>45	41 (55.41)	56 (67.47)		
Weight (kg)			0.004	0.947
≤60	29 (39.19)	39 (46.99)		
>60	45 (60.81)	44 (53.01)		
Anemia			2.575	0.109
Yes	56 (75.68)	53 (63.86)		
No	18 (24.32)	30 (36.14)		
Hematemesis			0.716	0.398
Yes	27 (36.49)	25 (30.12)		
No	47 (63.51)	58 (69.88)		
Alcohol abuse			0.801	0.371
Yes	31 (41.89)	29 (34.94)		
No	43 (58.11)	54 (65.06)		
Bleeding location			0.117	0.733
Esophageal variceal	35 (47.30)	37 (44.58)		
Gastric fundus varices	39 (52.70)	46 (55.42)		

Table II. Comparison of mean hemostasis time and hospitalization time between the octreotide and the combination group.

Index	Octreotide group (n=74)	Combination group (n=83)	t value	P-value
Mean hemostasis time (h)	29.54±3.28	21.18±2.76	17.340	<0.001
Hospitalization time (days)	11.02±3.13	7.27±2.67	8.100	<0.001

significantly higher than that in the combination group, and the difference was statistically significant ($t=17.340$, $P<0.001$). The hospitalization time of the octreotide group was significantly higher than that of the combination group, and the difference was statistically significant ($t=8.100$, $P<0.001$) (Table II).

Comparison of blood transfusion during hospitalization between the octreotide and the combination group. The blood transfusion volume of the octreotide group (425.68 ± 68.35 ml) was significantly higher than that of the combination group (251.41 ± 51.23 ml), and the difference was statistically significant ($t=18.200$, $P<0.001$) (Fig. 1).

Comparison of hemostatic efficacy between the octreotide and the combination group after treatment. The overall effective rate of the combination group was 97.59% (58 patients with significant efficacy, 23 patients with certain efficacy, 2 patients with no efficacy); and the overall effective rate of the octreotide group was 89.19% (47 patients with significant efficacy, 19 patients with certain efficacy, 8 patients

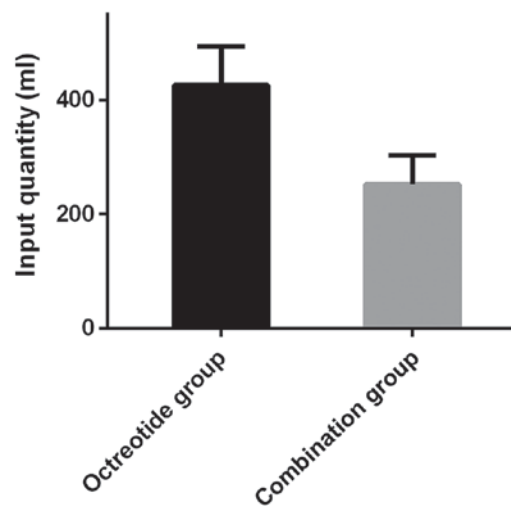


Figure 1. Comparison of the blood transfusion volume during hospitalization between the octreotide and the combination group. The transfusion volume of the octreotide group was 425.68 ± 68.35 ml, which was significantly higher than that of the combination group (251.41 ± 51.23 ml), and the difference was statistically significant ($t=18.200$, $P<0.001$).

Table III. Comparison of the overall effective rate between the octreotide and the combination group after treatment.

Groups	Significant efficacy	Certain efficacy	No efficacy	Overall effective rate
Octreotide group (n=74)	47 (63.51)	19 (25.68)	8 (10.81)	66 (89.19)
Combination group (n=83)	58 (69.88)	23 (27.71)	2 (2.41)	81 (97.59)
Chi-square test	-	-	-	4.630
P-value	-	-	-	0.031

Table IV. Comparison of VAS scores between the octreotide and the combination group before and after treatment.

Groups	Octreotide group (n=74)	Combination group (n=83)	t value	P-value
Before treatment	6.54±1.76	6.47±1.87	0.241	0.810
24 h after treatment	5.15±1.24 ^a	4.82±1.33 ^a	2.087	0.039
72 h after treatment	2.91±0.84 ^{a,b}	2.14±0.92 ^{a,b}	2.054	<0.001
F value	139.400	194.600		
P-value	<0.001	<0.001		

^aP<0.05, compared to the VAS score before treatment; ^bP<0.05, compared to the VAS score at 24 h after treatment. VAS, visual analog scale.

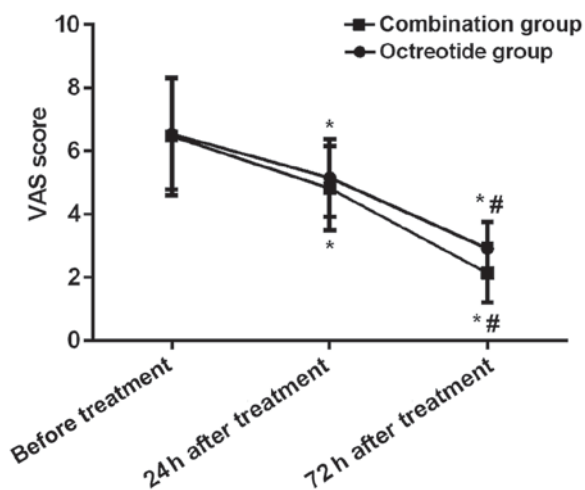


Figure 2. Comparison of VAS scores before and after treatment between the octreotide and the combination group. The VAS scores of both the octreotide and the combination group at 24 and 72 h after treatment were significantly lower than those before treatment, and the VAS scores at 72 h after treatment were significantly lower than that at 24 h after treatment, and the differences were statistically significant (P<0.05). ^aP<0.05, compared to the VAS score before treatment; ^bP<0.05, compared to the VAS score at 24 h after treatment. VAS, visual analog scale.

with no efficacy. The difference in the overall effective rate between the two groups was statistically significant (P<0.05) (Table III).

Comparison of VAS scores between the octreotide and the combination group before and after treatment. The VAS scores of the combination group at 24 and 72 h after treatment were lower than those of the octreotide group, and the differences were statistically significant (P<0.05); the VAS scores of both the octreotide and the combination group at 24 and 72 h after

treatment were significantly lower than those before treatment, and the VAS scores at 72 h after treatment were significantly lower than that at 24 h after treatment. The differences were statistically significant (P<0.05) (Table IV and Fig. 2).

Discussion

Liver cirrhosis is a diffuse liver damage caused by repeated incidence of liver disease due to one or more etiologies, leading to dysfunction of normal liver lobules and vascular structures, and causing liver fibrosis (14). Patients with liver cirrhosis, which is a common and serious disease in the clinic, have a very high risk of liver cancer, with liver cancer incidence of 2-5%/year (15,16). As the society is becoming more modernized, the cause of liver cirrhosis has increased, leading to an increasing trend in the number of patients with liver cirrhosis. As a serious complication of liver cirrhosis, portal hypertension with symptoms, such as, blocked blood flow or increased blood flow, and increased hydrostatic pressure in the portal vein, may cause esophageal and gastric varices bleeding, with an incidence of ~23.13% (17-19). According to the statistics by Lyles *et al* (20), liver cirrhosis with gastrointestinal hemorrhage has a mortality rate of ~8.4%, which seriously jeopardizes the life of patients.

This study retrospectively analyzed 157 patients with liver cirrhosis complicated with gastrointestinal hemorrhage that were admitted to Weifang People's Hospital, from March 2012 to September 2014. Seventy-four patients were treated with octreotide acetate and 83 patients were treated with octreotide acetate and thrombin, and then comprehensively compared factors between the two groups, such as, the treatment efficacy, mean hemostasis time, hospitalization time, blood transfusion volume during hospitalization, and VAS score, were investigated. The results revealed that the mean hemostasis time and hospitalization time of the combination group were

significantly shorter than the that of the octreotide group. Octreotide and thrombin can increase the contractile force of the low esophageal sphincter, can assist to reduce the reflux of gastric contents, protect the esophageal mucosa, promote platelet aggregation, and increase the coagulation rate (21).

DeLaney and Greene (22), in their study on the efficacy of octreotide and thrombin treatment in patients with upper gastrointestinal bleeding, have pointed out that the average hemostasis time and symptom-relieving time of patients treated with octreotide acetate and thrombin are significantly reduced, which further corroborates our research. The present study found that the patients in the octreotide group have significantly more blood transfusion during hospitalization than those in the combination group; the overall effective rate of combination group (97.59%), was found to be significantly greater than that of the octreotide group (89.19%). The above differences were all statistically significant. Since octreotide acetate can reduce the production and release of vasodilators (such as, glucagon, vasoactive intestinal peptide), it can reduce the total blood flow to the liver, reduce the blood flow of the portal vein, and keep the human hemodynamics relatively stable (23).

The efficacy of octreotide was discovered by Zhou *et al* (24) who reported on the hemostasis efficacy of lansoprazole combined with different dosages of octreotide in the treatment of liver cirrhosis with upper gastrointestinal bleeding. However, due to the pharmacological properties of octreotide acetate, such as, the short onset time and some adverse reactions, octreotide was not recommended to be used alone. Thrombin, a somatostatin analogue that can quickly convert the blood acting on the surface of the lesion into a stable blood clot after local application and have a relatively small incidence of adverse reactions, is suitable for the hemostasis of small blood vessels, capillaries and parenchymal viscera in which it is difficult to achieve hemostasis by ligation (25).

Friedlander *et al* (26) have reported that the combination of octreotide acetate and somatostatin significantly improves the recovery of white blood cells, blood glucose and blood calcium in patients with pancreatitis, compared to the single use of octreotide acetate or somatostatin, and achieves a reduction in the incidence of complications, which is supportive of the results of the present study. No literature exists on lower VAS scores of patients treated with octreotide acetate combined with somatostatin compared to those of patients treated with octreotide acetate alone, which is therefore of research value to be further studied. The severe liver damage and obvious systemic symptoms, such as, jaundice, fatigue and poor coagulation function may worsen the depression of patients with liver cirrhosis, so, medical staff should promptly give a psychological guide to patients and patiently respond to questions from patients and/or their families (27). Since upper gastrointestinal bleeding may cause shock or even death of the patient, the medical staff need to pay attention to the patient's vital signs in a timely manner, strengthen the basic nursing, implement predictive care, and prepare a series of nursing interventions, such as, emergency care for possible bleeding (28). Good communication between nurses and patients and nursing interventions, if combined with drug treatment, will benefit patients' compliance and rehabilitation, worthy of clinical promotion and application.

In this experiment, the sample size was relatively small due to the small number of patients with liver cirrhosis complicated with upper gastrointestinal hemorrhage in the above hospital, and therefore, the results might have some contingency. Thus, the authors will continue the follow-up for a longer period of time.

In summary, octreotide acetate and thrombin in the treatment of liver cirrhosis complicated with gastrointestinal bleeding can relieve the clinical symptoms of patients and achieve good efficacy and high safety, worthy of promotion in clinical practice.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XW was responsible for the writing of the manuscript. XW and JZhang recorded and analyzed the observation indicators. YL and JZhao acquired and interpreted the patients' general data. XW assisted with the evaluation of the treatment efficacy and the VAS scoring. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Weifang People's Hospital (Weifang, China). Patients who participated in this research had complete clinical data and cooperated with the medical staff to complete the relevant medical treatment. Signed informed consents were obtained from the patients and/or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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