A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock

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Abstract

Background & Aims: The choice of vasopressor for treating cirrhosis with septic shock is unclear. While noradrenaline in general is the preferred vasopressor, terlipressin improves microcirculation in addition to vasopressor action in non-cirrhotics. We compared the efficacy and safety of noradrenaline and terlipressin in cirrhotics with septic shock.

Patients and Methods: Cirrhotics with septic shock underwent open label randomization to receive either terlipressin (n=42) or noradrenaline (n=42) infusion at a titrated dose. The primary outcome was mean arterial pressure (MAP) >65 mm Hg at 48 h.

Results: Baseline characteristics were comparable between the terlipressin and noradrenaline groups. SBP and pneumonia were major sources of sepsis. A higher proportion of patients on terlipressin were able to achieve MAP >65 mm Hg (92.9% vs 69.1%, P= .005) at 48 h. Subsequent discontinuation of vasopressor after hemodynamic stability was better with terlipressin (33.3% vs 11.9%, P<.05). Terlipressin compared to noradrenaline prevented variceal bleed (0% vs 9.5%, P=.01) and improved survival at 48 h (95.2% vs 71.4%, P=.003). Percentage lactate clearance (LC) is an independent predictor of survival [P=.0001, HR=3.9 (95% CI: 1.85-8.22)] after achieving the target MAP. Therapy related adverse effects were comparable in both the arms (40.5% vs 21.4%, P=.06), mostly minor (Grade II-88%) and reversible.

Conclusions: Terlipressin is as effective as noradrenaline as a vasopressor in cirrhotics with septic shock and can serve as a useful drug. Terlipressin additionally provides early survival benefit and reduces the risk of variceal bleed. Lactate clearance is a better predictor of outcome even after achieving target MAP, suggesting the role of microcirculation in septic shock.

Keywords

cirrhosis, septic shock, terlipressin, vasopressor

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network classification; AVB, acute variceal bleed; CRRT, continuous renal replacement therapy; HRS, hepato renal syndrome; LC, lactate clearance; MAP, mean arterial pressure; SLED, slow low-efficient dialysis.

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1 | INTRODUCTION

Septic shock is the leading cause of death in intensive care units (ICUs) in general population with a mortality rate up to 60%.

Cumulative mortality in decompensated cirrhosis increased from 13.5% in the absence of infection to 43.5% with infection and up to 70% in the presence of septic shock. Cirrhosis is a state of hyperdynamic circulation which worsens with onset of infection. In septic shock, there is relative deficiency of vasopressin; though the receptor sensitivity and vasoconstrictive effects are preserved. In a meta-analysis, vasopressin was found to be effective, safe and helpful in weaning of catecholamine.

Terlipressin, a congener of vasopressin has equal efficacy for use as a vasopressor in septic shock, besides being effective in acute variceal bleed (AVB) and hepatorenal syndrome (HRS). Terlipressin constricts the vascular smooth muscles directly and also by increasing the responsiveness to catecholamine by inhibition of vascular smooth muscle nitric oxide production and K1-ATP channels. The catecholamine resistance in the setting of septic shock is due to metabolic acidosis, tissue hypoxia with receptor internalization. The vasopressin effects are, however, preserved with receptor hypersensitivity. The TERLIVAP trial supported the use of terlipressin monotherapy. Later the VAASST trial supported the early use of vasopressin as a rescue therapy or add-on therapy for better outcome. Consideration of terlipressin in critically ill cirrhotics with septic shock is a potential new application of terlipressin.

This study was conducted in a liver intensive care unit (LICU) to study the efficacy and safety of terlipressin as a vasopressor against noradrenaline for improving the haemodynamic parameters and its impact on survival outcome in cirrhotics with septic shock.

2 | PATIENTS AND METHODS

Patients of decompensated cirrhosis with septic shock, admitted to LICU at the Institute of Liver and Biliary Sciences (ILBS) from March 2013 to September 2014 were consecutively screened and those fulfilling the criteria were enrolled.

Septic shock was defined by the presence of two or more diagnostic criteria for the systemic inflammatory response syndrome, proven or suspected infection, hypotension non-responsive to fluid resuscitation for 2 h and need of a vasopressor to achieve a target mean arterial pressure (MAP) of ≥65 mm Hg. Patients with age <18 years, valvar heart disease, coronary artery disease, acute mesenteric ischaemia, peripheral vascular disease, pregnancy, chronic kidney disease, uncontrolled or refractory variceal bleed and on immunosuppressive drugs and lack of consent from family members were excluded.

This single centre study protocol conformed to the Declaration of Helsinki and was approved by the ILBS Institutional Ethics Committee vide letter no F25/5/43/AC/ILBS/2013/456, followed the CONSORT guidelines and was registered (NCT01836224). An informed written consent was taken from the spouse or the first degree relative of the patient as appropriate at the time of enrolment.

2.1 | Primary and secondary objectives

This study was conducted with a hypothesis that terlipressin is as good as noradrenaline for use as a vasopressor in cirrhotics with septic shock.

The primary objective was to achieve a MAP of >65 mm Hg and maintenance of the same for initial 48 h. The secondary objectives were: (i) early (≤48 h) and late (28-day) survival (ii) improvement in microcirculation and tissue perfusion, (iii) effect of vasopressor on acute kidney injury (AKI), acute variceal bleed (AVB) during the 28 days follow-up (iv) length of ICU stay and (v) safety of the drug.

2.2 | Patient enrolment and randomization

Cirrhotics suspected of septic shock received fluid resuscitation in the emergency room by 0.9% normal saline at 15 mL/kg over 30 min followed by 5% albumin at 50 mL/h for 6 h. Fluid response was assessed at 2 h. Responders excluded and only the fluid non-responsive hypotension that satisfied the selection criteria, were openly randomized to receive either terlipressin or noradrenaline in a 1:1 ratio using block randomization with a block size of 6. A total of 20% albumin was given subsequently at 1.5 gm/kg on first day followed by 1 mg/kg for next 2 days except those anuric or on renal replacement therapy. The allocation concealment (SNOSE technique) was done by the clinical trial coordinator blinded of patient and treatment. The medication was formulated and administered by the ICU staff.

2.3 | Drug administration

Terlipressin was titrated and infused at a rate of 1.3-5.2 μg/min, that is, 2-8 mg over 24 h and noradrenaline at a rate of 7.5 μg/min and gradually increased to maximum dose of 60 μg/min. Maintenance fluid was 0.9% NS and 5% albumin, and dose adjustment for vasopressor was done every 15 min to achieve MAP≥65 mm Hg. The dose of noradrenaline was used as per standard recommendation.
and was adopted from the VAAST trial. However, the dose of terlipressin was adopted from the existing articles on patients without cirrhosis. Patients unable to maintain MAP > 65 mm Hg despite the assigned dose or the highest tolerated dose of the single inotrope were switched to salvage therapy, that is, combination of noradrenaline of 7.5 μg/min to a maximum of 30 μg/min and terlipressin of 1.3 μg/min to a maximum of 2.6 μg/min. The septic dose of steroid, that is, intravenous hydrocortisone 50 mg every six hourly was given upon failure of monotherapy. The third vasopressor, that is, adrenaline or phenylephrine was used as per the clinical need.

Standard medical therapy included IV fluid, antibiotics on empirical basis as per our institute's microbiological epidemiology and subsequent revision based on culture positivity. Renal replacement therapy is by SLED (slow low-efficient dialysis) and was done in cases with acidosis, worsening azotemia or anuria. CRRT was not available during this study period.

### 2.4 Monitoring and study definitions

The macro-hemodynamic parameters were MAP, heart rate and hourly urine output.

Global tissue perfusion adequacy and microcirculation assessment was done by:

1. **Central venous O2 saturation (SCVO2) with a target of SCVO2>70%**

2. **Delta PCO2** that is Venus Blood and Arterial Blood Gas PCO2 difference in paired samples from CVP line and arterial line with target of < 5 mm Hg

3. **Lactate of Blood Gas preferably <1 mmol/L**

4. **Lactate clearance (defined by lactate baseline—lactate at time point/baseline lactate ×100)**

All these parameters were assessed at baseline, 6, 12, 24 and 48 h after enrolment then as per clinical need. The monitoring of these in non-ventilated patients was by CVP, Blood gas analysis from arterial and CVP line, IVC collapsibility and pulse pressure variation. In ventilated patients, we used FloTrac (EV1000). No peripherally inserted central catheter (PIC) line or Swan Ganz catheter used. Periodic microbiologic screening for infection was done every 48 hourly till last follow-up.

### 2.5 Study definitions

#### 2.5.1 Failure of therapy

(i) Development of adverse events leading to withdrawal of the drug, (ii) MAP < 65 mm Hg with maximum vasopressor dose, (iii) Need of additional/second vasopressor, that is, salvage therapy or death.

#### 2.5.2 Rebound hypotension

Development of new onset hypotension within 48 h of cessation of vasopressor requirement.

### 2.5.3 Adverse events

New onset events those were considered as a part of intervention which may not be present in the absence of any such intervention. The adverse events (AE) were graded 1-5 (Grade 1-Mild AE, Grade 2-Moderate AE, Grade 3-Severe AE, Grade 4-Life-threatening or disabling AE, Grade 5-Death) as per Common Terminology Criteria for Adverse Events (CTCAE) recommendation.

### 2.6 Safety of the therapy

Strict monitoring for the adverse events was done. The guidelines for stopping the protocol included: (i) arrhythmia, (ii) acute myocardial infarction, (iii) cardiomyopathy, (iv) peripheral cyanosis, (v) bowel ischaemia, (vi) refractory GI bleed, bowel perforation or need of any surgical intervention. In the presence of therapy related adverse events, switching of vasopressor was done.

### 2.7 Statistical analyses

This study was a single centre prospective randomized trial. The existing literature supports the use of catecholamine as standard therapy, the vasopressin analogue as single agent and in cirrhotic is the novel approach that cannot be considered as superior or equivalent. Hence, this study was a non-inferiority trial and the sample size was calculated by considering the hemodynamic improvement of 40% in the Noradrenaline group and 25% in terlipressin group, a non-inferiority limit of 15%, a parallel study with binary outcome (hemodynamic improvement, i.e. yes or no), two-sided alpha error of .05 and a power of 90%, we needed to enrol 82 cases and randomly allocated to two arms by block randomization method with block size of 6. The data were represented as proportion, median with inter-quartile range and mean±SD. The categorical data were compared between two groups using Chi-square test. The continuous data were compared using Student’s t test or Mann-Whitney test. The logistic regression was applied to determine predictors of 48 h and 28 day mortality. Kaplan-Meier curve analysis was used to estimate the probability of survival in the two treatment groups and was compared via log-rank test. The intention to treat (ITT) and per protocol (PP) analysis also carried out. The trend of parameters over period of time was assessed using the Generalized Estimating Equation (GEE) model. Analysis was performed using SPSS for Windows version 22.0. The significance was considered at 5% level of probability.

### 3 Results

A total of 511 cirrhotic patients presenting with shock were screened during the enrolment period from March 2013 to September 2014; of these 362 patients were excluded due to various reasons (Figure 1) and other 62 (12.1%) were fluid responsive and excluded. A total of 84 subjects were enrolled and randomized to receive either terlipressin
(N=42) or noradrenaline (N=42). This study was completed and notified on September 2014.

The patients in both the groups were comparable with respect to demographic, clinical and laboratory parameters (Table 1). Infection at presentation to ICU was classified as “first hit” sepsis. The predominant source of sepsis was different at enrolment, (Table S1) in the terlipressin group spontaneous bacterial peritonitis (SBP) (50%) followed by pneumonia (21.4%) and in the noradrenaline group; it was pneumonia (47.6%) followed by SBP (26.2%). However, the interaction between the source of infection and the intervention was not significant (P=.35). The mortality in terlipressin and noradrenaline group was comparable [P=.31, OR=1.81 (95% CI: 0.57-5.73)] when adjusted for different sources of infection.

3.1 | Primary outcome

It was to maintain a MAP of >65 mm Hg for the initial 48 h.

At 48 h of therapy, maintenance of MAP of >65 mm of Hg was achieved in majority of patients on Terlipressin compared to noradrenaline (92.9% vs 69.1% P=.005) on ITT analysis. However, the success of therapy, that is, maintenance of target MAP without adverse effects or switching of therapy was comparable (48% vs 36%, P=.27). This difference was due to little increase in adverse effect (P=.06, see Table 3) with terlipressin that required change in therapy. Use of Terlipressin compared with noradrenaline was associated with greater withdrawal of the vasopressor at 48 h (33.3% vs 11.9, P<.02) due to achievement of target MAP, with comparable switching to salvage therapy (45.4% vs 51.8%, P<.66; Table 2). However, after adjusting for the mortality in relation to need of salvage therapy, both the groups were comparable [P=.61, OR=0.73 (95% CI: 0.22-2.39)].

As a result of dynamicity of shock, the early hemodynamic stability, that is, at 6 h of protocol, the target MAP at 6 h was achieved in most (90.5% vs 78.6, P=.13) patients using either agent (Table 2). The mean time to achieve the target MAP was 1.24±0.43 and 1.26±0.50 h respectively (P=.82). The median dose of terlipressin was 2.9±1.8 μg/min and of noradrenaline was 22.7±8.6 μg/min (Table 2). The trend of MAP in both the cohort was comparable on ITT analysis (Figure 2).
TABLE 1  Baseline characteristics in the two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Terlipressin group (N=42)</th>
<th>Noradrenaline group (N=42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>46.76±12.11</td>
<td>48.29±12.53</td>
<td>.57</td>
</tr>
<tr>
<td>Gender (Male:Female)</td>
<td>35:7</td>
<td>34:8</td>
<td>.78</td>
</tr>
<tr>
<td>Aetiology of Liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>27 (64.3%)</td>
<td>22 (52.4%)</td>
<td>.31</td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>5 (11.9%)</td>
<td>3 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Chronic Hepatitis C</td>
<td>4 (9.5%)</td>
<td>4 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic and NASH related</td>
<td>6 (14%)</td>
<td>13 (31%)</td>
<td></td>
</tr>
<tr>
<td>Child–Turcotte–Pugh score</td>
<td>12.48±1.13</td>
<td>12.29 ± 1.44</td>
<td>.50</td>
</tr>
<tr>
<td>MELD score</td>
<td>32.14±6.37</td>
<td>32.21±7.44</td>
<td>.96</td>
</tr>
<tr>
<td>MELD Na score</td>
<td>33.14±6.38</td>
<td>32.98±7.05</td>
<td>.91</td>
</tr>
<tr>
<td>SOFA score</td>
<td>13.74±3.07</td>
<td>14.78±2.66</td>
<td>.11</td>
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<tr>
<td>Heart rate per minute</td>
<td>104.86±16.32</td>
<td>104.6±17.72</td>
<td>.96</td>
</tr>
<tr>
<td>Mean arterial pressure in mm Hg</td>
<td>60.67±2.79</td>
<td>60.29±3.05</td>
<td>.55</td>
</tr>
<tr>
<td>Lactate at baseline</td>
<td>3 (IQR=2.0-5.0)</td>
<td>3 (IQR=2.5)</td>
<td>.99</td>
</tr>
<tr>
<td>ScvO2</td>
<td>75.55±5.50</td>
<td>76.95±5.54</td>
<td>.25</td>
</tr>
<tr>
<td>VBG-ABG PCO2 difference</td>
<td>4.22±2.00</td>
<td>4.33±1.83</td>
<td>.82</td>
</tr>
<tr>
<td>Hb in gm/dL</td>
<td>8.98±1.67</td>
<td>9.14±1.41</td>
<td>.62</td>
</tr>
<tr>
<td>Total WBC Count/cc</td>
<td>13.95±6.39</td>
<td>14.50±5.36</td>
<td>.67</td>
</tr>
<tr>
<td>Platelet × 10^9/cc</td>
<td>66.52 (IQR=41.53-122)</td>
<td>68.03 (IQR=48.0-146.25)</td>
<td>.26</td>
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<tr>
<td>INR</td>
<td>2.0 (IQR=2.0-3.0)</td>
<td>2 (IQR=2.3-3.25)</td>
<td>.78</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>10.0 (IQR=6.75-18.00)</td>
<td>18.50 (IQR=5.0-31.0)</td>
<td>.36</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>5 (IQR=3.0-8.0)</td>
<td>10.0 (IQR=2.75-16.25)</td>
<td>.18</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>118.53 (IQR=90.73-164.24)</td>
<td>112.5 (IQR=79.10-188.21)</td>
<td>.62</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>2.31±0.71</td>
<td>2.43±0.70</td>
<td>.44</td>
</tr>
<tr>
<td>Blood urea (mg/dL)</td>
<td>103.0 (IQR=63.50-158.0)</td>
<td>83.0 (IQR=46-127.71)</td>
<td>.12</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.0 (IQR=1.0-4.0)</td>
<td>2.0 (IQR=1.0-4.0)</td>
<td>.82</td>
</tr>
<tr>
<td>Sodium (meq/lit)</td>
<td>134.64±9.81</td>
<td>136.07±9.75</td>
<td>.51</td>
</tr>
<tr>
<td>Potassium (meq/lit)</td>
<td>4.21±1.03</td>
<td>4.17±0.96</td>
<td>.83</td>
</tr>
</tbody>
</table>

*Detail work up was negative for aetiology.

**Diabetic, obese (Probable NASH) and biopsy proven cases.

3.2 | Secondary outcomes

3.2.1 | Global microcirculation and tissue perfusion parameters

Microcirculation was assessed as regional and global. The surrogate markers of global microcirculation and tissue perfusion, that is, Central Venous Oxygen Saturation (ScvO2), difference of PCO2 between paired central venous and peripheral arterial sample, lactate level and the percentage lactate clearance (LC) were assessed at baseline, 6, 12, 24 and 48 h into the protocol (Figure 3). The lactate level at the above mentioned time points showed a declining trend (P=.58) as was the percentage lactate clearance (P=.06) with the use of terlipressin. The decrease in ScvO2 (P=.07) and difference in Venus Blood and Arterial Blood Gas PCO2 with time (P=.07) also showed a trend towards improved tissue perfusion and better microcirculation with the use of Terlipressin over noradrenaline. The LC was found to be an independent predictor of outcome [P=.0001, HR=3.9 (95% CI: 1.85-8.22)] after achieving the target MAP, that is >65 mm Hg (Figure 4). A sharp decline in LC was noted among non-survivors at 12 h (58% vs 4%, P=.01).

3.2.2 | Effect on complications of cirrhosis

Organ failure as assessed by SOFA score on daily basis did not differ in both the groups, as were the length of ICU stay [6 (IQR=2-11.2) vs 5 (IQR=3-10.2) days, P=.99] and overall hospital stay [13 (IQR=8-17.5) vs 10 (IQR=7-14.5) days, P=.17] (Table 2). The use of terlipressin showed resolution of AKI (as assessed by AKIN score) from AKIN 3 to AKIN1 on day five (6/16, 37.5% vs 1/12, 8.3%, P=.08) suggesting a role of terlipressin in sepsis induced HRS and AKI. New onset variceal bleed was significantly lower while on terlipressin (0 vs 7/42, 9.5%, P=.01; Table 2).
3.2.3 | Survival

The survival in the whole cohort was 20.2% (17/84); comparable in both groups (26.2% vs 14.3%, P=.17). The median survival was 11 days [(95% CI: 8.9-13.04) and 7 days (95% CI: 3.8-10.2), P=.08 in terlipressin and noradrenaline group, with a significantly greater proportion surviving at 48 h in the former (95.2% vs 71.4%, P=.003) (Figure 5). Hospital stay prior to enrolment (59.5%...
FIGURE 3 Global Microcirculation and Vasopressors: Trend of various parameters used for the global microcirculation assessment showed a favourable trend with use of terlipressin but not statistically significant

FIGURE 4 Lactate clearance among Survivor vs Non-survivor (Total Cohort): The percentage lactate clearance (LC) is an independent predictor of outcome even after achieving the MAP i.e. >65 mm Hg. A sharp decline noted among non-survivors at 12 h (58% vs 4%, *P* = .01). GEE model. # Lactate clearance (lactate baseline - lactate at time point/baseline lactate ×100)
vs 64.3%, \( P= .36 \), and second hit sepsis (50% vs 40.5%, \( P= .19 \)) and mortality in relation to hospital stay, development of second hit sepsis and resolution of infection were comparable. But when the total cohort was considered for outcome in relation to sepsis, prior hospitalization (88.5% vs 65.6%, \( P= .007 \)), development of second hit sepsis (97.4% vs 65.2%, \( P< .001 \)) and non-resolution of infection (100% vs 70.7%, \( P< .001 \)) associated with high mortality (Table S2).

### 3.2.4 Adverse effects

The occurrence of drug related AEs was 40.5% (17/42) and 21.4% (9/42) \( (P= .06 \) in terlipressin and noradrenaline group respectively (Table 3). These AEs occurred earlier upon use of terlipressin [median time; 6 (range 2-60) vs 21 (range 6-72) hours, \( P= .01 \)]. The predominant AE was peripheral cyanosis (70.5% vs 44.4%, \( P= .19 \)) in both the group (Table 3). Terlipressin related adverse events were seen in 17 patients and discontinuation of the drug early enough in 16 of 17 and reduction in dose in one patient lead to complete reversal of the adverse events in 80% of cases. After adjusting for the mortality in relation to occurrence of AE both the groups were comparable \( (P= .06, \text{OR}=0.32 (95\% \text{ CI: 0.10-1.01}) \).

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Terlipressin group (n=42)</th>
<th>Noradrenaline group (n=42)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of adverse effects</td>
<td>17 (40.5%)</td>
<td>9 (21.4%)</td>
<td>.06</td>
</tr>
<tr>
<td>Time to adverse event in hrs (median)</td>
<td>6 (IQR=2-60)</td>
<td>21 (IQR=6-72)</td>
<td>.01</td>
</tr>
<tr>
<td>Severity of adverse events (CTACE Grade)</td>
<td>N=17</td>
<td>N=9</td>
<td></td>
</tr>
<tr>
<td>GRADE-2</td>
<td>15</td>
<td>6</td>
<td>.39</td>
</tr>
<tr>
<td>GRADE-3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>GRADE-4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Type of adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral cyanosis</td>
<td>12 (70.5%)</td>
<td>4 (44.4%)</td>
<td>.19</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>2 (11.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (11.8%)</td>
<td>1 (11.1%)</td>
<td>.99</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (5.9%)</td>
<td>3 (33.3%)</td>
<td>.07</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>0</td>
<td>1 (11.1%)</td>
<td>.16</td>
</tr>
</tbody>
</table>

### 3.3 Per protocol analysis comparing the monotherapy or combination

#### 3.3.1 Monotherapy

In the per protocol analysis (Table S3), when we compared the patients who were able to be maintained on monotherapy till the outcome, terlipressin, noradrenaline were comparable as far as the success of therapy at 6 h (100% vs 89%, \( P= .26 \)) and 48 h (100% vs 82%, \( P= .07 \)) concerned. The use of terlipressin showed a 28 days survival benefit (47% vs 11%, \( P= .002 \)) and greater reversal of septic shock (54.8% vs 33.3%, \( P= .04 \)) but at the cost of increased adverse effects (33% vs 12%, \( P= .02 \)). The early survival, that is <48 h were comparable (100% vs 89%, \( P= .26 \)) with the both the therapies. In our study protocol, 37 of 84 (44%) required change in therapy at any time point reflecting the dynamic nature of septic shock. Rebound hypotension, persistent or new onset tachycardia were comparatively less and resolution of AKI was better with terlipressin, though the difference was not significant.
3.3.2 | Combination (salvage therapy)

Comparison of terlipressin or noradrenaline alone against the salvage therapy showed that the combination had a significantly poor early as well as 28 days survival (P<.01). The combination was associated with higher tachycardia (P=.03) without any benefit in term of prevention of variceal bleed or resolution of AKI. The rebound hypotension was seen in 42%, 61% and 35% (P=.13) respectively in terlipressin, noradrenaline and salvage therapy. The terlipressin group required more frequent change to salvage therapy [23/42 (54.7%) vs 14/42 (33.3%), P=.03]. The adverse effects of therapy were higher with the salvage therapy than the monotherapy (P=.05).

4 | DISCUSSION

The results of this study on advanced cirrhatics with septic shock showed that terlipressin is as effective as noradrenaline in achieving a MAP of >65 mm Hg at 6 and 48 h, with early survival advantages in addition to prevention of variceal bleed and trend towards improvement in sepsis associated AKI and microcirculation. However, since cirrhosis with septic shock are very sick with high MELD and SOFA score, despite achieving hemodynamic stability at 48 h in nearly 90% patients, the mortality was still very high i.e. 79.8% due to multiorgan failure.

The type and the amount of fluid for resuscitation is undefined for cirrhosis as the surviving sepsis guideline and Early Goal directed therapy is not applicable for cirrhosis.12,17 Jalan et al.18 showed that even in compensated cirrhosis and after TIPS, there is always a defective handling of sodium challenge. Use of 0.9% NS vs 5% albumin as a resuscitation fluid in cirrhosis with septic shock is not standardized. But the use of isotonic NS for resuscitation in decompensated cirrhosis, critically ill cirrhotic and in the presence of AKI to a volume of 30 mL/kg is a challenge19 and supported recently against it.12,17 Under strict monitoring (use of FloTrac and other noninvasive methods), we provided fluid resuscitation with 0.9% NS up to 15 mL/kg followed by 5% albumin for maintenance. This approach showed that 12.1% of cirrhotics with septic shock were fluid responsive and achieved a target MAP of >65 mm Hg like in other studies.14

Like reported in non-cirrhotic patients,8 we observed that terlipressin infusion is effective for achieving and maintaining target MAP in cirrhosis with septic shock. Recently, CLIF SOFA score advocated the use of terlipressin, but further studies are needed before considering it as standard of care. It permits early withdrawal of vasopressor and lesser need of combination therapy than with the use of noradrenaline. This is possibly due to the synergistic effect of vasopressin supplementation in addition to catecholaminergic effect. The use of combination therapy upon failure of monotherapy did not show advantage in maintaining target MAP, tachycardia20 and rebound hypotension15 or survival. This may be due to the patient cohorts in our study were comparatively sick with high lactate and multiorgan failure from the beginning where it is expected to have adrenergic receptor internalization and hyposensitivity in addition to relative vasopressin deficiency.5,6,21 This necessitated the need for early introduction of the second vasopressor agent rather than after failure of monotherapy and is in line with the VAAST trial.11

Tissue microcirculation needs to be maintained in sepsis, more so in cirrhotics who are already in vasodilatory state. Our data favour lactate clearance as a good surrogate marker of microcirculation in predicting survival even after maintenance of MAP>65 mm Hg. And is supported by the fact that despite achieving a target MAP, the patients who had better tissue perfusion had better survival.22 High lactate level, poor lactate clearance, low SCVO2 or wide Venous Blood and Arterial Blood Gas PCO2 gradient (>5) reflect poor global microcirculation.23 We have not assessed the regional microcirculation.22,24 Our study cohort had patients with gross microcirculatory dysfunction (evidenced by the surrogate markers) in the background of advanced cirrhosis. Terlipressin in present study showed a trend towards improvement in microcirculation and possibly the restored sensitivity to catecholamine, as shown in earlier studies.25 This could not achieve statistical significance, but opened a window for future studies.

Terlipressin resolved renal failure by day 5 from AKIN-3 to AKIN-1 (P=.08). Sepsis worsens the systemic vascular resistance in a cirrhotic and hence can lead to a hepatorenal syndrome like pre-renal AKI. Rodriguez et al.26 showed that Type-1 HRS develops in the setting of active sepsis improved with terlipressin and albumin, an added benefit of terlipressin when used as a vasopressor in septic shock.

Sepsis increases the risk of variceal bleeding several folds due to increase in portal pressure.27 In these sick patients, occurrence of variceal bleed poses greater challenge due to coagulopathy, risk of rebleeding and unstable hemodynamics. In this study, none of patients in terlipressin group had variceal bleed compared to noradrenaline group possibly due to reduction in portal pressure and redistribution of splanchic blood.

In a retrospective analysis of 322 patients,28 we had shown that terlipressin is relatively safe with adverse events in 7.5% patients. Used as a bolus with catecholamine, Acevedo et al.29 showed a higher rate of adverse effects with terlipressin among patients of cirrhosis with septic shock. In this study, we used terlipressin in an infusion form; the adverse events were comparable to noradrenaline, mostly minor and often got reversed upon withdrawal. Our study recorded comparable AEs, that is, 40% (35.3% in Cavallin et al.30 when used for HRS) despite relatively much sicker group of patients. So while the concern for AE is well conceived, a select group of sickest patients, that is, cirrhosis with septic shock and vasoplectic have limited options, hence evaluation and use of terlipressin is justified.

Terlipressin achieved early survival advantage at 48 h; more so in severe septic shock sub-group. This reiterates that early and stable hemodynamic parameters result in subsequent recovery of organ(s) failure.

The present randomized trial raises a challenge as how to improve the survival from a mere 20% in cirrhotics with septic shock. Future trials to define early failure may be at 2-3 h and early introduction or use of a combination of terlipressin and vasopressin. The impact of relative adrenal insufficiency in septic shock and the role of nutrition on gut microbial translocation could provide new directions. It would have been good if serum cortisol levels were checked for detecting
possible relative adrenal insufficiency and monitoring of plasma levels of terlipressin in our study.

In summary, the present randomized trial shows that terlipressin is a good and safe alternative vasopressor agent to noradrenaline in patients of cirrhosis with septic shock, and can be used as a first line vasopressor. It is another issue that despite achieving a target MAP, the mortality is very high in cirrhotics with septic shock. Future trials could define early treatment failure at 2-3 h and assess early introduction or de novo use of a combination of terlipressin or vasopressin with or without an ionotrope.

CONFLICTS OF INTEREST

The authors do not have any disclosures to report.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.