



RESEARCH ARTICLE

# Use of terlipressin in the treatment of hepatorenal syndrome: Intravenous infusion versus intravenous boluses; An Open Label, Pilot, Randomized Controlled Study

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## OPEN ACCESS

### PUBLISHED

31 December 2025

### CITATION

Tiwari, PS., Aryal, M., et al., 2025. Use of terlipressin in the treatment of hepatorenal syndrome: Intravenous infusion versus intravenous boluses; An Open Label, Pilot, Randomized Controlled Study. Medical Research Archives, [online] 13(12).

<https://doi.org/10.18103/mra.v13i12.7147>

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### DOI

<https://doi.org/10.18103/mra.v13i12.7147>

### ISSN

2375-1924

## ABSTRACT

**Introduction:** The purpose of this study was to evaluate the role of terlipressin in the management of hepatorenal syndrome, focusing on the efficacy of its infusion and bolus regimens.

**Objectives:** To determine the efficacy and safety of terlipressin intravenous infusion and bolus regimens in treating hepatorenal syndrome.

**Materials & Methods:** The study employed an open-label, randomized controlled trial design. A total of 56 patients with hepatorenal syndrome were randomly assigned to two groups. The infusion regimen of terlipressin was administered to the TERLI-I group, while the bolus regimen was given to the TERLI-B group. The drug response and its adverse effects were analyzed.

**Result:** Among the 56 patients, 83.9% responded to the treatment. In the TERLI-I group, 71.4% had a complete response, 14.2% had a partial response, and 14.2% were non-responders. In the TERLI-B group, 60.7% had a complete response, 21.4% had a partial response, and 17.8% were non-responders. Overall, the response to treatment (partial plus complete response) was observed in 85.7% of the TERLI-I group and 82.1% of the TERLI-B group. No significant treatment-related adverse events were observed.

**Conclusion:** Terlipressin remains the standard of care for the management of patients with hepatorenal syndrome. Both administration regimens were equally effective, with no significant adverse effects.

**Keywords:** Cirrhosis, Hepatorenal syndrome, Terlipressin.

## Introduction

Hepatorenal syndrome (HRS) is a potentially reversible, volume-non-responsive, functional renal impairment that can occur in patients with advanced chronic liver disease, i.e., cirrhosis with ascites.

HRS is classified into types 1 and 2. Type 1 HRS is characterized by rapid progressive renal failure, usually accompanied by multiorgan failure. Type 2 HRS manifests as a slowly progressive functional renal failure associated with refractory ascites<sup>1</sup>. The 2-week mortality rate is as high as 80% in untreated Type 1 HRS patients, with only 10% of patients surviving for 3 months. The prognosis of Type 2 HRS patients is slightly better, with a median survival of 6 months<sup>2</sup>. Overall, HRS carries a dismal prognosis, but in recent years, there has been a trend toward a slight improvement in prognosis with the advent of vasoconstrictors.

The peripheral arterial vasodilation theory<sup>3</sup> is the most widely accepted explanation for the pathophysiology of HRS. The role of vasoconstrictors has been studied as a medical treatment or as a bridging therapy until definitive treatment with liver transplantation can be performed. Among the vasopressin analogs, terlipressin is the most widely studied drug.

Terlipressin improves renal perfusion and glomerular filtration in patients with HRS by inducing vasoconstriction of the splanchnic circulation<sup>4</sup>. Several studies have shown that terlipressin is an effective drug in the medical treatment of HRS<sup>5</sup>. Thus, it is recommended as the first-line drug in combination with plasma expansion with albumin by the Acute Dialysis Quality Initiative (ADQI) work group<sup>6</sup>.

However, terlipressin is an expensive drug; its high cost makes it less practical to use when used for prolonged durations. Alternative agents such as

noradrenaline are widely available and relatively inexpensive, but there are fewer studies supporting their efficacy. Moreover, most studies have used terlipressin in a bolus regimen and have reported adverse events in up to 22%<sup>7,8</sup>. However, a randomized study by Angeli P<sup>9</sup> showed that terlipressin, when given by continuous intravenous infusion rather than intravenous bolus, required a lower dosage and yet showed equal efficacy and is better tolerated. However, the intravenous terlipressin regimen in HRS requires further validation.

Thus, this study aimed to compare the efficacy of terlipressin when used as a continuous intravenous infusion versus intravenous boluses for treating HRS.

## Methodology

This was a hospital-based, open-label, pilot, randomized controlled study of the Hepatology unit, Nobel Medical College, from September 2023 to March 2024.

**Patients:** All consecutive patients with decompensated chronic liver disease (CLD) with acute kidney injury (AKI) admitted to the Hepatology unit, Nobel Medical College, were included in the study.

Chronic liver disease was diagnosed on clinical grounds, including laboratory tests, endoscopic evidence, sonographic findings, and liver histology, if available.

The study included patients diagnosed with HRS. The diagnosis of HRS was determined using the criteria proposed by the International Ascites Club (IAC)<sup>9</sup> as shown in Table 1.

**Table 1.** Diagnostic criteria for hepatorenal syndrome

Diagnostic criteria for HRS	*Diagnosis of AKI: IAC AKI Criteria
<ol style="list-style-type: none"><li>1. CLD with Ascites</li><li>2. Diagnosis of AKI according to the IAC AKI Criteria (*)</li><li>3. No improvement of serum creatinine concentration (decrease to <math>\leq 1.5</math> mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin at 20 g/day</li><li>4. Absence of shock</li><li>5. No current or recent treatment with nephrotoxic drugs</li><li>6. Absence of parenchymal kidney disease as indicated by proteinuria with a protein concentration <math>&gt;500</math> mg/day, microhematuria with <math>&gt;50</math> erythrocytes per high-power field, and/or abnormal renal findings on ultrasonography.</li></ol>	<p>Definition of AKI: Serum creatinine (SCr) concentration increase <math>\geq 0.3</math> mg/dl in <math>\leq 48</math> hours, from the baseline.</p> <p>Baseline SCr concentration: Stable SCr concentration for <math>\leq 3</math> months. If not available, a stable SCr concentration closest to the current one. If there is no previous SCr concentration measurement, use the admission SCr concentration.</p>

The exclusion criteria included:

- a. Improvement in renal function after albumin infusion for 2 days
- b. History of coronary artery disease, ventricular arrhythmia, obliterative arterial disease of the limbs, or other severe extrahepatic disease.
- c. Septic shock
- d. Contraindications to the use of terlipressin
- e. CLD with herbal-induced liver injury
- f. Acute on chronic liver failure (ACLF)

The study was an open-label, randomized controlled trial, approved by the institutional ethics committee (IIRC/NMCTH/492/2021). Written informed consent was obtained before inclusion in the study.

**Treatment Protocols:** All consecutive patients diagnosed with CLD fulfilling the AKI criteria received initial resuscitation and supportive care as needed. Diuretics and beta blockers were stopped. Before randomization into the two groups, each patient received a first-line treatment for 48 h consisting of an intravenous albumin infusion (20 g). After 48 h, the patient's AKI status was reassessed. If creatinine did not decrease, they were included in the randomization group. Patients were randomized into two treatment groups, A and B, using the coin flip method. Patients in Group A received an infusion regimen of terlipressin (TERLI-I), whereas those in Group B received a bolus regimen (TERLI-B). Diagram 1 explains the flow chart, below.

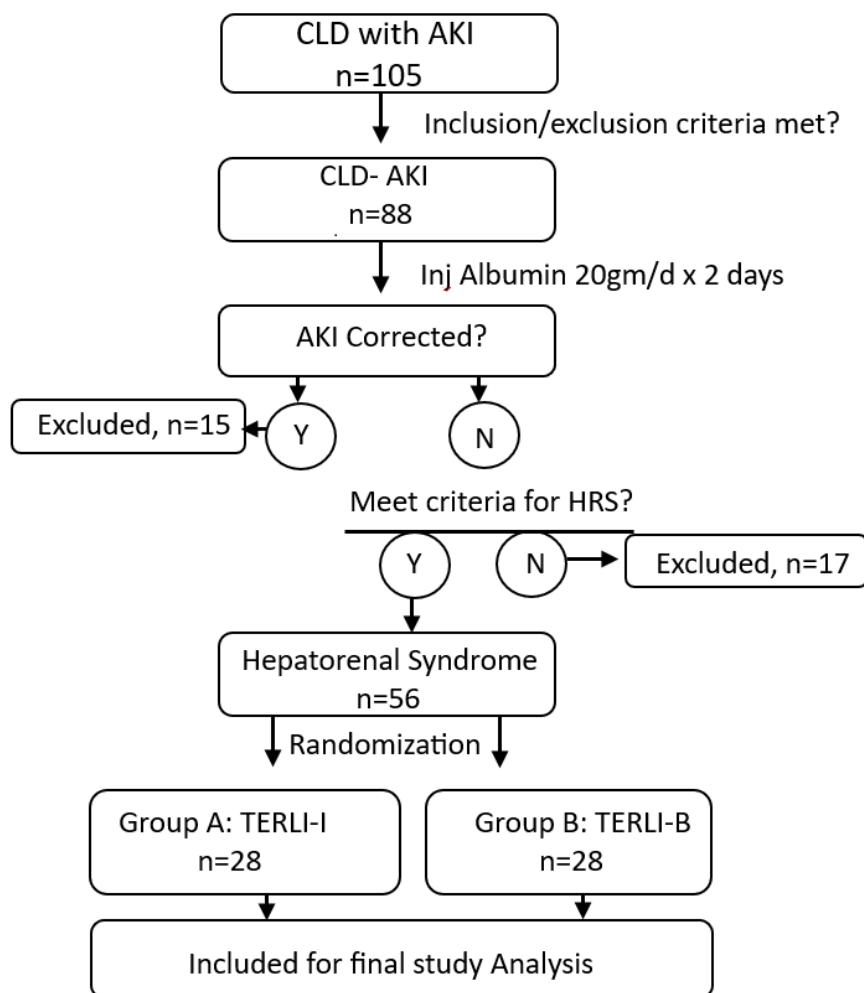


Diagram 1. Flow Chart

For TERLI-I, terlipressin (starting at 2 mg) was dissolved in 50 mL of 5% dextrose solution and infused over 24 h using a pump. For TERLI-B, the standard practice recommendation was used: terlipressin (starting at 0.5 mg) given as an intravenous bolus every 6 h. In both groups, terlipressin was continued until a complete

response occurred or discontinued if any adverse events occurred. The treatment response (defined below) was assessed every 3rd day. For partial responders or non-responders, the dose was doubled and reassessed on the 3rd day. The maximum dose of terlipressin was 12 mg/day, and the maximum treatment duration was 15 days.

Both groups received daily intravenous albumin (20 g/day) along with terlipressin. Blood samples were taken before the initiation of therapy and at days 1, 3, 5, 7, and 15 of treatment to measure standard liver and renal function tests, and blood pressure and weight were recorded. In patients with tense ascites, paracentesis was performed.

Stages of Acute kidney injury<sup>9</sup>

Stage 1: SCr concentration increase  $\geq 0.3$  mg/dL up to 2 times the baseline level.

Stage 2: SCr concentration  $>2$ -3 times the baseline level.

Stage 3: SCr concentration  $>3$  times the baseline level or SCr concentration  $\geq 4.0$  mg/dL or initiation of renal replacement therapy.

Progression: Progression of AKI to a higher stage or the need for renal replacement therapy.

Regression: Regression of AKI to a lower stage.

Definitions of Response<sup>9</sup>

NO RESPONSE: No regression of AKI despite complete treatment protocol

PARTIAL RESPONSE: Regression of the AKI stage with a decrease in SCr concentration, but to a value  $\geq 0.3$  mg/dl above the baseline.

COMPLETE RESPONSE (REVERSAL OF HRS): decrease in the SCr concentration to  $<0.3$  mg/dl from the baseline.

End Points

PRIMARY END POINT. Complete response (*i.e.*, reversal of HRS).

Table 2. Baseline characteristics

Features	TERLI-I		P value
	Group A: n=28	Group B: n=28	
Age (years)	51.00 $\pm$ 6.76	51.71 $\pm$ 9.07	0.740 (NS)
Sex(m/f)	22/6	19/9	0.820 (NS)
Etiology, Alcohol/not Alcohol	25/3	23/5	0.705 (NS)
MAP, mm Hg	84.14 $\pm$ 11.30	82.54 $\pm$ 13.47	0.630 (NS)
White blood cell, /ul	7776.75 $\pm$ 4606.42	9028.57 $\pm$ 4577.96	0.312 (NS)
Serum Na, mmol/L	125.68 $\pm$ 3.47	126.79 $\pm$ 3.08	0.212 (NS)
Serum Creatinine, mg/dl	2.61 $\pm$ 0.92	2.95 $\pm$ 1.25	0.252 (NS)
Serum total bilirubin, mg/dl	1.26 $\pm$ 1.16	1.65 $\pm$ 1.42	0.263 (NS)
AST, U/L	93.18 $\pm$ 44.11	74.21 $\pm$ 53.64	0.154 (NS)
ALT, U/L	69.29 $\pm$ 34.29	61.18 $\pm$ 39.19	0.413 (NS)
Albumin, g/L	2.49 $\pm$ 0.34	2.30 $\pm$ 0.45	0.080 (NS)
INR	1.66 $\pm$ 0.22	1.63 $\pm$ 0.34	0.612 (NS)
CTP score	9.46 $\pm$ 1.04	9.68 $\pm$ 1.34	0.505 (NS)
MELD score	21.43 $\pm$ 4.83	22.36 $\pm$ 5.34	0.501 (NS)
MELD-Na score	27.54 $\pm$ 3.51	27.79 $\pm$ 4.20	0.810 (NS)

Abbreviations: MAP, mean arterial pressure; AST, Aspartate transaminase; ALT, Alanine transaminase; INR, international normalized ratio; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD including sodium; NS, not significant; TERLI-BOL, terlipressin by intravenous boluses; TERLI-INF, terlipressin by intravenous infusion.

**Statistical Analyses:** The sample size was 56, which is consistent with the pilot trial sample sizes reported by Julious<sup>10</sup> and Kieser and Wassmer.<sup>11</sup> A proforma was used to collect data from the patients enrolled in the study. The data from the proforma were entered into Microsoft Excel. After coding, the data were then exported to the Statistical Package for Social Sciences (SPSS) version 25 software for analysis. A p-value  $< 0.05$  was considered significant. Descriptive analysis consisted of presenting the continuous data in mean and standard deviation, while frequency and percentages were reported for categorical data. The results were analyzed at baseline, day 3, day 5, the end of treatment, and day 30 of the study. We enrolled 56 patients, 28 in each treatment group. The characteristics of the responders and non-responders were analyzed regardless of the treatment regimen. Univariate and multivariate analyses were performed to determine the baseline predictors of response.

## Results

One hundred and five patients presented with a diagnosis of CLD and AKI. Fifty-six patients met the criteria of hepatorenal syndrome and were thus included in the study after randomization (Diagram 1). Twenty-eight patients were included in each group: Group A (TERLI-I) and Group B (TERLI-B). There were no significant differences between the two groups in the clinical and laboratory data at the time of randomization (Table 2).

### Response to treatment

Of the 56 patients, 47 (83.9%) responded to treatment. In the TERLI-I group, 20 patients (71.4%) had a complete response, four patients (14.2 %) had a partial response, and 4 patients (14.2%) were non-responders. In the TERLI-B group, 17 patients (60.7%) had a complete response, 6 patients (21.4%) had a partial response, and 5 patients (17.8%) were non-responders. Overall, the response to treatment (partial plus complete response) was seen in 85.7 % of the TERLI-I group and 82.1 % of the TERLI-B group. Note: For partial-responders or non-responders, the dosing of terlipressin was doubled and further reassessed on the next 3rd day.

Among the responders, the mean daily dose of terlipressin  $2.43 \pm 0.63$  mg and  $2.35 \pm 0.57$  mg in Groups A and B, respectively, and the duration of treatment was  $6.14 \pm 1.48$  and  $5.79 \pm 1.37$  days, but no significant difference was observed regarding the dose and length of treatment. Similarly, no significant differences were observed in the mean increase in mean arterial pressure or in the mean reduction in serum creatinine between the two groups (Table 3).

**Table 3.** Details of Assigned Treatment in Responders (Complete and Partial)

Features	TERLI-I Group A: n=28	TERLI-B Group B: n=28	P value
Duration of treatment (days)	$6.14 \pm 1.48$	$5.79 \pm 1.37$	0.354 (NS)
Mean daily dose of terlipressin (mg)	$2.43 \pm 0.63$	$2.35 \pm 0.57$	0.610 (NS)
SCr, at end of treatment (mg/dl)	$1.63 \pm 1.08$	$1.93 \pm 1.39$	0.365 (NS)
Delta MAP, mm Hg	$89.07 \pm 11.75$	$85.46 \pm 13.78$	0.297 (NS)
Delta CP-score	$0.214 \pm 0.63$	$0.429 \pm 0.63$	0.210 (NS)
Delta-MELD	$5.18 \pm 4.20$	$5.46 \pm 3.90$	0.793 (NS)
Delta Meld-Na	$3.93 \pm 3.43$	$4.14 \pm 3.23$	0.811 (NS)
Delta MAP			
Day 3 of treatment versus baseline	$-2.5 \pm 3.40$	$-2.82 \pm 6.03$	0.807 (NS)
End of treatment versus baseline	$-4.93 \pm 4.03$	$-2.79 \pm 6.41$	0.140 (NS)

Abbreviations: CP: Child Pugh score; MAP: mean arterial pressure; MELD: Model for End-Stage Liver Disease; MELD-Na: MELD including sodium

### Adverse Events

Infection was present in 16 (28.5%) patients in the form of spontaneous bacterial peritonitis (SBP) and urinary tract infection. All patients received intravenous cefotaxime (2 g) three times a day.

A total of 3 patients (10.7 %) in the TERLI-I group and 5 patients (17.8%) in the TERLI-B group developed diarrhea, although it was not statistically significant. No other treatment-related adverse events were observed.

Among the five patients who developed diarrhea in the Terli-B group, one patient achieved a complete response on Day 3; thus, terlipressin was stopped. In the other 4 patients, terlipressin was continued for another 24 h. Among the 4 patients, 1 had a partial response, and 3 showed no response and were thus discontinued.

In the Terli-I group, three patients had diarrhea; however, a complete response was observed in 1 patient on Day 3. Terlipressin was continued to

observe the tolerance, and 2 patients tolerated well until Day 7; however, 1 patient had a partial response, and the third was a non-responder and thus stopped.

### Predictors of Response

Baseline mean arterial pressure, total bilirubin, serum albumin, and CP, MELD & MELD-Na scores were significantly associated with the response (Table 4).

**Table 4.** Predictors of Response

Univariate Analysis	Responders	Non-responders	P value
Treatment: bolus/infusion	23/28, 24/28	5/28, 4/24	1.00
Infection (yes/no)	13/16, 34/40	3/16, 6/40	0.705
Baseline MAP, mm Hg	86.09±11.51	69.00±3.08	<0.001
Baseline white blood cell count	7518.06±3400.62	13022.22±7070.32	0.001
Baseline serum creatinine, mg/dl	2.623±0.91	3.58±1.63	0.016
Baseline total serum bilirubin, mg/dl	1.034±0.47	3.67±1.96	<0.001
Baseline international normalized ratio	1.60±0.28	1.89±0.20	0.004
Baseline albumin, g/L	2.48±0.37	1.98±0.32	<0.001
Baseline serum Na, mmol/L	126.38±3.28	125.44±3.47	0.439
Baseline CP-Score	9.24±0.88	11.44±0.73	<0.001
Baseline MELD	20.66±4.27	28.33±4.27	<0.001
Baseline MELD-Na	26.79±3.39	32.22±2.73	<0.001
Multivariate Analysis	OR	95% CI	p
Baseline serum creatinine, mg/dl	0.163	0.031 – 0.865	0.033

## Discussion

Renal dysfunction is not uncommon in chronic liver disease. Almost 50% of CLD patients with ascites develop AKI during their illness<sup>12</sup>. In the study by Garcia et al., 19% of hospitalized patients with CLD had AKI, and among those, 17% had HRS<sup>13</sup>.

Hepatorenal syndrome has a grave prognosis. Gines and Arroyo have previously reported a 2-week mortality rate as high as 80% in untreated T1 HRS patients, with only 10% of patients surviving for 3 months.<sup>1,2</sup> In recent years, however, there has been a trend toward a slight improvement in HRS prognosis. For example, in a multicenter study by Salerno et al., the 3-month survival was 20% and 40% for T1 and T2 HRS, respectively<sup>14</sup>.

Based on all studies to date, terlipressin has been the cornerstone therapy for HRS. Terlipressin causes splanchnic vasoconstriction, diverting the blood to the systemic circulation, lowering the sympathetic nervous system and Renin-Angiotensin-Aldosterone System activation, decreasing the production of arginine vasopressin, and eventually leading to improved renal perfusion<sup>15-20</sup>.

Terlipressin has been studied in several randomized controlled trials (RCT) in patients with HRS comparing its bolus doses plus albumin versus either albumin alone<sup>7,21</sup> or placebo with or without albumin<sup>8,22,23</sup>. The studies showed that terlipressin was able to significantly improve renal function in 24-80% of patients. Overall, terlipressin is considered effective in 40-50% of cases. In a meta-analysis of terlipressin trials, there was an overall 29% reduction in mortality<sup>24</sup>.

Terlipressin is used for HRS in many parts of the world and is included in the Clinical Practice

Guidelines in Europe<sup>25</sup>. However, it was not approved in the US until September 2022 owing to its adverse effects. Later, following the results of 3 major studies OT-0401, REVERSE<sup>26</sup>, and CONFIRM<sup>27</sup>, the drug became the first FDA-approved medication for the treatment of HRS, but with a box warning due to the safety issues over respiratory failure.

Terlipressin can be administered both as intravenous boluses. The continuous infusion regime was shown to be associated with a significantly lower incidence of adverse effects such as pain in the abdomen, persistent diarrhea, peripheral ischemia, cardiovascular abnormalities, and circulatory overload<sup>28</sup>. These results could be due to the short-term effect (3–4 h) of terlipressin on the portal pressure<sup>29</sup>.

Traditionally, terlipressin is administered as a slow IV bolus injection in the hospital setting, although the 2021 American Association for the Study of Liver Diseases (AASLD) guideline<sup>30</sup> has recommended administering it either as an IV bolus or continuous IV infusion. There are fewer studies of increased interest in using terlipressin as a 24-h infusion. Furthermore, there are no adequate data on the stability of terlipressin in infusor devices suitable for 24 h continuous infusion. In the only study by Bui et al., it was reported that terlipressin was physically and chemically stable when used by the infusion method and all reconstituted infusor concentrations retained above 90% of the original concentration over the test conditions<sup>31</sup>. In our study, we used a syringe pump as an infusor device to give terlipressin by continuous infusion.

Cavallin et al.<sup>32</sup> reported that terlipressin administered by continuous infusion was better tolerated and effective at lower doses than those required for bolus administration. In that study, patients received a 1 mg terlipressin bolus followed by a 4 mg infusion over 24 h. This study followed a similar infusion protocol. Cavallin<sup>32</sup> revealed that the infusion group experienced fewer adverse effects (35%) than the bolus group (62%,  $p < 0.025$ ). In the present study, a total of 3 patients (10.7%) in the TERLI-I group and 5 patients (17.8%) in the TERLI-B group developed diarrhea, although it was not statistically significant. No other treatment-related adverse events were observed. In the study by Cavallin<sup>32</sup>, in terms of response, the rate of response to treatment, including both complete and partial responses, was not significantly different between the two groups (76.47% versus 64.85%;  $P$  value not significant). In this study, 83.9% of the total patients responded to treatment. In the TERLI-I group, 71.4% had a complete response, while 14.2% had a partial response. In the TERLI-B group, 60.7% had a complete response, while 21.4% had a partial response. Overall, the response to treatment (partial plus complete response) was seen in 85.7% of the TERLI-I group and 82.1% of the TERLI-B group.

In addition, the mean required dose was also found to be lower in the infusion regime. In Cavallin's study<sup>32</sup>, the mean daily effective dose of terlipressin was lower in the TERLI-I group than in the TERLI-B group ( $2.23 \pm 0.65$  versus  $3.51 \pm 1.77$  mg/day;  $P < 0.05$ ). In the present study, among the responders, the mean daily dose of terlipressin was  $2.43 \pm 0.63$  mg and  $2.35 \pm 0.57$  mg in Groups A and B, respectively, and the duration of treatment was  $6.14 \pm 1.48$  and  $5.79 \pm 1.37$  days; however, no significant difference was observed regarding the dose and length of treatment. Similarly, in another study by Gerbes et al.<sup>33</sup>, patients who received the continuous infusion regime achieved better results than those who were administered the bolus regime (42% vs. 35%). Also, in Mukhtar et al.<sup>34</sup> Terlipressin was used for 48 h in continuous infusion among the patients undergoing liver transplantation. The results revealed that these patients showed renal protection within 2 days after surgery. Ding et al.<sup>35</sup> conducted a randomized comparison study to evaluate the hemodynamic effects of continuous versus bolus infusion of

terlipressin for portal hypertension. The study concluded that continuous infusion of terlipressin stably reduces the portal venous pressure and may become an alternative to the traditional bolus injection. In summary, results from most of the studies done with continuous infusion of terlipressin have shown better to similar results and lesser adverse effects.

The discussion would still be incomplete without mentioning a few important points. One important comment regarding the adverse effects of terlipressin is fluid overload or respiratory failure, as noted in other international studies as well. According to AASLD<sup>30</sup>, in conjunction with terlipressin, albumin is infused at a dose of 1 g/kg on day 1 of therapy, followed by 40-50 g/day, continued for the duration of treatment. In our clinical practice, we use a lower volume of albumin because of its high price and unaffordability. There have been no studies to compare low-volume versus high-volume albumin infusion in HRS in our settings. In the three trials conducted by Guevara M<sup>36</sup>, Thevenot T<sup>37</sup> and Fernandez J<sup>38</sup>, when the recommended dose of albumin was used for SBP, which were empirical: 1.5 g/kg of body weight on day 1 and 1 g/kg of body weight on day 3, pulmonary edema was the main complication, which makes it evident that the recommended dose is too high and should not only be weight based. In the most recent and the largest RCT, i.e., the CONFIRM trial<sup>27</sup>, HRS-AKI reversal occurred in a significantly higher proportion of patients randomized to terlipressin plus albumin (32% vs 17%). However, deaths from cardiopulmonary complications, mainly pulmonary edema, occurred more frequently in patients who received terlipressin and albumin (11%) compared with those in the placebo group (2%). Therefore, it is plausible that albumin infusion was a major contributor to these cardiopulmonary complications. The issues with fluid overload and respiratory distress associated with a large volume of albumin have been well documented in the literature. Common adverse effects, such as abdominal cramps and diarrhea, noted in this study have also been reported in most studies.

Overall response rates (complete and partial) to terlipressin therapy range from 40% to 60%, with some real-world studies observing as high as 73%<sup>39</sup>. The higher response rate in this study

(83.9%) could be due to several factors. This study consisted of a small number of patients. None of the CLD patients with acute-on chronic liver failure (ACLF) were included, which could be a significant contributing point unless other studies have included ACLF patients. Another critical point concerns the varying response criteria across studies. Furthermore, in the present study, patients with CLD, ascites, and AKI were excluded if there was a history of recent (within the past 3 months) consumption of any herbal medications to avoid cases with possible acute tubular necrosis. In the present context, the outcome of severe alcoholic hepatitis and ACLF has been better understood and well established, which was not clearly defined in the studies of the previous decade. Thus, in this study, patients were carefully selected to avoid heterogeneity.

#### Limitations of the study

As this study was a pilot project, the number of patients was small. The upcoming study, with a larger patient enrollment, will reveal the clearer efficacy and adverse effects of the drug.

## Conclusion

Terlipressin remains the standard of care for the management of patients with hepatorenal syndrome. Both administration regimens demonstrated equal efficacy, with no significant adverse effects. However, the cautious use of terlipressin is recommended in patients with evidence of volume overload.

## Conflict of Interest Statement:

None.

## Funding Statement:

None.

## Acknowledgements:

Authors want to extend sincere gratitude to the resident doctors of the Department of Medicine at the Nobel Medical College for their support.

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