Terlipressin Administered Only Prior To Endoscopic Therapy in The Management of Bleeding Esophageal Varices Does Not Increase the Risk of Re-bleeding Compared to Standard 3-5 Days Regime

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ABSTRACT

Background & Aims: Terlipressin is recommended therapy for 3-5 days in esophageal variceal bleeding. The aim of this study was to determine the feasibility of administering terlipressin only prior to band ligation. **Methods:** Patients with esophageal variceal bleeding received terlipressin 2mg intravenous bolus followed by 1mg 6 hourly until undergoing endoscopic band ligation. They were monitored for re-bleeding for 5 days. **Results:** 67 patients, 38 (57%) male and 29 (43%) female, mean age 50+4 years, received terlipressin until undergoing endoscopic band-ligation. Etiology of liver disease was HCV in 62 (92.5%), HBV & HCV in 2 (3%), HCV & ethanol in 2 (3%) and unknown in 1 (1.5%) patient. 13 (19%) patients underwent band ligation after a single 2 mg dose of terlipressin, 16 (24%) after two doses (6 hours therapy), 11 (16%) after 3 (12 hours therapy), 6 (9%) after 4 (18 hours therapy), 6 (9%) after 5 doses (24 hours therapy) and 15 (22%) after more than 24 hours therapy. Banding was done within 12 hours in 40 (60%) patients and within 24 hours in 12 (18%) patients. Endoscopy was delayed beyond 24 hours in 15 (22%) patients due to Sengstaken-Blakemore tube placement, encephalopathy and blood transfusion requirements. 3 (4.9%) patients had rebleeding. Repeat endoscopy showed post-banding ulcers in 2 patients (managed with I.V omeprazole and oral sucralfate). One patient had varices with red signs requiring repeat band ligation. Two patients died due to hepatorenal syndrome and persistent encephalopathy. No drug related adverse effects were noted. **Conclusion:** Once band-ligation has been performed, terlipressin may be safely discontinued. This can result in reduction in cost of treatment with no significant increase in morbidity and mortality.

Keywords: Liver cirrhosis, Portal hypertension, Variceal bleeding, Terlipressin

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INTRODUCTION

Cirrhosis of the liver is extremely common worldwide.[1,2] The most common cause remains viral hepatitis. Pakistan is one of the worst affected countries as regards viral hepatitis.[3,4,5] Complications of cirrhosis, especially variceal bleeding secondary to portal hypertension, lead to a large number of hospital admissions. Once varices have formed, bleeding occurs in up to 30% of patients within 24 months[7] leading to considerable patient morbidity and mortality[7] and increased health-care cost.[8] Treatment of bleeding esophageal varices includes an organized approach constituting vasoactive drugs such as terlipressin or octreotide, blood transfusions and timely endoscopic therapy.[9,10,11,12,13,14] Vasoactive drugs have been proven, in a meta-analysis of 30 trials involving over 3000 patients, to be effective in reducing morbidity and mortality in variceal bleeding.[15] Vasoactive drugs act by affecting vasomotor tone. Depending on the type of effect, vasoactive drugs are subdivided into vasoconstrictors and vasodilators. Terlipressin and octreotide are both vasoconstrictors. Terlipressin is a synthetic analogue of vasopressin and its main vasoconstrictor effect is by acting on the V1a receptor. It produces mesenteric vasoconstriction and thus decreases portal venous inflow and pressure. This reduces the blood pressure within the varices. In variceal bleeding, terlipressin is usually given for up to 5 days, the period during which the risk of rebleeding is the highest.[16] The usual dosage of terlipressin used is 2 mg intravenously (I.V) 4 hourly that prevents rebleeding in over 92% of patients. Terlipressin is usually administered in

conjunction with endoscopic treatment following a variceal bleed. Some trials have reported success with lower dose and/or duration of terlipressin therapy.[17,18] At our centre, we have routinely successfully treated patients with terlipressin regimes comprising lower doses (1 mg 6 hourly instead of 2 mg 4 hourly) and far shorter duration than the recommended 3-5 day course.[19]

OBJECTIVES

To determine the safety and efficacy of administering terlipressin only prior to endoscopic therapy in the management of bleeding esophageal varices.

HYPOTHESIS

It is feasible to stop terlipressin once definitive endoscopic therapy has been administered.

METHODOLOGY

Study Design: Open label interventional study.
Setting: Department of Gastroenterology & Hepatology, Shaikh Zayed Hospital, Lahore
Duration: 3 months
Sample Size: A sample size of 47 patients was calculated with a 95% confidence level, a 5% margin of error and taking an expected percentage efficacy of terlipressin coupled with endoscopic band ligation i.e. 98%[17] in patients presenting with variceal bleeding. We opted for a larger sample size of 70 patients.

INCLUSION CRITERIA:

- All adult patients aged 18 to 60 years regardless of sex with esophageal variceal bleed secondary to cirrhosis of the liver

EXCLUSION CRITERIA:

- Upper gastrointestinal bleed due to causes other than esophageal varices such as gastric varices, bleeding ulcers, malignant lesions and vascular ectasias as seen during upper gastrointestinal endoscopy
- Patients on anti-coagulants
- Patients with a history of active angina, ischemic heart disease or dynamic EKG changes
- Failure to control variceal bleed on initial endoscopy

DATA COLLECTION PROCEDURE:

After obtaining approval from institutional review board, 70 patients with a history of liver disease and presenting with upper GI bleed (manifest as hematemesis or malena or both) to the emergency received terlipressin 2mg I.V bolus followed by 1mg 6 hourly until undergoing endoscopy. Informed consent was obtained. 3 patients were excluded from the study due to refusal to undergo band ligation and refusal for terlipressin therapy. The remaining 67 with only esophageal varices as the cause of bleeding underwent EVBL and were included in the study. Data including age, sex and etiology of liver disease were recorded. Terlipressin therapy was stopped following EVBL in these patients. No patient received terlipressin following band ligation. They were then monitored for the occurrence of re-bleeding for 5 days following endoscopic band ligation. Failure to control bleeding or rebleeding was defined as fresh hematemesis or NG aspiration of 100 ml or more of fresh blood 2 hours or more after the start of a specific drug treatment or therapeutic endoscopy; development of hypovolemic shock; 2g or higher drop in hemoglobin (9% drop of hematocrit) within any 24 h period if no transfusion was administered. All patients had a daily check of their hemoglobin levels. Vital signs including blood pressure and pulse were checked every 8 hours. Further hemorrhage, including that which may have necessitated surgery, was also defined as rebleeding. Efficacy was be labeled if rebleed did not occur within 5 days of treatment. All information was collected through a specifically designed proforma.

DATA ANALYSIS:

IBM SPSS version 22 was used to analyze the data. Variables included age, sex and efficacy. Nominal data (sex and efficacy) was represented as frequency percentages. Numerical data (age) was represented as mean$\pm$ standard deviation.

ETHICAL CONSIDERATIONS:

- Informed consent was obtained from all patients
- The study was initiated after approval from the Institutional Review Board

RESULTS

67 patients received terlipressin until undergoing endoscopic band ligation. 38 (57%) were male and 29 (43%) female. Mean age was 50$\pm$4 years. Etiology of liver disease was hepatitis C in 62 (92.5%), Hepatitis C and hepatitis B co-infection in 2 (3%), hepatitis C and ethanol in 2 (3%) and unknown in 1 (1.5%) patient (Table I).

Table 1: Etiology of liver disease in study population

Patient Number (Total 67)	Etiology of liver disease
62 (92.5%)	HCV
2 (3%)	HBV & HCV
2 (3%)	Ethanol & HCV
1 (1.5%)	Unknown

13 (19%) patients underwent band ligation after a single 2 mg dose of terlipressin, 16 (24%) patients after two doses (6 hours therapy), 11 (16%) patients after 3 doses (12 hours therapy), 6 (9%) patients after 4 doses (18 hours therapy), 6 (9%) patients after 5 doses (24 hours therapy), 4 (6%) patients after 6 doses (36 hours therapy), 4 (6%) patients after 8 doses (48 hours therapy), 2 (3%) patients after 10 doses (60 hours therapy), 1 (1.5%) patients after 12 doses (72 hours therapy), 1 (1.5%) patient after 16 doses (96 hours therapy) and 3 (4%) patients after 20 doses (120 hours therapy) of terlipressin (Table II).

Table 2: Distribution of patients according to duration of terlipressin prior to undergoing endoscopic band ligation

Patient Number (Total 67)	Duration of terlipressin (2mg bolus followed by 1 mg 6 hourly)
13 (19%)	Single 2mg dose
16 (24%)	2 doses (6 hours therapy)
11 (16%)	3 doses (12 hours therapy)
6 (9%)	4 doses (18 hours therapy)
6 (9%)	5 doses (24 hours therapy)
4 (6%)	6 doses (36 hours therapy)
4 (6%)	8 doses (48 hours therapy)
2 (3%)	10 doses (60 hours therapy)
1 (1.5%)	12 doses (72 hours therapy)
1 (1.5%)	16 doses (96 hours therapy)
3 (4%)	20 doses (120 hours therapy)

Band ligation was done within 12 hours in 40 (60%) patients and within 24 hours in 12 (18%) patients (Table III). Endoscopy was delayed beyond 24 hours in 15 (23%) patients (Table IV). This delay was due to Sengstaken Blakemore tube placement in 1 (1.5%) patient, encephalopathy of grade III and above in 7 (10.5%) patients and blood transfusion requirements in 7 (10.5%) patients (Table IV). Rebleeding was seen in 3 (4%) patients. Repeat endoscopy on patients who re-bled showed ulcers on sites of band ligation with no active ooze in 2 patients. These were managed conservatively with intravenous proton pump inhibitor infusion (8mg/hour continuous infusion for 72 hours) and oral sucralfate suspension (10 mL 8 hourly). One (1.5%) patient had varices with red signs which required repeat band ligation. Two patients died; one secondary to hepatorenal syndrome and another due to persistent encephalopathy. No drug related adverse effects were noted.

Table 3: Time interval between presentation to emergency and endoscopy

Patient Number (Total 67)	Time between presentation to emergency and endoscopy
40 (60%)	Within 12 hours
12 (18%)	Within 24 hours
15 (22%)	More than 24 hours

Table 4: Causes of delay in endoscopy beyond 24 hours

Patient Number (Total 67)	Cause of delay
7 (10.5%)	Encephalopathy of grade III and above
7 (10.5%)	Blood transfusion requirements
1 (1.5%)	Sengstaken-Blakemore tube placement

DISCUSSION

Vasoactive agents in combination with endoscopic therapy remain a vital combination in the treatment of esophageal variceal bleeding. The current recommendations advise a management plan for all patients with variceal bleeding that stretches to at least 4 to 6 days of therapy: one day for initial emergency management with endoscopic therapy followed by 3 to 5 days of vasoactive agents.[16] This increases bed occupation time with associated increases in cost of treatment. We have, at our centre, practiced a faster cycling time for such patients. The basic approach is early resuscitation and endoscopic therapy and discharge as soon as the patient is hemodynamically stable and malena cleared. We administer vasoactive agents to our patients until they are fit to undergo endoscopy. Vasoactive agents are discontinued as soon as endoscopic band ligation is performed. Patients are discharged on oral beta-blockers (propranolol or carvedilol) plus a 5-day course of oral antibiotics (usually ciprofloxacin). This is followed by a recall for a repeat endoscopy after 14 days. In many cases our patients are discharged within 72 hours of presentation to the hospital. It is also routine to discharge patients within 24-36 hours if they are hemodynamically stable on presentation. In such

cases endoscopy is done immediately and the patient discharged directly from the emergency department or after an overnight stay in the ward. We also follow a practice to start the patient on oral treatment as soon as endoscopy is performed, provided his/her conscious level allows. To date we have found this practice to be effective and efficient. As reported in the results earlier, delay in endoscopy is due to encephalopathy, blood transfusion related delays and placement of Sengstaken Blakemore tube. At our centre it is standard practice to delay endoscopy until encephalopathy has recovered completely or at least at grade II level (according to the Westhaven criteria). We do not engage in early endoscopy on patients with grade III or higher encephalopathy by sedating and intubating them. These patients are managed on vasoactive agents for their bleeding along with the standard management for encephalopathy, which includes antibiotics, lactulose, branched chain amino acids and L-ornithine L-aspartate.[20] Once the patient's conscious level is deemed feasible, endoscopy is performed.

Blood transfusion related issues also delay endoscopy. In Pakistan, government hospitals rarely carry adequate stocks of screened blood products. It falls to the patients and their attendants to arrange the required transfusions. Endoscopy is performed once hemoglobin is 7 g/dL or higher.[21,22]

Sengstaken Blakemore tube placement is done in cases where there is continuous and heavy hematemesis on presentation to the hospital or seen during endoscopy of a severity that impedes proper visualization. The tube is kept in situ for 24 hours before endoscopy is performed.[23]

In our experience, the greatest number of delays is due to transfusion products arrangement and encephalopathy.

We suggest that in the light of this study's finding, the following important points are noted in the management of patients with liver cirrhosis presenting with bleeding esophageal varices. These points merit study in larger randomized clinical trials:

- Terlipressin can be administered at a lower dose than recommended, with a 2 mg IV bolus followed by 1 mg 6 hourly.
- In patients with esophageal varices confirmed as source of bleeding and having undergone endoscopic band ligation, terlipressin (or any other vasoactive agent) may be stopped following endoscopic treatment.
- Patients who are conscious, alert and hemodynamically stable can be started on oral treatment with beta-blockers plus a short antibiotic course following endoscopic treatment.
- Such patients may be discharged after a 12-24 hour monitoring period following endoscopic therapy.
- Patients should be recalled for repeat endoscopy 14 days following discharge.

CONCLUSION

Terlipressin is an important therapeutic intervention in management of bleeding esophageal varices. Once band ligation has been performed, terlipressin may be safely discontinued. This can result in reduction in cost of treatment with no significant increase in morbidity and mortality.

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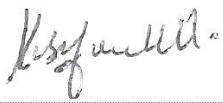
Dr. Kashif Malik Associate Professor, Gastroenterology & Hepatology, Shaikh Zayed Hospital, Lahore	Literature search	
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