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Comparison of Endoscopic Variceal Sclerotherapy Alone and in Combination With Octreotide in Controlling Acute Variceal Hemorrhage and Early Rebleeding in Patients With Low-Risk Cirrhosis

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OBJECTIVE: Efficacy of endoscopic variceal sclerotherapy (EVS) alone and in combination with octreotide in controlling acute variceal bleeding and preventing early rebleeding was compared in a double-blind study.

METHODS: Consecutive patients presenting with variceal bleeding with low-risk liver cirrhosis were randomized into two groups. Group A received EVS with 3–5 ml of ethanolamine oleate per varix and placebo injection at 50 μg/h; group B received the combined therapy of EVS and octreotide 50 μg/h continuously for 5 days. A total of 70 patients (mean age, 38.4 $\pm$ 8.6 yr) were selected for the study, which included 56 men (mean age, 37.9 $\pm$ 8.5 yr) and 14 women (mean age, 40.6 $\pm$ 9.0 yr). Thirty-five patients were allocated in each group.

RESULTS: In group A bleeding was controlled in 30 patients (85.7%) and in group B in 33 (94.3%) ($p = 0.24$). The number of patients who rebled during the first 5 days after sclerotherapy was eight (22.9%) and two (5.7%) in groups A and B, respectively ($p = 0.04$). The mean packs of blood transfused to the patients of groups A and B were 2.1 $\pm$ 1.2 packs and 1.5 $\pm$ 0.7 packs, respectively ($p = 0.03$). The mean hospital stay of group A was 6.6 $\pm$ 1.3 days, whereas that in group B was 5.9 $\pm$ 1.2 days ($p = 0.04$). One patient from each group died during the course of the study.

CONCLUSIONS: No significant difference was observed in arrest of bleeding in the two groups, but episodes of early rebleeding, blood transfusions, and hospital stay was significantly less in group B. (Am J Gastroenterol 2000;95: 768–771. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Management of the variceal bleeding is a challenge to the gastroenterologists and physicians. Many methods are in practice with variable results (1, 2). Somatostatin and its analogue octreotide are being used in the management of the varices. Somatostatin was originally isolated from the hypothalamus, but subsequently has been found throughout the entire GI tract (3). Somatostatin has a very short plasma half-life and requires administration by continuous infusion to maintain therapeutic levels. Stable long-acting analogues, like octreotide, have been shown to have a plasma half-life of 113 min (3). The mechanisms of action of somatostatin and octreotide in the therapy of bleeding esophageal varices are mainly mediated by a splanchnic vasoconstrictive effect (3). Furthermore, gastric acid suppression and potential enhancement of platelet aggregation may contribute to the beneficial outcome after treatment of esophageal varices with somatostatin (3). The problem of early rebleeding in the management of varices has gained much importance as about 50% of patients rebleed and its attributable mortality is reported as high as 30% in the early weeks of therapy (4, 5). Recently, many studies have been published with varying results regarding the efficacy of these drugs in the management of variceal bleeding (6). In this prospective study, we compared the efficacy of endoscopic variceal sclerotherapy (EVS) alone and in combination with octreotide in controlling acute variceal bleeding and early rebleeding.

MATERIALS AND METHODS

Patients

Consecutive patients presenting with a first episode of variceal bleeding from esophageal or gastric junctional varices between December 1, 1994, and April 30, 1998, to Almas GI Complex Larkana and Medical Department of Chandka Medical College Larkana were recruited into the study. Patients with massive tense ascites not responding to diuretics, patients presenting in Child's class C, patients with known hypersensitivity to octreotide, patients in chronic encephalopathy, and those who have already had a session of EVS earlier were excluded from the study.

Active bleeding was defined if at least one of the following criteria was present: 1) hematemesis or melena in the previous 3 h; 2) hematemesis or melena $>$3 h before if the systolic blood pressure was $<$80 mm Hg; and 3) presence of fresh blood in stomach on emergency esophagastroduodenoscopy (EGD).

The source of bleeding was defined by the following

criteria (7): 1) active bleeding from a lesion; 2) signs of recent bleeding from a lesion (white nipple sign or adherent clot); and 3) single lesion without any other potential source of bleeding.

Bleeding source was labeled undefined if the EGD was not feasible at the time of admission or was delayed for >24 h and no active bleeding or signs of recent bleeding were found.

Bleeding control was defined as (7, 8): 1) absence of hematemesis and melena for 24 consecutive h; 2) stable Hb concentration and hemodynamic conditions for 24 consecutive h without blood transfusions; or 3) absence of blood at control EGD.

Blood was transfused only if Hb levels were ≤8.0 g/dl. In case of rebleeding, patients were rescoped within 24 h of rebleeding.

Informed consent was obtained from patients who were conscious and oriented, and it was obtained from relatives/attendants of those who were not oriented.

Randomization

Patients were randomly allocated into two groups with the help of a random number table. A double-blind protocol was used. Treatment type was sealed in the cardboard cartons containing octreotide or placebo ampules of similar appearance. The boxes were serially numbered and were given allotted code numbers as per randomization. The randomization code list was kept in a locker and opened only after completion of trial.

Study Protocol

After oral informed consent has been obtained 10-ml of blood was collected for complete blood cell count, liver function test, A:G ratio, PT, urea, creatinine, electrolytes, and cross-matching. All patients were endoscoped and only patients with varices were selected. Clinical data from the emergency room evaluation, including the history, results of physical examination, results of investigations and endoscopy were recorded as part of detailed protocol by the physicians in the emergency room. Patients were evaluated for Child-Pugh score of the severity of liver disease. Patients were started with the treatment protocol as per the randomization list and the corresponding treatment box opened. Group A received EVS with 3–5 ml of ethanolamine oleate per varix with a total dose of 20 ml per session (9) and placebo injections at the dose of 50 μg/h for 5 days. Group B received EVS as described for group A and 50 μg/h of octreotide continuously for 5 days. Patients were followed until discharge from the hospital. Study endpoints were discharge from the hospital or death. All patients received lansoprazole 30 mg *p.o.* for at least 2 wk after EVS therapy. Patients who developed rebleeding were rescoped within 24 h and if the source was variceal, the patients were injected again. Patients with esophageal ulcers were advised to take succralfate syrup 2 g *b.i.d.* 1 h before meal for at least 8 wk.

Table 1. Age and Etiological Pattern of Liver Disease

Characteristics	Group A (n = 35)	Group B (n = 35)
Age (mean ± SD yr)	38.2 ± 9.4	38.7 ± 7.8
HbsAg + ve	28 (80.0%)	26 (74.3%)
HCV + ve	5 (14.3%)	6 (17.1%)
Alcohol consumption (>100 ml/day)	2 (5.7%)	3 (8.6%)

Outcome Measures

1. Control of bleeding after sclerotherapy.
2. Rebleeding during the first 5 days after sclerotherapy.
3. Number of blood packs transfused during hospitalization.
4. Duration of hospitalization.

Analytic Techniques

Endoscopy was done using Fujinon F-7 fiberoptic endoscope (Fujinon Diagnostics, Japan), observing standard procedure and precautions (10). Xylocaine 10% spray (Astra Pharmaceuticals, UK) was used for anesthesia. Varices were injected with 3–5 ml of ethanolamine oleate per varix with maximum total dose of 20 ml per session (11). No sedation was used during the procedure. The complete blood cell count were done on Sysmex K-4500 (Toa Medical Electronics Co., Japan) automated cell counter; electrolytes were done by Ciba-Corning 644 ISE electrolyte analyzer (Ciba-Corning Diagnostics Ltd.). The biochemistry was done using Boehringer Mannheim reagents on BM Photometer 5010 (Boehringer Mannheim Diagnostics, Germany).

Statistical Analysis

All results for continuous variables are expressed as means ± SD. The Pearson's χ^2 test and *t* test were used to compare continuous variables between different groups. The *p* values for comparisons of categorical variables were generated by the χ^2 test for proportions with appropriate degrees of freedom, and *p* values of <0.05 according to the two-sided McNemar test were considered to indicate statistical significance. All calculations were done with SPSS 8.0 (SPSS, Chicago, IL).

RESULTS

A total of 138 patients presented with history of acute hematemesis of <24 h in the studied duration. One hundred sixteen were endoscoped within 24 h of admission and 22 patients died before EGD. Of these 94 patients, 70 patients (mean age, 38.4 ± 8.6 yr) fulfilling the selection criteria were included. These included 56 men (mean age, 37.9 ± 8.5 yr) and 14 women (mean age, 40.6 ± 9.0 yr). Thirty-five patients were allocated in each group. Mean ages (± SD) in group A was 38.2 ± 9.4 yr and that in group B was 38.7 ± 7.8 yr. No significant difference in the age of two groups was observed. The cause of liver disease in the selected patients is given in Table 1 and the endoscopic findings of these patients in Table 2.

Table 2. Details of Endoscopic Findings in the Two Groups

Endoscopic Findings	Group A	Group B
Escophageal varices	35 (100%)	35 (100%)
Gastric fundal varices	15 (42.9%)	19 (54.3%)
Gastric junctional varices	20 (57.1%)	18 (51.4%)
Congestive gastropathy	26 (74.3%)	24 (68.6%)

Bleeding Control

In group A bleeding was controlled effectively in 30 patients (85.7%), whereas it could not be controlled in five (14.3%). In group B, hemostasis was achieved in 33 patients (94.3%), whereas bleeding could not be controlled in two (5.7%) ($p = 0.24$).

Rebleeding

The number of patients who rebled during the first 5 days after sclerotherapy was eight (22.9%) and two (5.7%) in groups A and B, respectively. On repeat endoscopy the source of bleeding was found to be varices in all patients and no other cause was found. Statistical analysis by two-sided Pearson's χ^2 test gave $p = 0.04$ showing a significant difference between the two groups. Analyzing the patients after excluding for uncontrolled initial bleeders, eight of 30 in group A and two of 33 in group B patients rebled (Pearson's χ^2 with continuity correction, $p = 0.06$ showing only borderline significance). But if the data are analyzed considering the dual endpoints of initial bleeding control and prevention of early rebleeding, then by Pearson's χ^2 ($p = 0.001$, two-sided) gives a highly significant difference in the outcome of the two groups.

Transfusions

The mean packs of blood transfused to the patients of groups A and B were 2.1 ± 1.2 packs and 1.5 ± 0.7 packs, respectively. Statistical analysis by two-tailed *t* test shows $p = 0.03$ and 95% confidence interval (CI) of mean were 0.58 and 1.03. The number of transfusions received by group B patients was significantly less. The amount of blood transfused in the patients who rebled was 3.3 ± 0.9 packs and that in those who did not was 1.6 ± 0.8 packs ($p < 0.001$; 95% CI −2.4 and −1.0).

Duration of Hospitalization

The mean hospital stay of group A was 6.6 ± 1.3 days, whereas that in group B was 5.9 ± 1.2 days. Statistical analysis by two-tailed *t* test shows $p = 0.04$ and 95% CI 0.029 and 1.228. The hospital stay in group A was significantly more than in group B.

Child-Pugh Score

Child-Pugh scoring for the severity of liver disease done at the time of induction into the study shows that the mean ± SD score in group A was 5.9 ± 0.6 and in group B was 5.7 ± 0.8. No statistical difference was observed by two-tailed *t* test for equality of means in two groups ($p = 0.5$; 95% CI −0.237 and 0.466).

Table 3. Side Effects Seen After Sclerotherapy

Side Effects	Group A	Group B
Pneumonia	2 (5.7)	1 (2.9)
SBP	1 (2.9)	1 (2.9)
Chest pain	3 (8.6)	2 (5.7)
Pharyngeal irritation	5 (14.3)	7 (20.0)
Dysphagia	3 (8.6)	4 (11.4)
Pleural effusion	0	1 (2.9)

SBP = spontaneous bacterial peritonitis.

Mortality

One patient from each group died during the course of the study. One patient from group A died due to recurrent variceal bleeding and succumbed to portosystemic encephalopathy. The second patient was from group B, who also developed encephalopathy.

Side Effects

The side effects after EVS therapy in the studied patients are given in Table 3. No significant side effect related to octreotide was observed.

DISCUSSION

In recent years several studies have shown the efficacy of giving octreotide in the management of variceal hemorrhage along with EVS (12, 13). In the present prospective double-blind study, the efficacy of controlling variceal hemorrhage by EVS alone and in combination with octreotide is compared, as well as the rate of rebleeding, length of hospital stay, and the number of packs transfused. In the present series no significant difference was seen in the arrest of variceal bleeding with EVS and placebo. But the combination of EVS and octreotide has shown significant benefit in frequency of rebleeding, less transfusions, and shorter length of hospital stay.

In the current series the mean hospital stay was longer in group A compared to group B patients. They required more transfusions and their encephalopathy grade was increased. They required intensive treatment and their hospital stay was extended until they showed improvement in their encephalopathy grade and they remained hemodynamically stable for 48 h.

Octreotide alone has also been shown to be as effective in controlling the variceal hemorrhage as sclerotherapy (14). In a series reported elsewhere (15), no significant difference in bleeding control with variceal ligation alone and in combination with octreotide has been reported ($p = 1.0$), but significant difference were observed in the rates of rebleeding (38% *vs* 9%; $p = 0.0007$). Better efficacy and lower complication rates of octreotide have been reported in various studies (16–18). In a recent study the rebleeding rate in patients without octreotide is reported at 50% (19), but we found it at 22.9%. This could be attributable to the short duration of observation period (6 wk *vs* 5 days) and lower Child-Pugh score in our study. The cause of liver disease is

also different in our study than the one reported by D'Amico *et al.* (19). We found a low percentage of alcohol-related disease (this may be because of religious beliefs) and a higher frequency of hepatitis B (there is a very high prevalence in the upper portion of the Sindh province in Pakistan).

In contrast, some gastroenterologists have not found any beneficial effect of using octreotide with EVS in bleeding control and prevention of early rebleeding (20). The majority of the investigators (16–18, 21, 22) believe that octreotide shows promising results when used in combination with EVS. Octreotide has also been shown to have a beneficial effect in controlling the variceal bleeding until sclerotherapy, banding, or ligation is also added (23–25).

Because of the unavailability of the necessary data at the time of initiation of the study, correct sample size estimations could not be performed and the study was stopped when 70 patients were inducted and the code of randomization was opened.

We conclude that the combination of EVS and octreotide is the better treatment option in patients who are fit to undergo this procedure and the addition of octreotide significantly reduces the risk of early rebleeding.

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REFERENCES

1. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta analysis. Ann Intern Med 1995;123:280–7.
2. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. Hepatology 1995;22:466.
3. Hanisch E, Doertenbach J, Usadel KH. Somatostatin in acute bleeding oesophageal varices. Pharmacology and rationale for use. Drugs 1992;44(suppl 2):24–35; discussion 70–2.
4. D'Amico G, Morabito A, Pagliaro L. Six-week prognostic indicators in upper gastro-intestinal haemorrhage in cirrhosis. In: Dianzani MU, Gentilini P, eds. Frontiers in gastrointestinal research: Chronic liver disease. Basel: Karger, 1986:247–57.
5. Smith JL, Graham DY. Variceal hemorrhage. A critical evaluation of survival analysis. Gastroenterology 1982;82:968–73.
6. Planas R, Quer JC, Boix J, et al. A prospective randomized trial comparing somatostatin and sclerotherapy in the treatment of acute variceal bleeding. Hepatology 1994;20:370–5.
7. De Franchis R, Pascal JP, Ancona E, et al. Definitions, methodolgy, and therapeutic strategies in portal hypertension. A consensus development workshop, Baveno Lake Maggiore, Italy, April 5–6, 1990. J Hepatol 1992:15:256–61.
8. Burroughs AK, Alexandrino P, Cales P, et al. "Sore points." A rereview of the points where there was disagreement at Baveno I, and an attempt to reach consensus. In: De Franchis R, ed. Portal hypertenstion II, Proceedings of the 2nd Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford: Blackwell Science, 1996:19–17.
9. Ethamolin package insert (Reed, Carnrick, Canada), Rev, Rec 3/95, 1993.
10. Kirk RM. Diagnostic upper gastrointestinal endoscopy. In: Dudley H, Paries WJ, Cartes DC, eds. Rob and Smiths's operative surgery, 4th ed. London: Butterworths, 1983:1–7.
11. Kang JH, Kambayashi J, Sakon M, et al. Mechanism of the haemostatic effect of ethanolamine oleate in the injection sclerotherapy for oesophageal varices. Br J Surg 1987;74: 50–3.
12. Sung JJ. Non surgical treatment of variceal hemorrhage. Br J Hosp Med 1997;57:162–6.
13. Chan LY, Sung JJ. Review article: The role of pharmacotherapy for acute variceal hemorrhage in the era of endoscopic haemostasis. Aliment Pharmacol Ther 1997;11:45–50.
14. Jenkins SA, Shields R, Davies M, et al. A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. Gut 1997;41:526–33.
15. Sung JJ, Chung SC, Yung MY, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. Lancet 1995;346:1666–9.
16. Avgerinos A, Armonis A, Raptis S. Somatostatin and octreotide in the management of acute variceal hemorrhage. Hepatogastroenterology 1995;42:145–50.
17. Cello JP. Medical management of acute variceal hemorrhage. Int Surg 1995;80:82–6.
18. Gotzsche PC, Gjorup I, Bonnen H, et al. Somatostatin vs placebo in bleeding oesophageal varices: Randomised trial and meta analysis. BMJ 1995;310:1495–8.
19. D'Amico G, Politi F, Morabito A, et al. Octreotide compared with placebo in a treatment strategy for early rebleeding in cirrhosis. A double blind, randomized pragmatic trial. Hepatology 1998;28:1206–14.
20. Primignani M, Andreoni B, Carpinelli L, et al. Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: A randomized, double blind, placebo controlled, multicenter trial. New Italian Endoscopic Club. Hepatology 1995;21:1322–7.
21. Williams SG, Westaby D. Management of variceal hemorrhage. BMJ 1994;308:1213–7.
22. Holstege A, Palitzsch KD, Scholmerich J. The role of drug treatment in variceal bleeding. Digestion 1994;55:1–12.
23. Sung JJ, Chung SC, Lai CW, et al. Octreotide infusion or emergency sclerotherapy for variceal hemorrhage. Lancet 1993;342:637–41.
24. Cello JP, Chan MF. Octreotide therapy for variceal hemorrhage. Digestion 1993;54(suppl 1):20–6.
25. Avgerinos A. Approach to the management of bleeding esophageal varices: Role of somatostatin. Digestion 1998;59(suppl 1):1–22.