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 ClinicalTrials.gov vide [NCT01267669](https://clinicaltrials.gov/ct2/show/study/NCT01267669). (J CLIN EXP HEPATOL 2015;5:204–212)

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 gastro-esophageal 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 ≥ 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

were analyzed by Fisher's exact test or Pearson chi-square test. Univariate analysis was performed to assess the variables predicting treatment failure. Variables found significant on univariate analysis were entered into multivariate analysis by backward conditional method to determine the independent predictors of treatment failure. Statistical analysis was done using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL).

RESULTS

Patients

During the study period, November 2005 to November 2009, 158 consecutive patients with portal hypertension and AVB were admitted. Ninety-seven patients were excluded for following reasons: non-cirrhotic portal hypertension ($n = 22$); age <12 or >75 years ($n = 6$); hepatic encephalopathy grade 3 or 4 ($n = 13$); renal failure with serum creatinine >2 mg/dL ($n = 8$); evidence of bleeding from additional source apart from esophageal varices ($n = 5$); patients already on vasoactive drugs like somatostatin or terlipressin during the current episode of bleeding ($n = 9$); patients already received EVL or endoscopic sclerotherapy elsewhere during the current episode of bleeding prior to presenting to our hospital ($n = 7$); patients with history of surgery for portal hypertension or TIPS ($n = 1$); concomitant coronary artery disease ($n = 2$); concomitant hepatocellular carcinoma ($n = 4$); HVPg not possible within 24 h of presentation ($n = 17$); and patients refusing to participate in the study ($n = 3$). Hence, remaining 61 patients were enrolled in the trial.

Randomization and Treatment Received

EVL was successfully performed in all patients. Thirty-one patients were randomized to receive somatostatin infusion and the rest thirty patients received placebo infusion.

Baseline Characteristics

The median age of included patients was 42 (range 12–73) years and 79% were males. The etiology of cirrhosis was alcohol in 22 (36%), viral in 20 (33%), and cryptogenic in 19 (31%). The median CTP score was 10 (range 5–13) and 31 (51%) patients had MELD ≥ 16 . Ninety percent of patients had large esophageal varices and in 22 (36%) patients, there was active bleed on endoscopy. The median HVPg was 20 (range 13–33) mm Hg. The baseline characteristics, including baseline HVPg, were similar in the two groups (Table 1).

Primary Endpoint: Treatment Failure Within Five Days

Within a period of five days, 15 (25%) patients had treatment failure. 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%]; $P = 1.000$). All episodes of treatment failure were due to fresh hematemesis (Table 2).

All patients with treatment failure were resuscitated, stabilized and underwent repeat endoscopy when the bleeding site was sought and was endoscopically treated with injection sclerotherapy. The bleeding could be controlled in all 15 patients with treatment failure, except one patient who died of exsanguination on the first day.

Secondary Endpoints (Table 2)

In-hospital Mortality

Six patients died during the hospital stay and the mortality was similar in the two groups (3/31 [10%] vs. 3/30 [10%]; $P = 1.000$). Five deaths occurred due to liver failure following AVB and one death occurred due to exsanguination. The median time to death since admission was 6 days (range 1–15 days). Of these, 2 deaths had occurred at 6th and 15th day following the *index bleeding* and 4 deaths had occurred following *treatment failure* at 1st, 5th, 7th and 12th day after admission.

Transfusion Requirement

The median (range) units of requirement of packed cells (2 [0, 8] versus 2 [0, 8]; $P = 0.230$) and FFP (4 [2, 16] vs. 4 [2, 15]; $P = 0.136$) were similar in the two groups.

ICU Stay

The median (range) ICU stay was also similar in the two groups (5 [1, 17] vs. 5 [1, 15] days; $P = 0.256$).

Adverse Effects

There were no significant drug related adverse effects in any group.

Follow-up HVPg

Thirteen (42%) patients in the somatostatin group and 9 (30%) patients in the placebo group had repeat HVPg after 5 days of therapy. HVPg response as defined by $\geq 10\%$ reduction could be achieved in 3 of 13 (23%) in the somatostatin group and 3 of 9 (33%) in the placebo group ($P = 0.655$). Only, one patient in each group could achieve a $\geq 20\%$ reduction in HVPg.

Predictors of Treatment Failure

Of the 61 patients, 15 (25%) had treatment failure. The results of univariate analysis of predictors of treatment failure are shown in Table 3. Serum albumin level ≤ 2.9 g/dL, CTP score ≥ 10 , baseline HVPg >20 mm Hg and active bleeding on initial endoscopy were significant predictors of treatment failure. Notably, the treatment received (EVL+ somatostatin versus EVL+ placebo) or

Table 1 Baseline Characteristics of Patients in the Two Groups.

Parameter	EVL plus somatostatin (n = 31)	EVL plus placebo (n = 30)	P value
Median (range) age, years	45 (26, 73)	42 (12, 65)	0.568
Sex, n (%)			1.000
Males	24 (77%)	24 (80%)	
Females	7 (23%)	6 (20%)	
Median (range) BMI, kg/m ²	21.8 (19.0, 31.2)	21.2 (18.4, 27.9)	0.902
Etiology, n (%)			0.657
Alcohol	12 (39%)	10 (33%)	
Viral	11 (35%)	9 (30%)	
Cryptogenic	8 (26%)	11 (37%)	
Ascites, n (%)	21 (68%)	18 (60%)	0.600
Hepatic encephalopathy (grade I–II), n (%)	4 (13%)	6 (20%)	0.508
Median (range) Hb, g/dL	7.5 (4.0, 11.9)	7.0 (3.5, 10.5)	0.686
Median (range) platelets, ×10 ⁹ cells/L	140 (90, 220)	130 (85, 190)	0.154
Median (range) creatinine, mg/dL	0.9 (0.3, 2.0)	0.8 (0.4, 2.0)	0.395
Median (range) sodium, meq/L	134 (122, 157)	136 (123, 146)	0.198
Median (range) bilirubin, mg/dL	2.4 (0.6, 17.0)	1.8 (0.6, 42.0)	0.564
Median (range) albumin, g/dl	2.9 (2.0, 3.4)	2.9 (2.0, 4.4)	0.788
PT prolongation, n (%)			1.000
≤6 s	13 (42%)	13 (43%)	
>6 s	18 (58%)	17 (57%)	
Median (range) CTP score	10 (7, 13)	10 (5, 13)	0.704
CTP class, n (%)			0.195
A	0 (0%)	3 (10%)	
B	13 (42%)	11 (37%)	
C	18 (58%)	16 (53%)	
Median (range) MELD	16 (9, 28)	16 (8, 33)	0.623
Large esophageal varices, n (%)	27 (85%)	28 (93%)	0.671
Active bleed on endoscopy, n (%)	10 (32%)	12 (40%)	0.600
Gastric varices, n (%)	6 (19%)	6 (20%)	1.000
PHG, n (%)	19 (61%)	16 (53%)	0.609
Median (range) HVPg, mm Hg	19 (13, 33)	21 (13, 30)	0.470
Patients with first bleed, n (%)	24 (77%)	21 (70%)	0.570
Patients with previous EVL, n (%)	7 (23%)	9 (30%)	0.570
Patients on beta-blockers, n (%)	5 (16%)	2 (7%)	0.425

Abbreviations: BMI body mass index, CTP Child-Turcotte-Pugh, EVL endoscopic variceal ligation, Hb hemoglobin, HVPg hepatic venous pressure gradient, MELD model for end-stage liver disease, PHG portal hypertensive gastropathy.

follow-up HVPg ($\geq 10\%$ reduction versus $<10\%$ reduction) did not predict treatment failure.

On multivariate analysis only baseline HVPg and active bleeding on initial endoscopy were independent predictors of treatment failure (Table 4). On receiver operating characteristic (ROC) curve the area under curve for HVPg in predicting treatment failure was 0.731 (95% CI 0.593, 0.870). The best cut-off obtained by ROC curve was an HVPg value of ≥ 19 mmHg for predicting treatment failure. The sensitivity, specificity, positive predictive value,

negative predictive value, and accuracy of HVPg ≥ 19 mmHg in predicting treatment failure were 93%, 48%, 61%, 58%, and 59%.

DISCUSSION

The results of this pilot study show that addition of somatostatin infusion for five days does not decrease the probability of treatment failure in patients being

Table 2 Primary and Secondary Endpoints.

Endpoint	EVL plus somatostatin (n = 31)	EVL plus placebo (n = 30)	P value
Primary endpoints			
Fresh hematemesis ≥2 h after start of therapy	8 (26%)	7 (23%)	1.000
Death	3 (10%)	3 (10%)	1.000
Secondary endpoints			
Median (range) PC units transfused	2 (0, 8)	2 (0, 8)	0.230
Median (range) FFP units transfused	4 (2, 16)	4 (2, 15)	0.136
Median (range) ICU stay, days	5 (1, 17)	5 (1, 15)	0.256
Drug related adverse effects, n (%)	0 (0%)	0 (0%)	1.000
HVPG response (≥10% reduction), n (%)	3/13 (23%)	3/9 (33%)	0.655

Abbreviations: EVL endoscopic variceal ligation, PC packed cells, FFP fresh frozen plasma, ICU intensive care unit, HVPG hepatic venous pressure gradient.

treated by emergency EVL for AVB. Further, addition of somatostatin also does not decrease the in-hospital mortality, requirement of FFP or packed cells, or the ICU stay in these patients. We have also shown that independent risk factors for treatment failure are active bleeding at endoscopy and high portal pressure (as manifested by high baseline HVPG).

It has been shown that combination therapy of vasoactive drugs with endoscopic therapy is better than either therapy alone in improving the five-day success rate.¹³⁻¹⁵ Hence, a combination of pharmacologic and endoscopic therapy is generally recommended for the treatment of AVB.^{4,16-18} The hypothesis being that two separate mechanisms of actions are at play: reduction in portal pressure by vasoactive drugs and mechanical hemostasis by endoscopic therapy. These recommendations are based on numerous trials which have shown that the efficacy of endoscopic therapy is significantly improved when they are associated with pharmacologic treatment. However, these trials have been heterogenous and most of these trials had used endoscopic sclerotherapy which is inferior to EVL in efficacy.^{5,6,13,14} Even in the meta-analysis by Banares et al trial, six out of eight included trials used injection sclerosis as the endoscopic therapy, and only two trials used band ligation. The meta-analysis, as expected, showed that combined treatment improved initial control of bleeding and 5-day hemostasis.¹⁴

Table 3 Univariate Analyses of Predictors of Failure to Control Bleed.

Variable ^a	Patients with failure to control bleed (n = 15)	Patients without failure to control bleed (n = 46)	P value
Age in years, n (%)			0.554
≤42	9 (60%)	22 (48%)	
>42	6 (40%)	24 (52%)	
Sex, n (%)			0.275
Males	10 (67%)	38 (83%)	
Females	5 (33%)	8 (17%)	
BMI in kg/m ² , n (%)			0.073
≤21.3	11 (73%)	20 (44%)	
>21.3	4 (27%)	26 (56%)	
Etiology, n (%)			0.610
Alcohol	4 (27%)	18 (39%)	
Viral	5 (33%)	15 (33%)	
Cryptogenic	6 (40%)	13 (28%)	
Ascites, n (%)			1.000
Present	10 (67%)	29 (63%)	
Absent	5 (33%)	17 (37%)	
Hepatic encephalopathy, n (%)			1.000
Present	2 (13%)	8 (17%)	
Absent	13 (87%)	38 (83%)	
Hb in g/dL, n (%)			1.000
≤7	8 (53%)	23 (50%)	
>7	7 (47%)	23 (50%)	
Platelets in × 10 ³ cells/mm ³ , n (%)			1.000
≤130	8 (53%)	23 (50%)	
>130	7 (47%)	23 (50%)	
Creatinine in mg/dL, n (%)			1.000
≤0.9	9 (60%)	26 (56%)	
>0.9	6 (40%)	20 (44%)	
Sodium in meq/L, n (%)			1.000
≤134	8 (53%)	26 (56%)	
>134	7 (47%)	20 (44%)	
Bilirubin in mg/dL, n (%)			0.079
≤1.9	5 (33%)	28 (61%)	
>1.9	10 (67%)	18 (39%)	
Albumin in g/dl, n (%)			0.033
≤2.9	13 (87%)	25 (54%)	
>2.9	2 (13%)	21 (46%)	
PT prolongation, n (%)			0.550

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Table 3 (Continued)

Variable ^a	Patients with failure to control bleed (n = 15)	Patients without failure to control bleed (n = 46)	P value
≤6 s	5 (33%)	21 (46%)	
>6 s	10 (67%)	25 (54%)	
CTP score, n (%)			0.038
<10	3 (20%)	24 (52%)	
≥10	12 (80%)	22 (48%)	
CTP class, n (%)			0.083
A	0 (0%)	3 (6%)	
B	3 (20%)	21 (46%)	
C	12 (80%)	22 (48%)	
MELD, n (%)			0.554
<16	6 (40%)	24 (52%)	
≥16	9 (60%)	22 (48%)	
Esophageal variceal size, n (%)			1.000
Small	1 (7%)	5 (11%)	
Large	14 (93%)	41 (89%)	
Active bleed on initial endoscopy, n (%)			0.034
Present	9 (60%)	13 (28%)	
Absent	6 (40%)	33 (72%)	
Gastric varices, n (%)			0.262
Present	1 (7%)	11 (24%)	
Absent	14 (93%)	35 (76%)	
PHG, n (%)			0.770
Present	8 (53%)	27 (59%)	
Absent	7 (47%)	19 (41%)	
HVPG in mm Hg, n (%)			0.019
≤20	4 (27%)	29 (63%)	
>20	11 (73%)	17 (37%)	
Bleed history, n (%)			1.000
Presenting with first bleed	11 (73%)	34 (74%)	
Presenting with rebleed	4 (27%)	12 (26%)	
EVL history, n (%)			1.000
Patients with previous EVL	4 (27%)	12 (26%)	
No previous EVL	11 (73%)	34 (74%)	
Beta-blocker history, n (%)			0.670
Patients on beta-blockers	1 (7%)	6 (13%)	
Not on beta-blockers	14 (93%)	40 (87%)	
Treatment received, n (%)			1.000

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Table 3 (Continued)

Variable ^a	Patients with failure to control bleed (n = 15)	Patients without failure to control bleed (n = 46)	P value
EVL + somatostatin	8 (53%)	23 (50%)	
EVL + placebo	7 (47%)	23 (50%)	
Follow-up HVPG (n = 22), n (%)			1.000
≥10% reduction	1/4 (25%)	5/18 (28%)	
<10% reduction	3/4 (75%)	13/18 (72%)	

Abbreviations: BMI body mass index, CTP Child-Turcotte-Pugh, EVL endoscopic variceal ligation, Hb hemoglobin, HVPG hepatic venous pressure gradient, MELD model for end-stage liver disease, PHG portal hypertensive gastropathy, PT prothrombin time.

^aFor continuous variables patients have been categorized as per their median values.

Endoscopic sclerotherapy has been gradually replaced by EVL, which has now become the treatment of choice both for controlling variceal hemorrhage and for variceal obliteration in secondary prophylaxis.^{4,16,17} This may be because of greater hemostatic effect with EVL, less adverse effects, and absence of rise in HVPG with EVL which is noticed with endoscopic sclerotherapy.^{9,19} Villanueva et al compared endoscopic sclerotherapy with EVL in patients admitted with AVB, receiving somatostatin infusion for five days. Therapeutic failure, failure to control bleeding, and side-effects were less common with EVL than with endoscopic sclerotherapy. Moreover, six-week survival probability without therapeutic failure was better with EVL.¹⁰ A meta-analysis has shown that EVL is better than endoscopic sclerotherapy for all major outcomes including initial control of bleeding, recurrent bleeding, side effects, time to variceal obliteration, and survival.⁷

Till date, trials that have used EVL as the endoscopic therapy for AVB are very few; hence, we used EVL combined with vasoactive drug in this trial. The reason why we chose somatostatin as the vasoactive agent for our study is manifold. The commonly used vasoactive drugs for AVB are terlipressin, octreotide and somatostatin. Though

Table 4 Results of Multivariate Analysis for Predictors of Failure to Control Bleed. Baseline HVPG, CTP Score, and Albumin were Entered into the Analysis.

Variable	P value	Odds ratio	95% CI
Baseline HVPG ≤20 vs. >20 mm Hg	0.021	4.915	1.272–18.997
Active bleeding on initial endoscopy	0.036	4.016	1.098–14.706

Abbreviations: CI confidence interval, HVPG hepatic venous pressure gradient.

terlipressin had shown survival benefit compared to placebo,²⁰ but it is prohibitively costly and not universally available. Moreover, head to head comparison of terlipressin with somatostatin in a controlled trial had not shown any significant difference.²¹ Another vasoactive drug is octreotide which is safe and few major side effects have been reported. However, a limitation of octreotide is that data from meta-analyses are inconclusive and controversial.²² Tachyphylaxis is another limitation of octreotide.²³ Somatostatin inhibits the release of glucagon, a vasodilator hormone, which leads to splanchnic vasoconstriction and decreased portal inflow. In a Cochrane meta-analysis which included 21 trials (enrolling 2588 patients) comparing somatostatin with placebo, units of blood transfused were less with somatostatin and the number of patients failing initial hemostasis was also reduced.²² There has been no trial that has compared somatostatin in combination with EVL against EVL alone. So we aimed this study to define the benefit of combination of somatostatin and EVL.

However, our study failed to show any benefit of addition of somatostatin to EVL. There are two major reasons why this combination did not decrease the probability of treatment failure in our study: First, EVL is a much more powerful technique to control bleeding, and second, somatostatin is relatively a weak vasoactive agent. Hence the marginal and ill-sustained portal pressure lowering effect of somatostatin could not add to the large benefit of EVL in controlling the AVB. In previous trials,^{13–15} the reason why somatostatin could show benefit in combination was that it was used with endoscopic sclerotherapy, which not only is an inferior and less effective endoscopic technique than EVL⁷ it also leads to sustained rise in portal pressure¹⁹ which required somatostatin to control.²⁴ In a trial comparing EVL with somatostatin, EVL was found much superior to somatostatin in treating AVB, with fewer requirements of transfusion and a tendency toward shorter hospital stay.²⁵

Having stated that our study failed to show any benefit of addition of somatostatin to EVL due to the two important reasons as stated above, we must interpret our results with caution due to small sample size. Large multi-centric trials should be conducted to confirm the findings of our study.

The weak or ill-sustained effect of somatostatin was well demonstrated in our study. A five day continuous infusion of somatostatin was not effective in keeping the portal pressure significantly low. HVPG response as defined by $\geq 10\%$ reduction could be achieved in only 3 of 13 (23%) in the somatostatin group which was similar to the placebo group (3 of 9 (30%); $P = \text{NS}$). This HVPG ill-sustained response must be due to desensitization to the effects of somatostatin because of tachyphylaxis as is well reported previously with somatostatin²⁶ as well as its analog octreotide.^{23,27}

Because of its weak action, somatostatin is also not cost-effective. In a study, the average aggregated treatment cost per person for all medical interventions at 1 year was lower for terlipressin-treated patients (£2623) compared with those treated using octreotide (£2758) or placebo (£2890).²⁸ One year simulations indicate somatostatin is the most expensive treatment option and terlipressin the least costly.²⁹

As per the available data in literature, the other vasoactive drug terlipressin seems to be more effective compared to somatostatin. A randomized trial from Italy showed that terlipressin was superior to octreotide when pharmacotherapy was used alone in AVB.³⁰ It has also been shown that terlipressin, but not somatostatin, maintains liver blood volume, increases thorax blood volume and improves the hyperdynamic state in cirrhosis.³¹ The portal pressure reducing effect of terlipressin are more sustained as compared to octreotide.²⁷ These effects can be beneficial in acute variceal bleeding, particularly in patients with advanced liver disease in preventing liver failure and death. On the basis of a 34% relative risk reduction in mortality, terlipressin was recommended by a Cochrane systemic review to be the vasoactive agent of choice in AVB.³² Combination of banding ligation and terlipressin infusion for 2 days was superior to only infusion of terlipressin for 5 days in the reduction of very early rebleeding and treatment failure in patients with inactive variceal bleeding at endoscopy.¹⁵ No other vasoactive agent, like somatostatin or octreotide, has been shown to reduce mortality in single studies or meta-analyses.

Contrary to our results, Sung et al found better results when they studied combination of octreotide with EVL vs. EVL alone in AVB.³³ They found better results with co-administration of octreotide in terms of need for transfusions, balloon tamponade and the rate of rebleeding. However, there was no benefit in terms of control of acute hemostasis or improvement in mortality. The reason for these dichotomous results between the study by Sung and our study is the difference in technique of performing EVL. Sung's study was performed in 1995 when multiband ligators were not available. The investigators ligated the varices with single elastic rings applied to the end of the endoscope using an overtube [the "single-shot" technique using Stiegman-Goff ligators³⁴]. In recent years, with the introduction of multiband devices, that allow 5–10 bands positioning in a single session, has simplified the EVL technique, avoiding the use of overtube and inherent complications.^{35,36} With better EVL technique available now, the need for additionally using a vasoactive drug to control acute variceal bleeding seems unwarranted.

In another study using vapreotide and endoscopic therapy,³⁷ the combination was found to be superior to the endoscopic therapy. However, in this study also, EVL was used in only minority of patients (31%), and in the rest,

depending on physician's preference, endoscopic sclerotherapy, cyanoacrylate or no endoscopic procedure was used. Thus, again in this trial due to less than optimal effectiveness of endoscopic therapy used, the portal pressure reducing effect of vasoactive agent came into play.

In our study failure to respond to combination therapy was determined by high baseline HVPG and active bleeding at endoscopy. Patients with high baseline HVPG had five-fold increased risk of treatment failure and those with active bleeding at endoscopy had four-fold higher risk. These patients should be categorized as 'high-risk' for failure of control of bleeding and an alternative therapy should be planned at the earliest.

High HVPG is an important and sensitive baseline predictor of treatment failure. In our study, an HVPG value of ≥ 19 mmHg had a sensitivity of predicting treatment failure in 93% of patients. In previous studies^{10,38,39} also high HVPG has been found to be independent predictor of treatment failure. If feasible, an early HVPG should be done in all patients with active variceal bleeding, to improve the outcome of patients with AVB. It has been shown that patients with an HVPG of 20 or above have a better outcome if they undergo early TIPS procedure.⁴⁰

Our finding of active bleeding at endoscopy as an independent predictor of treatment failure is supported by previous studies by D'Amico et al,¹ Ben-Ari et al,⁴¹ and Bambha et al.⁴² In such patients also a low threshold for choosing TIPS procedure within 24–72 h would certainly help reduce the rebleeding and mortality. In a seminal recent trial,⁴³ García-Pagán et al have shown that in patients with Child–Pugh class C disease or class B disease with active bleeding who were admitted for AVB, the early use of TIPS with an e-PTFE-covered stent was associated with significant reductions in the failure to control bleeding, in rebleeding, and in mortality, with no increase in the risk of hepatic encephalopathy.

The results of our study clearly suggest that there is a need to revise our current management strategy of these difficult-to-treat patients, who either have active variceal bleeding seen at the index endoscopy or have the baseline HVPG above 19 mm Hg. Further randomized controlled trials need to be undertaken in patients with AVB based on these two variables identified in the present study. There is also a need to probably evaluate more potent and longer acting portal pressure reducing drugs in combination with EVL.

CONFLICTS OF INTEREST

The authors have none to declare.

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