Addition of Somatostatin After Successful Endoscopic Variceal Ligation Does not Prevent Early Rebleeding in Comparison to Placebo: A Double Blind Randomized Controlled Trial

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Background: **Efficacy of endoscopic sclerotherapy in controlling acute variceal bleeding is significantly improved when vasoactive drug is added. Endoscopic variceal ligation (EVL) is superior to sclerotherapy. Whether efficacy of EVL will also improve with addition of somatostatin is not known. We compared EVL plus somatostatin versus EVL plus placebo in control of acute variceal bleeding.** ***Methods:*** **Consecutive cirrhotic patients with acute esophageal variceal bleeding were enrolled. After emergency EVL, patients were randomized to receive either somatostatin (250 mcg/hr) or placebo infusion. Primary endpoint was treatment failure within 5 days. Treatment failure was defined as fresh hematemesis ≥2 h after start of therapy, or a 3 gm drop in Hb, or death.** ***Results:*** **61 patients were enrolled (EVL plus somatostatin group, n = 31 and EVL plus placebo group, n = 30). The baseline characteristics were similar. Within the initial 5-day period, the frequency of treatment failure was similar in both the groups (EVL plus somatostatin group 8/31 [26%] versus EVL plus placebo group 7/30 [23%]; *P* = 1.000). The mortality was also similar in the two groups (3/31 [10%] vs. 3/30 [10%]; *P* = 1.000). Baseline HVPG ≥19 mm Hg and active bleeding at index endoscopy were independent predictors of treatment failure.** ***Conclusions:*** **Addition of somatostatin infusion to EVL therapy does not offer any advantage in control of acute variceal bleeding or reducing mortality. The reason for this may be its failure to maintain sustained reduction in portal pressure for five days. Active bleeding at index endoscopy and high baseline HVPG should help choose early alternative treatment options.**

Trial registered with ClincalTrials.gov vide NCT01267669. **(J Clin Exp Hepatol 2015;5:204–212)**

Variceal Bleeding

Acute variceal bleeding (AVB) is an important complication of cirrhosis.[1] With the use of vasoactive agents, endoscopic therapy, and antibiotics, the overall prognosis has improved in patients with AVB.[2,3] However, it is still associated with high rates of early rebleed and mortality.[2,4]

Standard treatment of AVB is a combination of endoscopic therapy and vasoactive drugs,[4] both of which have different mechanism of action: endoscopic therapy by direct effect while vasoactive drug reduces the portal pressure. Previous trials have shown that the efficacy of endoscopic sclerotherapy in achieving initial control of bleeding and 5-day hemostasis is significantly improved when vasoactive drug treatment is added to therapeutic regimen.[5,6] Endoscopic variceal ligation (EVL) is technically a superior endoscopic procedure with better results in acute bleed.[7–10] However, there is limited data whether addition of somatostatin to EVL improves the efficacy of EVL. This information is especially relevant because used independently both treatment modalities have been shown to be effective with comparable success rates.[11,12] Data is also lacking in terms of the effect on portal hemodynamics of this combination strategy and its influence on rebleed or mortality. We therefore undertook a randomized controlled trial to compare EVL plus somatostatin infusion versus EVL plus placebo in the control of acute variceal bleeding. We also correlated the baseline hepatic venous pressure gradient (HVPG) measurement with the outcome and determined the variables which are responsible for failure of control of AVB.

Keywords: Variceal bleeding, Endoscopic therapy, Band ligation, Octreotide, Terlipressin

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Abbreviations: AVB: Acute variceal bleeding; CTP: Child Turcotte Pugh; EVL: Endoscopic variceal ligation; FFP: Fresh frozen plasma; HVPG: Hepatic venous pressure gradient; ICU: Intensive care unit; ROC: Receiver operating characteristics

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PATIENTS AND METHODS

Patients

The study was conducted in the Gastroenterology Department of G.B. Pant Hospital, New Delhi, India.

Inclusion Criteria

Consecutive patients of portal hypertension with acute variceal bleeding from esophageal varices admitted to the Department were enrolled in the trial. Patients were included only if the clinical evidence of hematemesis and/or melena was within the 24-h period before admission.

Exclusion Criteria

Following group of patients were excluded: (i) non-cirrhotic cause of portal hypertension; (ii) age <12 or >75 years; (iii) hepatic encephalopathy grade 3 or 4; (iv) renal failure with serum creatinine >2 mg/dL; (v) any evidence of bleeding from additional source apart from esophageal varices (like gastric varices, portal hypertensive gastropathy, erosions or ulcers including variceal ulcers); (vi) patients already on vasoactive drugs like somatostatin or terlipressin during the current episode of bleeding; (vii) patients already received EVL or endoscopic sclerotherapy elsewhere during the current episode of bleeding prior to presenting to our hospital; (viii) patients with history of surgery for portal hypertension or TIPS; (ix) concomitant severe cardio-pulmonary disease; (x) concomitant malignancy; (xi) HVPG not possible within 24 h of presentation; and (xii) patients refusing to participate in the study.

Initial Resuscitation

All patients presenting with acute variceal bleeding underwent initial resuscitation which included protection of airway, care of breathing and fluid resuscitation. Care was taken not to over-infuse fluids and central venous pressure measurement was used, whenever indicated, to guide the fluid management. All patients received at least two units of fresh frozen plasma (FFP) initially and further FFP infusions were guided by the ongoing bleeding status and report of the prothrombin time. Packed cell infusions were given when indicated and the target hemoglobin was kept at 8 g/dL. All patients received prophylactic intravenous antibiotics (third generation cephalosporins).

Upper Gastrointestinal Endoscopy and Emergency EVL

All patients after initial resuscitation were taken up for upper gastrointestinal endoscopy as soon as possible, but definitely within 6 h of admission. *Esophageal* variceal bleeding was defined when endoscopy showed active bleeding from esophageal varices, or esophageal varices with an adherent clot, other signs of recent hemorrhage or esophageal varices but no other source of bleeding. Any evidence of bleeding from additional source apart from esophageal varices (like gastric varices, portal hypertensive gastropathy, erosions or ulcers including variceal ulcers) was sought and these patients were excluded from the trial as mentioned earlier.

EVL was done using a multiband ligator. Generally 4–6 bands were placed on the varices starting from the gastroesophageal junction and progressing upwards in a helical manner for approximately 5 cm.

Baseline Evaluation

After initial resuscitation and emergency EVL, the baseline evaluation of the patients was done which included detailed history, physical examination, liver function tests, kidney function tests, complete blood count, and investigations for cause of portal hypertension and etiology of cirrhosis, and HVPG measurement.

Randomization

Immediately after HVPG, patients were randomized to receive either somatostatin or placebo. The randomization was done by the statistician using computer generated random numbers and the investigators as well as the patients were blinded to the treatment allotted. The randomization sequence remained with the statistician, and the sequence remained concealed from the investigators.

Treatment

Somatostatin (250 mcg/hr, with an initial bolus of 250 mcg) or placebo infusion was given continuously through an infusion pump. The patients received the infusion for five days or till treatment endpoint. All patients were initially admitted to the intensive care unit (ICU) and they were shifted out of ICU once they were hemodynamically stable and melena started clearing.

Endpoints

The primary endpoint was treatment failure, defined as the occurrence of any of the following within a period of 120 h (5 days) from the time of admission: (i) fresh hematemesis $\geq$2 h after EVL; or (ii) a 3 g drop in Hb (9% drop in hematocrit) if no transfusion is administered; or (iii) death within 5 days. The secondary end-points of the study were in-hospital mortality, amount of packed cell or FFP infusions, ICU stay in days, any drug-related adverse effects, and HVPG response as defined by $\geq$ 10% reduction from baseline. This repeat HVPG was done after 5 days of treatment in patients consenting for repeat HVPG.

Statistical Methods

Quantitative data were expressed as median (range) and analyzed using Mann–Whitney U test. Qualitative data