INTRODUCTION

Terlipressin has been used extensively for effective control of bleeding from esophageal varices.\textsuperscript{1,2} However, this is an expensive medicine and the usual recommended regime of up to 5 days found in literature is a costly package.\textsuperscript{3,4} Viral hepatitis is extremely common in Pakistan.\textsuperscript{5,6} A large number of patients with viral hepatitis progress to liver cirrhosis. The complications of liver cirrhosis lead to a large number of hospital admissions, a significant number being due to variceal bleeding.\textsuperscript{2}

Treatment of bleeding esophageal varices includes an organized approach constituting vasoactive agents such as Terlipressin or Octreotide, blood transfusions and timely endoscopic therapy.\textsuperscript{7,8} In such circumstances, Terlipressin is usually given for up to 5 days, the period during which the risk of rebleeding is the highest, preventing rebleeding in over 92\% of patients.\textsuperscript{9}

Vasoactive agents affect vasomotor tone. Depending on the direction of such effect, vasoactive agents can be subdivided into vasoconstrictors and vasodilators. Terlipressin and Octreotide are both vasoconstrictors. Terlipressin is a synthetic analogue of vasopressin. Its main vasoconstrictor effect is by acting on the V1a receptor causing mesenteric vasoconstriction decreasing portal venous inflow and pressure, finally reducing blood pressure within the varices.\textsuperscript{10} Octreotide is a synthetic analogue of Somatostatin. The mechanism of action of Somatostatin and Octreotide is unclear. These may work either by preventing postprandial hyperemia or by reducing portal pressure through effects on vasoactive peptides (i.e., substance P or glucagon).\textsuperscript{11}

Endoscopic treatment options include variceal band ligation (EVBL) or sclerotherapy.\textsuperscript{7,8} It is the standard practice to administer Terlipressin for up to 5 days following a variceal bleed. At the study centre, patients have been successfully treated for variceal bleeding using Terlipressin regimes far shorter than the recommended 3- 5-day course. A pilot study has already been carried out at the study department.\textsuperscript{12} If proven effective, a shorter regime will allow for reduced hospital stay and less financial burden on both the patient and healthcare services.

The objective of this study was to determine whether Terlipressin given for 12-hour is as effective as 72-hour of Terlipressin therapy in preventing rebleed after endoscopic control of variceal bleeding.
METHODOLOGY
This was a parallel arm study and was carried out at the Department of Gastroenterology & Hepatology, Shaikh Zayed Hospital, Lahore from January to March 2016. A sample size of over 48 patients was calculated with a 95% confidence level, a 7% margin of error and taking an expected percentage efficacy of Terlipressin (coupled with endoscopic therapy) of 98% in treating patients presenting with variceal bleeding. For this study, a larger sample size of 93 patients was opted. All adult patients aged 18 years and above were included regardless of gender with esophageal variceal bleed (as per operational definition) secondary to cirrhosis of the liver (cirrhosis confirmed on abdominal ultrasound). Patients with upper gastrointestinal bleed due to causes other than esophageal varices such as gastric varices, bleeding ulcers and vascular ectasias as seen during upper gastrointestinal endoscopy were excluded from the study. Patients with a history of active angina, recent myocardial infarction or dynamic EKG changes were not included due to risk of Terlipressin in exacerbating coronary ischemia. Finally, patients in whom there was a failure to control variceal bleed on initial endoscopy were also excluded. Written and informed consent was obtained from all patients. After formal approval from the Institutional Review Board, patient recruitment was initiated.

All patients with a history of liver cirrhosis presenting to the hospital with upper gastrointestinal bleeding, manifest as hematemesis or melena or both, received Terlipressin starting with a 2mg intravenous bolus, followed by 1mg 6 hourly. Patients with esophageal varices alone, as the cause of bleed, underwent band ligation and were included in the study. The patients were then randomized into two groups, A and B. Randomization was done by lottery method. Group-A continued to receive Terlipressin at a dose of 1mg 6 hourly for 72 hours. Terlipressin was stopped in Group-B after 12 hours.

Esophageal variceal bleed was defined as hemorrhage from varices, which are dilated veins in the distal esophagus caused by elevated pressure in the portal venous system, typically from cirrhosis of the liver. Efficacy of prevention of rebleeding was determined in terms of prevention of rebleeding. Patients were followed for a period of 5 days after starting treatment with Terlipressin for the presence or absence of rebleed. Rebleeding was defined as a new episode of bleeding during hospitalization, after the initial bleeding had stopped, that manifested as recurrent hematemesis, hematochezia, fresh blood in the nasogastric aspirate, drop in hemoglobin ≥2 g/dL or circulatory instability. If rebleeding did not occur, the medicine would be labelled as efficacious. Both groups were monitored for occurrence of rebleeding for 5 days following band ligation. All patients had a daily check of their hemoglobin levels. Vital signs, including blood pressure and pulse, were checked every 8 hours. All information was collected through a specifically designed proforma and analysed using Windows SPSS version 23. Nominal data (gender and efficacy) was represented as frequencies and percentages and analysed by Chi-square test. Quantitative data (age) was represented as mean± standard deviation. Child Pugh Score was analysed in both groups using independent sample t-test. For all analyses, a p-value of less than 0.05 was considered significant.

RESULTS
A total of 93 patients were included in the study. Three patients were excluded due to refusal for further inpatient treatment following endoscopy. The remaining 90 patients were then randomized into two groups, A and B, with 25 (27.8%) patients randomized to group A and 65 (72.2%) allocated to Group B. Group A was the control group and received standard-of-care duration of Terlipressin for 72 hours. Group B was the intervention group and received Terlipressin for only 12 hours. Mean age was 53.56 ±11.11 years in Group-A and 51.35 ±11.46 years in Group-B with 51 (57%) patients being male and 39 (43%) female. Cause of liver disease was predominantly (82 patients: 91%) infection with HCV and D/each (1.5%) HBV, combined HBV, HVC, Idiopathic and alcohol abuse. Mean MELD score was 19 ±3 in Group-A and 20 ±2 in Group-B. Of the total 90 patients, 65 (72%) had a MELD score below 20, whereas 25 (28%) had MELD score above 20. Most patients (49 patients: 54%) had Child Class B disease (Table I). Most patients (87: 97%) had high-grade varices (Grade III-IV) on endoscopy (Table II). Diabetes mellitus was the most common comorbidity with 44 (49%) affected patients. Sixteen (18%) patients had hepatocellular carcinoma and systemic hypertension was found in 11 patients. Rebleeding occurred in 4 patients, 1 (4%) patient in Group-A (72-hour Terlipressin group) and 3 (4.6%) patients in Group-B (12-hour Terlipressin group), during the 5-day observation period. All 4 patients had Child Class C stage liver disease. The 4 rebleeders underwent repeat endoscopic evaluation to ascertain the cause of bleeding. The single (4%) Group-A patient and 2 (3%) of the 3 Group-B patients showed ulcers over sites of band ligation as sources of bleeding. Total incidence of post-bandning ulcer bleed was 3 out of 90 patients: 3.3%. These patients were treated conservatively with an I.V Omeprazole infusion (8mg/hour, continued for 48 hours followed by shift to oral Omeprazole, 40mg daily) and Antacid oral suspension (Aluminum hydroxide plus magnesium carbonate 10 mL, 8 hourly). The third Group-B patient showed varices with red signs that required repeat band ligation. Hence, only one patient
Among all rebleeders required repeat EVBL. Frequency of bleeding in Group-A, (4%), vs. Group-B, (4.6%) was statistically insignificant (p=0.899). One patient in Group-A died after developing progressive hepatic encephalopathy, following band ligation, which was refractory to treatment. No deaths were noted in Group-B.

No treatment-related adverse effects were seen in either group.

**DISCUSSION**

This study shows that a short (12-hour) duration of Terlipressin, as an adjunct to endoscopic band ligation, provides similar results to standard of care 72-hour therapy. Previous studies have explored a shorter Terlipressin regime as compared to the standard 72- to 120-hour therapy and have shown that shorter courses can be as effective as standard with no decrease in safety.12,13

Of the two groups compared in this study, actual variceal rebleeding requiring repeat EVBL was only seen in one patient. It was also seen that the other 3 rebleeders had bled from ulcers that had formed on the sites of EVBL. Ulcer formation on variceal ligation sites is a known complication.14,15 These ulcers can be managed efficiently using proton pump inhibitor infusion and oral Antacid suspensions.16,17

A shorter duration of Terlipressin translates to shorter hospital stay. This in turn means a reduction in other IV medications (such as antibiotics, proton pump inhibitors) and associated bed occupation expenses. In order to further elaborate the reduction in cost of treatment, we noted that the price per milligram of Terlipressin in Pakistan is approximately Rs1400 (14 USD). The cost of the recommended 3- 5-day treatment (assuming 2 mg bolus followed by 1mg 6 hourly) with a total of 13-21 mg Terlipressin administered is about Rs 20,000 - 30,000 (200- 300 USD) for a single patient. One the other hand, the cost of 12-hour regime is approximately 70 USD per patient. The number of endoscopies performed for acute upper GI bleeding at the hospital is 130 ±15 every month. Out of these, esophageal varices constitute 70±9; gastric fundal varices 20±5 and ulcers/erosions make up 40±3. This translates to a monthly cost, for the 3- 5-day regime of Rs 1.4-2.2 million (14000 - 22000 USD) at the study centre. The estimated monthly cost for 12-hour regime comes out to Rs 500,000 (5000 USD). This results in a cost saving of Rs 0.9-1.7 million (9000-17000 USD) per month, only in the cost of Terlipressin at the centre, not taking into account costs saved in associated expenses. These figures have not been corrected for subsidized rates of treatment at government hospitals. The actual cost of treatment is thus much higher. This is reflected by studies done in centres in the East as well as the West, which show cost of treatment of variceal bleeding, per patient, of approximately 3000 US dollars in Taiwanese centres and over 6000 US dollars for centres in the United States.18,19 These costs are also significant that they rise to 6000-23000 dollars respectively for Taiwanese and US centres, if a patient requires treatment for other complications related to his/her liver disease. Although the authors practice and support the use of short-term regimes associated with short admission times in the management of variceal bleeding, it is also understood that patients with liver cirrhosis represent a complex clinical entity. Frequently, these patients have other complications, related to advanced liver disease, in addition to variceal bleeding due to portal hypertension. These mainly include ascites (which may itself be complicated by spontaneous bacterial peritonitis), hepatic hydrothorax, hepatorenal syndrome and portosystemic encephalopathy.20,21 The management of these additional pathologies requires definitive therapies such as abdominal paracentesis, intravenous albumin, culture specific antibiotics, lactulose (orally and as enemas).22,23 This, therefore, leads to increased admission time, duration of which is dictated by when a patient's clinical condition improves.

The study was not without its limitations, as the re-bleeding and mortality not monitored beyond the 5-day observation period. We, therefore, recommended that a patient group needs to be assessed along the same

### Table I: Severity/stage of liver disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group A (72 Hours)</th>
<th>Group B (12 Hours)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score (Mean ± SD)</td>
<td>19 ±3</td>
<td>20 ±2</td>
<td>0.977</td>
</tr>
<tr>
<td>&lt;20</td>
<td>18 (77.7%)</td>
<td>47 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>7 (28%)</td>
<td>18 (72%)</td>
<td></td>
</tr>
<tr>
<td>Child Pugh class</td>
<td>None</td>
<td>None</td>
<td>0.773</td>
</tr>
<tr>
<td>A</td>
<td>13 (52%)</td>
<td>36 (55.4%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>12 (48%)</td>
<td>29 (44.6%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1 (4%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Child Pugh score (Mean ±SD) 9.32 ±1.65 8.9 ±1.4 0.279

**Pearson Chi-square test:** *Independent sample t-test

### Table II: Esophageal variceal findings on endoscopy.

<table>
<thead>
<tr>
<th>Varices</th>
<th>Group A (72 Hours)</th>
<th>Group B (12 Hours)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varices grade</td>
<td>25 patients</td>
<td>65 patients</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>None</td>
<td>None</td>
<td>0.674</td>
</tr>
<tr>
<td>II</td>
<td>1 (4%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>13 (52%)</td>
<td>28 (43%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11 (44%)</td>
<td>35 (53.8%)</td>
<td></td>
</tr>
<tr>
<td>No. of variceal columns</td>
<td>25 patients</td>
<td>65 patients</td>
<td>0.812</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (4%)</td>
<td>5 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16 (64%)</td>
<td>39 (60%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8 (32%)</td>
<td>21 (32.3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Pearson Chi-square test.**
parameters; and rebleeding and mortality be checked for a period of five days, six weeks, and 24 weeks following primary endoscopic therapy for variceal bleeding. Furthermore, mortality needs to be correlated with patient factors such as Child Pugh score, MELD score, presence or absence of hepatorenal syndrome, spontaneous bacterial peritonitis and encephalopathy at time of admission with variceal bleeding.

**CONCLUSION**

Esophageal variceal bleeding can be efficiently managed with a short 12-hour regime of Terlipressin coupled with variceal band ligation. This practice will serve to achieve similar efficacy and safety as the current standard of care 72-hour regime.

**REFERENCES**

12. Salim A, Khan AA, Alam A, Butt AK, Anjum S. 12 hours terlipressin is as effective as 72 hours therapy in the management of bleeding esophageal varices. *Gut* 2010; 59 (Suppl III): a 44.