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A Prospective Randomized Controlled Clinical Trial Comparing the Effects of Somatostatin and Vasopressin for Control of Acute Variceal Bleeding in the Patients with Liver Cirrhosis

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Background : Acute variceal bleeding is a serious complication of liver cirrhosis, which has an attendant mortality of approximately 60% over two years, and a variety of treatments, such as balloon tamponade, endoscopic varix ligation, sclerotherapy, histoacryl injection and vasoactive drugs, have been used. The aims of the present trial were to compare the effectiveness and complications of somatostatin and vasopressin in the treatment of acute variceal bleeding.

Methods : Forty-three cirrhotic patients, with endoscopically proven acute variceal bleeding, were included in this trial. Both drugs were given as continuous intravenous infusions for 48 hours. Twenty patients received the somatostatin (250 mcg per hr after a bolus of 50 mcg) and twenty-three the vasopressin (0.4 units per min).

Results : There were no significant differences between the two groups in relation to age, sex, etiology of cirrhosis, Child-Pugh classification, characteristics of bleeding episode, laboratory findings before randomization and units of transfused blood during therapy. Rebleeding, within 6 hours after beginning of therapy, was regarded as failure to control initial bleeding, and was observed in 3 (13.0%) of the patients who received vasopressin and in 1 (5.0%) treated with somatostatin ($p>0.05$). Five patients in both the somatostatin (25.0%) and vasopressin (21.7%) groups rebled during the first 5 days following the initial therapy ($p>0.05$). Meaningful complications related to the use of vasopressin were observed in 5 patients (chest pain or abdominal pain requiring nitroglycerin), but no complications were associated with the use of somatostatin ($p<0.05$). The mortalities during hospitalization were similar in both the treatment groups. Two of the vasopressin and 1 of the somatostatin group died due to the uncontrolled rebleeding, and 1 of the vasopressin group died due to hepatic failure (2 weeks later after theropy).

Conclusion : This study showed no differences in the effectiveness of somatostatin and vasopressin, but the somatostatin group had a lower risk of the complications.

Key Words : Variceal bleeding, Somatostatin, Vasopressin

INTRODUCTION

Variceal bleeding, due to portal hypertension, is an important complication of liver cirrhosis, occurring in 20~70% of the patients. The variceal bleeding recurrence rates are above 70%, with a 2 year-mortality rate of over 60%[1, 2]. The management of variceal bleeding is aimed at control of acute bleeding and the prevention of rebleeding. Methods of treatment that consist of decompression therapy of portal pressure and a local hemostatic therapy have been used.

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Standard therapies used for variceal bleeding include sclerotherapy or ligation therapy combined with a vasoconstrictor. Pharmacological therapy for the early treatment of variceal bleeding reduces the portal pressure, which in turn decreases rebleeding and stabilizes the patient enabling local therapy for varix to be performed. Single therapy with vasopressin infusion or the combination therapy of vasopressin and nitroglycerin are usually used to control of variceal bleeding, and reduce the splanchnic blood flow and a portal pressure, resulting in a hemostatic effect for the acute bleeding. The efficacy of drug therapy is about 50%, with reported systemic side effects in 25%[3, 4]. Somatostatin is a peptide, containing 14 amino acids, which reduces the splanchnic blood flow and hepatic venous pressure, and has been used for the treatment of variceal bleeding. It has been reported as the drug that has the lowest side effects as it acts mainly on the splanchnic blood flow[5, 6]. A prospective randomized controlled clinical trial was conducted to compare the effectiveness of somatostatin and vasopressin for the control of active variceal bleeding in patients with liver cirrhosis.

MATERIALS AND METHODS

Between March 1997 and April 1999, 43 patients were admitted to the Chungnam National University Hospital or the Youngnam University Hospital for the treatment of acute variceal bleeding. Patients were included in the study if they met the following conditions; they were aged between 18 years and 70 years, had hematemesis or proven bleeding by gastric lavage, had moderate to severe bleeding, which required a transfusion of above 500 mL of blood, and with variceal bleeding confirmed by endoscopy before or after the drug infusion (somatostatin or vasopressin). Other patients were excluded from the study for the following conditions; their age was below 17 or above 71 years, they had mild bleeding, needed an emergency operation for severe bleeding, had had a previous decompressive operation of portal pressure, had another coagulopathy, with the exception of liver disease, had a systemic disease (cardiovascular, respiratory, renal, neurologic disease) or had received a therapeutic endoscopy within 6 hours following the drug infusion.

Selected patients were evaluated for their vital signs, CBC, prothrombin time, liver function, degree of hemorrhage and Child-Pugh classification before the drug infusion. Variceal bleeding was confirmed by endoscopy either before or after the drug infusion. The informed consent was obtained from each patient, or a relative, after a full explanation of the nature and purpose of the study. The patients were randomized, using a table of random numbers, to receive either vasopressin or somatostatin. The vasopressin was given as a continuous intravenous infusion, at a rate of 0.4 IU per min for 48 hours, and the somatostatin was administered as a continuous intravenous infusion, following a 50 mcg bolus, at a rate of 250 mcg per hr.

Over the initial 5 day following admission, the vital signs were checked every 2-4 hours after a trial drug infusion, and a nasogastric tube was kept in place to check for rebleeding and the CBC and prothrombin time also checked. The side effects associated with the drug infusion were observed, and endoscopic ligation therapy or sclerotherapy were carried out after the trial of drug infusion.

During the drug infusion, following conditions regard as absence of rebleeding; the systolic blood pressure was maintained above 80 mmHg, with the reduction in the systolic blood pressure being no more than 20 mmHg, the increase in the pulse rate was no more than 20 beats/min, the hematocrit was kept above 9 g/dL, with a reduction of no more than 1 g/dL and here was no evidence of fresh blood via the nasogastric suction. During the 5 days' trial of drug administration, the early rebleeding and side effects had been examined and then evaluated. Paired *t*-and chi-squared tests were used for the statistical analysis of the results.

RESULTS

1. Characteristics of patient

Forty-three patients were selected, with 23 receiving the vasopressin and 20 the somatostatin. No statistically significant differences existed between the two groups in relation to age, sex and etiology of cirrhosis. Alcoholic cirrhosis was present in 67.4% of the patients (65.2 and 70.0% in the vasopressin and somatostatin groups, respectively), and viral origin was 23.3% (26.1% and 20.0% respectively). There was no significant difference between the two treatment groups in relation to their Child-Pugh classification. Respectively 25.6%, 60.5% and 11.4% of patients belonged to Child-Pugh A, B and C. And distribution rates of Child-Pugh class between the two groups were not different in statistically (Table 1).

There was no significant difference in relation to the characteristics of the bleeding episode at the time of admission between the two treatment groups (Table 2). The interval between the time of admission and the initiation of the drug infusion, the units of blood transfused during this interval, the hematocrit, the blood pressure, the heart rate and the sites of bleeding were similar for the two groups. About 86.0% of the patients bled from esophageal varices: 82.6 and 90.9% of the vasopressin and somatostatin groups, respectively, with

no statistically significant difference between the two groups.

Table 1. Clinical features of patients at the time of randomization

	Vasopressin (n=23)	Somatostatin (n=20)	*p*
Age (yr)	54.0±2.2	51.4±2.2	NS
Sex ratio (M/F)	17/6	18/2	NS
Etiology of cirrhosis			
Alcohol related	15	14	NS
Viral	6	4	NS
Cryptogenic	2	2	NS
Child-Puch Class			
A	5	6	NS
B	14	12	NS
C	4	2	NS
Laboratory data			
Bilirubin (mg/dL)	2.6±0.7	2.6±0.4	NS
Albumin (gm/dL)	2.8±0.1	3.1±0.1	NS
Prothrombin time (sec)	14.1±0.4	14.4±0.8	NS

NS, The difference between the two group was not significant.

Table 2. Characteristics of the bleeding episode

	Vasopressin (n=23)	Somatostatin (n=20)	*p*
Data on admission			
Blood pressure (mmHg)	100.9±4.2	114.0±5.0	NS
Heart rate (beats/min)	90.4±3.7	87.4±3.0	NS
Hemoglobin (gm/dL)	8.6±0.6	8.8±0.5	NS
Classification of hemorrhage			
Massive	7	4	NS
Serious	4	7	NS
Moderate	12	9	NS
Source of bleeding			
Esophageal/gastric varix	19/4	18/2	NS
Units of blood transfused during therapy	3.6±0.4	3.9±0.5	NS

NS, The difference between the two group was not significant.

2. Comparison of the treatment effects

Three of the patients treated with vasopressin and one treated with somatostatin re-bled within 6 hours following the beginning of the drug infusion, with no statistically significant difference between two groups (Table 3).

During the interval from 6 to 120 hours after the beginning of the drug infusion, 2 of 20 patients treated with vasopressin and 4 of 19 patients treated with somatostatin re-bled, with the exception of those patients that re-bled within 6 hour of the drug infusion, with no statistically significant difference between the two groups (Table 3).

For the 5 days after the drug infusion, 5 of the 23 patients treated with vasopressin and 5 of the 20 treated with somatostatin re-bled, with no statistically significant difference between the two groups (Table 4).

Table 3. Results of Vasopressin and Somatostatin treatments for the control of acute variceal bleeding

	Successful	Not Successful	*p*-Value
during initial 6 hours			
Vasopressin (n=23)	20	3	0.37
Somatostatin (n=20)	19	1	
from 6 to 120 hours			
Vasopressin (n=20)	18	2	0.35
Somatostatin (n=19)	15	4	

Table 4. Results of Vasopressin and Somatostatin treatments for the control of acute variceal bleeding

	Successful	Not Successful
Vasopressin (n=23)	18	5
Somatostatin (n=20)	15	5

p=0.80, The difference between the two group was not significant.

3. Side effects

During the drug infusion, the mild side effects observed were bradycardia and elevation of blood pressure in 5 of the 23 patients treated with vasopressin (21.7%) and in 6 of the 20 treated with somatostatin (30.0%). There was no statistically significant difference between the two groups. Abdominal or chest pains were observed in 5 of the 23 patients treated with vasopressin and none of the 20 with somatostatin, with a statistically significant difference between the two groups (p<0.05) (Table 5).

Table 5. Complications of treatments

	Vasopressin (n=23)	Somatostatin (n=20)
Abdominal pain or Chest pain	5	0$^{\Omega}$
Bradycardia	3	2
Elevated blood pressure	2	4

Ω, p<0.05

4. Mortality

Two of the 23 patients treated with vasopressin and one of the 20 treated with somatostatin died of variceal bleeding. One patient in the vasopressin group died of hepatic failure 2 week later after treatment. No significant difference was

observed in the causes of death between the two groups (Table 6).

Table 6. Causes of death during therapy

	Vasopressin (n=23)	Somatostatin (n=20)
Variceal bleeding	2	1Ω

Ω, p>0.05

DISCUSSION

Portal hypertension and varix occursd in 50～70% of the cirrhotic patients, with variceal bleeding occurring within 2 years in 30% of the patients with varices[7, 8]. Both medical and surgical therapies exist for the managements of the variceal bleeding. The medical therapy is composed of endoscopic treatments, mechanical coagulation using a Sangstaken-Blakemore tube and pharmacological agents, such as vasoconstrictors and nonselective beta receptor blockers. Other methods for the managements of variceal bleeding are a surgical operation and transjugular intrahepatic portosystemic shunt (TIPS).

Endoscopic sclerotherapy has been shown to have a high control rate of variceal bleeding when the sclerosant (ethanolamine oleate or polidocanol) was directly injected into the varices, with an alternative technique involving a submucosal injection adjacent to the varices. Repeated endoscopic sclerotherapy has excellent effects, these being complete remission and the prevention of rebleeding[9].

Since Stiegmann and colleagues first carried out endoscopic ligation therapy, endoscopic ligation has been broadly used for variceal bleeding. This method involves the aspirations with a vacuum, and mechanical ligations with 'O' shaped rubber bands. Compression with the rubber band induces a necrosis of ligated tissue, shallow ulceration, fibrosis and scar formation. Endoscopic variceal ligation therapy has shown excellent results[11]. Compared with sclerotherapy, endoscopic ligation shows no differences in hemostatic, rebleeding and survival rates, but tends to be simpler and lower complication rates[12]. These two endoscopic therapics achived hemostasis and prevention of rebleeding in 85～95% of patients.

Many drugs have been used for the treatment of variceal bleeding. Of these β-blockers are useful for the long-term preventive therapy of variceal bleeding[15]. With acute bleeding, vasoconstrictors have been used to facilitate sclerotherapy and the surgical treatment for this condition[16, 17]. Vasopressin, which constricts the visceral arteries and reduces the splanchnic blood flow, has been used, and consequently this drugs decompresses the portal pressure and has hemostatic effects on variceal bleeding.

The effectiveness of vasopressin for acute variceal bleeding is about 50%, but major adverse effects, such as myocardial infarction and systemic adverse effects, have been noted, which are still areas of debate[3, 4, 16, 17]. Somatostatin inhibits the secretion of growth hormone and most gastrointestinal, hormones, but has an effect in the treatment of variceal bleeding by reducing the splanchnic blood flow in patients with liver cirrhosis as also as in normal subjects[5, 6, 19, 21, 22]. This reduction in the splanchnic blood flow leads to a significant falling of the portal pressure, but does not induce alterations in the systemic hemodynamics which results in the advantage of the diminution of the systemic adverse effects differently to vasopressin[5 6, 20-22].

Sonnenberg et al[20] reported that the reducing effect of somatostatin on the portal pressure was significantly less than that of vasopressin, and had no effect unless somatostatin was infused as an initial bolus injection. Raptis et al[23, 24] has reported the failure to control esophageal bleeding. Conversely, Jenkins et al[25] and Bagarani et al[26] have reported the excellent effect of somatostatin on esophageal variceal bleeding, and also Kravetz et al[27] reporting that somatostatin was as effective as vasopressin in the control of variceal bleeding.

This study was a prospective randomized study for the comparison of the effectiveness and complication rates of somatostatin and vasopressin infusions as pharmacological therapies for the treatment of acute variceal bleeding. Rebleeding within 6 hours after the beginning of the therapy was observed in 3 of the 23 patients (13.0%) receiving vasopressin and in 1 of the 20 (5.0%) receiving somatostatin, but there was no significant difference between the two groups (p>0.05). The linitial hemostatic effects, which prevented rebleeding within 6 hours of therapies, were noted in 87.0 and 95.0% of the vasopressin and somatostatin infusion groups, with both drugs achieving high rates for the control of bleeding during the early post-bleeding stages. The initial hemostatic effects in the present study were higher than those of Jenkins et al[25], Bagarani et al[26] and Kravet et al[27], who reported 28-74 and 45～85% in the vasopressin and somatostatin infusion groups, respectively. The reason for the rebleeding in some patients during therapy, after the initial control of bleeding, has been reported to be due to drug resistance, but this is still unclear.

In this study, most of the patients had been examined with therapeutic endoscopy, such as endoscopic variceal ligation or endoscopic intravenous injection of a sclerosing agent (histoacryl), from 6 hours after the drug infusion. Somatostatin

or vasopressin were infused for 48 hours, and the patient's hospital course relating to these drugs observed,. but it was unclear whether the therapeutic endoscopy and the duration of the drugs administration had any effects on occurrence of rebleeding.

Five of the 23 patients (21.7%) receiving vasopressin, and 5 of the 20 (25.0%) treated with somatostatin, re-bled during the initial 5 days following the therapy, but with no significant difference (p>0.05), which was similar to the results of other reports[25-27]. In this study, the administration of somatostatin and vasopressin, within 6 hours and for the initial 5 days following the infusion, had similar hemostatic effects.

Mild complications, such as bradycardia and elevation of blood pressure, during the treatments were observed in 5 (21.7%) and 6 (30.0%) patients in the vasopressin and somatostatin groups respectively, but with no significant difference. Cardiovascular and gastrointestinal ischemic complications, such as chest and abdominal pains which required nitroglycerin, were observed in 5 of the patients treated with vasopressin, but not found in the somatostatin group. The somatostatin infusion group had a lower rate of associated significant complications than the vasopressin infusion group, which was no different from the results in other studies[25-27]. These lower rates of induced complications are thought to be due to the more selective action of the somatostatin on the splanchnic vascular bed[5, 6, 20-22]. This suggests that the complications of vasopressin could be reduced by decreasing the dose and length of the infusion or the simultaneous administration of nitroglycerin[4].

In this study, two patients in the vasopressin and one in the somatostatin groups died due to uncontrolled rebleeding during trial, with one of the vasopressin group dying due to hepatic failure 2 weeks later after therapy. Three of the patients who died were included in Child-Puch class C group, with this group also having a higher mortality rate in previous studies[25-27].

In conclusion, this study has shown that somatostatin and vasopressin were no different in the prevention of rebleeding due to acute variceal bleeding, but that somatostatin had a lower risk of the serious complications.

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