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

Short title: Terlipressin hemodynamic profile in portal hypertension

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Abstract

Background and aims: Continuous infusion (CI) 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 CI.

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: 1mg bolus of terlipressin + CI of placebo (TERLBOL n=12), bolus of placebo + CI of terlipressin (2mg/day or 4mg/day if <10% reduction in hepatic venous pressures gradient (HVPG) at 30min of infusion) (TERLINF n=14) or a bolus of octreotide (50mcg) + CI of octreotide (50mcg/h) (OCTR n=12) as an additional control group. HVPG, cardiopulmonary pressures and cardiac output were measured at baseline, after 30, 60 and 120 minutes.

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

Conclusion: There were non-significant reductions in HVPG with the three therapeutic strategies. Further investigations are warranted to determine the optimal dosing strategy for CI of Terlipressin in patients with cirrhosis and portal hypertension.

Impact and Implications

The results of our study do not show a significant reduction in portal pressure, at least in the first two hours after the selected dose. Although the study was not performed in the setting of acute variceal bleeding and terlipressin is used as a standard therapy, these results do not support the treatment strategy of terlipressin infusion alone at the doses studied for 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 continuous 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 in the future to support its use in managing variceal bleeding.

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 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 of portal pressure is the gold standard treatment. Current pharmacological treatments of acute decompensation include the use of somatostatin, terlipressin and/or octreotide (3,4,5,6). Studies of pharmacological treatment have not yet revealed significant discrepancies in efficacy, re-bleeding rates, or survival outcomes among vasoactive agents (7). Octreotide is typically administered via bolus followed by continuous infusion. Nonetheless, its effects are transient, lasting about 5 minutes, despite continuous infusion, and subsequent administrations exhibit shorter durations and diminished efficacy compared to the initial bolus (6). Terlipressin in AVB is administered by bolus injection every 4-6 hours, however despite an almost immediate portal pressure reduction, this reduction tapers off gradually and usually lasts less than 4 hours (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 that can lead to its discontinuation. Continuous infusion of terlipressin, on the other hand, may sustain a more prolonged reduction in portal pressure with fewer adverse effects, as evidenced by its benefits in conditions like hepatorenal syndrome (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, the evaluation of the effects of this treatment 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 versus continuous infusion, and octreotide administered as a bolus followed by continuous infusion.

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 to 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 <130mmol/l, serum creatinine >2mg/dl, serum bilirubin >5mg/dl, INR >2.5 and refusal to provide informed consent.

The study took place 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. In order 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 non-selective beta-blockers as primary or secondary prophylaxis was held at least 4 days prior to 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-hour 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 mcg) followed by continuous infusion of octreotide (50 mcg/h) (n=12; group OCTR). Subsequent HVPG and cardiopulmonary pressure measurements were performed at 30 minutes, 60 minutes, and 120 minutes. At 30 minutes of treatment, an independent observer, aware of the medications groups, reviewed the reduction in HVPG, and in the TERLINF group if less than 10% reduction in HVPG was observed at 30 minutes, the infusion rate was increased by doubling it to 4 mg/day. Thus, 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 hours before hospital discharge and one 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. Adverse events (AE) were classified as grade 1 mild-AE, grade 2 moderate-AE, grade 3 severe-AE, grade 4 life-threatening or disabling-AE.

All participants provided informed consent in accordance with the International Guideline for Ethical Review of Epidemiological Studies and 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 to clarify the inclusion criteria and the second to change the final recruitment date.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. To compare baseline measurements between groups we used the Student's t-test or Wilcoxon rank sum test when appropriate. Categorical variables are expressed as total number with percentages and compared between groups using Pearson's Chi-squared test or Fisher's exact test when appropriate. We analyzed trajectories between treatment groups in the longitudinal follow-up using generalized multilevel mixed effects models (GLMM) 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 done with 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).

Results

We enrolled 57 patients, of whom 40 fulfilled the inclusion criteria (HVPG ≥ 12 mmHg), with 38 patients undergoing analysis **(Figure 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 in the OCTR group 20.2 ±5.1 mmHg.

In the TERLBOL group, there was a non-significant reduction in HVPG from 18.4 to 17.5 mmHg at 120 minutes (-4.9%; p: 0.14) **(Figure 2)**. HVPG reduction of more than 10% was achieved in 3/12 (25%), 3/12 (25%), and 4/12 (33.3%) patients at 30, 60, and 120 minutes, respectively**.** However, most cardiopulmonary measurements significantly increased at 30 and 60 minutes, tending to return to baseline values at 120 minutes, pulmonary artery pressure (PAP) increased from 17.2 to 19.5 mmHg (+13.4%; p: 0.03) at 30 minutes, peaked at 20.2 mmHg (+17.4%; p: 0.0065) at 60 minutes, and then returned to baseline at 120 minutes (17.0 mmHg). PCP increased from 11.9 to 14.7 mmHg at 30 minutes (+23.5%; p: 0.0097), reached 15.5 mmHg at 60 minutes (+30.2%; p: 0.0097), and returned to 12.2 mmHg at 120 minutes. Right atrial pressure (RAP) increased from 7.2 to 8.2 mmHg at 30 minutes, peaked at 8.6 mmHg at 60 minutes (+19.5%; p: 0.0.15), and reduced to 6.9 mmHg at 120 minutes **(Supplementary figure 1, 2, 3**). Mean arterial pressure increased significantly at 30 minutes 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 minutes (-14.3%; p: 0.002), further decreased to 4.9 l/min at 60 minutes (-12.5%; p: 0.008) and remained at 4.5 l/min at 120 minutes (-19.6%; p: <0.001). Heart rate significantly decreased at 120 minutes from 69.5 to 60.8 bpm (-12.5%; p: 0.0104) **(Supplementary Table 1)**.

In the TERLINF group, a mild reduction in cardiac output was observed at 60 minutes from 6.3 to 5.8 l/min (7.9%; p: 0.01) **(Supplementary table 2)**. There were no significant changes in cardiopulmonary pressures **(Supplementary figures 1, 2 and 3)**, only one patient achieved an HVPG response with a reduction of 17.9% at 30 minutes of administration, but overall, there were no significant changes in HVPG values despite doubling the dose after 30 minutes of infusion in 13/14 no responder patients **(Figure 2)**. HVPG reduction of more than 10% was achieved in only 1/14 (7.1%), 3/14 (21.4%), and 3/14 (21.4%) patients at 30, 60, and 120 minutes, respectively **(Supplementary table 2)**.

In the OCTR group, there was a non-significant reduction in HVPG from 20.2 to 19.2 mmHg at 120 minutes (-4.9%; p: 0.08) **(Figure 2)**. However, significant changes were observed in wedge 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 minutes (-3.4%; p: 0.032). Pulmonary capillary pressure (PCP) also significantly decreased at 120 minutes from 12.4 to 10.3 mmHg (-16.9%; p: 0.0045) **(Supplementary figures 1, 2 and 3)**. No significant changes in other cardiopulmonary parameters were noted **(Supplementary table 3**). Patients that achieved a HVPG reduction

of more than 10% were 4/12 (33.3%), 5/12 (41.7%), and 5/12 (41.7%) at 30, 60, and 120 minutes, respectively.

The difference in the reduction of the HVPG 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 adverse events observed.

Discussion

In the management of acute decompensations in cirrhosis, the utilization 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 hours, has been shown to be clinically effective (4). The bolus of terlipressin promotes a quick but transient reduction of HVPG, returning to baseline values at 4 hours, 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 adverse events, 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 a more homogeneous and targeted hemodynamic effect with less systemic adverse events (9). As a result, it is used as a continuous infusion with a stepwise increase to achieve hepatorenal syndrome reversal (9). However, the adequate dose regimen of continuous infusion of terlipressin and its effects on HVPG and in 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 in the TERBOL group it was associated with significant systemic hemodynamic effects, including a notable increase in PCP (to 30%) after one hour 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 less adverse events. Several relevant differences between both studies may explain the discrepancies in the obtained results. Among those, our study was blinded vs open label; all patients in Arora's study received a bolus dose of 2mg, at a mean time of around 3 hours before the first HVPG and therefore, the "baseline HVPG" may not represent a "true" baseline HVPG. However, most importantly, the terlipressin infusion group had a different dose and timing of HVPG response assessment. Indeed, our initial dose terlipressin infusion of 2mg/day, which is effective in the treatment of hepatorenal syndrome (9), was lower than the 4mg/day used in the study by Arora (10). We doubled the dose to 4mg/day in most of our patients after 30 minutes, however our HVPG measurements were performed 90 minutes after doubling the dose (total terlipressin dose in 120 minutes of 290 ug) while the first HVPG in Arora's study was done 12 hours after the 4mg/day dose (total terlipressin dose of 2mg). This dosing strategy in the setting of AVB therefore likely explains the differences with 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 hours) to produce a faster and significant reduction in HVPG. It should also be noted that in Arora's study the influence on HVPG measurements of hemodynamic stability secondary to hemorrhage and anemia were not evaluated. Other studies, such as the one performed by Jha et.al in AVB, conclude as well 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 (12). Similarly, the randomized clinical trial of bolus versus continuous infusion

delivery of terlipressin by Ding et al, evaluating changes on direct portal pressure in the setting of TIPS placement, reported a rapid and stable reduction in portal pressure compared to bolus delivery, and a significant reduction in heart rate and increase in mean arterial blood pressure in the bolus group (13). However, most of the patients included in this study did not have cirrhosis.

Our study's observations, albeit limited by a small sample size, indicate that both octreotide and terlipressin, when administered as bolus over 120 minutes, 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 lack of information on flexible and or increasing doses of continuous terlipressin in this 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 two hours (even at double the usual dose) this does not change. This indicates that if we want to use it 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 versus continuous infusion. These findings, while 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 adverse events 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.

Abbreviations: CO: Cardiac Output, HVPG: Hepatic Venous Pressure Gradient, HR: heart rate, MAP: Mean Arterial Pressure, PAP: Pulmonary Arterial Pressure, PCP: Pulmonary Capillary Pressure and RAP: Right Atrium Pressure.

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Figure Legends

Figure 1. Consort diagram of the total study cohort.
HVPG: Hepatic Venous Pressure Gradient.

Figure 2. HVPG changes during two hours of treatment administration in the three groups.

- Treatment groups were analyzed in the longitudinal follow-up using generalized multilevel mixed effects models with an intereaction P-value of 0.85. HVPG: Hepatic Venous Pressure Gradient.

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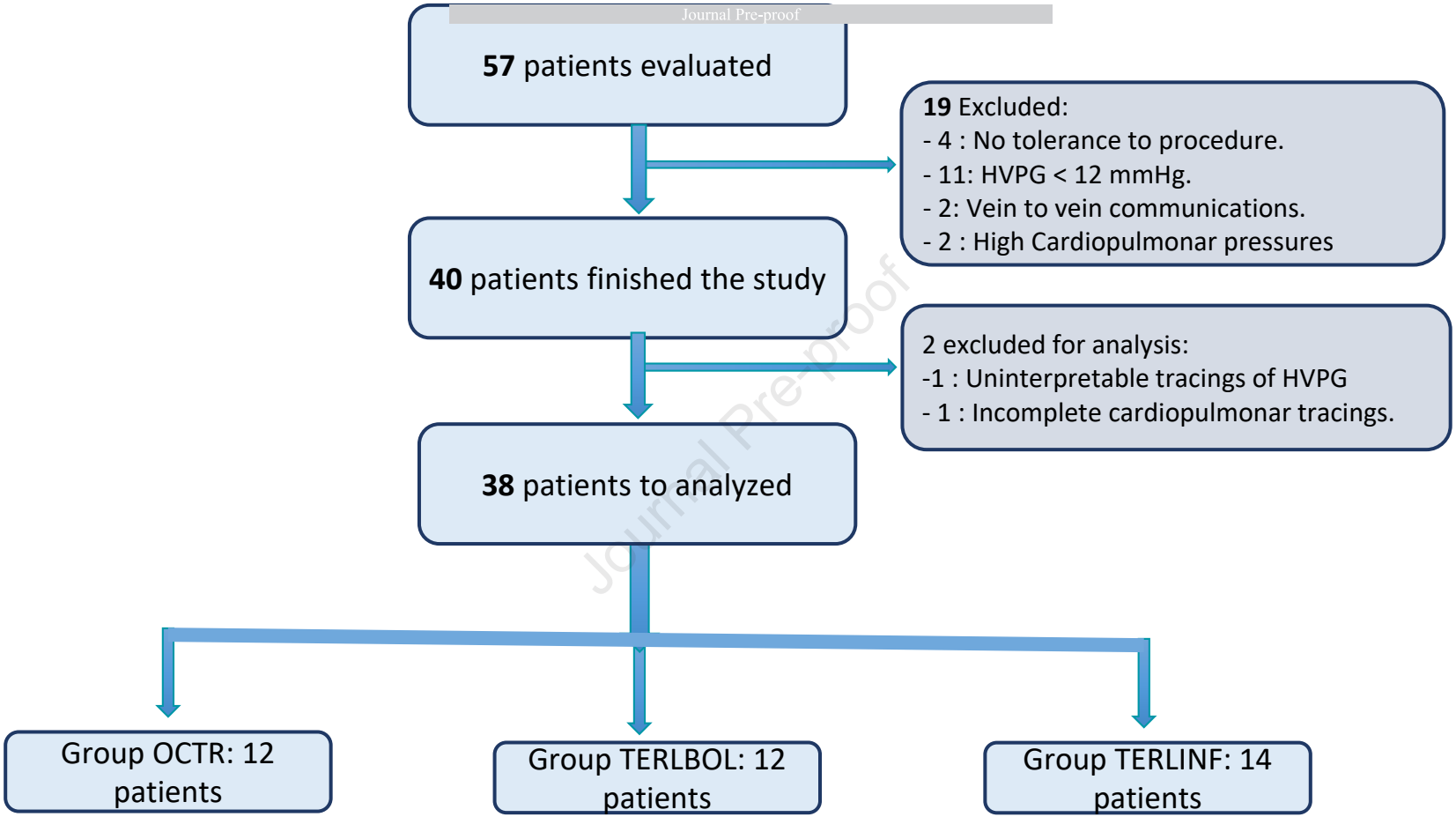
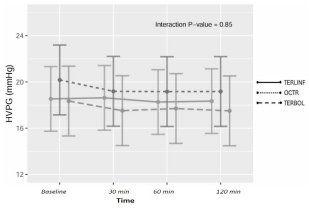
Table 1. Baseline characteristics of the overall cohort and in the 3 groups.

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				
Betablocker 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)
Portal Hypertension				
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 expressed as mean ± standard deviation, Student's t-test or Wilcoxon rank sum test were used. Qualitative variables expressed as "n" and relative frequencies (percentage), Pearson's Chi-squared test or Fisher's exact test were used.

PHT: Portal hypertension, ALD: Alcohol related Liver Disease, HCV: Hepatitis C Virus, SVR: Sustained Virological Response, MASLD: Metabolic Associated Steatotic Liver Disease, MetAld: Metabolic and Alcohol Related Liver disease, HVPG: Hepatic Venous Pressure Gradient.





HIGHLIGHTS

- 2 hours Terlipressin infusion(2-4mg/day) did not reduce significantly portal pressure.
- Continuous infused terlipressin regimen is well tolerated.
- Terlipressin administered as infusion has a better cardiopulmonary safety profile.
- Futher strategies of terlipressin infusion for ABV should be evaluated.

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

SUBJECTS AND METHODS

38 patients with cirrhosis

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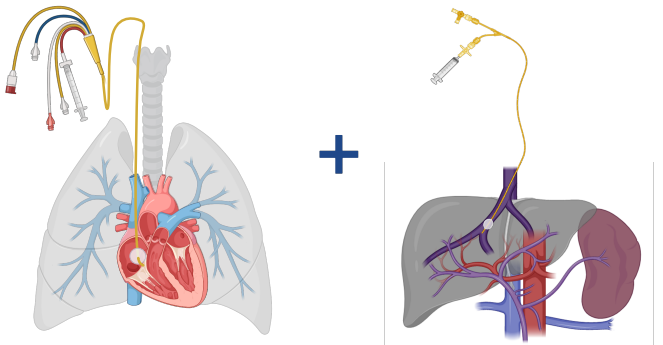
Portal hypertension (**12 mmHg**)

TERLINF group
(infusion 2mg/day)
n = 14

TERLBOL group
(bolus 1mg)
n = 12

OCTR group
(50 mcg bolus + 50 mcg/h infusion)
n = 12

Cardiac and Hepatic catheterization



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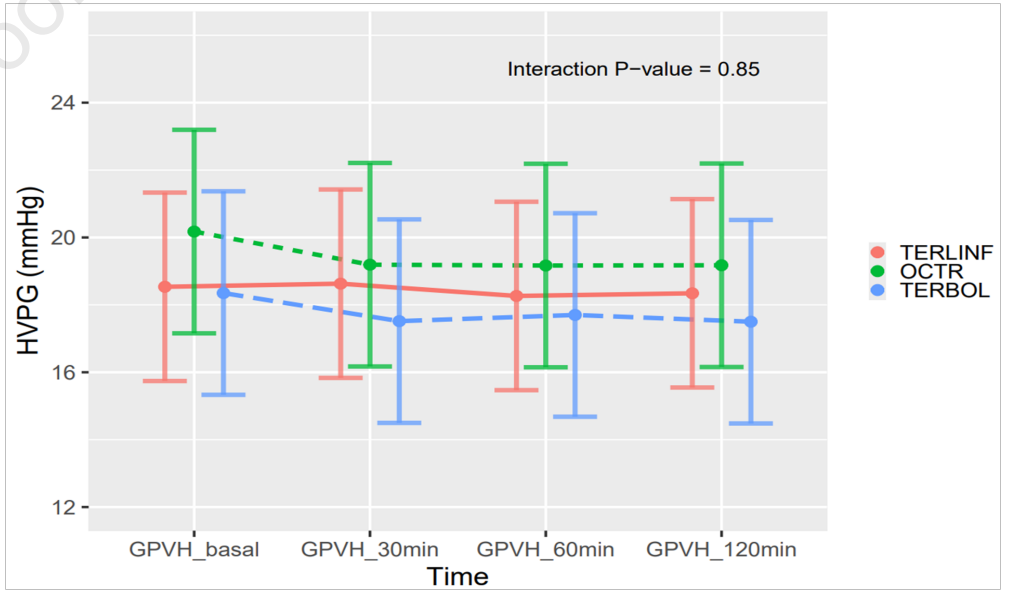
Baseline — 30 minutes — 60 minutes — 120 minutes — 1 week clinical follow-up

TERLINF group
If <10% HVPG reduction: increase 4mg/day

RESULTS

There were non-significant reductions in HVPG with the 3 therapeutic strategies



TERLBOL group: cardiopulmonary and mean arterial pressures significantly increased, while cardiac output and heart rate significantly decreased.

TERLINF group: Continuous infused terlipressin regimen is well tolerated and appears to have a better cardiopulmonary safety profile.

Further investigations are warranted to determine the optimal dosing strategy for Terlipressin infusion in patients with cirrhosis and portal hypertension