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Sclerotherapy plus octreotide versus sclerotherapy alone in the management of gastro-oesophageal variceal hemorrhage

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SCLEROTHERAPY PLUS OCTREOTIDE VERSUS SCLEROTHERAPY ALONE IN THE MANAGEMENT OF GASTRO-OESOPHAGEAL VARICEAL HEMORRHAGE

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Background: There are different ways for controlling oesophageal variceal bleed which include pharmacological and endoscopic methods. In this study we compare efficacy of octreotide (50 μg/hr for 48 hours) combined with sclerotherapy versus sclerotherapy alone in patients with acute bleeding from gastro-oesophageal varices (GOV). **Methods:** It was a randomized clinical controlled trial conducted at Aga Khan University Hospital, Karachi, from January1997 to December 1998. We evaluated the role of octreotide (50 μg/hr for 48 hours) combined with sclerotherapy versus sclerotherapy alone in a total of 105 adult cirrhotic patients who had acute bleeding from GOV. Patients were assigned to receive octreotide plus sclerotherapy or sclerotherapy alone. Primary outcome measure was 5-day survival without rebleeding. The hospital stay in days and blood transfusion requirements were also compared in the combined treatment group versus sclerotherapy alone group. **Results:** Initial control of bleeding was achieved in 46/51 (90.2%) patients who received combined treatment compared to 41/54 (75.9%) patients (p=0.05) in sclerotherapy alone group. Rebleeding after the first 48 hours was less in the octreotide treated patients 2/46 vs. 8/41 patients (p=0.003). The octreotide treated patients had a better short term (5 days) survival without rebleeding 44/51 vs. 33/54 (p=0.003) and shorter hospital stay, 5.31 ± 3.87 days vs. 6.63 ± 3.86 (p=0.008) as compared to sclerotherapy alone group. The blood transfusion requirement was also less in the combined treatment group 3.88 ± 2.80 vs. 5.37 ± 3.15 units (p=0.002). **Conclusion:** 1) The combination of sclerotherapy and octreotide infusion over 48 hours is more effective than sclerotherapy alone in the treatment of acute variceal bleeding and prevention of early rebleed in cirrhotic patients. 2) It leads to shorter hospital stay and 3) less blood transfusion requirements. 4) Although early survival without rebleeding is improved, the overall mortality at the end of hospitalization period is similar in the two groups of treated patients.

Key words: Varices, Esophageal, Sclerotherapy, Octreotide, Cirrhosis.

INTRODUCTION

Hemorrhage from gastroesophageal varices is an important complication of portal hypertension due to cirrhosis of liver. Despite the improvements in therapeutic techniques employed in the management of acutely bleeding varices, the mortality remains in the range of 30-50% [1-6]. Sclerotherapy is considered an efficient modality of treating acutely bleeding varices in most institutions of the world [7]. The effectiveness of this technique depends on the availability of well-trained personnel and sophisticated instruments.

Bleeding is controlled in the short term in upto 90% of patients [8, 9]. The rate of rebleeding in such patients is high, upto 50% in the short term following admission. It has therefore been recommended that treatment for variceal bleed should not only be aimed at arresting the acute bleed but also at preventing early rebleed and thus improving morbidity and mortality. Various techniques have been used in the treatment of variceal hemorrhage including pharmacological measures, balloon tamponade, band ligation of varices; trans-jugular intra-hepatic portosystemic shunts (TIPSS) and emergency surgery apart from sclerotherapy. Combination of various procedures have also been tried so as to improve outcome in acutely bleeding patients.

Octreotide is a synthetic somatostatin analogue which is a potent vasoconstrictor agent in the splanchnic circulation without any significant systemic hemodynamic effects and has been used to control hemorrhage from ruptured gastroesophageal varices. Reduction in portal pressure after octreotide has been shown [10] and a decrease in azygos blood flow in patients with cirrhosis has also been consistently reported.[11-13] Octreotide has been compared with balloon tamponade [10], Vasopressin [14], Glypressin [15, 16] and sclerotherapy [17, 18]. Two recent studies, [19, 20] on the use of octreotide in combination with sclerotherapy in an attempt to improve outcome in the acutely bleeding patients have shown encouraging results. The available literature has used octreotide for a longer time period (5

days) in an attempt to improve outcome in the acutely bleeding varices. There is paucity in literature on short term use of octreotide (48 hours) in the treatment of acute gastro-oesophageal variceal bleed [21].

In a randomized study, we have compared sclerotherapy alone with a combination of sclerotherapy and octreotide infused over 48 hours in controlling acute variceal bleed and preventing early rebleeding in patients with cirrhosis of liver.

MATERIAL AND METHODS

This study was conducted at Aga Khan University Hospital (AKUH), Karachi from January 1997 to December 1998. It was a randomized clinical controlled trial. A total of 105 patients were enrolled into the study. Fifty-one patients received octreotide plus sclerotherapy whereas 54 patients received sclerotherapy treatment alone.

All adult patients admitted to the AKUH with a history of hematemesis or melena (or both) within 24 hours prior to admission were evaluated. Cirrhosis of the liver had either been diagnosed previously or on current admission on the basis of clinical signs of chronic liver disease such as ascites, palmar erythema, spider angiomas, splenomegaly and biochemical evidence of derangement of liver function, abdominal ultrasound and / or liver biopsy where possible.

An upper gastrointestinal endoscopy was done within 12 hours of admission, following resuscitation. Patients were enrolled in the trial if they were found to have active esophageal variceal bleeding; active esophageal variceal bleeding was taken as spurt or ooze from a varix seen at endoscopy. Non-bleeding esophageal varices with signs of recent bleed in the upper gastrointestinal tract like presence of blood, red marks on varices and no other source of upper gastrointestinal bleed were also enrolled.

Patients were excluded from the study if they had had previous sclerotherapy within the last eight days; evidence of severe liver failure i.e. prothrombin time greater than 10 seconds prolong, serum albumin less than 1.5 grams per d/l, serum bilirubin greater than 5 mg% and / or significant impairment of renal function i.e. serum creatinine greater than 4 mg%. Age above 85 years and non-cirrhotic portal hypertension were also considered as exclusion criteria.

A complete blood count including hemoglobin, white blood cell count, platelet count, and hematocrit, blood urea nitrogen, serum creatinine, blood sugar and electrolytes were done initially and repeated if needed during hospital stay of patients. Liver function tests of all patients were also done on admission to assess the degree of impairment of liver function. Endoscopic esophageal variceal sclerotherapy was performed with 3-5 ml of 5% injection ethanolamine oleate per varix (total of 20 ml) during initial endoscopy. Randomization was carried out after initial endoscopy. A sealed envelope containing the treatment option was opened and treatment given accordingly. Patients were distributed in two arms; one arm was given octreotide infusion in a dose of 50 mcg/hr and other was started on normal saline infusion as placebo for 48 hours in a randomized manner. Supportive measures like lactulose, I/V fluids, oxygen etc were administered where indicated. Both groups received packed cells and / or fresh frozen plasma as and when required. We did not injected the cardia varix as they were not actively bleeding.

Patients, who rebled evidenced by a drop in systolic BP of > 20 mm Hg with a rise in pulse rate of > 110/minute or a drop in > 2 gm of hemoglobin, were re-endoscoped and repeat sclerotherapy done. Failure of control of bleeding following second sclerotherapy session led to surgical referral and emergency surgery where possible.

The primary outcome measure was survival without rebleeding at 5 days after sclerotherapy which was taken as either control of acute variceal bleeding, without rebleeding or death. The other end points were to determine the blood transfusion requirements following endoscopy and difference in hospital stay in the two groups of treated patients. Variceal bleeding was considered to have been controlled, if the blood pressure stabilized and there was no drop in systolic blood pressure exceeding 20 mmHg (supine) and the hemoglobin concentration and hematocrit also stayed stable after the initial control of hemostasis.

Statistical analysis was performed on all patients who underwent randomization. The two treatment groups were compared on the basis of primary outcome measure using Mantel-Haenszel test. Various prognostic variables were tested against the primary outcome measure using Mantel-Haenszel test and Pearson's Chi Square test wherever appropriate and difference of means was compared by using independent sample t-test. All p values were two tailed, p values of equal to or less than 0.05 were considered to indicate statistical significance. Analysis was performed using SPSS 10.0 version.

This study was approved by the ethical review committee of AKUH and any ethical concern was dealt before the start of study. Patients were allocated to sclerotherapy along with octreotide and sclerotherapy with placebo (normal saline) by simple sealed envelope randomization containing the treatment groups on one to one basis to reduce possibility of bias. There was no conflict of interest among any of the authors.

RESULTS

A total of 105 patients were enrolled into the study after the inclusion and exclusion criteria were met. Fifty-one patients received octreotide plus sclerotherapy whereas 54 patients received sclerotherapy treatment alone. The two groups had similar baseline characteristics (table 1). The mean total dose of 5% ethanolamine oleate injected per patient was also similar in the two groups. Twenty-four patients in the combined treatment group and 27 in the sclerotherapy alone treated group had inactive bleeding at initial endoscopy, respectively. After five days, the proportion of patients who had survived without rebleeding was significantly higher in the octreotide treated group, 44 of 51 patients (86.82%) vs. 33/54 (61.1%) in the sclerotherapy alone group; p=0.003 (table 2). Similarly, the rate of survival at five days without rebleeding was higher in the octreotide treated patients than in the sclerotherapy alone, group when the data were analyzed according to the Child-Pugh class of hepatic function. However, the difference was not statistically significant in the Child-Pugh class A patients (table 2). The difference in survival remained significant after simultaneous adjustment for the Child-Pugh class of hepatic function, the presence or absence of acute bleeding at initial endoscopy, and previous treatment with propranolol or the absence of such treatment, sex, hemoglobin, and creatinine (p=0.001 by the Mantel-Haenszel test). In patients who rebled after the initial control of bleeding, 2 in combined treatment and 8 in sclerotherapy alone underwent re-secelrotherapy; none in the combined group and 2 in the sclerotherapy group were referred for surgery.

Table 1: Demographic features in two Study Groups

Characteristics	Sclerotherapy + Octreotide (n=51)	Sclerotherapy alone (n=54)
Age Mean (yrs)	49.5 ±14.2	50 ± 12.3
Sex (M:F)	32:19	36:18
Etiology: Viral	49	52
Alcoholic	02	02
Child pugh class A	09	07
B	31	33
C	11	14
Active EV bleed	23	24
Gastric Varices	04	03
Hepatic Encephalopathy		
Absent	33	38
Stage I-II	15	14
Stage III-IV	02	02
Bilirubin (mg/dl)	1.44 ± 0.83	1.85 ± 0.90
Albumin (gm/dl)	2.49 ± 0.61	2.34 ± 0.53
Creatinine (mg/dl)	1.12 ± 0.44	1.29 ± 0.68
Prothrombin Time (Secs. Prolonged)	3.73 ± 1.56	4.28 ± 2.17
Hemoglobin (gm%)	8.54 ± 1.97	8.92 ± 1.75
Interval b/w start of bleeding & endoscopy	All within 24 hrs	All within 24 hrs.
Previous Propranolol therapy	17	15

Table 2: Comparison of Outcomes in the Two Study Groups

Outcomes	Sclerotherapy + Octreotide n=51 (%)	Sclerotherapy alone n=54 (%)	p-values
Controlled bleeding in 24 hrs.	46 (90.2%)	41 (76%)	0.05
Rebleeding b/w 24 hrs – 5 days	02 (3.9%)	08 (14.8%)	0.003
Controlled bleeding during hospital stay	37 (72.5%)	28 (51.8%)	0.03
Survival without rebleeding @ 5 days			
Child pugh class:	44 (86.3%)	33 (61%)	0.003
A			
B	08/09	06/07	-
C	27/31	22/33	-
Total blood transfusions: (Units)	09/11	05/14	0.05

Death with uncontrolled bleeding	3.88 ± 2.80	5.37 ± 3.15	0.002
Death with controlled bleeding	07 (13.7%)	09 (16.6%)	NS
Hospital Stay (days)	03 (5.8%)	03 (5.5%)	NS
	5.31 ± 3.87	6.63 ± 3.86	0.008

NS= Not Significant

The total number of units of blood transfused during hospital stay of the patients following endoscopy was significantly less in the octreotide treated patients than the sclerotherapy group (mean no. of units 3.88 ± 2.80 vs. 5.37 ± 3.15; p=0.002). The hospital stay was similarly shorter in the octreotide treated patients than sclerotherapy alone treated patients (5.31 ± 3.87 days vs. 6.63 ± 3.86 days; p=0.008).

Logistic regression analysis, incorporating all the characteristics in table 1 indicated that the factors independently associated with survival without rebleeding at 5 days were the treatment assigned (p=0.002) and the presence of active esophageal variceal bleeding (p=0.02).

DISCUSSION

Bleeding from gastroesophageal varices is associated with a major risk of death.[22,23] Currently available modalities of treatment such as sclerotherapy help control bleeding in up to 90% of patients.[8, 10] However, the risk of rebleeding and complications is high. Hence, there is a need for use of adjuvant measures to improve the mortality rate as well as decrease the risk of rebleeding in cirrhotic patients.

In this, randomized clinical trial involving 105 patients, we have evaluated efficacy of octreotide infusion given to 51 patients intravenously for short period (48 hours), following sclerotherapy for the control of acute gastroesophageal variceal bleeding in a group of patients suffering from cirrhosis of the liver, mostly (96%) due to viral causes. Octreotide treated group was seen to be associated with a significantly higher rate of survival without rebleeding at 5 days compared to the sclerotherapy alone group. This finding has been demonstrated in other studies but most of these studies have used octreotide infusion for 5 days.[24-26] In our setting where cost constraint is a major problem, short duration of octreotide infusion as shown in our study, can be as effective as 5 day treatment. The difference in control of bleeding and rebleeding is statistically significant, however, only in the child B and C class of patients. This is because such patients are at a higher risk of rebleed than child A class of patients and more likely to benefit from an adjuvant treatment. The overall death rate at the end of the hospitalization period is however similar in the two groups of treated patients (Table 2). This means that octreotide use for a 48 hours period did not significantly alter the course of events after the first 5 days following start of treatment.

We have used octreotide intravenously as an infusion for a 48 hour period following sclerotherapy. Besson et al[19] and Zuberi and Baloch [20] in their published studies have maintained the infusion for five days. This length of time would increase the cost of patient care and add to the burden on health care resources of the unit, in a third world country like Pakistan by a large proportion. We have shown that using the medication for a shorter period maintains the benefit of control of bleeding after discontinuation of treatment. This may be because the risk of rebleed is maximal in the first 48 hours after a bleed and declines thereafter[22,23]. In a study reported from Peshawar[27] author has compared octreotide alone in a dose of 25 ug / hour infusion followed by 50 ug / hour for another 48 hour, with injection sclerotherapy which is found effective in only first 24 hours but not at all beyond that point although the treatment was given for 3 days. In this study every 6th patient would need sclerotherapy after 24 hours along with a possibility to restart vasoactive substance which can be expensive, time consuming approach rather than a cost effective way.

The blood transfusion requirement as well as hospital stay of the surviving patients is also decreased in our study, when octreotide is used for only 48 hours as compared to other study where it is used for five or more days.[28] This is of tremendous importance in situations where blood and blood products as well as hospital beds are in short supply.

Our study has clearly demonstrated benefit of a short term pharmacological therapy in conjunction with injection sclerotherapy, which is simple to use, devoid of major side effects, relatively cheap and non-invasive in a patient care area where a lot of work is being done worldwide to find ways and means of improving outcome following treatment. There is still a need to devise adjuvant treatment to be used with sclerotherapy, which could improve late mortality following gastroesophageal variceal bleed.

CONCLUSIONS

- Octreotide infusion for 48 hours in conjunction with injection sclerotherapy compared with sclerotherapy alone improves initial control of bleeding and bleeds free survival at five days.
- There is significant decrease in the requirement of packed red blood cells and blood product transfusions in patients where octreotide is used as an adjunct treatment along with injection sclerotherapy.
- Combination of octreotide with sclerotherapy leads to shorter hospital stay as compared to sclerotherapy alone treatment.

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