“Comparison of Octreotide and Terlipressin Efficacy in Prevention of Early Variceal Rebleed after Endoscopic Variceal Band Ligation”

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ABSTRACT

Objectives: Terlipressin and octreotide are both used as adjuvant therapy to endoscopic variceal band ligation however data is scarce on the head-to-head efficacy of terlipressin and octreotide in prevention of early variceal rebleed. The aim of this study was to compare the efficacy of terlipressin with octreotide as an adjuvant therapy to endoscopic variceal band ligation in patients with esophageal variceal bleeding.

Methods: This study (a comparative interventional study) was conducted in Medical Unit II, Jinnah hospital Lahore from December 2012 to June 2013 and 150 patients were included in this study. Cirrhotic patients with esophageal variceal bleed were randomized on admission to receive octreotide (group A) or terlipressin (group B) after endoscopic variceal band ligation. The two groups were compared for prevention of early variceal rebleed. “Control of variceal bleed” was the measure of efficacy of terlipressin and octreotide.

Results: One hundred and fifty patients were included in the study. Re-bleeding occurred in 16 patients (21.33 %) in study group A and in 12 patients (16 %) in study group B (p = 0.402).

Conclusion: It is concluded that terlipressin is as effective in prevention of early variceal rebleed after endoscopic band ligation as octreotide, with minor superiority. Therefore both drugs can be used for prevention of early variceal rebleed after band ligation.

INTRODUCTION

Cirrhosis is a chronic disease of the liver resulting into disorganization of hepatic lobule and vascular architecture leading to as cites, spontaneous bacterial peritonitis, and hepatic encephalopathy etc.1 Cirrhosis affects hundreds of millions of patients worldwide.2 It is also a common cause of mortality among Pakistani population and frequent cause of admission in our hospitals. Cirrhosis develops in 10 to 20% within 5 to 30 years, the most common cause being viral hepatitis3. In Pakistan, prevalence of cirrhosis is 2.4 – 6.5 % and incidence is 240 patients per million of inhabitants3. Chronic hepatitis C is the commonest cause of cirrhosis (47%) followed by chronic hepatitis B (32%); 3 % have both hepatitis B and C4.

Gastro esophageal varies develop in consequence of progressively increasing blood flow entering the vasodilator splanchnic bed and the portal vein where blood flow meets intrahepatic resistance. Porto-systemic collateral veins are formed having high pressure causing the venous walls to expand into esophageal varices, which eventually may rupture and bleed5.

Esophageal variceal bleeding occurs in 10-20% of cirrhotic patients per year and more frequently in patients with large varices6. Up to 30 percent of initial bleeding episodes are fatal and as many as 70 percent of survivors have recurrent bleeding. Mortality within 2 weeks after acute bleeding episode is 30%7.

Acute esophageal variceal bleeding is a common problem in Pakistan with a high risk of death. Management of patients with bleeding oesophageal varices includes treatment of acute variceal bleeding and prevention of re-bleeding after an initial bleeding episode6. An early endoscopy helps in confirming the diagnosis and thereafter performing the therapeutic procedures like esophageal variceal band ligation or injection sclerotherapy. Drug treatment such as octreotide and terlipressin can be used in combination with these procedures8.

This study was aimed to see the comparison of octreotide and terlipressin efficacy in prevention of
Comparison of Octreotide and Terlipressin Efficacy in Prevention of Early Variceal Rebleed after Band Ligation

SUBJECTS AND METHODS
In this study, 150 patients with acute variceal bleeding were included, of which 75 patients were randomly assigned to group A and 75 patients to group B. Group A received octreotide at a rate of 50 microgram per hour and group B received terlipressin 1 milligram intravenously every 6 hours for 5 days after band ligation. Both groups were monitored for evidence of early variceal rebleed for five days after banding.

Sample Selection:
INCLUSION CRITERIA
Patients of either gender between 28 to 65 years of age were included with following pre requisites:
1. Had coarse shrunken liver with irregular margins with or without ascites (on ultrasound) due to chronic viral hepatitis.
2. Presented within 24 hours with history of hematemesis, melena or both.
3. Had upper gastrointestinal bleed due to esophageal varices.
4. Had received band ligation.

EXCLUSION CRITERIA
Following patients were excluded from study:
1. Known patients of renal failure, ischemic heart disease or congestive heart failure
2. Had non variceal bleed on endoscopy.

Operational Definitions
1. Efficacy. Ability of octreotide or terlipressin to prevent re-bleed after banding, based on the absence of hematemesis, melena and shock (pulse rate > 100 beats/min, systolic pressure < 90 mm of Hg) after five days of treatment.
2. Early Variceal Rebleed. Bleeding within 5 days after band ligation.

RESULTS
One hundred and fifty patients were included in the study, which were randomly assigned into two groups by block randomization. The overall mean age was 52.07±8.52. In group A, mean age was 51.88 ± 8.80 and in group B, mean age was 52.40 ± 8.40 (Table No. 1).

Out of these 150 patients, 77 (51.33%) presented with hematemesis, 16 (10.66%) had melena while 57 (38%) had both hematemesis and melena. In group A, 27 patients (36%) had hematemesis, 9 (12%) had melena and 39 (52%) had both hematemesis and melena. In group B, 30 patients (40%) presented with hematemesis, 7 (9.3%) with melena and 38 (50.66%) with both hematemesis and melena. (Table No. 2)

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>n</th>
<th>%</th>
<th>Group A</th>
<th>%</th>
<th>Group B</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematemesis alone</td>
<td>77</td>
<td>51.33</td>
<td>27</td>
<td>36</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Melena alone</td>
<td>16</td>
<td>10.66</td>
<td>9</td>
<td>12</td>
<td>7</td>
<td>9.33</td>
</tr>
<tr>
<td>Hematemesis and melena both</td>
<td>57</td>
<td>38</td>
<td>39</td>
<td>52</td>
<td>38</td>
<td>50.66</td>
</tr>
<tr>
<td>Total</td>
<td>150</td>
<td>75</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: n = number of patients, (%) = percentage
The viral cause of cirrhosis was determined in all 150 patients. In group A, 52 patients (69.33%) were Anti-HCV positive, 16 patients (21.33%) were HBsAg positive while in 7 patients (9.33%) both viral markers were positive. In group B, 52 patients (69.33%) were Anti-HCV positive, 19 patients (25.33%) were HBsAg positive while in 4 patients (5.33%) both viral markers were positive.

Endoscopic grading of varices was done which showed that in group A, 11 patients (14.66%) had grade I esophageal varices, 28 (37.33%) had grade II varices and 36 (48%) had grade III varices. In group B, 12 patients (16%) had grade I esophageal varices, 25 (33.33%) had grade II varices and 38 (50.66%) had grade III varices. (Table No.3)

Table 3: Endoscopic Grades of Varices in Both Groups n = 150

<table>
<thead>
<tr>
<th>Grade of varices</th>
<th>Study group A</th>
<th>Study group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade –I</td>
<td>11 (14.66%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Grade –II</td>
<td>28 (37.33%)</td>
<td>25 (33.33%)</td>
</tr>
<tr>
<td>Grade –III</td>
<td>36 (48%)</td>
<td>38 (50.66%)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Key:
n = number of patients
(%) = percentage
Grade –1 = Straight veins
Grade –2 = Tortuous veins occluding less than 1/3rd of lumen
Grade –3 = Tortuous veins occluding more than 1/3rd of lumen

Endoscopic variceal band ligation (by applying 4-6 bands) was performed by the head of department of the medical unit. After band ligation, group A received octreotide while group B received terlipressin. Both groups were monitored for 5 days for prevention of early variceal rebleed. It was noted that in group A, 59 patients (78.66%) didn’t rebleed (no hematemesis, melena or both), 8 patients (10.66%) had hematemesis, 4 patients (5.33%) had melena and 4 patients (5.33%) had both hematemesis and melena. In group B, it was noted that 63 patients (84%) didn’t rebleed, 7 patients (9.33%) had hematemesis, 3 patients (4%) had melena while 2 (2.66%) patients had both hematemesis and melena. (Table No. 4)

So it is concluded that both octreotide and terlipressin are effective in prevention of early variceal rebleed after band ligation with minor superiority of terlipressin. Therefore both drugs can be used for prevention of early variceal rebleed after band ligation.

Table 4: Post Band Ligation Early Variceal Re Bleed Symptoms in Both Groups n = 150

<table>
<thead>
<tr>
<th>Re bleeding status</th>
<th>Study group A</th>
<th>Study group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>No re bleed</td>
<td>59 (78.66%)</td>
<td>63 (84%)</td>
</tr>
<tr>
<td>Hematemesis alone</td>
<td>8 (10.66%)</td>
<td>7 (9.33%)</td>
</tr>
<tr>
<td>Melena alone</td>
<td>4 (5.33%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Hematemesis and melena both</td>
<td>4 (5.33%)</td>
<td>2 (2.66%)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Key:
n = number of patients
(%) = percentage
DISCUSSION
The study shows that both terlipressin and octreotide are comparable as adjuvant therapy to prevent esophageal variceal rebleed in cirrhotic patients after band ligation.

One hundred and fifty patients were entered in this study with a mean age of 52.07±8.52 years, minimum age being 28 years and maximum being 65 years. Ali H, et al10 who used endoscopic intervention as adjuvant to octreotide for prevention of early variceal rebleed reported a mean age of 56.7±12 years (40 –70 years), which is comparable to our mean age. In our study group A, mean age was 51.88±8.80(29—65 years) while in group B it was 52.40±8.40(28—65 years). After proper randomization, it was appreciated that mean age was similar in both groups. This suggests that esophageal variceal bleed is more common in this group.

Among 150 patients 102 patients (68%) were males and 48 patients (32%) were females. Umer M, et al11 followed cases of acute variceal bleeding due to cirrhosis of liver, out of which 62.5% patients were males 37.5% patients were females. Similar results were reported in Ali H, et al10 where 64.70% patients were males and 35.29 % were females. These results are similar to our study groups. This suggests that upper GI bleed due to esophageal varices is more common in males than females.

Chronic viral hepatitis is the most common cause of liver cirrhosis in Pakistan. In our study, 104 patients (69.33%) were Anti-HCV +ve, 35 patients (23.33%) patients were HBsAg +ve while in 11 patients (7.33%) both viral markers were positive. Farooq JI, et al12 reported in their study that 63% patients were Anti-HCV +ve and 37% patients were HBsAg +ve. This suggests that hepatitis C is the most common cause of cirrhosis in our country.

Patients were randomly allocated in two groups and after band ligation were monitored for the efficacy of octreotide and terlipressin in prevention of early variceal rebleed (within 5 days). It was noted that overall re-bleeding occurred in 28 patients (18.66%). In group A, re-bleeding was seen in 16 patients (21.33%) while in group B re-bleeding was seen in 12 patients (16%) which was not statistically significant (p=0.402). Augustin, et al13, after monitoring the patients for 5 days, noted in their study that in group A (band ligation alone) control of bleeding was achieved in 62% patients while in group B (band ligation plus octreotide) control of bleeding was achieved in 91 % patients (re-bleeding occurred only in 9% patients). So they concluded that octreotide plus band ligation is efficient and safe in the initial control of re-bleeding from esophageal varices.

Chen, et al14 in their study of low dose terlipressin plus band ligation versus terlipressin alone in the prevention of early variceal rebleed observed that combined therapy (band ligation plus terlipressin) was superior to terlipressin alone and after 48hrs homeostasis was achieved in 98% patients(p=.0002). Abid S, et al15 in a randomized double blind palcebo control trial compared the efficacy of terlipressin and octreotide with endoscopic intervention and found terlipressin and octreotide to be 92.60% and 95% effective respectively in controlling esophageal variceal rebleeding.

The results of some of these studies are different probably due to different duration of observation as in Ali H et al10 and Chen et al studies, it was 2 days while in Farooq JI, et al12 study, this duration was 10 days as opposed to our duration of observation which was 5 days. Definition of early variceal rebleed was also different in different studies. We defined early variceal rebleed as bleeding within five days after banding. In study of Farooq et al11 it was 10 days while it was 2 days in Ali H, et al10 and Chen et al14 studies.

The dosages of drugs used were also different in other study groups as opposed to our study. Ali H, et al10 used octreotide analogue in dose of 25 microgram per hour and terlipressin in dose of 2 milligram intravenous every 4 hour. Muhammad SR, et al16 used octreotide infusion at 25 microgram per hour. Patients were kept under observation in hospital for 5 days. They concluded that combination therapy of octreotide or terlipressin with endoscopic intervention is effective method of controlling and preventing early variceal rebleed.

Regarding the overall efficacy of these drugs, it was 78.6% in group A (band ligation plus octreotide group) while it was 84 % in group B (band ligation plus terlipressin group). So both drugs can be used.

CONCLUSION
It is concluded that terlipressin is as effective in prevention of early variceal rebleed after band ligation as octreotide with minor superiority. Therefore both drugs can be used for prevention of
early variceal rebleed after banding. Use of any of these two drugs in combination with endoscopic band ligation is more effective in prevention of early variceal rebleed than band ligation alone.

REFERENCES