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Shorter and Economical Terlipressin Regime for Esophageal Variceal Bleeding

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MS and MT managed the analyses of the study. Author MT also managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To compare the effectiveness of treatment with Terlipressin for 12-hour and for 72-hour in inhibiting the episodes of rebleeding once endoscopic band ligation is done.
Study Design: Randomized Clinical Trial.
Place and Duration of Study: Department of Medicine (Unit of Gastroenterology and Hepatology) at District Headquarter (DHQ) Teaching Hospital, Sahiwal (Pakistan) during February to April, 2018.
Methodology: Patients with cirrhosis presenting to emergency of our hospital with upper GI (gastrointestinal) bleeding was given Terlipressin 2 mg IV bolus, followed by 1mg every 6-hourly until endoscopy was done. Those with proven esophageal varices as the cause of bleeding were managed with band ligation and were enrolled. 54 enrolled patients were randomized into 14 (25.9%) in control Group-A and 40 (74.1%) in experimental Group-B. Group-A was treated for 72-

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hour with Terlipressin while Group-B was treated for 12-hour. Both groups were observed for episodes of rebleeding for at least 5 days.
Results: Rebleeding was observed in 1 (7.1%) patient in Group-A and 2 (6.7%) in Group-B during the 5-day period. All 3 (5.5%) underwent second endoscopy. The Group-A patient and 1 (3.3%) of 2 Group-B patients showed ulcers around the sites of band ligation as cause of bleeding. The second patient in Group-B showed esophagus varices requiring repeated banding.
Conclusion: 12-hour Terlipressin treatment along with banding is cheaper while as effective as 72-hour regime.

Keywords: Terlipressin; variceal bleeding; portal hypertension; liver cirrhosis.

ABBREVIATIONS

DHQ : District Headquarters
EVBL : Endoscopic Variceal Band Ligation
GI : Gastro-Intestinal
g/dL : gram per deci-litre
HBV : Hepatitis B Virus
HCC : Hepato-Cellular Carcinoma
HCV : Hepatitis C Virus
HTN : Hypertension
mg : milligram
MELD : Model for End-stage Liver Disease
NG : Naso-Gastric
SBP : Spontaneous Bacterial Peritonitis
SD : Standard Deviation
SPSS : Statistical Package for Social Sciences

1. INTRODUCTION

Terlipressin is an effective therapy to limit upper gastrointestinal (GI) bleeding caused by esophageal varices [1,2]. But the 5-day regimen recommended in literature is rather costly for patients in low-income countries like Pakistan where even government hospitals are poor in resources [3,4]. Cirrhosis induced by chronic stages of viral hepatitis is fairly common in Pakistan [5,6]. There is a huge number of hospital admissions due to variceal bleeding in cirrhosis patients on the background of chronic hepatitis.

Management of upper GI bleed includes resuscitation with blood transfusion or plasma spreaders, supportive treatment with proton pump inhibitors, interventions like upper GI endoscopy with variceal band ligation and treatment with vasoactive agents until availability of interventions. Terlipressin is an effective vasoactive agent [7,8]. Across the Pakistan, many hospitals lack the facility of endoscopy and 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 [9]. Vasoactive agents affect vasomotor tone. Depending on the direction of such effect, vasoactive agents can be subdivided into vasoconstrictors and vasodilators.

Terlipressin is a vasoconstrictors and a synthetic analogue of vasopressin. Mechanism of action of Terlipressin is by acting upon V1a receptors of the mesenteric vessels leading to decreased blood flow in the portal vein. Decreased portal venous pressure leads to low pressure in esophageal varices [10]. The standard regimen is to administer Terlipressin for around 5 days following an upper GI bleed caused by esophageal varices. At this study center, patients have been effectively treated, for variceal bleeding, with Terlipressin regimens which are shorter than the recommended 5-day schedule. If proven effective is this study, a shorter regimen will allow for shorter hospital stay and decreased financial burden on both the healthcare services and the patient.

The purpose of this study was to define whether Terlipressin given only for 12-hour is as effective as 72-hour of Terlipressin treatment in inhibiting rebleed after endoscopic intervention of variceal bleeding.

2. METHODOLOGY

A randomized clinical trial was carried out, during February 2018 to April 2018, in the Department of Medicine (Unit of Gastroenterology and Hepatology) at District Headquarter (DHQ) Teaching Hospital, Sahiwal which is a district level tertiary care healthcare facility in Pakistan. Approval from the ethical committee of the hospital was followed by inclusion of patients who presented during February to March 2018 based on following criteria:

2.1 Inclusion Criterion

- Patients with age above 18 years.
- Patients presenting with Upper GI bleed.

- Patients with liver cirrhosis of ultrasound scan of abdomen.
- Patients with a history of viral hepatitis.

2.2 Exclusion Criteria

- Patients who were having gastric varices, bleeding peptic ulcer or vascular ectasias on endoscopy.
- Patients with any form of acute coronary syndrome or a recent thrombotic event.
- Patients who were not willing for indoor stay after endoscopic intervention.
- Patients who didn't consent to inclusion in the study.

A sum of 54 patients were selected for the sake of this study after calculation of sample size in the population of Sahiwal District (Sahiwal District has 831,468 people over the age of 18 years) using WHO sample size calculator for Bio Medical research and studies by taking 95% confidence level with 7% margin of error and considering the expected percentage efficacy of Terlipressin (along with endoscopic band ligation) of 98% in the treatment of patients presenting with upper GI bleed caused by esophageal varices.

All patients with known liver cirrhosis presenting to the hospital emergency with upper GI bleed, manifested as hematemesis or melena or both, were given Terlipressin loading dose of 2 mg intravenous bolus, and then maintenance dose of 1 mg every 6 hourly. Patients who had esophageal varices alone, as the mechanism for bleeding, were treated with band ligation and were selected for the study. Preceding the signing of informed consent with all necessary details, patients were counseled regarding both the treatment options and were then randomized into two groups, A and B. Group A was constituted by 14 patients and Group B had the rest of 40 patients. Randomization was done by the process of simple random sampling technique. Group-A was treated with Terlipressin at the dose of 1mg every 6 hourly for a total of 72 hours while Terlipressin was stopped in Group-B after treatment for only 12 hours. In both the groups, a few patients also received the antibiotic treatment if there was a suspicion of Spontaneous Bacterial Peritonitis (SBP) while all of the patients received some other drugs as well. To name one, Rifaximine was given as 550 mg tablet to all patients orally. But these medicines were same to all the patients included in the study and hence were not considered to affect the results of the study in anyway.

Bleeding from esophageal variceal was defined, for the purpose of this study, as hemorrhage from dilated veins in the lower part of esophagus caused by increased pressure in the portal vein that happens commonly due to end stage cirrhosis of the liver. Patients were monitored for at least 5 days after the first dose of Terlipressin for any rebleeding episode. Rebleeding episode was defined as a new bleeding during subsequent hospitalization, after the initial bleeding had ceased completely or fresh red blood in the nasogastric (NG) tube aspirate or decrease in hemoglobin level of more than 2 g/dL. If there was no such rebleeding episode, the treatment given would be labelled as effective in that patient. Both the study groups were observed for 5 days after band ligation. All patients were subjected to daily check of their bloods for hemoglobin level. All information was gathered on a specifically designed proforma and Version 21 of the software Statistical Package for Social Sciences (SPSS) was used to analyze all this data. Nominal data like gender as well as efficacy was analyzed as frequencies along with percentages and was subjected to Chi-square test. While the quantitative data like age was represented as mean along with its standard deviation. However, Child Pugh Score was analyzed in both the study groups by applying independent sample t-test. P value below 0.05 was considered significant statistically, for the purpose of this study.

3. RESULTS

54 patients included in the study were randomized into two groups, A and B, group A was formed by 14 (25.9%) patients and group B was formulated by 40 (74.1%) patients. Group A was selected to be the control group and was treated with longer regime of Terlipressin for 72 hours. Group B was the experimental group and was given Terlipressin for only 12 hours.

Mean age for Group-A was 54.26 ±09.25 (Lower age limit: 41 years, Upper age limit: 66 years) in years and 53.86 ±08.91 years for Group-B (Lower age limit 39 years, Upper age limit: 68 years) while 32 (59.2%) patients were male (Group A: 9, Group B: 23) and 22 (40.8%) patients were female (Group A: 5, Group B: 17). Predominant cause for liver disease was infection with Hepatitis C Virus (HCV) for 49 patients (90.7%) while rest of the patients had

Hepatitis B Virus (HBV) infection (2 patients), Hepatitis D and B virus co-infection (1 patient) Hepatitis D and C virus co-infection (1 patient) and alcoholic liver disease (1 patient). Mean MELD score for group A was 18 ±3 while for group B it was 19 ±2. Out of the total 54 patients, MELD score for 39 (72.2%) patients was below 19, while MELD score for 15 (27.8%) patients was above 19.

Most patients (30 patients: 55.5%) were found out to have Child Class B disease (Table 1). Most patients (52: 96.2%) were found of having high-grade varices (Grade III-IV) on upper GI endoscopy (Table 2). Diabetes mellitus was the most common comorbidity in this patient group with 26 (48%) patients having this. Nine (16.6%) patients had hepatocellular carcinoma (HCC) and systemic hypertension (HTN) was found in 5 (9.2%) patients. Rebleeding episode happened in 3 patients, 1 (7.1%) of these patients was in in Group-A (72-hour treatment with Terlipressin) and 2 (6.7%) of these patients were in Group-B (12-hour treatment with Terlipressin group), during the period of 5-day after endoscopic band ligation. All 3 patients were already classified as Child Class C stage liver disease. The 3 rebleeders had to undergo second endoscopic evaluation to confirm the cause of this second episode of bleeding. The one (7.1%) Group-A patient and one (3.3%) of the 2 Group-B patients showed formation of ulcers around the sites of band ligation as sources of this episode of bleeding. Overall incidence of this kind of ulcer bleed secondary to band ligation was 2 out of 54 patients (6.7%). These patients were subjected to conservative treatment with an intravenous (IV) Omeprazole infusion and Antacid oral suspension. The second Group-B patient showed that varices had red signs and required another band ligation.

Therefore, only one patient among those 3 rebleeders required second Endoscopic Variceal Band Ligation (EVBL). Observed frequency of second episode of bleeding in Group-A, (7.1%)

Table 1. Stage and severity of liver disease in both groups

Stage	Group A (14 Patients of 72-Hr Group)	Group B (40 Patients of 12-Hr Group)	P-Value*
MELD Score (Mean ± SD)	18 ±3	19 ±2	0.981
<19	10 out of 39 (25.6%)	29 out of 39 (74.4%)	
>19	4 out of 15 (26.6%)	11 out of 15 (73.4%)	
Child Pugh Class			
A	None	None	
B	8 out of 14 (57.1%)	22 out of 40 (55%)	0.812
C	6 out of 14 (42.9%)	18 out of 40 (45%)	
Child Pugh Score (Mean ± SD)**	8.32 ±1.58	9.8 ±1.42	0.41

**Pearson Chi-Square test; **Independent sample t-test*

Table 2. Findings of endoscopy regarding esophageal varices

Stage	Group A (14 Patients of 72-Hr Group)	Group B (40 Patients of 12-Hr Group)	P-Value*
Variceal Grading			
I	None	None	
II	1 out of 14 (7.1%)	1 out of 40 (2.5%)	0.762
III	7 out of 14 (50%)	18 out of 40 (27%)	
IV	6 out of 14 (52.9%)	21 out of 40 (70.5%)	
Variceal Column			
1	None	None	
2	1 out of 14 (7.1%)	2 out of 40 (5%)	0.708
3	8 out of 14 (57.1%)	26 out of 40 (65%)	
4	5 out of 14 (35.8%)	12 out of 40 (30%)	

**Pearson Chi-Square test*

compared with Group-B (6.7%) was statistically insignificant (p=0.913). There was one death in Group-A owing to development of hepatic encephalopathy, following the management with band ligation but this happened on 7th day following EVBL and hence patient was labelled as successfully treated for the purpose of this study. There was no death in Group-B. None of the patients observed any treatment related adverse effects.

Comparison of the cost of treatment with Terlipressin showed that Group-A patients who needed 14 ampoules of Terlipressin (1 mg) had a total treatment cost of this individual drug to be PKR15,400 while the cost of complete treatment for this individual drug for Group-B was PKR4,400 for a total of 4 ampoules of Terlipressin (1 mg).

4. DISCUSSION

This study concluded that a shorter (12-hour) duration of Terlipressin treatment, in addition to endoscopic variceal band ligation, offers similar results to typical 72-hour treatment. Earlier studies have discovered a shorter Terlipressin management in comparison to the regular 72- to 120-hour treatment and have publicized that shorter options can be as effective as regular with no decease in protection [11,12].

Of the two groups matched in this study, real variceal rebleeding needing repeated EVBL was only seen in one patient. It was also comprehended that the other 2 rebleeders had bled from ulcers that had originated around the sites of EVBL. Ulcer formation on the site of variceal ligation is a recognized complication [13,14]. Those ulcers can be treated efficiently using infusion of proton pump inhibitor and oral therapy with Antacid suspensions [15,16].

The short duration of treatment with Terlipressin means a shorter hospital admission. This results in decrease in other IV medicines (namely antibiotics, proton pump inhibitors) and accompanying bed occupation expenditures. In order to elaborate the decrease in budget of therapy, we noticed that the price per 1 milligram ampoule of Terlipressin in Pakistan is approximately PKR1,100 (11 USD). The cost of the recommended 3- 5-day treatment (supposing 2 mg then followed by 1 mg every 6 hourly) with a total of 14-22 mg Terlipressin administered is around PKR15,400 to 24,200 (150-250 USD) for one patient. One the flip side of the coin, the price of 12-hour administration is around PKR4400 (USD 44) per patient.

But it must also be considered that the study was not without limitations. The foremost thing was limited follow-up as after the 5-day period a lot of patients went to visit other specialized care hospitals (higher centers) and similarly during the study sometimes same drug was provided by different brands as study center is a government owned hospital. So the reader should keep these things in mind. At the same time, authors would welcome any new researchers to feel free to contact us for any kind of discussion.

5. CONCLUSION

Bleeding from esophageal varices can be effectively controlled with a shorter 12-hour regimen of IV Terlipressin together with endoscopic variceal band ligation. This intervention will help to attain comparable effectiveness and protection as the existing regular 72-hour regimen of Terlipressin, hence, cutting a lot of hospital expenses.

CONSENT

Preceding the signing of informed consent with all necessary details, patients were counseled regarding.

ETHICAL APPROVAL

Approval from the ethical committee of the hospital was followed by inclusion of patients who presented during February to March 2018.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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