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Hemodynamic profile of terlipressin and octreotide in patients with cirrhosis and portal hypertension: a randomized, single-blind clinical trial

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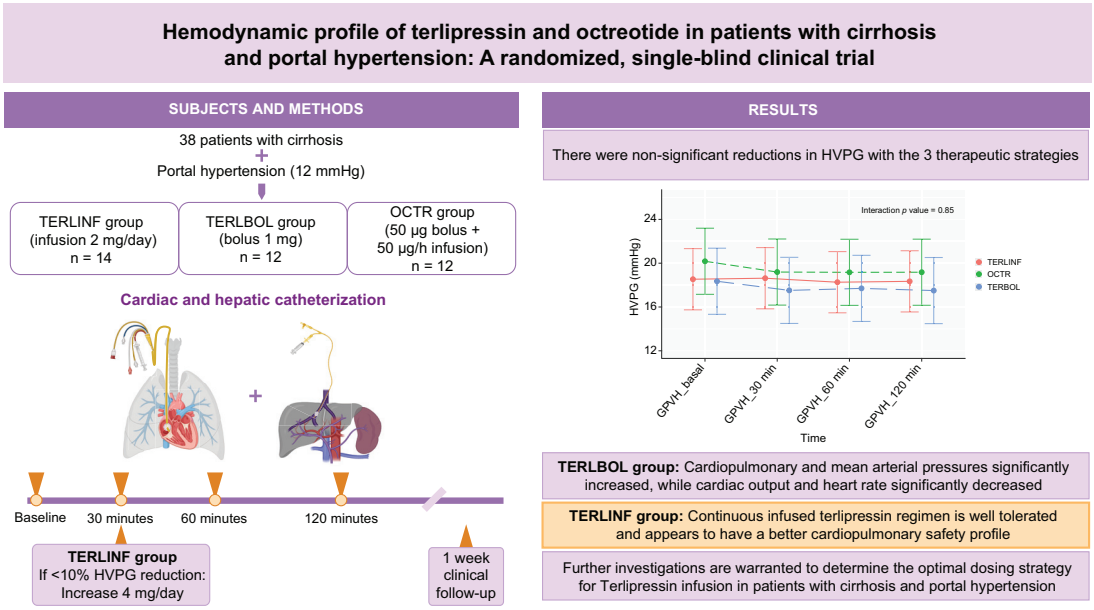
Graphical abstract



Highlights:

- Two-hour terlipressin infusion (2–4 mg/day) did not significantly reduce portal pressure.
- The continuously infused terlipressin regimen is well tolerated.
- Terlipressin administered as an infusion has a better cardiopulmonary safety profile.
- Further strategies of terlipressin infusion for acute variceal bleeding should be evaluated.

Impact and implications:

The results of our study do not show a significant reduction in portal pressure, at least in the first 2 h after the selected dose. Although the study was not performed in the setting of acute variceal bleeding and terlipressin was used as a standard therapy, these results do not support the treatment strategy of terlipressin infusion alone at the doses studied for the management of acute variceal bleeding, where a quick reduction in portal pressure is thought to play a major role controlling variceal bleeding. It is important to highlight that the continuously infused terlipressin regimen is better tolerated and appears to have a better cardiopulmonary safety profile. Other treatment strategies of continuous terlipressin infusion, such as initial bolus administration or higher infusion doses, should be evaluated to support its use in managing variceal bleeding.

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Research article

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Hemodynamic profile of terlipressin and octreotide in patients with cirrhosis and portal hypertension: a randomized, single-blind clinical trial☆

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Background & Aims: Continuous infusion of terlipressin may result in a more sustained reduction in portal pressure with fewer adverse effects than administered as a bolus. This study aimed to compare the hepatic and cardiopulmonary hemodynamic effects and safety profiles of bolus *vs*. terlipressin continuous infusion.

Methods: This is a single-center, single-blinded, double-dummy, parallel-group, clinical trial in which 38 patients with cirrhosis and portal hypertension were randomized to receive the following: 1 mg bolus of terlipressin + continuous infusion of placebo (TERLBOL, n = 12), a bolus of placebo + continuous infusion of terlipressin (2 or 4 mg/day if <10% reduction in hepatic venous pressure gradient [HVPG] at 30 min of infusion) (TERLINF, n = 14), or a bolus of octreotide (50 μg) + continuous infusion of octreotide (50 μg/h) (OCTR, n = 12) as an additional control group. HVPG, cardiopulmonary pressures, and cardiac output were measured at baseline and after 30, 60, and 120 min.

Results: Sixty-eight percent of patients were male, with a median age of 59 years. There were no significant differences in baseline characteristics. In the TERLBOL group, there was a nonsignificant reduction in HVPG (at 120 min, -4.9%; $p = 0.14$). However, cardiopulmonary and mean arterial pressures significantly increased, whereas cardiac output and heart rate significantly decreased. In the TERLINF group, there were nonsignificant changes in cardiopulmonary hemodynamics or HVPG (NS) despite doubling the infusion dose after 30 min in 13/14 patients. In the OCTR group, there was a nonsignificant reduction in HVPG (at 120 min, -4.9%; $p = 0.08$), and pulmonary capillary pressure significantly decreased. All treatments were well tolerated, and no adverse events were observed.

Conclusions: *T*here were nonsignificant reductions in HVPG with the three therapeutic strategies. Further investigations are warranted to determine the optimal dosing strategy for continuous infusion of terlipressin in patients with cirrhosis and portal hypertension.

Clinical trial identifier: EudraCT No. 2019-004328-39.

Introduction

In patients with cirrhosis, developing portal hypertension and its associated complications represents a major change in their prognosis.[1] Current management of acute decompensations, such as hepatorenal syndrome (HRS) and acute variceal bleeding, includes vasoactive drug therapy. Acute variceal bleeding (AVB) represents a decompensation that is associated with a high risk of mortality,[2] and lowering portal pressure is the gold standard treatment. Current pharmacological treatments of acute decompensation include the use of somatostatin, terlipressin, and/or octreotide.[3–6] Studies of pharmacological treatment have not yet revealed significant discrepancies in efficacy, rebleeding rates, or survival outcomes among vasoactive agents.[7] Octreotide is typically administered via bolus followed by continuous infusion. Nonetheless, its effects are transient, lasting approximately 5 min, despite continuous infusion, and subsequent administrations exhibit shorter durations and diminished efficacy compared with the initial bolus.[6] Terlipressin in AVB is administered by bolus injection every 4–6 h. However, despite an almost immediate portal pressure

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reduction, this reduction tapers off gradually and usually lasts less than 4 h.[8] In addition, repeated terlipressin bolus is usually associated with significant increases in arterial pressure and frequent manifestations of systemic and splanchnic ischemia. These are potentially serious adverse events (AEs) that can lead to its discontinuation. In contrast, continuous infusion of terlipressin may sustain a more prolonged reduction in portal pressure with fewer adverse effects, as evidenced by its benefits in conditions such as HRS.[9] A recent randomized open-label trial in the setting of AVB has suggested the effectiveness of continuous terlipressin infusion in reducing hepatic venous pressure gradient (HVPG).[10] However, the impact of terlipressin infusion requires further evaluation, specifically, its effects on the acute decrease in portal pressure in patients with cirrhosis. This study aimed to compare the hepatic and cardiopulmonary hemodynamic effects and safety of terlipressin administered as a bolus *vs*. continuous infusion and octreotide administered as a bolus followed by continuous infusion.

Patients and methods

We conducted a single-center, single-blinded, double-dummy, parallel-group clinical trial, enrolling patients meeting specific criteria. Inclusion criteria included individuals aged 18–75 years with cirrhosis, as defined by standard clinical, radiological, or histological criteria, a Child–Pugh score of up to 12 points, and an HVPG ≥12 mmHg during hepatic vein catheterization. Exclusion criteria included current or recent hepatic decompensation or infection within the past 10 days, use of vasoactive treatments or medications that can prolong QT interval, presence of hepatocellular carcinoma not fulfilling Milan criteria for transplant, morbid obesity, decompensated cardiopulmonary disease, history of ischemic heart disease, peripheral vascular disease or intestinal ischemia, concurrent HIV infection, decompensated chronic renal disease or under replacement therapy, current extrahepatic malignancies, pregnancy, plasma sodium <130 mmol/l, serum creatinine >2 mg/dl, serum bilirubin >5 mg/dl, international normalized ratio >2.5, and refusal to provide informed consent.

The study was conducted from May 2021 to December 2023, during which patients with cirrhosis and portal hypertension, who were under follow-up care at the outpatient clinic of Hospital Clinic of Barcelona, were recruited. To increase the quality of our study, during the performance of the hepatic catheterization, the physicians in charge of the procedure were not aware of the medication administered, thus establishing a double-blind design. Treatment with nonselective beta-blockers as primary or secondary prophylaxis was held at least 4 days before the catheterization. After baseline measurements confirming the presence of HVPG ≥12 mmHg, cardiopulmonary pressures and cardiac output were registered, and patients were randomly assigned (1:1:1) to three groups via sealed envelopes. Group allocation entailed receiving the following treatments over a 2-h period: (1) a bolus of terlipressin (1 mg) followed by continuous infusion of placebo (n = 12; group TERLBOL), (2) a bolus of placebo followed by continuous infusion of terlipressin (initially at a rate of 2 mg/day) (n = 14; group TERLINF) or (3) a bolus of octreotide (50 μg) followed by continuous infusion of octreotide (50 μg/h) (n = 12; group OCTR). Subsequent HVPG and cardiopulmonary pressure measurements were performed at 30, 60, and 120 min. At 30 min of treatment, an independent observer, aware of the medications groups, reviewed the reduction in HVPG. In the TERLINF group, if less than 10% reduction in HVPG was observed at 30 min, the infusion rate was increased by doubling it to 4 mg/day. Thus, the HVPG operator could not deduce the treatment that the patient was receiving. All hemodynamic measurements were meticulously recorded,[11] and assessments were blinded to evaluate the values and quality of tracings. Patients were prospectively followed up 24 h before hospital discharge and 1 week after with a second clinical visit to monitor and document any secondary effects. An online registry was established to collect baseline characteristics, including age, gender, comorbidities, chronic medications, prior hepatic decompensations, and previous HVPG measurements.

HVPG response was established as a reduction of 10% or more of baseline measurement. AEs were classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life-threatening or disabling).

All participants provided informed consent in accordance with the International Guideline for Ethical Review of Epidemiological Studies and the principles of the Declaration of Helsinki. The study protocol was approved by our ethics committee and registered at the EU Clinical trial register (EudraCT No. 2019-004328-39). During the study, we made two amendments to the protocol: the first was to clarify the inclusion criteria and the second was to change the final recruitment date.

Statistical analysis

Continuous variables are presented as the mean ± SD. To compare baseline measurements between groups, we used Student's *t* test or the Wilcoxon rank sum test, when appropriate. Categorical variables are expressed as total numbers with percentages and were compared between groups using Pearson's Chi-square test or Fisher's exact test, when appropriate. We analyzed trajectories between treatment groups in the longitudinal follow-up using generalized multilevel mixed-effects (GLMM) models for repeated measures fitting the time × treatment as fixed effects to assess the different trajectories over time. Residual plots were used to perform model validation. GLMM models were fitted using the library Lme4 (v. 1.1-35.3), and statistical estimations were performed using emmeans (v. 1.10.1). All analyses were addressed considering a two-tailed type I error of 5%. Statistical computations were performed using R (v. 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

We enrolled 57 patients, of whom 40 fulfilled the inclusion criteria (HVPG ≥12 mmHg), with 38 patients undergoing analysis (Fig. 1). In the overall cohort, 68% of patients were male, with a median age of 59 years. There were no significant differences in age, sex, etiology of liver disease, Child–Pugh score, or prior HVPG measurements among the three groups (Table 1). Baseline HVPG values were 18.4 ± 1.5 mmHg in the TERLBOL group, 18.5 ± 3.6 mmHg in the TERLINF group, and 20.2 ± 5.1 mmHg in the OCTR group.

In the TERLBOL group, there was a nonsignificant reduction in HVPG from 18.4 to 17.5 mmHg at 120 min (-4.9%; $p = 0.14$) (Fig. 2). HVPG reduction of >10% was achieved in 3/12 (25%), 3/12 (25%), and 4/12 (33.3%) patients at 30, 60, and 120 min,

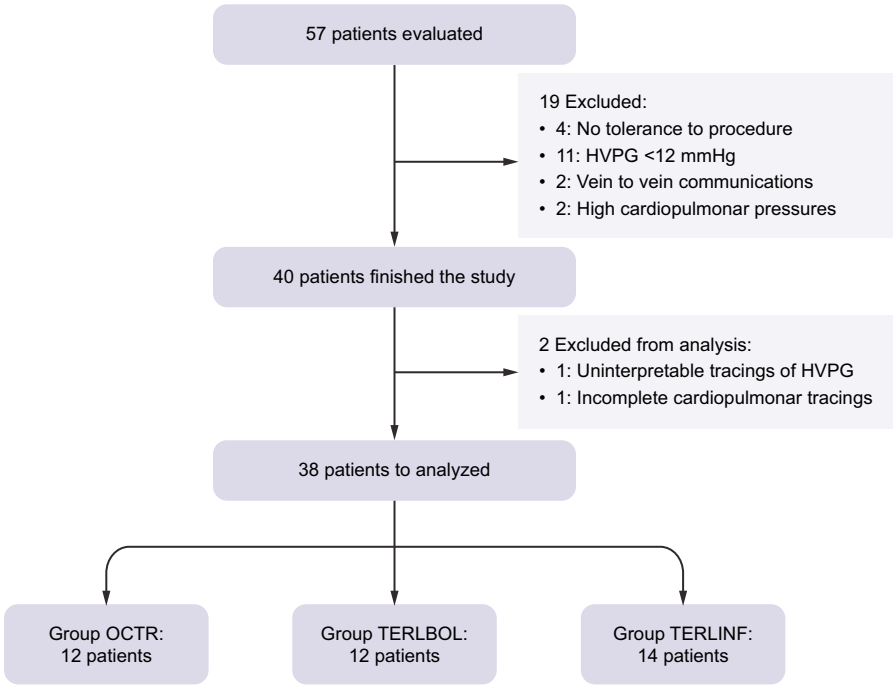

Fig. 1. CONSORT diagram of the total study cohort. HVPG, hepatic venous pressure gradient.

Table 1. Baseline characteristics of the overall cohort and the three groups.

Baseline characteristics	Overall cohort (N = 38)	TERLINF (n = 14)	OCTR (n = 12)	TERBOL (n = 12)
Sex (male)	26 (68%)	7 (50%)	11 (91.7%)	8 (66.7%)
Age (years)	59.2 ± 9.4	60.5 ± 11.9	57.9 ± 8.2	58.8 ± 7.5
No comorbidities	7 (18%)	2 (14.3%)	2 (16.7%)	3 (25%)
Arterial hypertension	13 (34%)	6 (42.9%)	5 (41.7%)	2 (16.7%)
Diabetes mellitus	13 (34%)	6 (42.9%)	4 (33.3%)	3 (25%)
Dyslipidemia	9 (24%)	4 (28.6%)	4 (33.3%)	1 (8.3%)
Cardiopathy	2 (5.3%)	2 (14.3%)	0	0
Medication PHT				
Beta-blocker treatment	24 (63%)	9 (64.3%)	8 (66.7%)	7 (58.3%)
Diuretic treatment	20 (53%)	9 (64.3%)	6 (50%)	5 (41.7%)
Etiology of cirrhosis				
ALD	24 (63.2%)	8 (57.1%)	8 (66.7%)	8 (66.7%)
HCV on SVR	4 (10.5%)	0	1 (8.3%)	3 (25.0%)
MASLD	5 (13.2%)	4 (28.6%)	0	1 (8.3%)
MetAld	5 (13.2%)	2 (14.3%)	3 (25.0%)	0
Liver disease				
Child–Pugh score	7.5 ± 1.9	7.7 ± 1.5	7.6 ± 2.3	7.2 ± 2.0
MELD	12.4 ± 4.7	12.8 ± 4.6	12.5 ± 5.6	11.8 ± 4.1
MELD-Na	13.7 ± 5.5	14.5 ± 6.3	14.0 ± 5.6	12.6 ± 4.7
Baseline HVPG	19.0 ± 5.1	18.5 ± 3.6	20.2 ± 5.1	18.4 ± 1.5
PHT				
Esophageal, gastric, or ectopic varices	30 (81%)	11 (78.6%)	11 (91.7%)	8 (66.7%)
Previous portal hypertension bleeding	17 (45%)	6 (42.9%)	4 (33.3%)	7 (58.3%)
Ascites at inclusion	28 (74%)	12 (85.7%)	10 (85.7%)	6 (50%)

Quantitative variables are expressed as mean ± SD, and Student's *t* test or the Wilcoxon rank sum test was used. Qualitative variables are expressed as *n* and relative frequencies (percentage), and Pearson's Chi-square test or Fisher's exact test was used. ALD, alcohol-related liver disease; HVPG, hepatic venous pressure gradient; MASLD, metabolic dysfunction-associated steatotic liver disease; MetAld, metabolic dysfunction- and alcohol-related liver disease; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease–sodium; PHT, portal hypertension; SVR, sustained virological response.

respectively. However, most cardiopulmonary measurements significantly increased at 30 and 60 min, tending to return to baseline values at 120 min, pulmonary artery pressure (PAP) increased from 17.2 to 19.5 mmHg (+13.4%; $p = 0.03$) at 30 min, peaked at 20.2 mmHg (+17.4%; $p = 0.0065$) at 60 min, and then returned to baseline at 120 min (17.0 mmHg). Pulmonary capillary pressure (PCP) increased from 11.9 to 14.7 mmHg at 30 min (+23.5%; $p = 0.0097$), reached 15.5 mmHg at 60 min (+30.2%; $p = 0.0097$), and returned to 12.2 mmHg at 120 min. Right atrial pressure (RAP) increased from 7.2 to 8.2 mmHg at 30 min, peaked at 8.6 mmHg at 60 min (+19.5%; $p = 0.0.15$), and reduced to 6.9 mmHg at 120 min

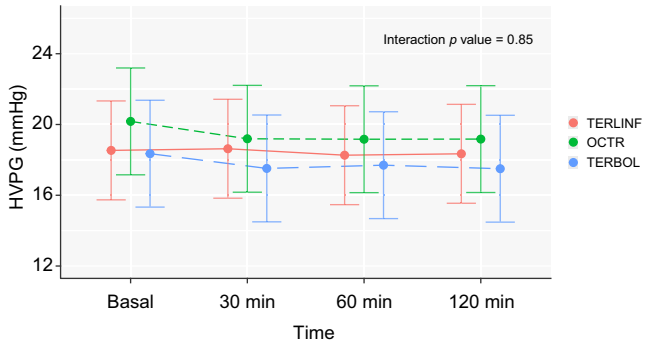

Fig. 2. HVPG changes during 2 h of treatment administration in the three groups. Treatment groups were analyzed in the longitudinal follow-up using generalized multilevel mixed effects models with an interaction *p* value of 0.85. HVPG, hepatic venous pressure gradient.

(Figs S1–S3). Mean arterial pressure increased significantly at 30 min from 91.1 to 101.4 mmHg (+11.3%; $p = 0.02$). Cardiac output decreased significantly from 5.6 to 4.8 L/min at 30 min (-14.3%; p = 0.002), further decreased to 4.9 L/min at 60 min (-12.5%; p = 0.008), and remained at 4.5 L/min at 120 min (-19.6%; p <0.001). Heart rate significantly decreased at 120 min from 69.5 to 60.8 bpm (-12.5%; $p = 0.0104$) (Table S1).

In the TERLINF group, a mild reduction in cardiac output was observed at 60 min from 6.3 to 5.8 L/min (7.9%; $p = 0.01$) (Table S2). There were no significant changes in cardiopulmonary pressures (Figs S1–S3). Only one patient achieved an HVPG response with a reduction of 17.9% at 30 min of administration, but, overall, there were no significant changes in HVPG values despite doubling the dose after 30 min of infusion in 13/14 no-responder patients (Fig. 2). HVPG reduction of >10% was achieved in only 1/14 (7.1%), 3/14 (21.4%), and 3/14 (21.4%) patients at 30, 60, and 120 min, respectively (Table S2).

In the OCTR group, there was a nonsignificant reduction in HVPG from 20.2 to 19.2 mmHg at 120 min (-4.9%; $p = 0.08$) (Fig. 2). However, significant changes were observed in the wedged hepatic vein, decreasing from 29.2 ± 1.7 to 27.8 ± 1.7 and 28.2 ± 1.7 mmHg at 60 (-4.8%; p <0.01) and 120 min (-3.4%; $p = 0.032$), respectively. PCP also significantly decreased at 120 min from 12.4 to 10.3 mmHg (-16.9%; $p = 0.0045$) (Figs S1–S3). No significant changes in other cardiopulmonary parameters were noted (Table S3). HVPG reduction of >10% was achieved in 4/12 (33.3%), 5/12 (41.7%), and 5/12 (41.7%) patients at 30, 60, and 120 min, respectively.

The difference in HVPG reduction between the groups was not significant ($p = 0.85$). We found no predictive factors associated with reduced HVPG between groups. All treatments were well tolerated; only one patient in the TERBOL group experienced desaturation during the measurement of cardiopulmonary parameters at the end of the procedure. At the 7-day follow-up, all patients reported good general condition, with no gastrointestinal alterations or AEs observed.

Discussion

In the management of acute decompensations in cirrhosis, the use of vasoactive agents represents a cornerstone of medical therapy, as underscored by multiple practice guidelines.[2] The application of such therapies is particularly critical in AVB, a life-threatening complication. In this situation, terlipressin, administered as a bolus every 4/6 h, has been shown to be clinically effective.[4] The bolus of terlipressin promotes a quick but transient reduction in HVPG, returning to baseline values at 4 h. This decrease in HVPG, however, can be achieved again with a new bolus administration. This hemodynamic profile is associated with a similar pattern in changes in systemic parameters with fast, and sometimes significant, increases in arterial and cardiopulmonary pressures.[8] This pulse vasoconstrictive effect of terlipressin bolus is thought to be responsible for most of its ischemic AEs, which can be potentially severe and life-threatening. This prompted to test, in the setting of HRS, the efficacy and safety of continuous intravenous administration of terlipressin, aiming for a more homogeneous and targeted hemodynamic effect with fewer systemic AEs.[9] As a result, it is used as a continuous infusion with a stepwise increase to achieve HRS reversal.[9] However, the adequate dose regimen of continuous infusion of terlipressin and its effects on HVPG and cardiopulmonary pressures have not been properly evaluated. This study aimed to evaluate the splanchnic and systemic hemodynamic profile of terlipressin when delivered as a continuous infusion, thereby assessing whether these doses and regimens could achieve an early and optimal reduction in portal pressure. To maintain a blinded evaluation of the effects of terlipressin infusion, we also included two additional groups: one receiving a bolus of terlipressin followed by a continuous infusion of placebo and another receiving octreotide administered as an initial bolus followed by a continuous infusion.

Our findings revealed that continuous infusion of terlipressin did not significantly reduce HVPG or modify systemic hemodynamics, despite doubling the initial dose after 30 min of treatment. With respect to the other groups, both TERBOL and OCTR did not significantly decrease HVPG. It is worth noting that the TERBOL group was associated with significant systemic hemodynamic effects, including a notable increase in PCP (to 30%) after 1 h of administration.

A recent open-label study by Arora *et al.*,[10] performed in patients with AVB, showed a higher reduction in HVPG after tailored continuous terlipressin infusion than after the standard bolus administration. The total dose of terlipressin administered during the treatment period was lower after the intravenous infusion than after the bolus administration, and this fact was also associated with fewer AEs. Several relevant differences between the two studies may explain the discrepancies in the obtained results. Among those, our study was blinded, whereas the study by Arora *et al.*[10] was open label. All patients in the study by Arora *et al.*[10] received a bolus dose of 2 mg at a mean time of approximately 3 h before the first HVPG. Therefore, the "baseline HVPG" may not represent a "true" baseline HVPG. However, most importantly, the terlipressin infusion group had a different dose and timing for HVPG response assessment. Indeed, our initial-dose terlipressin infusion of 2 mg/day, which is effective in the treatment of HRS,[9] was lower than the 4 mg/day used in the study by Arora *et al.*[10] We doubled the dose to 4 mg/day in most of our patients after 30 min. However, our HVPG measurements were performed 90 min after doubling the dose (total terlipressin dose in 120 min of 290 μg), whereas the first HVPG measurement in the study by Arora *et al.*[10] was done 12 h after the 4 mg/day dose (total terlipressin dose of 2 mg). This dosing strategy in the setting of AVB likely explains the

differences from our findings and strongly suggests that, especially in the setting of AVB where a fast HVPG reduction would be desirable to control bleeding, it would be necessary to initiate terlipressin infusion at a higher dose (4 or even 6 mg/24 h) to produce a faster and significant reduction in HVPG. It should also be noted that in the study by Arora *et al.*,[10] the influence of hemodynamic stability on HVPG measurements, secondary to hemorrhage and anemia, was not evaluated. Other studies, such as the one performed by Jha *et al.*[12] in AVB, also conclude that continuous infusion of terlipressin may be more effective than intermittent infusion to prevent treatment failure in patients with variceal bleeding, although no cardiopulmonary or hepatic hemodynamics were evaluated in this study. Similarly, the randomized clinical trial of bolus *vs*. continuous infusion delivery of terlipressin by Ding *et al.*,[13] evaluating changes in direct portal pressure in the setting of TIPS (transjugular intrahepatic portosystemic shunt) placement, reported a rapid and stable reduction in portal pressure compared with bolus delivery and a significant reduction in heart rate and increase in mean arterial blood pressure in the bolus group. However, most of the patients included in this study did not have cirrhosis.

Our observations, albeit limited by a small sample size, indicate that both octreotide and terlipressin, when administered as bolus over 120 min, yield modest reductions in HVPG. Considerably, terlipressin at a 1-mg dose induces pronounced systemic hemodynamic changes. However, the continuous infusion of terlipressin did not demonstrate a significant impact on cardiopulmonary or hepatic hemodynamics. A longer infusion regimen could have an effective decrease in portal pressure. However, in the context of AVB, as the greatest risks occur in the first hours of presentation, the continuous infusion used in our study is not adequate. We acknowledge the limitation of the lack of information on flexible or increasing doses of continuous terlipressin in this specific protocol. Thus, we believe that our findings demonstrate that the strategy usually used in patients with HRS does not achieve an immediate effect on HVPG and that for at least 2 h (even at double the usual dose) this does not change. This indicates that if we want to use terlipressin as an infusion for AVB, either higher doses or an initial bolus may be required. Although in patients with HRS, the dose is gradually increased, and in some cases, it is started at a higher dose (*i.e.* arterial hypotension), this approach is not backed up by evidence. The findings of this study could have been optimized with a larger sample size. However, the current sample size should be large enough to detect the expected effect (at least an HVPG reduction of 10% from baseline) that it is supposed to be clinically relevant in the setting of variceal bleeding. Exploring different dosing regimens or combination therapies (including the hemodynamic profile of somatostatin instead of octreotide) could yield different results. However, the main objective of this clinical trial was to compare the hemodynamic effects of terlipressin in bolus *vs*. continuous infusion. These findings, although preliminary, underscore the need for further research to optimize terlipressin regimens for patients with cirrhosis, potentially involving combinations and varied dosing strategies to enhance therapeutic efficacy.

In conclusion, the safety profile observed in our study, with no serious AEs reported, provides a preliminary indication of the tolerability of these treatments. However, the safety of higher doses or different administration routes requires further investigation. The potential clinical relevance of the hemodynamic changes observed, despite their lack of statistical significance, warrants additional exploration in larger, more extended studies to ascertain their implications in the management of portal hypertension in patients with cirrhosis.

Affiliations

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Abbreviations

AE, adverse event; AVB, acute variceal bleeding; GLMM, generalized multilevel mixed-effects; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; PAP, pulmonary artery pressure; PCP, pulmonary capillary pressure; RAP, right atrial pressure.

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Conflicts of interest

JFA is a consultant for AstraZeneca. AC is a consultant for Mallinckrodt Pharmaceuticals, Boston Scientific Corp, and B. Braun; has participated on Advisory Boards for Mallinckrodt Pharmaceuticals; and has received grant support from Mallinckrodt and Boston Scientific Corp. JCGP is a consultant for Cook and AstraZeneca and has received speaker fees from GORE and Cook.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: JCGP, AC, VPC. Methodology: JCPG, AC, VHG, VPC. Investigation: VPC, PO, JFA, ST, ROB, ST, AB, LO, SS, AO, FT, VHG, AC, JCGP. Formal analysis: VPC, RB, JCGP. Project administration: AC, JCGP. Supervision: AC, JCGP. Writing original draft: AC, JCGP, VPC.

Data availability statement

The raw/processed data required to reproduce the findings cannot be shared at this time because of legal/ethical reasons.

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The graphical abstract was created in BioRender. Hernandez-gea, V. (2025) https://BioRender.com/v33p532.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101325.

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Author names in bold designate shared co-first authorship

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