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Rational for continuing terlipressin after endoscopic variceal ligation in acute variceal haemorrhage needs further evidence: a pilot study

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ABSTRACT – **Background** – Variceal hemorrhage (VH) is a medical emergency. Prompt endoscopic variceal ligation (EVL) is therapeutic. Terlipressin is used in VH and continued for 2–5 days even after EVL. As hemostasis is primarily achieved by EVL, the benefit of continuing trelipressin after EVL is unknown. **Objective** – To evaluate the efficacy of continuing terlipressin after EVL to prevent re-bleed and mortality. **Methods** – In this pilot study, after EVL 74 patients of VH were randomized into two treatment groups TG2 & TG5, received terlipressin (1 mg IV bolus q 4 hourly) for 2 days and 5 days respectively and one control group (TG0), received 0.9% normal saline (10 mL IV bolus q 4 hourly) and followed up for 8 weeks. **Results** – A total of 9 (12.6%) patients had re-bleed with maximum 4 (5.6%) patients in TG5 group followed by 3 (4.2%) in TG2 and 2 (2.8%) in TG0 groups (P=0.670). The overall mortality was 15 (21.1%) patients, 6 (8.5%) patients in TG0 group, followed by 5 (7.0%) in TG5 and 4 (5.6%) in TG2 group (P=0.691). Adverse drug reactions were significantly higher in treatment groups with maximum 18 (24.32%) patients in TG5, followed by 8 (10.8%) in TG2 and 2 (2.7%) in TG0 groups (P=0.00). Duration of hospital stay was also significantly higher in treatment group, 6.63 (±0.65) days in TG5 followed by 3.64 (±0.57) in TG2 and 2.40 (±0.50) days in TG0 groups (P=0.00). **Conclusion** – The rational for continuing terlipressin after EVL is doubtful as it didn't have any benefit for the prevention of re-bleed or mortality; rather it increased the risk of adverse drug reactions and duration of hospital stay. Further randomized clinical trials are encouraged to generate more evidence in support or against continuing terlipressin after EVL.

Keywords – Terlipressin; variceal hemorrhage; endoscopic variceal ligation; re-bleed; mortality; adverse drug reaction; portal hypertension; chronic liver disease; cirrhosis; gastrointestinal bleed.

INTRODUCTION

Upper gastrointestinal (UGI) bleed of variceal origin is a frequently encountered medical emergency. Prompt endoscopic variceal ligation (EVL) is therapeutic as well as diagnostic. Terlipressin is a vasopressin analog and widely used (intravenous, 2 mg q 4 hourly) in suspicious cases of variceal hemorrhage (VH) before endoscopic procedure is done, along with volume and blood resuscitative measures. As per guideline, after EVL terlipressin therapy (1 mg IV q 4 hourly) is continued for 2–5 days to prevent re-bleed and mortality[1]. But the extended use of terlipressin is not completely safe, as well as expensive also in resource constraint setting. At present there is no clinical trial available to authenticate the benefit of continuing terlipressin after EVL to prevent re-bleed or mortality in acute VH. During the post marketing surveillance terlipressin had been found to be associated with life threatening complications, like cardiac arrhythmia, myocardial ischemia, critical vasoconstriction of peripheral as well as internal organ leading to ischemia or gangrene, severe hyponatremia, hypertension, fluid overload and pulmonary edema[2-4]. So, the justification of continuing terlipressin for 5 days after EVL is questionable, as haemostasis is primarily achieved by EVL and the risk versus benefit of trelipressin therapy after EVL is still undiscovered. Continuing terlipressin after EVL also prolongs in-hospital care causing further expansion of the health care burden. There is still scarcity of evidence regarding efficacy of continuing terlipressin after EVL in preventing re-bleed or mortality and the incidence of adverse drug reaction in acute VH. The present study was about evaluating the benefit or risk associated with continuing terlipressin after EVL in acute VH.

METHODS

Aims

The aim of the study was to evaluate the efficacy of continuing terlipressin after EVL to prevent re-bleed and mortality in acute VH.

Site of study

The study was carried out in emergency medical outpatient department (EMOD) of post graduate institute of medical education and research (PGIMER), a tertiary care centre in northern India, with collaboration of department of internal medicine, gastroenterology, hepatology and pharmacology.

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Study design

It was an open label randomized controlled clinical trial. The study was carried out in three groups; denoting the duration of terlipressin therapy after EVL, two treatment group TG2 and TG5 and one control group TG0. The TG2 and TG5 groups received terlipressin for 2 days and 5 days respectively while the control group (TG0) received 0.9% normal saline (NS). All the patients of endoscopic proven acute VH presented at emergency were screened and subsequently enrolled in the study as per inclusion and exclusion criteria after taking written informed consent. The participants were followed up for 8 weeks telephonically or physically as and when required. The study was registered in the clinicaltrials.gov (clinicaltrials.gov PRS ID: NCT03584087).

Study duration

The study was conducted during the period of January 2018 to July 2019 after getting prior approval from Institutional Ethics Committee (IEC) of the under the n. IEC/2018/000684.

Inclusion and exclusion criteria

Irrespective of gender with age ≥18 years, all the patients with endoscopy proven acute VH with EVL done within 24 hours of admission were enrolled for the study. Patients with UGI bleed for more than 24 hours, past history of UGI bleed or EVL, chronic kidney disease, pregnancy were excluded from the study. Patients who didn't received pre-EVL terlipressin therapy, couldn't achieve haemostasis during EVL, EVL done beyond 24 hours of admission because of hemodynamic instability or encephalopathy were excluded from the study. Further patients who were receiving blood thinners like antiplatelets, anti-coagulation agents within 4 weeks of presentation, were also excluded from the study.

Methods and intervention

Clinical details were noted and base line blood investigations of all the patients were performed for risk stratification and to formulate further plan of management. For management, initial priority was given to secure airway, breathing and circulation. To ensure hemodynamic stability, crystalloid infusion was given as and when required. Blood transfusion was initiated at the threshold hemoglobin (Hb) of 7g/dL, to maintain target Hb of 7–9 g/dL or with signs of hemodynamic instability despite fluid resuscitation. Intra venous (IV) terlipressin (2 mg q 4 hourly) along with proton pump inhibitor and antibiotic were initiated promptly in all suspicious case of VH before endoscopy. Once the patient was hemodynamically stable and airway secured, endoscopy was done as soon as possible, within 24 hours of the presentation by the experienced gastroenterologists and hepatologists in the institute. Once variceal origin of hemorrhage was confirmed, EVL was done. After EVL patients satisfying the inclusion criteria were randomized into two treatment groups TG2 & TG5 and one control group (TG0) (FIGURE 1). The participants in TG2 and TG5 groups received IV terlipressin 1 mg IV bolus q 4 hourly for 2 and 5 days respectively and participants in control group (TG0) received 10 mL of 0.9% normal saline (NS) IV bolus q 4 hourly in place of terlipressin (FIGURE 1). All the participants were kept under observation and discharged subsequently after stabilization when haemostasis achieved and followed up for 8 weeks through OPD visits or telephonically. In case of re-bleed, terlipressin (1 mg IV bolus q 4 hourly) was re-started in those patients who were not receiving terlipressin at the time of re-bleed,

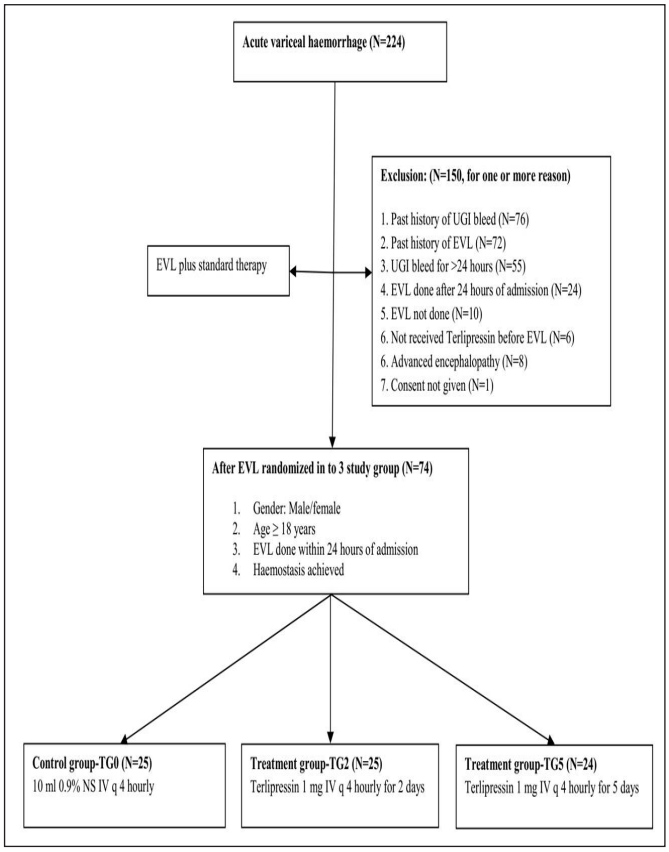

FIGURE 1. Study design.
EVL: endoscopic variceal ligation; UGI: upper gastrointestinal.

both in control as well as treatment groups. Re-bleed was defined as any significant UGI hemorrhage after EVL, leading to repeat endoscopy, hemodynamic instability and significant drop of Hb requiring blood transfusion. In case of re-bleed, another attempt was made for endoscopic hemostasis. Incidence of re-bleed, mortality, need for blood transfusions, duration of hospital stay and ADR were compared between the study groups. ADR incurred in the patients during the study were notified to ADR Monitoring Centre, PGIMER, under the Pharmacovigilance Programme of India (PvPI), National Coordination Centre (NCC) – Indian Pharmacopoeia Commission (IPC), Ministry of Health and Family Welfare, Government of India.

Outcome

Primary outcomes were incidence of re-bleed and mortality among the participant during the 8 weeks follow up. Secondary outcomes were incidence of ADR, duration of hospital stay, cost of therapy and in-hospital complication.

Sample size and statistical analysis

No previous RCT was available for the expected incidence of re-bleed or mortality in the treatment or control group. It was a pilot study. As per available epidemiological evidence, expecting 30% incidence of re-bleed in population with 15% incidence of re-bleed in treatment group, sample size was calculated to be around 70 patients after adjusting α-error of 0.05 with power of 80% and 10% drop out, for the final analysis[5]. A total of 224 patients with

acute VH were screened, out of which 150 patients were excluded as per exclusion criteria (FIGURE 1). Finally, 74 patients of acute VH were enrolled and randomized into three study groups (TG0, TG2, TG5) through computer generated block randomization. The data was managed in database system through Microsoft Excel and statistical analysis was performed by SPSS 24.0 version. The descriptive statistics were summarized as categorical data in the form of percentage, proportions and graphical presentations. The categorical endpoints were analyzed by non-parametric Pearson's chi-square test. Parametric data were presented in the form of mean, range and standard deviation. The mean values were compared for various groups using one-way ANOVA. The *P*-value of less than 0.05 was considered statistically significant. Outcomes were assessed for risk factor by using odds ratio, value more than one was considered significant.

RESULTS

Baseline data of the study population

• Age and Gender

Out of total 74 participants, 61 (82.4%) were male. The mean age of the study population was 48.15 (±11.12) years (range 25 to 71 years). Out of which 12 (16.2%) participants (6, 2 and 4 in TG0, TG2 and TG5 respectively) had age of ≥60 years and 62 (83.8%) participants (19, 23 and 20 in TG0, TG2 and TG5 respectively) were below 60 years of age and comparable between the groups (*P*=0.307). The mean body mass index (BMI) was 23.9 (±3.5) kg/m^2. The distribution of gender, age and BMI were comparable among the study groups (TABLE 1).

• Comorbidity

The most common comorbidity was chronic liver disease (CLD), in 64.9% participants, followed by diabetes mellitus (10.8%), chronic hepatitis C (10.8%) and chronic hepatitis B (9.5%). Two participants had hypertension and one participant had chronic obstructive airway disease (COAD). None of the participants were HIV positive. Total 20.3% participant were smokers and 73% were alcoholic, out of which 67.6% participants consumed alcohol in cirrhogenic dose. The distribution of comorbidities and risk factors were similar among the study groups (TABLE 1). At presentation 51.3% participants had tachycardia (PR ≥100), 20.3% had hypotension (SBP ≤90 mmHg) and 5.4% were hypoxic (SPO2 ≤90%), which were comparable among the study groups (TABLE 1).

• Investigations

Mean Hb, total leucocyte count (TLC) and platelet counts of the study population were 7.76 (±2.3) g/dL, 10.10x10^9/L (±4.8) and 108.5x10^9/L (±85.0) respectively. Clinically significant anemia

TABLE 1. Baseline data of the study population.

Baseline data	TG0 (N=25)	TG2 (N=25)	TG5 (N=24)	*P* value
Males (N=61)	20 (27%)	20 (27%)	21 (28.4%)	0.730
Females (N=13)	5 (6.8%)	5 (6.8%)	3 (4.1%)	0.730
Age (years ±SD)	48.28 (12.005)	48.12 (10.212)	48.04 (11.563)	0.997
BMI (kg/m^2)	23.9 (2.6)	24.1(3.3)	23.8(4.3)	0.906
CLD (N=48)	16 (21.6%)	16 (21.6%)	16 (21.6%)	0.975
DM (N=8)	1 (1.4%)	3 (4.1%)	4 (5.4%)	0.351
Hypertension (N=2)	0	0	2 (2.7%)	0.118
COAD (N=1)	1(1.4%)	0	0	0.370
Hepatitis B (N=7)	3 (4.1%)	2 (2.7%)	2 (2.7%)	0.867
Hepatitis C (N=8)	1 (1.4%)	3 (4.1%)	4 (5.4%)	0.351
Smoking (N=15)	5 (6.8%)	2 (2.7%)	8 (10.8%)	0.088
Alcoholic (N=54)	17 (23%)	17 (23%)	20 (27%)	0.380
Cirrhogenic dose of alcohol (N=50)	14 (18.9%)	16 (21.6%)	20 (27%)	0.111
Tachycardia (PR ≥100) (N=38)	12 (16.2%)	12 (16.2%)	14 (18.9%)	0.707
Hypotension (SBP ≤90) (N=15)	3 (4.05%)	6 (8.1%)	6(8.1%)	0.448
Hypoxia (SPO2 ≤90%) (N=4)	1 (1.4%)	2 (2.7%)	1 (1.4%)	0.780
Cirrhosis (N=66)	22 (29.7%)	22 (29.7%)	22 (29.7%)	0.893
Ascites (N=32)	12 (16.2%)	9 (12.2%)	11 (14.9%)	0.660
Spontaneous bacterial peritonitis (N=3)	1 (1.4%)	2 (2.7%)	0	0.365
Significant anemia (Hb ≤7 gm/dL) (N=28)	13 (17.6%)	7 (9.5%)	8 (10.8%)	0.186
Thrombocytopenia (N=52)	20 (27%)	18 (24.3%)	14 (18.9%)	0.246
Acute kidney injury (N=18)	6 (8.1%)	4 (5.4%)	8 (10.8%)	0.368
Transaminitis (N=48)	15 (20.3%)	18 (24.3%)	15 (20.3%)	0.547
Jaundice (N=40)	12 (16.2%)	15 (20.3%)	13 (17.1%)	0.696
Hypoalbuminemia (N=49)	14 (18.9%)	20 (27%)	15 (20.3%)	0.937
Coagulopathy (N=40)	15 (20.3%)	10 (13.5%)	15 (20.3%)	0.219

BMI: body mass index; CLD: chronic liver disease; DM: diabetes mellitus; COAD: chronic obstructive airway disease.

requiring PRBC transfusion was considered with a Hb ≤7 gm/dL, which was detected in 37.8% participants. Thrombocytopenia was present in 70.3% participants. In coagulation profile mean prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and prothrombin time index (PTI) were 22.9 (±6.5) second, 38.49 (±11.34) seconds, 1.63 (±0.43) and 61.12 (±14.75) % respectively. Coagulopathy (INR >1.5) was present in 54.6% patients. Mean serum urea and creatinine level were 52.5 (±26.06) mg/dL and 1.0 (±0.6) mg/dL respectively and 24.3% patients had renal dysfunction (creatinine of ≥1.5 mg/dL). Liver function test was comparable between the study groups with mean serum bilirubin, aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and albumin were 3.99 (±6.0) mg/dL, 91.69 (±68.4) IU/L, 57.21 (±39.5) IU/L and 2.87 (±0.5) g/dL respectively. Jaundice (total serum bilirubin ≥2 mg/dL) was present in 54.6% patients. Transaminitis (SGOT/SGPT>40 IU/L) and hypoalbuminemia (serum albumin <3.5 gm/dL) were present in 64.9% and 66.2% patients respectively. Baseline investigations were comparable among the study groups (TABLE 1 and 2). Ultrasonography proven cirrhosis with portal hypertension was present in 66 (89.2%) participants with 43.2% had ascites and 4.1% patients had spontaneous bacterial peritonitis (TABLE 1).

TABLE 2. Baseline investigations of the study population.

Baseline investigation	TG0 (N=25) (Mean ±SD)	TG2 (N=25) (Mean ±SD)	TG5 (N=24) (Mean ±SD)	*P* value
Hemoglobin (gm/dL)	6.93 (1.63)	8.22 (2.60)	8.14 (2.41)	0.086
TLC ($\times 10^9$/L)	9.22 (5.0)	10.62 (5.0)	10.48 (4.3)	0.529
Platelets($\times 10^9$/L)	87.56 (62.45)	115.2 (118.32)	123.38 (59.194)	0.304
Urea (mg/dL)	51.68 (25.32)	50.88 (30.37)	55.17 (22.66)	0.834
Creatinine (mg/dL)	0.91 (0.37)	0.89 (0.48)	1.22 (0.86)	0.120
Bilirubin (mg/dL)	3.13 (3.59)	3.31 (3.98)	5.60 (9.03)	0.285
SGOT (IU/L)	110.9 (84.78)	93.16 (69.83)	71.68 (43.42)	0.260
SGPT (IU/L)	60.64 (45.59)	61.39 (41.76)	48.58 (30.24)	0.563
Albumin (g/dL)	2.79 (0.71)	2.90 (0.56)	2.93 (0.45)	0.780
PT (seconds)	22.5 (5.4)	22.0 (6.2)	24.3 (7.9)	0.446
PTI (%)	61.08 (15.95)	63.56 (13.42)	58.52 (14.96)	0.503
INR	1.63 (0.39)	1.55 (0.40)	1.71 (0.50)	0.477
aPTT (seconds)	35.83 (5.79)	37.36 (7.93)	42.60 (16.98)	0.097

TLC: total leucocyte count; SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PTI: prothrombin time index.

TABLE 3. Comparison of outcome among the different treatment and control groups.

Outcomes	TG0	TG2	TG5	*P* value
Re-bleed (N=9)	2 (2.8%)	3 (4.2%)	4 (5.6%)	0.670
Early re-bleed (N=1)	0	0	1 (1.4%)	0.348
Late re-bleed (N=8)	2 (2.8%)	3 (4.2%)	3 (4.2%)	0.888
Mortality (N=15)	6 (8.5%)	4 (5.6%)	5 (7.0%)	0.691
Early mortality (N=2)	0	1 (1.4%)	1 (1.4%)	0.592
Late mortality (N=13)	6 (8.5%)	3 (4.2%)	4 (5.6%)	0.447
Mean units of PRBCs transfusion (N=40)	1.60 (± 1.22)	1.04 (±1.27)	1.00 (±1.38)	0.198
Mean units of FFPs transfusion (N=7)	0.36 (±0.99)	0.24 (±0.83)	0.25 (±0.89)	0.876
Patients with ADR (N=28)	2 (2.7%)	8 (10.8%)	18 (24.3%)	0.00
Diarrhoea (N=25)	2 (2.7%)	7 (9.5%)	16 (21.6%)	0.00
Hypokalemia (N=10)	0	2 (2.7%)	8 (10.8%)	0.002
Bradycardia (N=8)	0	2 (2.7%)	6 (8.1%)	0.016
Abdominal pain (N=7)	1 (1.4%)	3 (4.1%)	3 (4.1%)	0.518
Shock (N=7)	2 (2.7%)	0	5 (6.8%)	0.043
Encephalopathy (N=6)	1 (1.4%)	2 (2.7%)	3 (4.1%)	0.552
Sepsis (N=4)	1 (1.4%)	2 (2.7%)	1 (1.4%)	0.780
Mechanical ventilation (N=3)	0	1 (1.4%)	2 (2.7%)	0.335
Hospital acquired pneumonia (N=1)	0	0	1 (1.4%)	0.348
Duration of hospital stay (days)	2.40 (±0.50)	3.64 (±0.57)	6.63 (±0.65)	0.000
Cost of therapy (INR)	10480 (±3216)	15880 (±2437)	29166 (±4931)	0.000

PRBC: packed red blood cells; FFP: fresh frozen plasma; ADR: Adverse drug reaction; INR: Indian rupee.

Rest of the 8 (10.8%) participants had either Budd Chiari syndrome or extrahepatic portal venous obstruction or grade -3 fatty liver on Ultrasonography.

• Primary outcomes

Out of 74 participants, 71 participants could be followed up for 8 weeks. Three participants (2 in TG0 and 1 in TG5) were lost from follow up after 7 days.

• Re-bleed

Total 9 (12.6%) patients had re-bleed during 8 weeks follow up. Maximum re-bleed occurred in TG5 (5.6%) group followed by TG2 (4.2%) and TG0 (2.8%) groups (TABLE 3). But it was not statistically significant (*P*=0.670). Re-bleed was further divided into early re-bleed (within 7 days) and late re-bleed (after 1 week to 8 weeks). All 74 participants could be followed up for 7 days and early re-bleed occurred in only 1 (1.4%) patient, which was in TG5 group. Rest of 8 (11.3%) patients had late re-bleed, 2.8%, 4.2% and 4.2% in TG0, TG2 and TG5 groups respectively (TABLE 3), which was not statistically significant (*P*=0.888). We found that patients in treatment group (TG2 and TG5 groups) had higher incidence (N=7, 9.9%) of re-bleed as compared to the patients (N=2, 2.8%) in control group (TG0), but statistically insignificant (*P*=0.485). Re-endoscopy was done in six patients out of nine; two in each group. One patient in each group underwent repeat EVL and hemostasis was achieved.

• Mortality

The overall mortality was 21.1% (15 patients) during 8 weeks follow up. Maximum mortality was in TG0 group (8.5%), followed by TG5 (7.0%) and TG2 (5.6%) groups (TABLE 3). But it was not statistically significant (*P*=0.691). All 74 patients could be followed up for 7 days. Early mortality (within 7 days) occurred in 2 (2.7%) patients, one each in TG2 and TG5 groups and none in the control (TG0) group (TABLE 3), but it was not statistically significant (*P*=0.592). Rest of 13 (18.3%) patients had late mortality (after 7 days within 8 weeks), 8.5%, 4.2% and 5.6% in TG0, TG2 and TG5 groups respectively (TABLE 3), which was not statistically significant (*P*=0.447). When comparing the treatment groups (TG2 and TG5) with the control group (TG0), we found that mortality was higher in treatment group (N=9, 12.7%) than control group (N=6, 8.5%) but statistically insignificant (*P*=0.485).

• Cause of death

Most commonly patients died because of CLD related complications 9 (60.0%). Cause of death was re-bleed in 4 (26.7%) patients, hepatic encephalopathy in 3 (20%) patients, refractory shock in 1 (6.7%) patient and re-bleed with aspiration pneumonia in 2 (6.7%) patient. One (6.7%) patient died of traumatic head injury. Cause of death was not clear in 5 (33.3%) patients who died at home. Two patients had in-hospital early mortality due to hepatic encephalopathy (TG2 group) and refractory shock (TG5 group). Both of these patients did not have evidence of re-bleed. One patient under TG5 group had late mortality from in-hospital early re-bleed and subsequent aspiration pneumonia requiring mechanical ventilation.

Secondary outcomes

• Blood component transfusion requirement

Total 40 (54.1%) patients required Blood component transfusion in the form of packed red blood cells (PRBC) and fresh frozen plasma (FFP). FFP was transfused in 7 (9.5%) patients who also required PRBC and 33 (44.6%) patients required only PRBC transfusion. Mean number of PRBC and FFP units transfusion (TABLE 3) were not significantly different between the study groups (*P*=0.198). None of the patients required platelets transfusion.

• Adverse drug reaction

Out of 74 patients, ADR was noted in 28 (37.5%) patients. Most commonly in TG5 group (24.3%), followed by TG2 (10.8%) and TG0 (2.7%) study groups (TABLE 3). ADRs were significantly higher in treatment group than control group (*P*=0.000). Most Common ADR was diarrhea, followed by hypokalemia and bradycardia and 15 patients reported two or more ADR. ADR was significantly higher in treatment groups than control group (TABLE 3).

• In-hospital complications

Most common in-hospital complication was shock (seven patients), followed by encephalopathy (six patients) and sepsis (four patients). Total three patients required mechanical ventilation and one patient developed hospital acquired pneumonia (TABLE 3). Though the incidence of in-hospital complication was higher in TG5 group but it was statistically significant only for shock (*P*=0.043).

• Duration of hospital stay

Mean duration of hospital stay for all patients was 4.19 (±1.86) days. Mean duration of hospital stay was 2.40±0.50 days, 3.64±0.57 days and 6.63±0.65 days in TG0, TG2 and TG5 groups respectively (TABLE 3). Duration of hospital stay was significantly prolonged as the number of days of terlipressin therapy was increased (*P*=0.000).

• Cost of therapy

Mean cost of therapy for the study participants was INR 18364.86 (±8647.70) which was INR 10480 (±3216), INR 15880 (±2437) and INR 29166 (±4931) in TG0, TG2 and TG5 group respectively (TABLE 3). As the duration of hospital stay and duration of terlipressin therapy was increased, cost of therapy also significantly increased (*P*=0.000).

DISCUSSION

Acute VH is a medical emergency and mostly secondary to CLD leading to cirrhosis and portal hypertension. Mortality from VH varies from 20–80%, depending upon whether the patients present with isolated event of VH or with ascites or encephalopathy[6]. The immediate goal of therapy is to control bleeding, prevent early recurrence and prevent 6-week mortality[7]. Prompt EVL is therapeutic as well as diagnostic. Before EVL, the initial priority is to assess airway, breathing and maintain circulatory volume with crystalloids for hemodynamic stability. Blood transfusion is indicated to target Hb of ≥7 g/dL[8]. Endoscopy is done as soon as possible, preferably within 24 hours of the presentation. During endoscopy when variceal origin of bleeding is confirmed, EVL should be done promptly. But re-bleed is not unusual and it may be as high as 30–40% of cases[9]. In case of re-bleed another attempt of endoscopic hemostasis is tried. In refractory bleeding definite treatments with transjugular intrahepatic portosystemic shunt is

under taken. Terlipressin along with proton pump inhibitor and antibiotic have been widely used as adjuvant pharmacotherapy in acute VH. Terlipressin is a vasopressin analog. Its pharmacological effect is mediated through stimulation of vasopressin-1 receptors of vascular smooth muscle, causing vasoconstriction of splanchnic circulation leading to decrease in portal flow and hepatic venous pressure gradient[2]. As per guideline terlipressin (2 mg IV q 4 hourly) is promptly used in any suspicious case of VH before endoscopic procedure and continued (1 mg IV q 4 hourly) for 2–5 days after EVL to prevent re-bleed and mortality[1]. But the prolong use of terlipressin is not completely safe. It increases in-hospital care burden and expenses in resource constraint setting like India. Terlipressin is also known to be associated with some life threatening cardiovascular, ischemic, pulmonary and electrolytes imbalance like complication[2-4]. So the benefit of continuing terlipressin for 5 days after EVL is debatable, as haemostasis is primarily achieved by EVL. The present pilot study was a prospective, open label randomized controlled clinical trial. Primary end point of this study was to evaluate re-bleed and mortality benefit of terlipressin therapy after successful EVL in acute VH.

Re-bleed

In 1989, Freeman et al. found that 60% of VH were controlled with terlipressin compared to 37% with placebo[10]. Re-bleed was also more common in the placebo group and 5 days bleeding remained under control in 54% of patients with terlipressin therapy compared to 19% with placebo (P<0.025). Blood transfusion requirement was similar in the two groups. However, the sample size was 29 patients only. In 1990, Sodurlund et al. concluded that 90.3% of VH was controlled with terlipressin therapy for duration of 24 hours to 36 hours as compared to 58.6% with placebo[11]. Blood transfusion requirement was also fewer in terlipressin group. But unlike our study both of these studies did not consider EVL and use of terlipressin after EVL. Y Peng et al. in 2013, compared efficacy of EVL combined with 1 mg/day of terlipressin for 5 days and EVL combined with 10 mg/day of oral propranolol for 5 days[12]. Early (5-day) re-bleeding was significantly lower in EVL plus terlipressin group than in EVL plus propranolol group (2.1% vs 12.5%). There was no significant difference in 3-month re-bleeding rate between two groups (4.2% vs 14.6%). As compared to Y Peng et al. the dose of terlipressin used in our study was significantly higher. As per guidelines, terlipressin is continued for 2-5 days after EVL at a dose of 1 mg every 4 hours[1]. Presently there is no clinical trial available to define the duration & rational of terlipressin therapy after EVL. In our study, we compared the different duration of terlipressin therapy after successful EVL. There was no significant differences in the re-bleed rate (TABLE 3) in different groups in our study (P>0.05). In our study, re-bleed occurred in 9 (12.6%) patients. Only one patient had early re-bleed, which was in TG5 group, received terlipressin for 5 days. Overall 7 (9.9%) patients in treatment group (TG2 & TG5) had re-bleed as compared to 2 (2.8%) patients in control group (TG0). So re-bleed was more in patients who received terlipressin for longer duration after EVL, though the data was not statistically significant (P=0.485). Since all the patients underwent EVL within 24 hours of their arrival, early re-bleeding was less in our study compared to the above studies. Since hemostasis could be achieved with EVL, use of terlipressin after EVL to prevent re-bleed was not beneficial in our study. According to our study, using terlipressin after EVL did not offer advantage in terms of controlling re-bleed.

Mortality

Mortality from VH varies from 20–80%[6]. In 1992, Arcidiacono et al. found that re-bleed was significantly higher in sclerotherapy alone group than sclerotherapy plus terlipressin group (29.5% vs 12.7%) though the mortality rate was similar (10.5% vs 9.8%) in both the groups[13]. But in this study none of the patient underwent EVL. In our study, overall mortality was 21.1% (15 patients) and two patients had early mortality; one each from TG2 & TG5 groups. None of the patients in control group had early mortality. In present study there was no significant differences in the early or late mortality (TABLE 3) in different study groups (P>0.05). As per present study overall mortality was higher in treatment group (N=9, 12.7%) than control group (N=6, 8.5%) but statistically insignificant (P=0.485). As in other studies, most common cause of death in present study was also CLD related complications, like re-bleed and hepatic encephalopathy, followed by shock and aspiration pneumonia. At present there is no other major clinical trial available regarding mortality benefit of terlipressin therapy after EVL. As per present study continuing terlipressin after EVL did not yield any mortality benefits. Smoking, alcohol, presence of ascites, jaundice and coagulopathy were associated with increased risk of re-bleed and mortality as per our study (supplementary file).

Blood component transfusion

As per Freeman et al., PRBC transfusion requirement was similar in both terlipressin and placebo groups[10], whereas Soderlund et al. found that PRBC transfusion requirement was more in placebo group than in terlipressin group[11]. In present study mean number of PRBC (P=0.198) and FFP (P=0.876) units transfusion were not significantly different between the study groups (TABLE 3). According to present study, terlipressin therapy after EVL did not show any major benefit for the need for PRBC or FFP transfusion.

Adverse drug reactions and in-hospital complications

Sodurlund et al. noted gastrointestinal cramps, diarrhea, bradycardia and ECG changes, hypertension as common ADR associated with terlipressin therapy[11]. Similar side effects were also noted by Arcidiacono et al.[13]. Similar ADR was noted in the present study. Most common was diarrhea, followed by hypokalemia, bradycardia and non-specific abdominal pain (TABLE 3). There were some reports of terlipressin associated ischemic complication of peripheral as well as internal organ including heart[1,3,4]. None of the participants in our study complained of chest pain and features suggestive of ischemic heart disease, as well as peripheral ischemia. Most of the ADR was common in TG5 group as compared to TG2 and control group (P=0.000). So, our study showed using terlipressin for longer duration may result in number of ADR. These ADR were mainly minor, self-limiting and subsided, requiring close observation. Similarly, in-hospital complications such as need of mechanical ventilation, sepsis, encephalopathy, shock were more in the patients admitted for longer duration and received terlipressin therapy after EVL, though the data was statistically not significant.

Recently published meta-analysis with systematic review concluded that terlipressin along with EVL was effective in bleeding control and preventing in-hospital mortality in acute VH but terlipressin alone was not effective therapy for acute VH[14]. Same study also showed that terlipressin was not completely safe and free of complications[14]. So EVL is the definitive form of therapy to achieve primary hemostasis and terlipressin is bridging the interval before the definitive therapy with EVL is done. At present there is no

clinical trial available to prove the efficacy of continuing terlipressin after EVL in acute VH to prevent re-bleed or mortality. As per index study continuation of terlipressin after achieving haemostasis with EVL was not beneficial for preventing re-bleed, mortality and need for blood product transfusion, in fact it increased the risk of ADR, duration of hospital stay, in-hospital complications and cost of the therapy. Continuing terlipressin even after achieving hemostasis with EVL also prevents early discharge and increases health care burden for the already congested emergency facilities, like our institute. Further randomized double blind study with larger sample size is required to verify the efficacy of the continuing terlipressin after EVL in acute VH.

Limitations of the study were first, it was an open label study. We could not do blinded study because as per guidelines, in acute VH terlipressin is recommended to be continued after EVL for 2 to 5 days. So, we did not get ethical clearance for blinded study because of risk of re-bleed involved in the study participants. This study, which to our knowledge is the only clinical trial tried to evaluate the rational of continuing Trelipressin after EVL in acute VH. Secondly the sample size was small because of strict exclusion criteria. PGIMER, being tertiary care centre, caters many patients referred from multiple northern states of India and arrival in the institute for definitive therapy may take several hours. Acute VH is medical emergency and any delay in intervention may influence the outcome of the patients. So we excluded all the patients with recurrent bleed and bleeding for more than 24 hours to prevent bias and maintain uniformity in the study groups.

We conclude that in acute VH, terlipressin should be used as a bridging therapy before definite EVL is done to achieve haemostasis. Rational for continuing terlipressin after EVL in acute VH is doubtful as it did not have any benefit for prevention of re-bleed or mortality, rather it increased the risk of ADR, duration of hospital stay, in-hospital complications and cost of the therapy. However, further randomized control studies with larger sample size are recommended to establish and verify the rational of continuing terlipressin after EVL to prevent re-bleed or mortality in acute VH.

Authors' contribution

Poudel RC: plan execution, data analysis, protocol, and manuscript writing. Dhibar DP: concept, design, data analysis, protocol and manuscript writing. Sharma N: patient management and guidance. Sharma V: patient management, endoscopic intervention. Taneja S: patient management, endoscopic intervention. Prakash A: randomization, statistical analysis, ADR monitoring. Each author has contributed significantly to the submitted work.

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SUPPLEMENTAL

TABLE 4. Risk factors for re-bleed & mortality.

Risk factors	Re-bleed (N=9)	Risk factors	Mortality (N=15)
Male (N=8) vs female (N=1)	OR–1.597 95%CI 0.233–10.936	Male (N=14) vs female (N=1)	OR–2.847 95%CI 0.413–19.647
Alcoholic (N=7) vs non-alcoholic (N=2)	OR–1.234 95%CI 0.340–4.472	Alcoholic (N=13) vs non-alcoholic (N=2)	OR–2.277 95%CI 0.590–8.781
Smoker (N=3) vs non-smoker (N=6)	OR–1.234 95%CI 0.766–1.986	Smoker (N=5) vs non-smoker (N=10)	OR–1.259 95%CI 0.865–1.883
Hb ≤7 gm/dL (N=4) vs Hb >7 gm/dL (N=5)	OR–0.722 95%CI 0.213–2.453	Hb ≤7 gm/dL (N=8) vs Hb >7 gm/dL (N=7)	OR–1.454 95%CI 0.822–2.572
With TCP (N=5) vs without TCP (N=4)	OR–0.871 95%CI 0.320–2.374	With TCP (N=7) vs without TCP (N=8)	OR–0.853 95%CI 0.652–1.116
With CP (N=7) vs without CP (N=2)	OR–2.323 95%CI 0.668–8.073	With CP (N=12) vs without CP (N=3)	OR–2.768 95%CI 0.979–7.824
With jaundice (N=8) vs without jaundice (N=1)	OR–4.645 95%CI 0.721–29.945	With jaundice (N=11) vs without jaundice (N=4)	OR–1.942 95%CI 0.808–4.665
With ascites (N=5) vs without ascites (N=4)	OR–1.379 95%CI 0.647–2.939	With ascites (N=11) vs without ascites (N=4)	OR–2.545 95%CI 1.079–6.003

OR: odd ratio, CI: confidence interval, TCP: thrombocytopenia, CP: coagulopathy, Hb: haemoglobin.

Risk factors for re-bleed & mortality

In our study re-bleed (OR–1.597, 95%CI 0.233–10.936) and mortality (OR–2.847, 95%CI 0.413–19.647) were more common in males than in females. This may be due to the fact that most of the patients were male who were alcoholic with CLD. Similarly smoker (OR–1.234, 95%CI 0.766–1.986), alcoholic (OR–1.234, 95%CI 0.340–4.472), patient with jaundice (OR–4.645, 95%CI 0.721–29.945), ascites (OR–1.379, 95%CI 0.647–2.939) and coagulopathy (OR–2.323, 95%CI 0.668–8.073) had increased risk for re-bleed and mortality as compared to non-smoker (OR–1.259, 95%CI 0.865–1.883), non-alcoholic (OR–2.277, 95%CI 0.590–8.781),

patients without jaundice (OR–1.942, 95%CI 0.808–4.665), ascites (OR–2.545, 95%CI 1.079–6.003) and coagulopathy (OR–2.768, 95%CI 0.979–7.824) respectively. In our study patient with significant anemia (Hb ≤7 gm/dL) had increased risk of death within 8 weeks (OR–1.454, 95%CI 0.822–2.572) but there was no relation with re-bleed (OR–0.722, 95%CI 0.213–2.453) as compared to the patients with Hb >7 gm/dL. In our study there were no relation of re-bleed (OR–0.871 95%CI 0.320–2.374) and mortality (OR–0.853, 95%CI 0.652–1.116) with thrombocytopenia as compared to the patients without thrombocytopenia.

Poudel RC, Dhibar DP, Sharma N, Sharma V, Taneja S, Prakash A. O uso contínuo da terlipressina após a ligadura endoscópica em hemorragia varicosa aguda necessita de mais evidências: um estudo piloto. Arq Gastroenterol. 2022;59(1):89-96.

RESUMO – **Contexto** – A hemorragia varicosa (HV) é emergência médica. A ligadura endoscópica imediata das varizes (LEV) é terapêutica. A terlipressina é usada em HV e contínua por 2–5 dias mesmo após a LEV. Como a hemostasia é alcançada principalmente pela LEV, o benefício do uso contínuo da terlipressina após o evento é desconhecido. **Objetivo** – Avaliar a eficácia da terlipressina contínua após a LEV para evitar o ressangramento e a mortalidade. **Métodos** – Neste estudo piloto, após a LEV, 74 pacientes com HV foram randomizados em dois grupos de tratamento TG2 & TG5, que receberam terlipressina (1 mg EV em bolus a cada 4 horas) durante 2–5 dias, respectivamente, e um grupo controle (TG0), que receberam soro fisiológico normal de 0,9% (10 mL EV em bolus a cada 4 horas) e foram seguidos por 8 semanas. **Resultados** – Um total de 9 (12,6%) pacientes tiveram ressangramento, 4 (5,6%) no grupo TG5, seguidos por 3 (4,2%) no TG2 e 2 (2,8%) no grupo TG0 (*P*=0,670). A mortalidade geral de pacientes foi de 15 (21,1%), 6 (8,5%) no grupo TG0, seguidos por 5 (7,0%) no TG5 e 4 (5,6%) no TG2 (*P*=0,691). As reações adversas de medicamentos foram significativamente maiores em grupos de tratamento em 18 (24,32%) pacientes no TG5, seguidos por 8 (10,8%) no TG2 e 2 (2,7%) em grupo TG0 (*P*=0,00). A duração da internação hospitalar também foi significativamente maior no grupo de tratamento, 6,63 (±0,65) dias no TG5, seguido por 3,64 (±0,57) em TG2 e 2,40 (±0,50) dias em grupos TG0 (*P*=0,00). **Conclusão** – O uso racional para a continuação da terlipressina após a LEV é duvidoso, pois não teve qualquer benefício para a prevenção de ressangramento ou mortalidade; pelo contrário, aumentou o risco de efeitos adversos e duração da internação hospitalar. Outros ensaios clínicos randomizados são necessários para gerar mais evidências em apoio ou contra a terlipressina contínua após a LEV.

Palavras-chave – Terlipressina; hemorragia varicosa; ligadura endoscópica de varizes; ressangramento; mortalidade; reação adversa a medicamentos; hipertensão portal; doença hepática crônica; cirrose; sangramento gastrointestinal.

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