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Original article

A randomised controlled trial comparing octreotide vs octreotide plus sclerotherapy in the control of bleeding and early mortality from esophageal varices

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SUMMARY

Octreotide, the long-acting analogue of somatostatin, has been used as the initial treatment in acute variceal haemorrhage, with conflicting results. In this study we compared octreotide alone with octreotide and sclerotherapy combined in the control of acute variceal bleeding. The mortality within a six-week period after the acute variceal haemorrhage was also examined.

In a prospective trial 30 patients with cirrhosis and variceal haemorrhage confirmed by endoscopy, were randomized to two groups (A and B). All patients received octreotide after admission, in a continuous infusion (50 μg/h) for five days. The patients of group A underwent variceal sclerotherapy with ethanolanime 5% injection at emergency endoscopy.

At 120 hr bleeding was controlled in 100%(15/15) in group A and 93%(14/15) in group B (NS). Mean transfusion requirements were not significantly different between the two groups (group A=2,7 blood units and group B=3,1 blood units). No side effects were detected in either group and no deaths observed. The mortality from bleeding recurrence at six-weeks were: none of group A and 2/15(13%) of group B (NS).

In conclusion, the results of this study suggest that a five day course of octreotide alone, without the addition of sclerotherapy appears to be effective in the emergency control of active variceal bleeding in cirrhosis.

Key words: Octeotide, Sclerotherapy, Esophageal varices, Bleeding

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INTRODUCTION

Variceal bleeding accounts for only 10% of all hospital admissions with upper gastrointestinal bleeding.[1] Acute variceal bleeding is a life-threatening complication in patients with cirrhosis and portal hypertension, with a reported mortality rate of 30% to 50%.[2]

Early or late rebleeding rates and the severity of the underlying liver disease, mostly estimated by Child-Pugh score, determine prognosis. Moreover, mortality is still closely related to failure to control haemorrhage or early rebleeding, which occurs in as many as 50% of patients in the first days to 6 weeks after admission.[3]

The endoscopic management of variceal bleeding is currently based on sclerotherapy and more recently on band ligation. These methods are widely used to control acute variceal haemorrhage and to reduce recurrent bleeding, but rebleeding occurs in up to 50% of patients before variceal obliteration is achieved.[4] Since recent evidence suggests that those patients with high variceal or portal pressure are likely to continue bleeding or rebleed early, prolonged drug therapy that lowers portal pressure over days may be the optimal treatment.[5]

Recently, somatostatin and its long-acting analogue, octreotide have been used as the initial treatment in acute variceal haemorrhage with conflicting results.[6] Moreover, many studies show that the octreotide is safer and more effective than natural drugs.[7]

In this study, we compared octreotide with or without sclerotherapy to control acute variceal bleeding and prevent early rebleeding within 6 weeks of admission in patients with cirrhosis.

PATIENTS AND METHODS

Thirty patients (M=21, F=9, age=24-76 years) with cirrhosis and variceal haemorrhage confirmed by endoscopy, {active bleeding=13/30 (43%), stigmata of haemorrhage=17/30 (57%)}, were considered eligible for the trial.

The inclusion criteria of the study were: a) liver cirrhosis documented by needle biopsy on previous admissions, and b) presence of esophageal varices confirmed by endoscopy. Other causes of bleeding except bleeding from esophageal varices were excluded.

Furthermore, the exclusion criteria were: a) undergoing endoscopic variceal sclerotherapy in the week prior to entry, b) hepatic encephalopathy or severity of liver dysfunction which prevented endoscopy, c) administration of vasoactive drugs during the last 48 hours and d) previous surgical treatment of variceal bleeding.

All patients who satisfied the above criteria had an emergency endoscopy within 12 hours of admission and were randomised into two groups (group A and B).

The two groups of patients were balanced for Child-Pugh class and endoscopic appearance of varices. All patients received a continuous infusion of octreotide (50 μg/h) for five days. In addition all the patients of group A underwent variceal sclerotherapy with ethanolamine 5% injection during emergency endoscopy.

Control of bleeding was evaluated 120 hr after initiation of treatment. Thus, 120 hr was considered the primary end point and defined by at least one of the transfusion requirements, haemodynamic status, need of surgical intervention or death according to the Baveno III definitions.[8] Moreover, the secondary end point was the early mortality rate at 6 weeks after the initial episode of bleeding.

During hospitalisation all patients were monitored regularly for hematocrit, transfusion requirements and biochemical analysis of hepatic function and hemostasis. The study was terminated for each patient at the first rebleeding episode, at death or six weeks after admission.

The outcomes during the 120 hr treatment period were analysed by x^2-test and the overall survival up to 42 days by the log- rank test.

RESULTS

The two groups of patients were well matched for age, sex, cause and stage of liver disease and endoscopic findings, (Table 1).

In group A, at 120 hr bleeding was controlled in all

Table 1. Patient characteristics

Characteristic	Octreotide+Sclerotherapy Group A, n=15		Octreotide Group B, n=15		p-Value
Age (yr)	50	(24-75)	52	(27-76)	NS
Gender (M/F)	11/4		10/5		NS
Cause of cirrhosis (%)					
Alcoholism	8	(53)	5	(33)	NS
Chronic viral hepatitis	4	(27)	6	(40)	NS
Primary bilary cirrhosis	1	(7)	1	(7)	NS
Unknown	2	(13)	3	(20)	NS
Child-Pugh grade (%)					
A	2	(13)	4	(27)	NS
B	4	(27)	3	(20)	NS
C	9	(60)	8	(53)	NS
Variceal bleeding (%)					
Active	5	(33)	8	(53)	NS
Stigmata	10	(67)	7	(47)	NS

15 patients (100%) compared with 14 of 15 (93%) in group B, (NS). Transfusion requirements were not significantly different between the two groups (NS) and no patient died during this first 120 hr period or during hospitalisation and no one needed surgical treatment (NS), (Table 2).

During the six-week follow-up, 2 patients died in group B: one of haemorrhage and one of encephalopathy and none in group A (Table 2). A Kaplan Meier curve analysis of survival showed no statistical difference between the two groups (Figure). There were no side effects observed due to administration of octreotide infusion.

DISCUSSION

The mortality rate of acute variceal bleeding in cirrhotics ranges from 30 to 50%.[1] Early recurrence of bleeding occurs in as many as 50% of patients and it is reported that the one year survival in good risk patients (Child-Pugh grade A and B) is about 70%, whereas in bad risk patients (Child-Pugh grade C) it is about 30%.

Injection sclerotherapy is successful in controlling variceal bleeding in up to 90% of patients and it is reported to significantly reduce early rebleeding in comparison to vasoactive drugs and balloon tambonade.[9] This technique consists of an intravariceal or perivariceal injection of substances that provoke thrombosis of the varices and a fibrous reaction that tends to eliminate them. However, emergency sclerotherapy does not alleviate portal hypertension and the possibility of rebleeding remains.

The medical treatment of acute variceal bleeding has

Table 2. Results of treatment and patient outcomes during hospitalization

	Octreotide+Sclerotherapy Group A, n=15	Octreotide Group B, n=15	p-Value
Control of bleeding at 120 hr (%)	15 (100)	14 (93)	NS
Transfusion requirements:	2,7 (0-7)	3,1 (0-6)	NS
Death at 6 weeks	0	2	NS
Surgical ligation	0	0	NS

*Data expressed as mean (range)

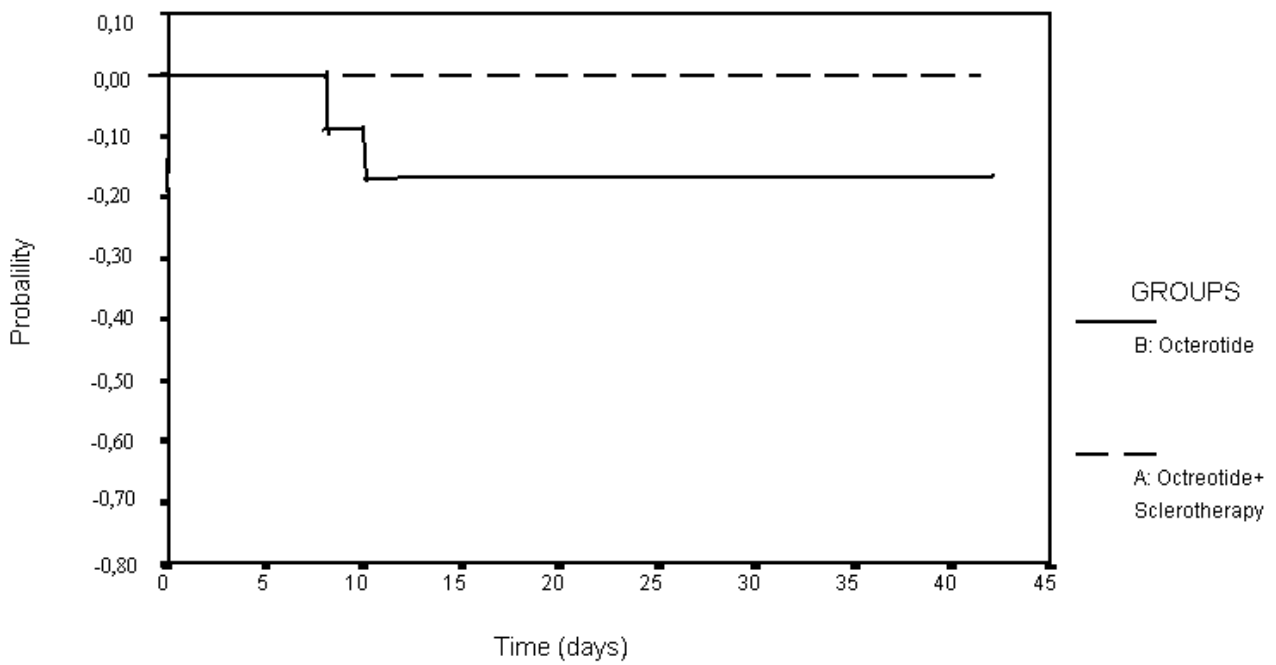

Figure. Kaplan Meier curve of overall survival.

been the subject of extensive investigation. The vasoactive drugs that are currently used in the management of acute variceal bleeding are vasopresin, glypressin, somatostatin and octreotide. Meta analysis of randomised controlled trials in which octreotide or somatostatin were compared with other vasoactive drugs revealed that both agents were associated with significantly higher effectiveness and a lower complication rate.[10]

Recently, attention has focused on octreotide as a treatment modality for patients bleeding from esophageal varices. In cirrhotics several studies have observed a significant decrease in estimated portal pressure after administration of somatostatin and octrerotide.[11,12] The responsible mechanisms are unknown but they may involve direct vasoconstriction of splachnic vasculature, vasodilation of the portal system or inhibition of vasoactive hormones such as glucagon.[13] However, octreotide has also been reported to cause a transient reduction in azygous blood flow,[14] but some studies did not confirm this observation, using similar or even greater doses of the drug.[15]

Furthermore, a close correlation appears to exist between variceal bleeding events and elevated intravariceal (I.V.) pressure but the effects of octreotide infusion on intravariceal pressure are under debate.[16] Both increases and decreases in I.V pressure have been reported. In any case, clinical trials demonstrated that intravenous infusion of somatostatin or octreotide was more effective than placebo in decreasing I.V. pressure.[17]

A number of published clinical trials demonstrated too, that the intravenous infusion of somatostatin, increased the effectiveness of emergency sclerotherapy, significantly reduced the incidence of rebleeding and improved survival.[10] Moreover, both somatostatin and octreotide were as effective as sclerotherapy and balloon tamponade in controlling initial bleeding.[18,19]

The results of this trial show the significant improvements that have taken place in the medical management of esophageal haemorrhage both in terms of initial outcome and long term prognosis. More specifically, our results suggest that octreotide is effective with or without sclerotherapy in the emergency control of acute variceal haemorrhage in portal hypertension of cirrhotic patients. It is noteworthy that there was only one case of failure in the emergency control of acute variceal bleeding and this patient refused surgical treatment. Thus, no patients died during hospitalisation despite the fact that bad risk patients (Child-Pugh grade C) were the majority in both groups. Comparison of patient outcomes during hospitalisation between the two groups showed no advantage in combining octreotide and emergency sclerotherapy versus administering octreotide alone in all tested parameters. More specifically there was no difference between the two groups in the control of bleeding 120 hr, the transfusion requirements, bleeding recurrence and hospital mortality. The reduced incidence of early rebleeding may have been associated with the octreotide infusion consistently reducing azygous blood flow and the intravariceal pressure more than portal pressure itself, effects that could have contributed to our results.[20,21]

Recent studies[22-25] conclude that combined endoscopic and pharmacologic treatment is more efficient than endoscopic therapy alone. This was not demonstrated in our study, possibly due to the relatively low number of patients included. Considering that about 40% of variceal haemorrhage stops without further intervention, we need a large number of patients to demonstrate statistically significant differences. Nevertheless, it appears that if emergency therapeutic endoscopy is not available, octreotide monotherapy is an effective therapeutic modality in the control of bleeding in patients with acute variceal haemorrhage.

In conclusion, octreotide with or without sclerotherapy appears to be effective in the emergency control of active variceal bleeding in cirrhotic patients. It should be considered a safe and effective adjunctive therapy to variceal obliteration techniques.[23]

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