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Comparison of 1-day versus 3-day intravenous terlipressin in cirrhosis patients with variceal bleeding: A pilot randomised controlled trial

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Summary

Background: In cirrhosis patients with acute variceal bleeding (AVB), the optimal duration of vasoconstrictor therapy after endoscopic haemostasis is unclear.

Aims: We aimed to compare efficacy of 1-day versus 3-day terlipressin therapy in cirrhosis patients with AVB post-endoscopic intervention. The primary objective was to compare rebleeding at 5 days between the two arms. Secondary objectives included rebleeding and mortality rates at 6 weeks.

Methods: In this open-label, randomised controlled trial, cirrhosis patients with AVB were randomised to either 1-day or 3-day terlipressin therapy.

Results: A total of 150 cirrhosis patients with AVB were recruited to receive either 1 day ($n=75$) or 3 days ($n=75$) of terlipressin therapy. One patient from 1-day arm was excluded. Modified intention-to-treat analysis included 149 patients. Baseline characteristics were comparable between the two groups. Rebleeding at 5 days: 3 (4.1%; 95% confidence interval [CI]: 0.4–9.0) versus 4 (5.3%; 95% CI: 2.0–10.0), risk difference (RD) $p=0.726$ and 5-day mortality rates: 1 (1.4%; 95% CI: 0–7.3) versus 1 (1.3%; 95% CI: 0.2–7.0), RD $p=0.960$ were similar. Rebleeding at 42 days: 9 (12.2%; 95% CI: 7.0–20.0) versus 10 (13.3%; 95% CI: 7.0–20.0), RD $p=0.842$ and mortality at 42 days: 5 (6.8%; 95% CI: 3.0–10.0) versus 4 (5.3%; 95% CI: 2.0–10.0), RD $p=0.704$ were also similar. Patients in the 1-day terlipressin therapy arm experienced significantly fewer adverse effects compared with those receiving 3 days of terlipressin therapy: 28 (37.8%) versus 42 (56%), $p=0.026$.

Conclusions: Our results suggest that 1 day of terlipressin therapy is associated with similar 5-day and 42-day rebleeding rates, 42-day mortality and an overall superior safety profile compared with 3-day of terlipressin therapy. These findings require to

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be validated in double-blinded, larger, multiethnic and multicentre studies across the various stages of cirrhosis (CTRI/2019/10/021771).

1 | INTRODUCTION

Acute variceal bleeding (AVB) is a common and potentially fatal complication of portal hypertension occurring in 10%–15% of patients with liver cirrhosis per year.[1,2] Despite the availability of effective pharmacotherapy and endoscopic interventions, failure of endotherapy occurs in 15%–20% of patients. The 42-day mortality rates following AVB vary between 15% and 20%, with the most common cause of death being uncontrolled haemorrhage, followed by sepsis.[3–7]

The standard treatment for AVB includes intravenous vasoactive drugs (terlipressin, somatostatin and octreotide) and endoscopic variceal band ligation (EVL).[3] Current recommendations suggest initiation of a vasoactive agent prior to endoscopic intervention. In the study by Lo et al., vasoactive agents alone were able to control variceal haemorrhage in 90% of cases within 48 h but were associated with a 5-day rebleeding rate of 15% compared with 0% in those receiving vasoactive agents along with endoscopic intervention for primary haemostasis.[8] Thus, while early initiation of vasoactive agents is the standard of care at most centres, the duration of treatment with vasoactive agents is variable and the optimal duration of pharmacotherapy after achieving endoscopic haemostasis remains unclear. The American Association for the Study of Liver Diseases (AASLD) and Baveno VII consensus statements recommend that vasoactive drugs be used for 2–5 days after achieving endoscopic haemostasis.[3,9] A longer duration of vasoactive drug use exposes the patient to the risk of drug-induced adverse effects. A prior randomised trial in 2012 reported no differences in 30-day rebleeding and mortality rates between patients receiving terlipressin as adjuvant therapy post-endoscopic haemostasis for 24 h compared to those receiving it for 72 h. Thus, there is data to suggest that a shorter duration of vasoactive drugs is as effective as a longer course in terms of rebleeding and mortality rates.[10–12]

In this randomised controlled trial, we compared the effect of a shorter duration (1-day) versus 3-day therapy with intravenous terlipressin in cirrhosis patients with AVB for differences in (1) rebleeding at 5 days, (2) rebleeding at day 42 and (3) mortality at day 42.

2 | MATERIALS AND METHODS

2.1 | Participants and settings

This was a single centre, investigator-initiated, parallel group, open-label randomised control trial conducted at the Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi between August 2020 and October 2022. The study protocol was approved by the institutional ethics committee and prospectively registered at the Clinical Trials Registry of India (CTRI) (Clinical trial ID: CTRI/2019/10/021771). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients with liver cirrhosis presenting with AVB between 18 and 65 years of age who had presented with acute oesophageal variceal bleeding and subsequent haemostasis after treatment with vasoactive agents and EVL were considered for inclusion in the trial. Cirrhosis was defined by clinical history, imaging evidence and endoscopic criteria. Exclusion criteria were age <18 years, acute-on-chronic liver failure, overt hepatic encephalopathy, chronic kidney disease, spontaneous bacterial peritonitis at presentation, known malignancy including hepatocellular carcinoma or other metastatic malignancy in the liver, variceal bleeding secondary to extrahepatic portal venous obstruction or hepatic venous outflow tract obstruction, patients with shock or on mechanical ventilation, active sepsis, patients on antiplatelets or vitamin K antagonists, active angina, recent myocardial infarction or dynamic electrocardiogram (ECG) changes, gastric variceal bleeding, pregnant women and those unwilling to participate in the trial. Informed written consent was obtained from each patient prior to enrollment in the study.

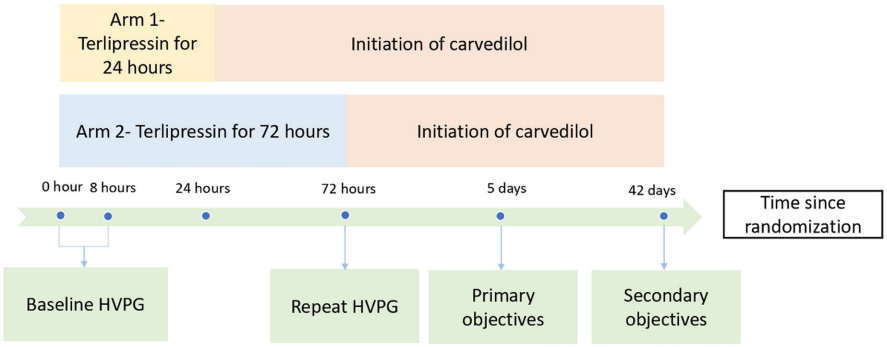
2.2 | Study design

After achieving endoscopic haemostasis, patients were randomised in a 1:1 ratio to receive an abbreviated duration of terlipressin therapy (for 24 h) or a standard duration of therapy (72 h) using a computerised randomisation sequence (Figure 1). Random Permuted Block randomization was performed by using a block size of 6. The Biostatistician (AKM) prepared the randomization plan and coded alpha-numerically. For example, for the first patient, it was coded as PT01. Allocation concealment was done by using sequentially numbered opaque-sealed envelopes prepared by an individual who was not a part of the treating team and blinded to the study results and outcomes.

2.3 | Study procedures

All patients were managed as per the AASLD and Baveno VI consensus statements and received intravenous terlipressin (2 mg every 4 h) prior to endoscopy.[3,9] Packed red blood cell transfusions were done to maintain a pre-endoscopy haemoglobin of 7–8 g/dL. All patients received intravenous ceftriaxone 1 g once daily for 5 days. All endoscopies were performed within 12 h of admission to emergency. All patients underwent ultrasound of abdomen with colour Doppler evaluation of the splenoportal axis to rule out hepatocellular carcinoma (HCC) and portal vein thrombosis (PVT). In patients with

FIGURE 1 Study design.



suspicion of HCC or PVT, a multiphase contrast-enhanced computerised tomography scan (MPCT) was done to verify the findings. At endoscopy, all patients found to have bleeding from oesophageal varices underwent EVL application for primary haemostasis. Bleeding was attributed to oesophageal varices if the following were noted: (i) active bleeding noted from the column of oesophageal varices and (ii) pre-existing varices with high-risk stigmata of recent bleeding such as red spots or fibrin plugs, in the absence of any other source of bleeding. Endoscopic variceal ligation was performed by OmniView multiple band ligator set. After endoscopic haemostasis was achieved, patients were randomised into two groups—groups 1 and 2.

Patients in group 1 received intravenous terlipressin (2 mg every 4 h) for 24 h after endoscopic haemostasis after which the drug was discontinued, whereas in group 2, the patients received intravenous terlipressin for 72 h after endoscopic haemostasis was achieved (2 mg every 4 h for the first 24 h after endotherapy followed by 1 mg every 6 h for 48 h). Patients were monitored for drug-related adverse events that were graded and managed as per the CTCAE criteria.[13] Patients experiencing grade 1 or grade 2 adverse events, had a dose reduction of terlipressin to 1 mg every 6 h or 1 mg every 12 h as tolerated. For those experiencing symptoms even after dose reduction, or those experiencing grade 3 or 4 adverse effects, terlipressin therapy was discontinued and alternative vasoconstrictor therapy was administered (somatostatin infusion 250 μg/h). After cessation of intravenous terlipressin, all patients were started on carvedilol 6.25 mg in two divided doses titrated up to 12.5 mg with a target systolic blood pressure ≥90 mm Hg and heart rate >50/min. HVPG measurement was done after endoscopic haemostasis was achieved. A repeat HVPG measurement was done after 72 h of the initial reading for patients who had undergone HVPG at baseline. All patients could not undergo the index HVPG measurement due to diversion of healthcare facilities during the COVID-19 pandemic or due to other logistic issues.

A dedicated member of the team was responsible for data collection which was made accessible to all authors for review. The primary investigator oversaw the running of the study.

2.4 | Rescue therapy

In the case of rebleeding post-endotherapy, a repeat upper endoscopy was done for endoscopic haemostasis. Transjugular intrahepatic portosystemic shunt (TIPS) or SX-ELLA stent Danis® (self-expanding metal stent) were considered when required for refractory variceal bleeding as a means of rescue therapy only. No patient received pre-emptive TIPSS or liver transplantation as a part of the study.

2.5 | Follow-up

After completion of therapy, patients in both groups were attached to the outpatient department for weekly physical follow-up. Any patient unable to follow up in person was contacted telephonically. All patients were put on an endotherapy schedule to undergo surveillance and EVL (if required) every 3 weeks till complete eradication was achieved. Additional endoscopic examination was done for patients in whom there was a clinical suspicion of rebleeding during outpatient visits or teleconsultation. At each visit, compliance with aetiology-specific medication was assessed and enforced.

Patients with ascites were started on oral diuretics with dose titrated to clinical response. All patients were assessed for adherence to beta blockers and tolerance.

2.6 | Study outcomes

The primary outcome of this study was to compare the efficacy of 1-day with 3-day intravenous terlipressin therapy after primary haemostasis of oesophageal varices in preventing rebleeding at 5 days. Secondary outcomes included rebleeding rates and mortality at 6 weeks post-intervention, and assessment of adverse events, in each arm.

2.7 | Study definitions

AVB was defined as per Baveno VI criteria.[14] Failure to control bleeding was defined as per Baveno VI consensus.[14] Time frame for the same was taken as 120 h (5 days) from the acute bleeding episode. Failure was defined as death or need to change therapy defined by one of the following: (i) fresh hematemesis or NG

aspiration of ≥100 mL of fresh blood ≥2 h after the start of a specific drug treatment or therapeutic endoscopy, (ii) development of hypovolemic shock or (iii) 3 g drop in Hb (9% drop of haematocrit) within any 24-h period if no transfusion is administered. Failure to prevent re-bleeding was defined as a single episode of clinically significant re-bleeding from portal hypertensive sources after day 5. Clinically significant re-bleeding was defined as recurrent melena or hematemesis resulting in any of the following: (i) hospital admission, (ii) blood transfusion, (iii) 3 g drop in haemoglobin or (iv) death within 6 weeks.

2.8 | Hepatic venous pressure gradient assessment

HVPG was measured on the day of the AVB within 8 h of endotherapy in fasting condition and repeated on day 3. The digital pressure transducer was calibrated to a baseline pressure of 0 mm Hg at the midaxillary line and atrial level. The procedure was done without the use of any sedative agent. Under strict aseptic precautions and noninvasive vital monitoring (pulse oximetry, electrocardiography and blood pressure), access to the right internal jugular vein was achieved under direct ultrasonographic guidance using Seldinger's technique after the application of a local anaesthetic agent (2% Lignocaine).[15] No sedation was given during HVPG measurement. A 7 Fr vascular sheath was placed in the internal jugular vein. An end-hole compliant balloon occlusive Swan Ganz catheter (Edward Life Sciences, USA) was passed under fluoroscopic guidance through the sheath into the right or middle hepatic vein. Ballon was inflated slowly with air to occlude the hepatic vein outflow. A small amount of contrast 3–5 mL was injected to confirm occlusion of hepatic vein and any intrahepatic veno-venous collaterals. Before any measurements, the catheter was flushed. Free hepatic venous pressure (FHVP) was measured by keeping the tip of the catheter in the hepatic vein approximately 2–4 cm away from the opening of the vena cava. Wedge hepatic venous pressure (WHVP) was measured after occluding the hepatic vein. After stabilisation of reading for at least 1 min, the value was taken as the final WHVP. All measurements were repeated, and a variance of up to 1 mm Hg was considered acceptable for each pressure reading. At least three consistent paired values (FHVP and WHVP) were taken for each patient.

2.9 | Statistical analysis

The sample size requirement for establishing non-inferiority of 1-day terlipressin (t1) relative to 3-day terlipressin (t3), assuming the failure to control rebleeding rates based on the previous study by Azam et al.[10] in the two arms as 12% [P_{t1} (0.12), P_{t3} (0.12)] a minimum of 1162, with 581 subjects in both arms (1:1) at 5% level of significance, 80% power, non-inferiority margin of 5% and accounting for non-response of 10%. We recruited 150 patients based on feasibility and expected patient numbers during the study period. Binomial and categorical data were represented as percentages and compared using the χ^2 test. The normally distributed continuous variables were expressed as mean ± SD or Median (interquartile range [IQR (Q_1, Q_2)]) and analysed using the independent sample *t*-test or Mann–Whitney *U* test, respectively. For paired analysis, non-parametric Wilcoxon signed ranks test was used. Kaplan–Meier graphs were used to represent the cumulative probability of 42-day rebleeding and 42-day mortality, with the log-rank test (group comparison of cumulative survival probabilities). The testing of hypothesis for two proportions (H_o = Risk Difference is zero; H_1 = Risk Difference is not zero) in both the arms was performed by two-sided *Z* test, for the primary (rebleeding at 5 days) and secondary (rebleeding and mortality at 42 days) objectives. Sub distribution hazard ratio (sHR) with 95% CI was calculated to assess the risk of rebleeding in the context of competing risks, where the possibility of death before rebleeding was considered. This analysis was performed using the competing risk regression approach outlined in the methods described by Fine and Grey.[16] Cox proportional hazard regression model was applied for predictors of mortality and results were interpreted by the estimated hazard rate (HR) and 95% confidence interval (CI). The two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed by utilising statistical software SPSS (version 25.0, SPSS Inc. Chicago, IL, USA) and MedCalc software (version 15.11.4, MedCalc Software, Ostend, Belgium).

3 | RESULTS

3.1 | Baseline characteristics

A total of 727 cirrhosis patients presented with portal hypertension-related bleeding during the recruitment period (Figure 2). A total of 150 patients met the inclusion criteria and were randomised to either Group 1 ($n = 75$) or Group 2 ($n = 75$). One patient from Group 1 was excluded from the final analysis as the diagnosis of extrahepatic portal venous occlusion was made on imaging after inclusion. Modified intention-to-treat analysis included 149 patients. No patient was lost to follow-up.

The baseline characteristics of patients randomised to Groups 1 and 2 are described in Table 1. No differences were noted in age, cirrhosis aetiology, severity of liver disease (as measured by median MELD [Model for End-Stage Liver Disease], Child–Pugh–Turcotte score [CTP]) and baseline haemoglobin. Alcohol was the most common aetiology of cirrhosis. The median duration of hospital stay in Group 1 was 4 (3–5) days, and in Group 2 was 4 (4–6) days.

3.2 | Primary outcomes

The primary outcome of the study was the rebleeding rate at 5 days (Table 2). None of the patients in Group 1 had rebleeding at

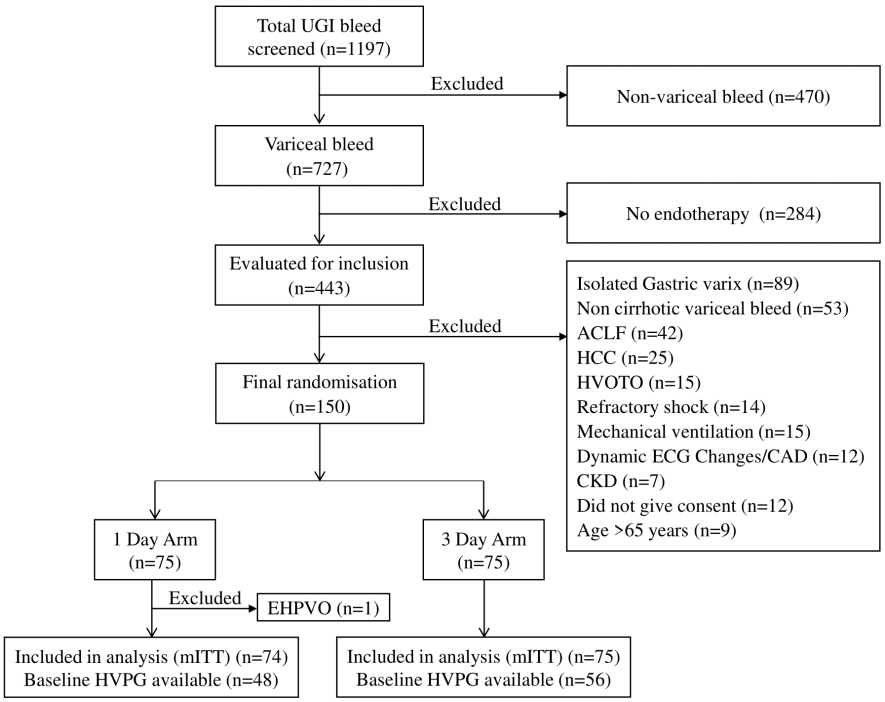


FIGURE 2 CONSORT chart showing flow of patients in the study.

24-h post-endotherapy, whereas 2 (2.7%) patients in Group 2 had rebleeding at 24-h post-endotherapy. The *Z* test for the observed risk difference (H_0: risk difference = 0; H_1: risk difference ≠ 0) was found to be statistically insignificant ($Z = -1.42$, $p = 0.155$). Both these patients were managed with rescue therapy in the form of TIPS due to active bleeding from post-EVL ulcers. Rebleeding at 5 days were similar, 3 (4.1%) in Group 1 and 4 (5.3%) in Group 2. The *Z* test for the observed risk difference was found to be statistically insignificant ($Z = -0.34$, $p = 0.726$).

3.3 | Secondary outcomes

3.3.1 | 42-day rebleeding and mortality

Nineteen (12.7%) patients had rebleeding within 42 days of follow-up: 9 (12.2%) patients in Group 1 and 10 (13.3%) patients in Group 2 (Figure 3A). Five (6.8%) patients from Group 1 and 4 (5.3%) patients from Group 2 died within 42 days (Figure 3B), totalling nine deaths at 42 days (6%) (Table 2). Five patients died due to rebleeding, while the cause of death in the remaining four patients was the progression of underlying liver disease. Only one patient had recidivism in the 1-day arm and had rebleeding at 40 days. The *Z* test for the observed risk difference was found to be statistically insignificant for rebleeding within 42 days ($Z = -0.20$, $p = 0.842$) and mortality ($Z = 0.38$, $p = 0.704$).

3.4 | Predictors of rebleeding and mortality

Group 2 compared to Group 1 was not significantly associated with rebleeding (sHR, 0.86; 95% CI, 0.31–2.37; $p = 0.77$; Table S1). Group 2 compared to group 1 was not significantly associated with death (HR 0.77; 95% CI, 0.21–2.86; $p = 0.693$).

3.5 | Hepatic haemodynamics

Baseline HVPG was available in 48 (64.9%) and 56 (74.7%) patients of Group 1 and Group 2, respectively (Table 3). The median interval between endoscopic therapy and HVPG measurement was 8 h. Median baseline HVPG was similar in Group 1 (16 mm Hg [14–19.8]) and Group 2 (18 [14–20]) mm Hg ($p = 0.338$). Error Plot illustrating mean ± 95% CI for baseline HVPG and day 3 HVPG in the two groups is shown in Figure 4. Change in HVPG was assessed in only those patients who had paired HVPG values of days 1 and 3 available (group 1, $n = 42$ [56.8%], group 2, $n = 48$ [64%]). Median change in HVPG at 3 days was similar between both the groups, that is, −1 (−4–0) mm Hg in group 1 compared with −2 (−4–0) mmHg in group 2 ($p = 0.620$). Patients having HVPG reduction of ≥10% from baseline were comparable in both groups, 20/42 (47.6%) in group 1 versus 30/48 (62.5%) in group 2 ($p = 0.156$). HVPG reduction of ≥20% from baseline was also comparable in both groups, 13/42 (31%) in group 1 versus 14/48 (29.2%) in group 2 ($p = 0.854$). In patients who achieved HVPG reduction of ≥10%, the 5-day rebleeding was 0 versus 2/40 (5%) in those who did not achieve HVPG reduction. The 42-day rebleeding was 3/50 (6%) versus 5/40 (12.5%), and mortality at 42 days was 1/50 (2%) versus 2/40 (5%).

3.6 | Adverse reactions

Adverse drug reactions of terlipressin were seen in 70 (47%) patients overall. They were more common in group 2 compared to group 1: 42

TABLE 1 Baseline characteristics.

Parameters	1-day Terlipressin arm (*N* = 74)	3-days Terlipressin arm (*N* = 75)
Age (years)	44 (36–51.5)	40 (37–48)
Sex (male)	63 (85.1)	67 (89.3)
Aetiology		
Alcohol	36 (48.6)	32 (42.7)
Hepatitis B virus	4 (5.4)	16 (21.3)
Hepatitis C virus	7 (9.5)	7 (9.3)
NAFLD	7 (9.5)	5 (6.7)
Others	20 (27.0)	15 (20.0)
Haemoglobin (g/dL)	8.0 ± 2.8	7.4 ± 2.3
Total leucocyte count (/mm^3)	7500 (5025–10,225)	7200 (4100–13,400)
Platelets (/mm^3)	77 (58–120)	79 (48–114)
INR	1.6 ± 0.5	1.6 ± 0.3
Creatinine (mg/dL)	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Total bilirubin (mg/dL)	1.8 (0.9–3.0)	1.8 (1.1–2.8)
Albumin (g/dL)	2.9 (2.5–3.3)	2.9 (2.4–3.2)
Sodium (mEq/L)	137 (134–140)	136 (134–139)
CTP score	8 (6–9)	8 (7–9)
Child Class		
Child A	21 (28.4)	17 (22.7)
Child B	41 (55.4)	48 (64)
Child C	12 (16.2)	10 (13.3)
MELD score	13.6 (10.4–17.1)	14.2 (11.7–16.8)
Mean arterial pressure (mm Hg)	84 (73–94)	81 (74–87)
Heart rate (/min)	102 (96–116)	100 (92–114)
PRBC transfusion requirement	35 (47.3)	38 (50.7)
PRBC units	0 (0–2)	1 (0–2)
Active bleeding (yes)	4 (5.4)	6 (8.0)
Varices grade		
Medium varices	31 (41.9)	24 (32.0)
Large varices	43 (58.1)	51 (68.0)
No. of EVL bands	4 (3–5)	4 (3–4)
Ascites	40 (54.1)	38 (50.7)
Prior GI bleed	33 (44.6)	37 (49.3)
Prior beta-blocker use	27 (36.5)	28 (37.3)

Note: All values are expressed as median (IQR) or *n* (%) unless otherwise specified.

Abbreviations: CTP, Child–Turcotte–Pugh; INR, international normalised ratio; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; PRBC, packed red blood cells.

(56%) compared with 28 (37.8%), respectively ($p = 0.026$). Diarrhoea was the most common adverse reaction seen in 19 (25.7%) patients in Group 1 compared with 28 (37.3%) patients in Group 2 (Table 4). Overall, 63 (42.3%) patients required dose reduction of terlipressin, which was more commonly seen in Group 2 compared to Group 1: 38 (50.7%) versus 25 (33.8%), $p = 0.037$. Most patients experienced improvement after the initial dose reduction and only three patients required cessation of terlipressin altogether—one patient in either arm due to the development of cardiac arrhythmias and one patient in Group 1 due to the development of hypersensitivity reaction.

4 | DISCUSSION

We compared the effects of an abbreviated duration of adjuvant terlipressin therapy post-endotherapy for 1-day with 3-day therapy in patients with liver cirrhosis presenting with AVB. Our results suggest that in a select group of AVB patients, a shorter duration of terlipressin regimen has a similar risk of rebleeding and mortality compared with 3-day terlipressin therapy. Our study thus supports the expert recommendations advocated by the AGA which supports a shorter duration of vasoactive drug use in a select group of patients (Child A and B patients with no active bleeding seen during endoscopy).[17] We found no differences in rebleeding at days 5 and 42 or 6-week mortality between the two groups. In addition, an abbreviated duration of therapy was associated with fewer adverse drug reactions.

The optimal duration of vasoactive therapy after endotherapy remains unclear across major society guidelines that recommend 2–5 days of vasoactive medications.[9] The studies on which these guidelines are based are dated and have often used a heterogenous combination of endoscopic band ligation and sclerotherapy.[18] Multiple studies have established that EVL is superior to endoscopic sclerotherapy and is associated with lower rebleeding rates post-endotherapy. Thus, while a prolonged course of vasoactive drugs may safeguard a patient undergoing endoscopic sclerotherapy against a variceal rebleed, the same may not apply to those undergoing EVL. Prolonged use of the drugs post-endotherapy in these patients increases the risk of potential drug-related adverse effects, as shown in our study. Over the last few decades, EVL has emerged as the preferred modality of endotherapy. However, the duration of vasoactive therapy required post-endotherapy has not been reviewed as there is a lack of studies evaluating optimal vasoactive therapy duration after EVL.[19] A recent meta-analysis by Yeh et al. comparing a short course of vasoconstrictor therapy (≤3 days) to that of 3–5 day therapy post-EVL showed no difference in 5-day rebleeding, mortality as well as 6-week mortality, similar to our results.[20] Available literature suggests that terlipressin and somatostatin have similar efficacy.[21] The reduction in HVPG after a single bolus dose of terlipressin is larger in magnitude and faster in onset compared to somatostatin and octreotide. This reduction in HVPG is also sustained for a longer duration of time compared with somatostatin and octreotide.[22,23] A prior Cochrane systematic review also reported a potential survival benefit with terlipressin use along with a similar adverse effect profile in comparison to somatostatin and octreotide.[24] This led us to choose terlipressin as the vasoactive agent of choice for our study. However, a recent update on the use of vasoactive drugs by the American Gastroenterology Association has highlighted the

TABLE 2 Primary and secondary outcomes.

Parameters	1-day terlipressin arm (*N* = 74)		3-days terlipressin arm (*N* = 75)		Risk difference			
	n (%)	95% CI	*n* (%)	95% CI	Difference[a]	*Z*-test (two-tail)	95% CI	*p* value
Failure to control bleeding at 24 h	0	0, 4.9	2 (2.7)	0.7, 9.0	−2.7	−1.420	−6.3, 0.97	0.155
Rebleeding 5 days	3 (4.1)	0.4, 9.0	4 (5.3)	2.0, 10.0	−1.2	−0.346	−7.99, 6.79	0.726
Mortality 5 days	1 (1.4)	0, 7.3	1 (1.3)	0.2, 7.0	0.1	0.053	−3.61, 3.81	0.960
Rebleeding 42 days	9 (12.2)	7.0, 20.0	10 (13.3)	7.0, 20.0	−1.1	−0.201	−11.81, 9.60	0.842
Mortality 42 days	5 (6.8)	3.0, 10.0	4 (5.3)	2.0, 10.0	1.5	0.384	−0.61, 9.16	0.704

Abbreviation: CI, confidence interval.

[a]1-day minus 3-day measurements.

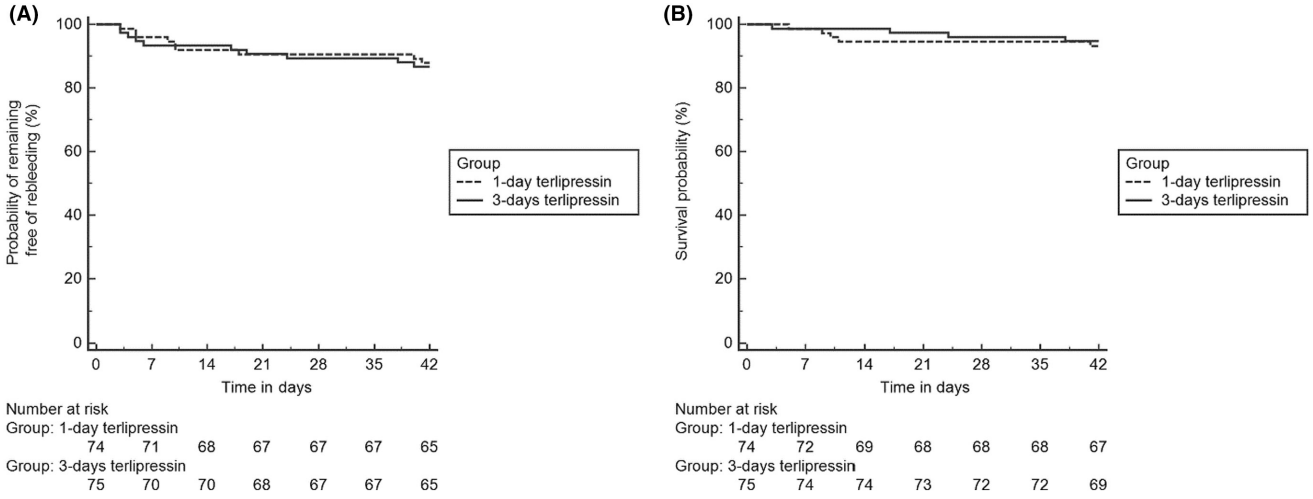


FIGURE 3 (A) Probability of remaining free from rebleeding in the 1-day and 3-day terlipressin groups (log-rank test $p = 0.820$). (B) Survival probability in the 1-day and 3-day terlipressin groups (log-rank test, $p = 0.691$).

TABLE 3 Portal hemodynamics and HVPG in the 2 study arms.

Parameters	1-day terlipressin arm (*N* = 74)	3-day terlipressin arm (*N* = 75)	*p* value
Baseline HVPG availability	48 (64.9)	56 (74.7)	0.413
Baseline HVPG value (mm Hg)	16 (14–19.8)	18 (14–20)	0.338
Day 3 HVPG availability	42 (56.8)	48 (64)	
Day 3 HVPG value (mm Hg)	15 (11.8–18)	15 (11.3–18)	0.964
Δ HVPG at day 3	−1 (−4–0)	−2 (−4–0)	0.620
HVPG at day 3			
Reduction	26/42 (61.9)	33/48 (68.8)	0.664
No change	7/42 (16.7)	5/48 (10.4)	
Increment	9/42 (21.4)	10/48 (20.8)	
HVPG decline ≥10%	20/42 (47.6)	30/48 (62.5)	0.156
HVPG decline ≥20%	13/42 (30.9)	14/48 (29.2)	0.854
Day 3 HVPG <12 mm Hg	11/42 (27.5)	16/48 (33.3)	0.461

Note: All values are expressed as median (IQR) or *n* (%) unless otherwise specified.

Abbreviation: HVPG, hepatic venous pressure gradient.

higher rates of adverse events with terlipressin use (which was also noted in our study) and advocated for the use of octreotide as a first-line agent for variceal haemorrhage citing a better safety profile and efficacy compared to terlipressin. We could not consider using octreotide as it was not routinely available at our centre at the time of the study.

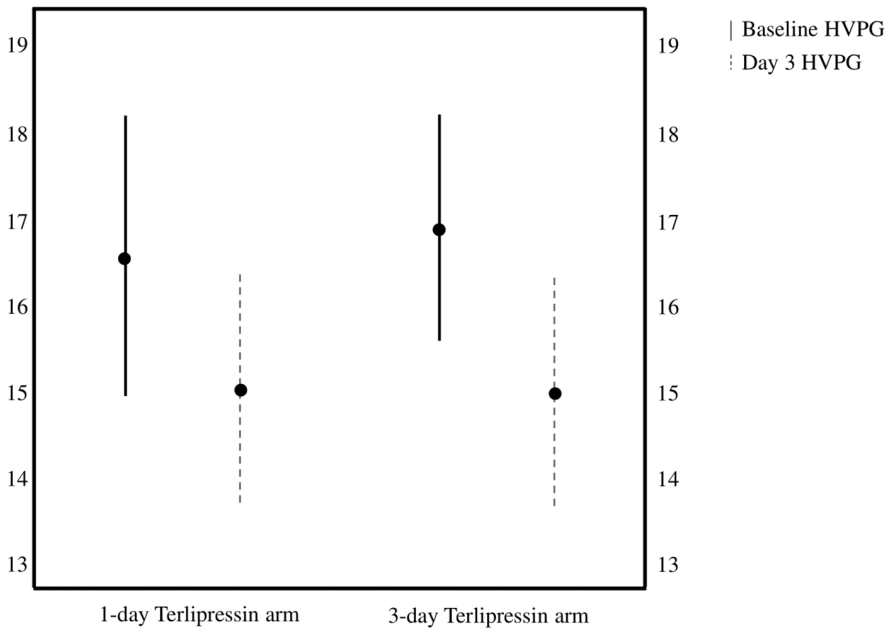


FIGURE 4 Error plot illustrating mean ± 95% confidence interval (CI) for baseline HVPG and day-3 HVPG in the two groups. Patients in the 1-day terlipressin arm received bolus terlipressin doses for 24 h (day-1 HVPG reading) followed by carvedilol after 24 h (day-3 HVPG reading). The patients in the 3-day arm received bolus terlipressin doses for 72 h (Day-1 and -3 HVPG readings) and carvedilol was started after that. Thus, carvedilol and terlipressin boluses resulted in similar HVPG reduction in both groups.

TABLE 4 Terlipressin side effects in the two groups.

Parameters	1-day terlipressin arm (*N* = 74)	3-day terlipressin arm (*N* = 75)	*p* value
Presence of any side effect[a]	28 (37.8)	42 (56.0)	0.026
Diarrhoea	19 (25.7)	28 (37.3)	0.126
Headache	4 (5.4)	10 (13.3)	0.097
Abdominal pain	1 (1.4)	1 (1.3)	1.000
Cyanosis	2 (2.7)	2 (2.7)	1.000
Cardiac arrythmia	1 (1.4)	1 (1.3)	1.000
Hyponatremia	0 (0.0)	1 (1.3)	NA

Note: All values are expressed as *n* (%).

Abbreviation: NA, not applicable due to zero cell frequency.

[a]Number of patients. The total of individual side effects is higher than the total number of patients.

Azam et al. compared 1-day versus 3-day terlipressin therapy in 130 patients (65 in each group) and reported similar rebleeding rates at 5 days (0% vs. 1.5%), 30 days (1.5% vs. 3.1%) and 30 days mortality (9.2% in each group) in both groups.[10] Lo et al. compared 0 versus 5 days of terlipressin therapy in a randomised control trial involving 118 patients and found that there was no difference in 5-day rebleeding (2% in each group), 42-day rebleeding (8.3% vs. 8.6%) and 42-day mortality (6.6% vs. 5.2%) in patients with similar cirrhosis severity as in our study.[11] Rebleeding and bleeding control rates were similar in these studies compared to our study.[10,11] The higher rebleeding rates in the study by Azam et al. is likely due to the higher number (90%) of patients with CTP B or C cirrhosis compared to our study, which had 74.5%.[10] An important limitation of both studies was the lack of HVPG assessment. In addition, rates of active bleeding seen in Lo et al. and Azam et al. were nearly 20% compared with our study, in which the rate of active bleeding was 6.7%. This may be because all of our patients received vasoactive agents prior to endoscopy, which may have controlled any active bleeding.

In our study, a decline in the HVPG by more than 20% in group 1 and group 2 was observed in 31% and 29.2% of patients, respectively, despite stopping terlipressin after 24 h in the 1-day arm. A possible explanation for this finding is the effect of carvedilol, which was started after 24 hours in the 1-day arm.[25–27] We also did not find any difference in HVPG at 72 h between group 1 (patients who received 24 h of terlipressin post-endotherapy followed by 48 h of carvedilol) as compared to group 2 (72 h of terlipressin post-endotherapy). We initiated oral beta-blockers early (24 h) in patients who received terlipressin for 24 h only. While this carries a theoretical risk of impacting the pathophysiological response of the body to AVB, we did not find any significant difference in mortality, anaemia or renal insufficiency among the patients in either group. Early use of beta blockers may contribute to the early mobilisation of the patients and our findings need to be verified in larger trials. None of the patients had any major adverse events requiring the stopping of carvedilol. The drug was withheld only in those patients who were admitted with rebleeding, to prevent hypotension and renal insufficiency associated

with acute blood loss and was restarted after endoscopic haemostasis was achieved.

Our results also suggest that almost 50% of patients receiving terlipressin experience drug-related adverse effects. The doses recommended by the guidelines for the management of AVB are not well tolerated, and dose reduction is required in almost 40% of all patients. This may have been prevented by using lower doses at initiation or the vasoactive agent as an infusion instead of bolus doses and is an area of further study.

We excluded some patients who were at high risk of rebleeding—as those with sepsis or organ failures. The presence of an active spurt from oesophageal varices on endoscopy—a high-risk feature for rebleeding which would mandate pre-emptive TIPSS as per current recommendations—was present only in 6.7% of patients.[28] We also noticed significantly fewer side effects with a shorter duration of therapy.

There are certain limitations in our study. Firstly, the study was unicentric, open-label and blinding was not done. We used terlipressin as a vasoactive agent although the current AGA expert review (2023) recommends the use of octreotide due to a better safety profile and efficacy.[17] Second, most patients did not have active variceal bleeding on endoscopy and had lower MELD and CTP distribution at presentation. We randomised 38.4% of eligible patients (150/390 cirrhosis patients), while excluding patients with overt hepatic encephalopathy, sepsis, HCC and acute-on-chronic liver failure, thereby limiting the generalizability of the results to these high-risk groups. Not all patients underwent HVPG due to the diversion of medical resources during the COVID-19 pandemic. In an ideal setting, we would prefer to perform the HVPG prior to initiating therapy with terlipressin. However, in a pragmatic scenario, endotherapy would be preferentially performed prior to the assessment of hepatic hemodynamics to control the variceal bleeding. As our centre provides 24-h gastroenterology services, delaying the initiation of vasoactive therapy for assessment of HVPG carries logistic and ethical concerns. We acknowledge that HVPG data should be interpreted in light of these observations. Fourth, the drug-related adverse effects of terlipressin were higher in our study, possibly due to bolus doses, which could be reduced by infusion, as highlighted in a recent study.[29] Fifth, the number of males recruited greatly outnumbered the females, which may contribute to sparse data bias and should be cautiously interpreted. The recent AGA guidelines (2023) recommend a shorter duration of antibiotic use in select cohorts unlike in our study where we continued the drug for 5 days in all patients. This may be incorporated in future studies. Our study is underpowered to detect the true difference in primary and secondary outcomes between the two study groups. as it is based on a relatively smaller sample size compared to that of minimally required (581 in each arm) for establishing the non-inferiority of 1-day terlipressin to 3-day terlipressin. However, the estimated risk difference for the primary and secondary outcomes was comparable across both treatment regimens. This can be further tested in the forthcoming studies by adopting a more robust design in terms of non-inferiority/superiority trials/individual patient meta-analysis, based on a large sample size, and involving multiple centres. Such studies will probably generate more robust evidence for optimisation of treatment.

5 | CONCLUSIONS

We found no differences regarding control of bleeding, rebleeding at day 5 and day 42 and 42-day mortality while noting a significantly higher number of adverse events in patients receiving a longer duration of terlipressin. Future studies addressing the shorter duration of terlipressin therapy compared with other vasoactive agents in AVB are warranted, and larger studies assessing the shorter duration of terlipressin may further support the results of this clinical trial.

AUTHOR CONTRIBUTIONS

Manas Vaishnav: Conceptualization; formal analysis; methodology; project administration; writing – original draft; writing – review and editing. **Sagnik Biswas:** Formal analysis; project administration; writing – original draft; writing – review and editing. **Abhishek Shenoy:** Writing – original draft. **Piyush Pathak:** Writing – original draft. **Abhinav Anand:** Project administration. **Shekhar Swaroop:** Project administration. **Arnav Aggrawal:** Project administration. **Umang Arora:** Project administration. **Anshuman Elhence:** Project administration. **Soumya Jagannath:** Project administration. **Deepak Gunjan:** Project administration. **Saurabh Kedia:** Project administration. **Ashwani Kumar Mishra:** Formal analysis; project administration; writing – original draft. **Shivanand Gamanagatti:** Project administration. **Baibaswata Nayak:** Project administration. **Pramod Garg:** Project administration; supervision; writing - review and editing. Shalimar: Conceptualization; data curation; formal analysis; methodology; project administration; supervision; writing – original draft; writing – review and editing.

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REFERENCES

1. Rout G, Sharma S, Gunjan D, Kedia S, Nayak B, Shalimar. Comparison of various prognostic scores in variceal and non-variceal upper gastrointestinal bleeding: a prospective cohort study. Indian J

Gastroenterol. 2019;38(2):158–66. https://doi.org/10.1007/s12664-018-0928-8
2. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med. 1988;319(15):983–9. https://doi.org/10.1056/NEJM198810133191505
3. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American association for the study of liver diseases. Hepatology. 2017;65(1):310–35. https://doi.org/10.1002/hep.28906
4. Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146(2):412–419.e3. https://doi.org/10.1053/j.gastro.2013.10.018
5. Lee HH, Park JM, Han S, Park SM, Kim HY, Oh JH, et al. A simplified prognostic model to predict mortality in patients with acute variceal bleeding. Dig Liver Dis. 2018;50(3):247–53. https://doi.org/10.1016/j.dld.2017.11.006
6. Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology. 2014;60(3):954–63. https://doi.org/10.1002/hep.27006
7. Augustin S, Altamirano J, González A, Dot J, Abu-Suboh M, Armengol JR, et al. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. Am J Gastroenterol. 2011;106(10):1787–95. https://doi.org/10.1038/ajg.2011.173
8. Lo GH, Chen WC, Wang HM, Lin CK, Chan HH, Tsai WL, et al. Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices. Gut. 2009;58(9):1275–80. https://doi.org/10.1136/gut.2008.165910
9. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII – renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959–74. https://doi.org/10.1016/j.jhep.2021.12.022
10. Azam Z, Hamid S, Jafri W, Salih M, Abbas Z, Abid S, et al. Short course adjuvant terlipressin in acute variceal bleeding: a randomized double blind dummy controlled trial. J Hepatol. 2012;56(4):819–24. https://doi.org/10.1016/j.jhep.2011.11.019
11. Lo GH, Perng DS, Chang CY, Tai CM, Wang HM, Lin HC. Controlled trial of ligation plus vasoconstrictor *versus* proton pump inhibitor in the control of acute esophageal variceal bleeding: prevention of early variceal rebleeding. J Gastroenterol Hepatol. 2013;28(4):684–9. https://doi.org/10.1111/jgh.12107
12. Chitapanarux T, Ritdamrongthum P, Leerapun A, Pisespongsa P, Thongsawat S. Three-day versus five-day somatostatin infusion combination with endoscopic variceal ligation in the prevention of early rebleeding following acute variceal hemorrhage: a randomized controlled trial: early variceal rebleeding, somatostatin. Hepatol Res. 2015;45(13):1276–82. https://doi.org/10.1111/hepr.12503
13. Common Terminology Criteria for Adverse Events (CTCAE). Published online 2017.
14. de Franchis R. Expanding consensus in portal hypertension. J Hepatol. 2015;63(3):743–52. https://doi.org/10.1016/j.jhep.2015.05.022
15. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol. 2009;6(10):573–82. https://doi.org/10.1038/nrgastro.2009.149
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509. https://doi.org/10.1080/01621459.1999.10474144
17. Garcia-Tsao G, Abraldes JG, Rich NE, Wong VWS. AGA clinical practice update on the use of vasoactive drugs and intravenous albumin in cirrhosis: expert review. Gastroenterology. 2024;166(1):202–10. https://doi.org/10.1053/j.gastro.2023.10.016
18. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology. 2002;35(3):609–15. https://doi.org/10.1053/jhep.2002.31354
19. Zhou X, Tripathi D, Song T, Shao L, Han B, Zhu J, et al. Terlipressin for the treatment of acute variceal bleeding: a systematic review and meta-analysis of randomized controlled trials. Medicine. 2018;97(48):e13437. https://doi.org/10.1097/MD.0000000000013437
20. Yeh JH, Lo GH, Huang RY, Lin CW, Wang WL, Perng DS. Short-course vasoconstrictors are adequate for esophageal variceal bleeding after endoscopic variceal ligation: a systematic review and meta-analysis. Sci Prog. 2021;104(3). https://doi.org/10.1177/00368504211031711
21. Wang C, Han J, Xiao L, Jin CE, Li DJ, Yang Z. Efficacy of vasopressin/terlipressin and somatostatin/octreotide for the prevention of early variceal rebleeding after the initial control of bleeding: a systematic review and meta-analysis. Hepatol Int. 2015;9(1):120–9. https://doi.org/10.1007/s12072-014-9594-9
22. Li B, Chen J, Zhang CQ, Wang GC, Hu JH, Luo JJ, et al. The pharmacodynamic effect of terlipressin versus high-dose octreotide in reducing hepatic venous pressure gradient: a randomized controlled trial. Ann Transl Med. 2021;9(9):793. https://doi.org/10.21037/atm-20-6774
23. Villanueva C, Planella M, Aracil C, López-Balaguer JM, González B, Miñana J, et al. Hemodynamic effects of terlipressin and high somatostatin dose during acute variceal bleeding in nonresponders to the usual somatostatin dose. Am J Gastroenterol. 2005;100(3):624–30. https://doi.org/10.1111/j.1572-0241.2004.40665.x
24. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev. 2003;(1):CD002147. https://doi.org/10.1002/14651858.CD002147
25. Bañares R, Moitinho E, Piqueras B, Casado M, García-Pagán JC, de Diego A, et al. Carvedilol, a new nonselective beta-blocker with intrinsic anti-alpha$_1$-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis: carvedilol, a new nonselective beta-blocker with intrinsic anti-Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol. Hepatology. 1999;30(1):79–83. https://doi.org/10.1002/hep.510300124
26. Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC. Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating β-blocker, in patients with cirrhosis and portal hypertension: low-dose carvedilol and portal hypertension. Aliment Pharmacol Ther. 2002;16(3):373–80. https://doi.org/10.1046/j.1365-2036.2002.01190.x
27. Lin HC, Yang YY, Hou MC, Huang YT, Lee FY, Lee SD. Acute Administration of Carvedilol is more effective than propranolol plus Isosorbide-5-Mononitrate in the reduction of portal pressure in patients with viral cirrhosis. Am J Gastroenterology. 2004;99(10):1953–8. https://doi.org/10.1111/j.1572-0241.2004.40179.x
28. Azam Z, Hamid S, Jafri W, Salih M, Abbas Z, Abid S, et al. Short course adjuvant terlipressin in acute variceal bleeding: a randomized double blind dummy controlled trial. J Hepatol. 2012;56(4):819–24. https://doi.org/10.1016/j.jhep.2011.11.019

29. Arora V, Choudhary SP, Maiwall R, Vijayaraghavan R, Jindal A, Kumar G, et al. Low-dose continuous terlipressin infusion is effective and safer than intravenous bolus injections in reducing portal pressure and control of acute variceal bleeding. Hepatol Int. 2023;17(1):131–8. https://doi.org/10.1007/s12072-022-10416-6

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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