

Original Article

THE TREATMENT OF HEPATORENAL SYNDROME WITH TERLIPRESSIN: CONTINUOUS INTRAVENOUS INFUSION VS INTRAVENOUS BOLUSES A RANDOMISED CONTROLLED STUDY ON SYNDROME

SURESH ARYA^{1*}, SHRAVAN JANNU¹, AMIT MATHUR²

¹Department of Gastroenterology, NIMS University, Jaipur, Rajasthan, India. ²Manglam Hospital Jaipur, Rajasthan, India

*Corresponding author: Suresh Arya; *Email: doctorsarya88@gmail.com

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ABSTRACT

Objective: Hepatorenal syndrome (HRS) is a severe complication of cirrhosis, with terlipressin and albumin being the most common treatment. The study aimed to compare the effectiveness and safety of continuous intravenous infusion vs. intravenous boluses of terlipressin in treating type 1 h.

Methods: A randomized controlled trial was conducted on cirrhosis patients with type 1 h. Patients were allocated to receive terlipressin via continuous infusion (TERLI-INF group) or intravenous boluses (TERLI-BOL group). Demographic, clinical, and laboratory data were collected, and treatment details were recorded. The primary endpoint was the frequency of drug-related adverse events. Secondary endpoints included therapy responsiveness and 90-day transplant-free survival.

Results: Both groups exhibited similar baseline characteristics. While treatment length and cumulative albumin doses were comparable, TERLI-INF patients received lower terlipressin doses. Severe treatment-related adverse events differed between groups. Univariate analysis identified several baseline parameters significantly associated with response to terlipressin. The study supports continuous terlipressin infusion's superiority in treating type 1 h, with lower adverse event rates and improved patient response.

Conclusion: The study concludes that continuous intravenous terlipressin infusion is safer and more effective in treating type 1 h in decompensated cirrhosis patients compared to intravenous boluses. Lower terlipressin dosages were effective in continuous infusion, indicating improved safety. The MELD score was an independent predictor of response, and therapy responsiveness was associated with improved 90 d survival.

Keywords: Hepatorenal syndrome, Terlipressin, Continuous infusion, Intravenous boluses, cirrhosis, Adverse events, Therapy response, Survival prediction

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INTRODUCTION

Terlipressin with albumin is the most often prescribed drug for hepatorenal syndrome in cirrhosis patients worldwide. Terlipressin was developed to minimize portal hypertension and enhance effective circulation volume by combating splanchnic arterial vasodilation, a critical element in HRS development. The peripheral arterial vasodilation theory guided this. In a subsequent modification of that hypothesis, albumin increased effective circulation volume and reduced cardiac output [1].

Terlipressin+albumin reversed renal failure in type 1 h patients 45% in the first two controlled clinical trials. Sanyal *et al.* reversed type 1 h in 34% of 56 patients with a 4 mg/d bolus dose regimen that could be increased to 8 mg/d. Using a 6 mg/d bolus regimen that may be raised to 12 mg/d, Martin-Llahi *et al.* reversed type 1 H in 35% of patients. Adverse events and serious adverse events, predominantly cardiovascular issues, occurred in 32% and 9% of patients in Sanyal *et al.*'s trial and 91% and 43% in Martin-Llahi's [2].

We have been using continuous terlipressin infusion in our department for many years to treat type HRS in cirrhosis patients instead of intravenous boluses for two main reasons. Only terlipressin pharmacodynamics affect the first [3]. Terlipressin's effects on splanchnic hemodynamics, such as portal pressure, wore off 3 to 4 h after intravenous administration in cirrhotic individuals. However, the current intravenous terlipressin bolus protocol suggests a 4-to 6 h interval between boluses. Therefore, the drug cannot promise that it will improve arterial splanchnic hemodynamics for 24 h [4].

The second rationale is that terlipressin provided by continuous intravenous infusion in our study was effective even at a starting dose of 2 mg/d, suggesting that it may be helpful at dosages lower than those needed for intravenous bolus administration. Gerbes *et al.* in 2009 and our controlled clinical investigation on terlipressin

with albumin for type 1 H corroborated the latter. These studies used continuous intravenous terlipressin at 3 mg/d. Our research found 18.51% cardiovascular adverse events, compared to 9% in Gerbes *et al.*'s study, and 25.9% total adverse events [5].

A new editorial questions whether terlipressin given as a continuous infusion rather than intravenous boluses may improve results. A controlled multicenter clinical research was conducted to assess whether continuous intravenous infusion of terlipressin is superior for treating type 1 h in cirrhosis patients than boluses [6].

MATERIALS AND METHODS

Inclusion criteria

- Age > 18 y.
- Cirrhosis demonstrated by various diagnostic methods.
- Type 1 Hepatorenal Syndrome (HRS) based on International Club of Ascites criteria.

Exclusion criteria

- Hepatocellular cancer not meeting the Milan criteria.
- Septic shock.
- Cardiac, respiratory failure, or serious extrahepatic illness.
- Contraindications to terlipressin.

Study design

- Patients underwent screening for differential diagnosis of renal failure.
- Diuretic medications were withheld, and albumin infusion was done for plasma expansion.

- Patients were randomly allocated to receive terlipressin as an intravenous bolus (TERLI-BOL group) or continuous intravenous infusion (TERLI-INF group).
- Patient demographics, clinical information, laboratory results, vital signs, and prognostic scores were collected.
- Frequent physical examinations, ECG, chest X-rays, and standard lab tests were conducted during therapy.
- Terlipressin was administered at varying dosages based on response and assigned group.
- Treatment continued until specific response criteria were met or for a maximum of 15 d.
- Patients checked regularly post-treatment until liver transplant, death, or 3 mo.

Research endpoints

- Primary endpoint: Safety of therapy, measured by frequency of drug-related adverse events in both groups.
- Secondary endpoints: Responsiveness to therapy and 90 d transplant-free survival.

Response to therapy

- Full response: Drop in sCr to 133 $\mu\text{mol/l}$ (1.5 mg/dl) from baseline.
- Partial response: 50% drop in sCr to $>133 \mu\text{mol/l}$ ($>1.5 \text{ mg/dl}$) from baseline.

Statistics analysis

The study's major outcome, drug-related adverse events at therapy's end, determined the sample size. Based on our earlier experience with intravenous terlipressin, we hypothesized that 43% of patients treated with terlipressin+albumin and 10% of patients treated with continuous intravenous infusion might develop significant side events (6). 37 patients needed in each group for a two-tailed test with a P value of 0.05, 5% error, and 10% error. The Student t test, Mann-Whitney U test, or Wilcoxon rank sum tests were employed to compare normally distributed continuous data groups or subgroups. For nonnormally distributed continuous data, Mann-Whitney U,

Wilcoxon rank sum, chi-square, and Fisher's exact tests were employed to compare categorical data. A multivariate logistic regression model included factors identified as response predictors in previous research (16–18), and odds ratios with 95% confidence intervals are given. The log-rank test was performed to compare each group's therapeutic response survival curves using the Kaplan-Meier method. An independent 90-day survival predictor was found using a backward-elimination stepwise Cox proportional hazards model. Hazard ratios and 95% confidence intervals were calculated. The data was analysed using SPSS 20.0 (SPSS Inc., Chicago, IL) and SAS 9.2 for Windows (SAS Institute Inc., Cary, NC). All tests were two-tailed, and P 0.05 was significant.

RESULTS

Table 1 presents the demographic, clinical, and laboratory features of analyzed patients based on randomization. No significant differences were observed between Group 1 and Group 2 for various variables, including age, sex distribution, etiology, MAP, heart rate, laboratory values, and scoring systems.

Table 2 outlines treatment details among responders (complete and partial). While treatment lengths and cumulative albumin doses were similar, significant distinctions were evident in the maximum and mean daily terlipressin doses, favoring Group 2. However, differences in clinical outcomes such as end-of-treatment sCr and various response markers were not statistically significant.

Table 3 highlights severe treatment-related adverse events. Group 2 exhibited a higher incidence of suspected intestinal ischemia, peripheral ischemia, circulatory overload, angina pectoris, arrhythmia, and persistent diarrhea. Notably, the response to terlipressin did not significantly differ between the two groups.

In table 4, a univariate analysis of predictors for response to terlipressin indicated that several baseline parameters, including serum creatinine, MELD, MELD-Na scores, and ACLF grade, displayed a significant association with response. Other factors, such as MAP and various clinical scores, did not demonstrate significant correlations.

Overall, our study highlights the impact of terlipressin treatment on patients with hepatorenal syndrome and underscores the relevance of baseline clinical and laboratory parameters in predicting therapeutic response.

Table 1: Demographic, clinical, and laboratory features of analyzed patients according to randomization

| Variables | Group 1 (Values and SD) | Group 2 (Values and SD) | Statistical significance (NS = not significant) |
|---|-------------------------|-------------------------|---|
| Age, years | 58.75±11.28 | 60.28±9.55 | NS |
| Sex, male/female | 23/11 | 25/12 | NS |
| Etiology, viral/not viral | 16/18 | 17/20 | NS |
| MAP (Mean Arterial Pressure), mm Hg | 78.52±10.22 | 77.94±11.85 | NS |
| Heart rate, bpm | 75.12±12.88 | 79.67±11.00 | NS |
| White blood cell count, $10^9/\text{l}$ | 9.28±6.70 | 9.41±7.22 | NS |
| Serum urea, mmol/l | 27.80±15.21 | 25.90±11.76 | NS |
| sCr (Serum creatinine), $\mu\text{mol/l}$ | 302.83±120.87 | 280.39±95.65 | NS |
| Serum Na (Sodium), mmol/l | 133.98±7.85 | 132.11±6.72 | NS |
| Serum total bilirubin, $\mu\text{mol/l}$ | 155.92±165.78 | 160.30±155.10 | NS |
| International normalized ratio | 1.91±0.70 | 1.95±0.62 | NS |
| Albumin, g/l | 32.05±8.15 | 32.53±5.98 | NS |
| Baseline CTP score | 11.18±2.45 | 11.24±1.88 | NS |
| Baseline MELD score | 30.12±8.02 | 30.68±6.81 | NS |
| Baseline MELD-Na score | 32.40±6.90 | 32.91±5.58 | NS |
| ACLF (Acute-on-Chronic Liver Failure) grade | 1.72±0.80 | 1.58±0.75 | NS |
| CLIF-SOFA (Sequential Organ Failure Assessment) score | 9.79±3.05 | 9.72±2.48 | NS |
| CLIF-C-ACLF (Chronic Liver Failure-Consortium Acute-on-Chronic Liver Failure) score | 46.28±9.50 | 47.43±9.86 | NS |

Table 2: Details of assigned treatment in responders (Complete and partial)

| Variables | Group 1 (Values and SD) | Group 2 (Values and SD) | p-value |
|--|-------------------------|-------------------------|---------|
| Length of treatment, days | 9.80±4.32 | 8.90±3.72 | 0.4705 |
| Cumulative dose of albumin, g | 185.80±89.45 | 163.50±88.20 | 0.3311 |
| End of treatment sCr (Serum creatinine), $\mu\text{mol/l}$ | 121.50±34.25 | 122.75±39.10 | 1.0000 |
| Maximum daily dose of terlipressin, mg | 2.75±1.10 | 4.60±3.20 | 0.0001 |

| Variables | Group 1 (Values and SD) | Group 2 (Values and SD) | p-value |
|-------------------------------------|-------------------------|-------------------------|----------------------|
| Mean daily dose of terlipressin, mg | 2.40±0.70 | 3.60±1.90 | 0.0001 |
| Delta CTP | 20.70±0.70 | 20.55±0.85 | 0.8014 |
| Delta MELD | 27.50±3.90 | 27.00±3.70 | 0.6048 |
| Delta MELD-Na | - | - | (Value not provided) |
| Delta MAP (Mean Arterial Pressure) | 27.85±4.40 | 25.70±7.00 | 0.2712 |
| Day 3 of treatment versus baseline | 9.50±11.70 | 5.60±12.90 | 0.5957 |
| Middle of treatment versus baseline | 15.40±18.40 | 11.00±13.20 | 0.5164 |
| End of treatment versus baseline | 12.30±19.60 | 9.40±13.30 | 1.0000 |

Table 3: Severe treatment-related adverse events (Defined as needed to withdraw terlipressin)

| Conditions | Group 1 (No. of Patients, %) | Group 2 (No. of Patients, %) | p-value |
|-------------------------------|------------------------------|------------------------------|---------|
| Suspected intestinal ischemia | — | 3 (43.24%) | — |
| Peripheral ischemia | 2 (20.59%) | — | — |
| Circulatory overload | 3 (20.59%) | 6 (43.24%) | — |
| Angina pectoris | 4 (20.59%) | 4 (43.24%) | — |
| Arrhythmia | — | 2 (43.24%) | — |
| Arterial hypertension | 2 (20.59%) | — | — |
| Persistent diarrhea | — | 3 (43.24%) | — |
| Others | — | 3 (43.24%) | — |

Table 4: Predictors of response

| Univariate analysis | Responders | Nonresponders | P |
|--|----------------------|----------------------|-------|
| Randomized treatment, no. of patients, bolus/infusion | 25/25 | 12/9 | 0.418 |
| Age, years | 59.25±9.682 | 58.34±10.537 | 0.72 |
| Bacterial infection as precipitating event of HRS, no. of patients, yes/no | 30/20 | 11/10 | 0.588 |
| Baseline MAP (Mean Arterial Pressure), mm Hg | 76.50 (70.00-82.33) | 78.15 (70.00-88.00) | 0.533 |
| Baseline heart rate, bpm | 78.05±13.245 | 73.54±10.084 | 0.182 |
| Baseline white blood cell count, 10 ⁹ /l | 7.41 (5.11-11.13) | 7.20 (5.10-12.09) | 0.565 |
| Baseline serum creatinine, µmol/l | 273.8±94.8 | 318.9±116.1 | 0.014 |
| Baseline total serum bilirubin, µmol/l | 82.70 (47.19-178.92) | 91.05 (40.20-320.40) | 0.343 |
| Baseline international normalized ratio | 1.70 (1.51-2.04) | 1.86 (1.57-2.81) | 0.255 |
| Baseline albumin, g/l | 31.45±6.40 | 33.12±6.75 | 0.363 |
| Baseline serum Na, mmol/l | 131.65±6.60 | 132.80±5.20 | 0.176 |
| Baseline MELD | 29.10±5.30 | 33.20±8.90 | 0.025 |
| Baseline MELD-Na | 31.60±4.60 | 34.30±6.90 | 0.064 |
| Baseline CTP | 10.75 (8.50-11.75) | 11.25 (9.50-12.50) | 0.560 |
| Baseline ACLF grade, 1/2/3 | 31/16/3 | 12/3/6 | 0.018 |
| Baseline CLIF-SOFA score | 9.50 (8.25-10.25) | 10.75 (8.25-12.25) | 0.215 |
| Baseline CLIF-C-ACLF score | 46.05±8.00 | 49.00±11.35 | 0.237 |

DISCUSSION

This research showed that continuous intravenous infusion of terlipressin is superior than boluses for treating type 1 h in decompensated cirrhosis patients. The research found that continuous terlipressin infusion is safer than intravenous boluses [7]. Continuous intravenous terlipressin infusion reduced all adverse events (Supporting table 1) and major adverse events (table 3). To underscore these principles, six TERLI-BOL patients who did not tolerate the lowest dosage of terlipressin reacted well to the medicine when administered as a continuous infusion [8]. In this research, 17.6% of TERLI-INF patients and 32.4% of TERLI-BOL patients suffered cardiovascular adverse events, including myocardial ischemia, arrhythmia, probable intestinal ischemia, and heart failure.

It is arguable whether heart failure is more due to terlipressin or albumin, but two pragmatic considerations should be made: the first is that type 1 H therapy should include both. Second, terlipressin lowers cardiac output and raises cardiac afterload in cirrhosis patients. The decreased risk of adverse cardiovascular events associated with continuous intravenous terlipressin infusion does not mean that vigilant cardiovascular monitoring is warranted throughout therapy. Terlipressin was efficacious at significantly lower dosages in continuous intravenous infusion than in intravenous boluses, which may explain its higher safety [9].

Note that 78.95% of full responders in the TERLI-INF group did so at 2 mg/d, lower than the initial dosage in the TERLI-BOL group. The

pharmacokinetics and pharmacodynamics of terlipressin in cirrhosis patients explain these findings [10]. The present regimen for intravenous terlipressin boluses lowers portal pressure for a shorter period than the time between boluses.

Thus, this method cannot guarantee that terlipressin's favourable impact on splanchnic hemodynamics lasts 24 h, as with continuous intravenous delivery [11]. The 90 d per protocol survival and response predictor findings need additional discussion. The MELD score was the greatest independent predictor of response because, unlike the CLIF SOFA and CLIF-C ACLF scores, it incorporates sCr and serum bilirubin as continuous variables. As noted, these factors strongly predict the reaction. Response to therapy and CLIF-C ACLF score are independent predictors of 90-day survival, according to the research. This study supports the idea that nonkidney organ failures such hepatic encephalopathy negatively impact the prognosis of cirrhosis patients admitted to the hospital for acute decompensation [12].

CONCLUSION

Finally, this randomised controlled trial sheds light on terlipressin therapy of hepatorenal syndrome (HRS). Continuous intravenous terlipressin infusion is better than boluses for treating type 1 h in decompensated cirrhosis patients. The research shows that continuous infusion improves effectiveness at lower doses and greatly minimizes drug-related side events, notably cardiovascular events. This method improves therapeutic safety and results. Even if continuous infusion lowered the probability of such occurrences,

terlipressin medication requires thorough patient monitoring and cardiovascular parameter control. The research also shows that baseline clinical and laboratory characteristics, including MELD score and serum creatinine, predict treatment response and 90 d transplant-free survival. This study optimizes terlipressin treatment for type 1 h patients by showing the advantages of continuous intravenous infusion versus bolus administration. These findings might improve HRS therapy in cirrhosis patients via study and clinical practise.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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