ORIGINAL ARTICLE

A COMPARATIVE STUDY OF EFFICACY OF OCTREOTIDE AND SCLEROTHERAPY IN VARICEAL BLEEDING

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ABSTRACT

Objective: To see the efficacy of octreotide and sclerotherapy and combination thereof in control of variceal bleeding.
Design: A prospective, open-label randomised study.
Place and Duration of Study: Department of Medicine, Chandka Medical College, Larkana and Lateef Medical Complex, Larkana, Pakistan.
Patients and Methods: This study was conducted from June, 1996 to June, 2001. In all, 564 patients were included in the study, 188 received sclerotherapy alone (group I), 196 sclerotherapy with octreotide (group II) and rest (180) were put on octreotide alone (group III). The patients of all groups were comparable regarding baseline characteristics and severity of disease. Sclerotherapy was given on day 1,8,15 and 29. Each varix was injected with 4-6 ml of ethanolamine separately at the same sitting. The octreotide was given 50 μg/ hour through infusion for 48 hours and then subcutaneously 8 hourly for total 5 days. All the patients were observed for 30 days.
Results: In group I, 48 patients (25.53%) showed re-bleeding, whereas in group II and III re-bleeding was noted in 20 patients (10.2%) and 24 patients (13.33%) respectively. The difference was statistically significant $p < 0.01$. The re-bleeding was remarkable in Child-Pugh s group B and C. Twelve patients (6.3%) died in group I, while 4 died in each group II (2.04%) and III (2.22%) respectively. The difference was statistically significant (p 0.03).
Conclusion: Octreotide appeared equally or superior over sclerotherapy in controlling bleeding and preventing early re-bleeding.

KEY WORDS: *Variceal bleeding.* *Sclerotherapy.* *Octreotide.*

INTRODUCTION

Variceal bleeding is the most serious complication in patients with cirrhosis liver and is associated with 30-50 percent risk of death.[1] Bleeding stops on its own in about 70% of the patients before they reach the hospital, however, early re-bleeding occurs within hours and days in at least 50 percent of the cases.[2-4] The risk of continued variceal bleeding or early rebleed within first 6 hours is related to the severity of liver disease.[2,5,6] The factors that sustain bleeding and that cause re-bleeding in individuals are not fully understood.[7-9] As the bleeding may precipitate hepatic encephalopathy, hepatorenal syndrome and death etc, therefore, these patients require urgent treatment. There is considerable debate regarding treatment of acute bleeding from esophageal varices. Esophageal tamponade has been shown to be an effective mean of control of bleeding, however, at least 50% of the patients experience re-bleeding within 24 hours of intervention, and procedure related complications (e.g. aspiration pneumonia, airway obstruction and perforation), tolerance of patients is poor and death occur in substantial number of cases.[10-11] Endoscopic sclerotherapy has proved beneficial for the control of active variceal bleeding.[12] It also prevents re-bleeding during the long-term management.[13-15] and improves survival of the patients.[16] However, sclerotherapy is associated with re-bleeding in 25-50% of patients. Variceal obliteration takes 6-11 sittings. Complications related to procedure are present in 15-50% of patients.[17] However, this requires endoscopic facility and expertise, which is not easily available everywhere. Vasopressin has been the mainstay of drug treatment over the past 30 years but the doubts have been raised as to its efficacy[18] and serious cardiac side effects (e.g. myocardial ischaemia, cardiac failure, pulmonary oedema) may occur. It has been suggested that in addition to vasopressin, a vasodilator like nitroglycerine may be added to reduce side effects.[19-20] It has been claimed that octreotide causes a 30% reduction in portal pressure in stable cirrhotic patients,[21,22] and has been shown to be at least as effective as vasopressin in controlling acute variceal haemorrhage without side effects. In the present study we have compared the efficacy of octreotide alone, or in combination with sclerotherapy and also sclerotherapy alone in early control of active variceal bleeding.

PATIENTS AND METHODS

This was a prospective, open-label randomized study conducted between January, 1996 and June, 2001 over 564 patients admitted to the Department of Medicine, Chandka Medical College, Hospital, and Lateef Medical Complex, Larkana, with an active bleeding from esophageal varices at endoscopy. Active bleeding was defined when blood was coming from varices or seen in the esophagus with cherry red spots on varices and no other haemorrhagic source was found in the stomach and duodenum. Cirrhosis of liver was documented

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TABLE I : Inclusion criteria

1.	Over 18 years age
2.	Active bleeding from varices
3.	No treatment for variceal haemorrhage in the last 15 days.
4.	Absence of end stage of cirrhosis liver or hepato-renal syndrome.
5	.No history of myocardial infarction within the preceding 6 months.
EXCLUSION CRITERIA	
1.	Bleeding due to other causes.
2.	Admission in the hospital 24 hours after the variceal bleeding.
3.	Hepatocellular carcinoma
4.	Age 75 years or above.
5.	Non-cirrhotic portal hypertension.

on the basis of liver biopsy performed during a previous admission or typical history and examination and laboratory findings with strong support of ultrasound. The inclusion and exclusion criteria are given in **Table I**. Over a period of 5 years, 564 subjects were selected for this study. They (or relatives) were explained the nature of trial. Following admission to hospital, patients were resuscitated with haemacel and blood transfusion. Upper gastrointestinal endoscopy (UGI) was performed with GIF XQ20 within 2-10 hours. Prior to endoscopy in patients suspected of having variceal haemorrhage, the trial was explained and written informed consent was obtained from the patient or relative. Having confirmed active bleeding from oesophageal varices at endoscopy, patients were randomized to treatment with sclerotherapy alone or in combination with octreotide or octreotide alone. The amount of blood transfused was recorded. Group I, which consisted of 188 patients, underwent sclerotherapy, group II of 196 patients was placed for sclerotherapy and octreotide and group III of 180 patients was put on octreotide only. All the 3 groups of patients were comparable regarding baseline characteristics and severity of disease **(Table II)**. Sclerotherapy was performed with the flexible Olympus GIF XQ20 with NM-1K needle. Each varix was injected with 4-6 ml of 50% ethanolamine separately at the same sitting. Sclerotherapy was given on day 1,8,15 and 29. Octreotide was given by intravenous infusion 50 µg/ hour for 48 hours or till stoppage of bleeding whichever was earlier. Later, it was given subcutaneously 50 µg 8 hourly with sclerotherapy or alone. It was given for 5 days only. All the patients were observed for 30 days. Vital signs were observed and checked for any fresh bleeding. Haemoglobin was checked on days 1,3,5,7,15 and 30. Blood transfusion was given as required along with injection cimetidine, vitamin K and other supportive measures. The significant bleeding was defined as haematemesis and/or malaena accompanied either by systemic disturbances like sudden drop in blood pressure >15 mmHg or systolic B.P was < 100 mmHg or with a rise in pulse > 100 per minute or a drop in haemoglobin (Hb) percent by > 1.5 gm or if two or more units of blood were required. The presence of oesophageal ulcer (grade 0=absent, grade I= moderate or grade II = large or necrotic) was recorded. B.P, pulse rate, haematocrit, and transfusion were monitored throughout the treatment and follow up period.

STATISTICAL ANALYSIS: Data in the text and tables were given as mean ± SD. To detect significant differences between baseline characteristics of two treatment groups and efficacy of treatment modalities were analyzed by the two tests, students T test and chi-square test. Statistical differences were considered significant when p was < 0.05.

RESULTS

Of the 564 patients, 188 received sclerotherapy, 196 received sclerotherapy plus octreotide and 180 received octreotide, grouped as I, II and III respectively. All the 3 groups were age, sex, and Child Pugh's classification matched and had similar baseline characteristics **(Table II)**. Most of the subjects were in the age group of 40-59 years **(Table III)**. Systolic B.P was in the range of 106± 35 mmHg for group I, group II was 101 ± 29 mmHg and for group III was 95 ± 27 mmHg at the time of admission. Hb was 7.6% Gm (range 5.4-11.8) with SD ± 2.3, 7.4 (5.2-11.3) with SD ± 2.3 and 7.5 (6.0-11.5) with SD ± 2.4 for group I, II and III respectively. HBs marker was aetiologically most significant in all the 3 groups.

Out of 188 patients in group I, 48 (25.5%) patients showed re-bleeding, whereas in group II (196 patients) re-bleeding was noted in 20 patients (10.2%) and in group III (180 cases) re-bleeding was observed in 24 patients (13.3%). The difference was statistically significant p < 0.01. The re-bleeding was

TABLE II : Patients characteristics at the time of randomization

	Group I (Scl)	Group II (Scl + Oct)	Group III (Oct)
Number (564)	(188)	196	180
Age (years)	41 ±12	39 ± 13	41 ± 14
Sex (m/f)	128/60	132/64	120/60
Etiology B/C/U	136/32/20	124/40/32	136/16/28
Variceal grade I/II/III	32/128/28	24/136/36	24/96/60
Pugh's classification			
A (5-6), B (7-5), C (10-15)	76/88/24	72/96/28	60/96/24
Level of			
S. Bilirubin (units)	2.4 ± 1.4	2.45 ± 1.45	2.5 ± 1.5
S. Albumin (units)	3.4 ± 1.5	3.6 ± 1.6	3.4 ± 1.5
B. Urea (units)	34 ± 16	36 ± 17	38 ± 16
S. Creatinine (units)	1.8 ± 1.3	1.7 ± 1.2	1.5 ± 0.5
Prothrombin time	19 ± 4	18 ± 6	18.5 ± 7.5
Platelets	108100 ± 43038	120000 ± 44310	133400 ± 47536
B.P			
Systolic (mmHg)	95 ± 27	106 ± 35	101 ± 29
Diastolic (mmHg)	65 ± 5	55 ± 20	57 ± 23
Blood Transfusion	1500 ± 450 ml	(500 – 4500)	1250 ± 700 ml
	(250 –3000)	750 ± 550 ml	(250 –1500)

Scl =Sclerotherapy; Oct = Octreotide; Pugh's = Child modified Pugh's classification; C = Hepatitis CV; U = Unknown.

TABLE III : Age and sex distribution of 564 cases

Age (yrs)	Group I		Group II		Group III	
	Male	Female	Male	Female	Male	Female
18-39	32	19	22	12	29	17
40-59	86	39	88	48	86	37
60	10	02	22	04	10	01
Total	188		196		180	

remarkable in Child-Pugh's[23] group B and C **(Table IV)**. Four patients died in each group II and III, while 12 died in group I (all in child's classification B and C). They died on day 2nd (groups II and III), 2nd, 3rd, 5th and 25th day in group I as a result of massive re-bleeding.

TABLE IV: Distribution of re-bleeding cases according to group and Pugh's classification

Pughs classification	Group I		Group II		Group III	
	R	N	R	N	R	N
A	0	24	0	28	0	24
B	28	60	8	80	12	84
C	20	56	12	68	12	48
Total	25.53	74.47	10.2	89.8	13.33	86.67

R = Re-bleeding; N = Non-re-bleeding.

Bleeding was controlled within first 4 hours of the start of treatment after admission in 170 of 180 patients treated with octreotide (group III), 188 of 196 with octreotide plus sclerotherapy (group II) and in 164 of 188 (group I) treated with sclerotherapy alone. However 14 patients in the octreotide group (III), 12 patients in octreotide plus sclerotherapy group (II) and 24 patients in sclerotherapy developed re-bleeding. Therefore complete control of bleeding at the end of 30 days period after trial was achieved in 156 of 180 (86.67%, 95 percent C.I.: 68-98%) in octreotide group, 176 of 196 (89%, 95 percent C.I.: 68-98%) in octreotide plus sclerotherapy, and 140 of 188 (74.5%, 95 percent C.I.: 68-98%) in sclerotherapy alone. The complete control of bleeding was better in the octreotide and/or in combination with sclerotherapy than sclerotherapy group. The difference was statistically significant (p=0.03).

There were significant differences among the three groups in respect of side effects. Retrosternal chest pain occurred in 71 patients (37%), fever in 73 (38%), and oesophageal ulcers in 38 patients of sclerotherapy group, whether alone or in combination. These side-effects were of transient nature and responded to symptomatic treatment. Twelve patients of octreotide group whether alone or in combination, developed transient nausea and abdominal pain. Octreotide group received less blood transfusion **(Table II)**, as compared to sclerotherapy. Hospital stay was 5.5 days with octreotide group (3-9 days) as compared to sclerotherapy alone (mean 6.7 days, range 4-11 days). Ninety- seven percent patients survived successfully in octreotide and in combination with sclerotherapy groups as compared to sclerotherapy only (94.6% survival).

Discussion

Esophageal variceal bleeding is a medical emergency with high risk of mortality. Therapy has four main purposes: control of initial haemorrhage, prevention of early bleeding, minimization of liver dysfunction and treatment of any complication caused by blood loss. The standard treatments are injection sclerotherapy and/or ligation; with balloon tamponade used as second line therapy in case if bleeding cannot be controlled by standard techniques. Octreotide therapy has been evaluated in rebleeding after sclerotherapy, as an adjunct to sclerotherapy or as an alternative to sclerotherapy for primary treatment of variceal bleeding.

In our study, infusion of octreotide showed significantly better control of bleeding than sclerotherapy (156/180, 176/196 versus 140/188) in cirrhotic patients. The difference in success rate was 13-15%(95% C.I. 8-60%) in favor of octreotide. Out of 188 patients in group I, 48 had re-bleeding (25.3%), in group II (196 patients) 20 (10.2%) had re-bleeding and out of 180 patients, re-bleeding was observed in 24 (13.3%). Our observation is consistent with the reported studies.[24,25] The success rate of sclerotherapy in controlling acute variceal haemorrhage was 74-95%. Shah *et al*[26] have also reported that the sclerotherapy control of bleeding was in 80.4%. Farooqi JI[27] observed immediate control of bleeding in 84%, re-bleeding in 18% and mortality in 8%. A meta-analysis has shown that sclerotherapy results in a significant (25%) reduction in overall mortality.[28] The earliest trial involving octreotide for acute variceal haemorrhage was conducted by McKee *et al*.[29] This was based on earlier demonstration that octreotide produced a 305 decrease in the porto-systemic pressure gradient.[30] They observed that within first 4 hours after admission bleeding was stopped in 18 out of 20 patients. The more recent randomized trial conducted by Hwang *et al*.[31] observed that bleeding was initially stopped in 21 out of 24 patients receiving octreotide, but 6 patients had re-bleeding. Other randomized trial has reported the control of bleeding in 78%, re-bleeding in 27% and death in 6%.[32] Successful control of bleeding was achieved in randomized trial by Sung *et al* in 84% of octreotide group.[33] In this trial, re-bleeding and mortality was 21% and 20% respectively. During the first 48 hours period of acute variceal bleeding, in another study,[34] the control of bleeding with octreotide was 85% and mortality was 3%. Sivri *et al*[35] evaluated the use of octreotide and found a control of bleeding, re-bleeding and mortality in 75%, 22% and 3% respectively. In our study, serious side effects associated with octreotide were insignificant as compared with sclerotherapy. Transient chest pain, fever, oesophageal ulcers and dysphagia were significantly associated with sclerotherapy, which resolved with symptomatic treatment. In our view octreotide appeared equally or superior over sclerotherapy in controlling bleeding and preventing in early re-bleeding.

Conclusion

Octreotide being cost effective and due to its easy availability is the first–line therapy for control of acute variceal bleeding and early re-bleeding either alone or as an adjuvant to sclerotherapy.

References

1. Bosch J, Burroughs AK. **Clinical manifestations and management of bleeding episodes in cirrhotic patients**. In: Bricher J, Benhamou JP, McIntyle N, Rizzeto M, Rodes J, (edi). **Clinical pharmacology**. 2nd ed. New York: *Oxford University Press* 1999: 671-93.
2. Burroughs AK, Mezzanotte G, Philips A, Mc Cormick PA, Mc Intyre N. *et al*. **Cirrhotic with variceal hemorrhage: the importance of the time interval between admission and start of analysis for survival and rebleeding rates**. *Hepatology* 1989; **9**: 801-7.
3. De Dombal FT, Clarke JR, Clamp SE, Malizia G, Kotwal

MR, Morgan AG. **Prognostic factors in upper GI bleeding**. *Endoscopy* 1986; **18**(suppl 2): 6-10.

4. Grahm DY, Smith JL. **The course of patients after variceal haemorrhage**. *Gastroenterology* 1981; **80**: 800-9.
5. Burroughs AK, Heygere F, Philips A, Mc Intyle N. **Predictive model for early failure to control variceal bleeding (abstract)**. *Hepatology* 1986; **6**:1153.
6. Northfield TC. **Factors predisposing to recurrent haemorrhage after acute gastrointestinal bleeding**. *BMJ* 1971: 26-8.
7. Pomier-Layragues G, Villenueve J, Willenis H, Huet PM, Marleu D. **Systemic and hepatic haemodynamics after variceal haemorrhage: effects of propranolol and placebo**. *Gastroenterology* 1987; **93**: 1218-24.
8. Vinel JP, Gassigneul J, Levade M, Boight JJ, Pascal JP. **Assessment of short-term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of porto hepatic gradient**. *Hepatology* 1986; **6**; 116-7.
9. Ready JH, Robertson AD, Golf JS, Rector WG. **Assessment of the risk of bleeding from oesophageal varices by continuous monitoring of portal pressure**. *Gastroenterology* 1991; **100**: 1103-10.
10. Panes J, Teres J, Bosch J, Rhodes J. **Efficacy of balloon tamponade in the tretment of bleeding gastric and oesophageal varices**. *Dig Dis Sci* 1988; **33**: 454-9.
11. Haddock G, Garden OJ, McKee RF, Anderson JR, Carter DC. **Oesophageal tamponade in the management of acute variceal haemorrhage**. *Dig Dis Sci* 1989; **34**: 913-8.
12. Pitcher JL. **Safety and effectiveness of the modified Sangstaken-Blakemoore tube: a prospective study**. *Gastrenterology* 1971; **61**: 291-8.
13. Bhargava DK, Dasarathy S, Atmakuri SP, Dwivedi M, **Comparative efficacy of emergency endoscopic sclerotherapy for active variceal bleeding due to cirrhosis of the liver, non-cirrhotic portal fibrosis and extrahepatic portal various obstruction**. *J Gastroenterol Hepatol* 1990; **5**: 432-7.
14. Bhargava DK, Dasarathy S, Sundaram KR, Ahuja RK. **Efficacy of endoscopic sclerotherapy on long-term management of oesophageal varices: a comparative study of results with cirrhosis of liver, non-cirrhotic portal fibrosis (NCPF), and extrahepatic portal venous obstruction (EHO)**. *J Gastroenterol Hepatol* 1991; **6**: 471-5.
15. Bhargava DK, Dwivedi M, Dasarathy S, Arora A. **Endoscopic sclerotherapy for portal hypertension due to extrahepatic obstruction: long-term follow-up**. *Gastrointestinal Endosc* 1989; **35**: 309-11.
16. Infante RC, Esanola S, Villeneuve JP. **Role of endoscopic variceal sclerotherapy in the long-term management of variceal bleeding: a meta analysis**. *Gastroenterology* 1989; **96**: 1087-92.
17. Kahn D, Jones B, Bornman PC, Terblanche J. **Incidence and management of complications after injection sclerotherapy: a ten year prospective evaluation**. *Surgery* 1989; **105**(2 pt1): 160-5.
18. Tsai YT, Lay CS, Lai KH. **A controlled trial of vasopressin plus nitroglycerin versus vasopressin alone in the treatment of bleeding oesophageal varices**. *Hepatology* 1986; **6**: 406-9.
19. Nader A, Grace ND. **Pharmacologic intervention during the acute bleeding episode**. *Clin North Am* 1999; **9**: 287-99.
20. Gimson AES, Westaby D, Hegarty J. **A randomized trial of vasopressin plus nitroglycerin in the control of acute variceal haemorrhage**. *Hepatology* 1986; **6**: 410-3.
21. Mottet C, Sieber CC, Neuer A, Drewe J, Fried R, Larsen F. *et al.* **Haemodynamic effects of somatostatin analog lanreotide in humans. Placebo–ranging echo– doppler study**. *Hepatology* 1998; **27**: 920-5.
22. Jenkins SA, Baxter JN, Corbett WA, Shields R. *et al.* **Effects of somatostatin analogue SMS 201–955 on hepatic haemodynamics in the pig and on intravariceal pressure in man**. *Br J Surg* 1985, **72**: 1009-12.
23. Andrew KB. **Pugh's modification of child's grading of the severity of liver disease, cited in "management of chronic liver disease"** In: Marinos Ella, Susan AJ, Humphrey JFH. **Nutrition-liver disorders**. Pakistan Edition–Medicine International.eds. 1994; **7**: 485-493.
24. Zuberi BF, Baloch Q. **Comparison of endoscopic variceal sclerotherapy and in combination with octreotide in controlling acute variceal haemorrhage and early rebleeding in patients with low risk cirrhosis**. *Am J Gastroenterol* 2000; **95**: 768-71.
25. **Drug topics red book 2000**. Montvale: *Medical Economics* 2000; 505-6.
26. Caps MT, Heelton WC, Johansen K. **Left upper quadrant devascularization for unshuntable portal hypertension.** *Arch Surg* 1996; **131**: 834-9.
27. Farooqi JI, Farooqi RJ, Najibul Haq, Siddiq-ur-Rehman, Mehmood S. **Treatment and outcome of variceal bleeding: a comparison of two methods**. *J Coll Physicians Surg Pakistan* 2000; **10**: 131-3.
28. Infante RC, Eanaola S, Villeneue JP. **Role of endoscopic variceal sclerotherapy in the long-term management of variceal bleeding; meta- analysis**. *Gastrenterology* 1989; **96**: 1087-92.
29. McKee RF, Garden OJ, Anderson JR, Carter DC. **A comparison of SMS 201-995 and oesophageal tamponade in the control of acute variceal haemorrhage**. *HBP Surg* 1992; **6**: 7-17.
30. McKee R. **A study of octreotide in oesophageal varices**. *Digestion* 1990; **45** (suppl 1): 60-5.
31. Hwang SJ, Lin HC, Chang CF, Lee FY, Lu CW, Hsia HC, *et al.* **A randomized controlled trial comparing octreotide and vasopressin in the control acute oesophageal variceal bleeding**. *J Hepatology* 1992; **16**: 320-5.
32. Silvain C, Carpentier S, Sautereau D, Czemichow B, Metreau JM, Fort E, *et al.* **Terlipressin plus transdermal nitroglycerine vs octreotide in the control of acute bleeding from oesophageal varices: a multicenter randomized trial**. *Hepatolgy* 1993;**18**: 61-5.
33. Sung JJ, Chung SC, Lai CW, Chank FK, Leung JW, Young MY, *et al.* **Octreotide infusion or emergency sclerotherapy for variceal haemorrhage**. *Lancet* 1993; **342**: 637-41.
34. Jenkins SA, Sheilds R, Davies M, Elias E, Turnbull AJ,

Bassendine MF, *et al.* **A multicentre randomized trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage.** *Gut* 1997; **41**: 526-33.

35. Sivri B, Oksuzoglu G, Bayraktar Y, Kayhan B. **A randomized trial from Turkey comparing octreotide vs injection sclerotherapy in acute variceal haemorrhage.** *Hepatol Gastroenterol* 2000; **47**: 1310-4.