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Comparison of Noradrenaline and Terlipressin for Type 1 Hepatorenal Syndrome Treatment: A Randomized Controlled Trial

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Introduction

Cirrhosis is characterized by fibrosis and the formation of nodules within the liver parenchyma, arising as a consequence of chronic liver injury. This pathological remodeling disrupts the normal lobular architecture of the liver. Cirrhosis is traditionally classified into two stages: compensated and decompensated. The transition from compensated to decompensated cirrhosis is primarily driven by the development of portal hypertension. The onset of decompensated cirrhosis is marked by the emergence of serious complications, including variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and hepatopulmonary syndrome.(1)

Hepatorenal Syndrome (HRS) is a significant renal impairment that affects 7–15% of patients with decompensated cirrhosis. HRS is characterized by three main components: liver dysfunction, circulatory abnormalities, and progressive renal failure. According to the updated 2021 guidance from the American Association for the Study of Liver Diseases (AASLD) on the diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis, and HRS, the definition of HRS-acute kidney injury (HRS-AKI) emphasizes the role of acute kidney injury (AKI) in its pathogenesis. HRS-AKI represents a functional renal failure in patients with decompensated cirrhosis, primarily driven by systemic hemodynamic abnormalities. New management recommendations are anticipated to improve patient outcomes significantly.(2)

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Hepatorenal syndrome represents the final stage of progressive kidney perfusion decline due to worsening hepatic injury. Diagnosing hepatorenal syndrome involves systematically ruling out other potential causes and is generally associated with a poor prognosis. In cirrhosis, hemodynamic changes and the subsequent decrease in kidney function are mainly due to arterial vasodilation in the splanchnic circulation, directly resulting from portal hypertension. This vasodilation is thought to be caused by an increased production or activity of vasodilatory agents, primarily within the splanchnic circulation, with nitric oxide playing a key role.(3)

HRS is classified into two types: type 1 (HRS-1) and type 2 (HRS-2). HRS-1 is the more severe form, characterized by multi-organ failure, rapid doubling of serum creatinine to more than 2.5 mg/dl within two weeks, and a swift decline in renal function. HRS-1 has a high mortality rate, with approximately 50% of patients succumbing within two weeks of diagnosis. In contrast, HRS-2 progresses more slowly and is generally associated with a less severe decline in renal function.(2)

The prevalence of HRS-AKI in hospitalized patients with decompensated cirrhosis ranges from 27% to 53%, with a 30-day mortality rate of 29% to 44%. (4)

Liver transplantation remains the most effective treatment for HRS-AKI in suitable candidates without contraindications; however, it is not always a feasible option. In liver diseases, the release of large amounts of vasoactive substances leads to reduced renal blood flow. This reduction activates the juxtaglomerular apparatus, stimulating the renin-angiotensin system and increasing renin secretion, which results in systemic and renal vasoconstriction. This pathophysiological mechanism underscores the severe impact of HRS on renal function in patients with advanced liver disease.(2)

At present, the treatment of hepatorenal syndrome (HRS) involves the use of vasoconstrictor agents that target the splanchnic circulation. Vasoconstrictor drugs combined with albumin are the preferred treatment for HRS-AKI to counteract splanchnic arterial vasodilation and enhance renal perfusion. Terlipressin and norepinephrine, specifically, have shown efficacy in improving kidney function in these patients. Drugs such as midodrine, an alpha-adrenergic agent, and vasopressin agonists like ornipressin and terlipressin, enhance renal perfusion and glomerular filtration in HRS patients by inducing splanchnic vasoconstriction. More recently, noradrenaline, a catecholamine with predominantly alpha-adrenergic activity, has also been suggested as an effective treatment for HRS. However, randomized trials directly comparing the efficacy of noradrenaline with terlipressin in the treatment of type 1 HRS remain limited.(5)

However, large head-to-head trials comparing these vasoconstrictors are lacking, making it difficult to definitively assess their comparative efficacy. Current guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend terlipressin as the preferred

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treatment, with norepinephrine as an alternative. Meanwhile, the American College of Gastroenterology endorses either drug as a first-line option.(4)

Given terlipressin's recent approval in the US and norepinephrine's established use, there is a need to evaluate their comparative effectiveness. In the absence of direct comparative studies, this study could provide crucial insights to guide the management of HRS-AKI, therefore we planned this study to compare the efficacy and safety of noradrenaline with terlipressin in the treatment of HRS.(4)

AIM OF THIS STUDY:

The aim of the study is to compare between the effect of Terlipressin and norepinephrine in the management of type I hepatorenal syndrome.

Materials and methods

A total of 40 consecutive patients with cirrhosis and HRS type 1, who presented at the Medicine department of the Smt SMS Multispeciality Hospital, Chandkheda, Ahmedabad between January 2024 and May 2024, were prospectively evaluated for inclusion in the study.

- **Study Design:** A prospective randomized controlled study.
- **Setting:** This study was conducted at Smt SMS Multispeciality Hospital, Chandkheda, Ahmedabad
- **Study Period:** January 2024 to May 2024 (5 months).
- **Study Population:**
  - **Inclusion Criteria:**
    - Age: 18-60 years
    - Patients with acute or chronic liver diseases
    - Patients with Type I hepatorenal syndrome, as defined by the Ascites Club criteria: rapidly progressive reduction in renal function, such as a doubling of serum creatinine to ≥ 2.5 mg/dL within less than 2 weeks, and lack of improvement in renal function following diuretic withdrawal and plasma volume expansion (Facciorusso, 2019).(6)

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- **Exclusion Criteria:**
  - Patients with Type II hepatorenal syndrome (progressive kidney failure in individuals with severe cirrhosis).
  - Evidence of obstructive or parenchymal renal disease (e.g., acute tubular necrosis, glomerular disease, interstitial nephritis, and urinary obstruction).
  - Patients with severe congestive heart failure or malignancies.

- **Sampling Method:** Random sampling.

- **Sample Size:** 40 patients, divided equally into two groups (20 patients per group).

- **Ethical Considerations:**
  - The study received approval from the ethics committee of the Smt SMS Multispeciality Hospital, Chandkheda, Ahmedabad
  - Informed consent was obtained from each participant or their families.
  - The study protocol, including the purpose of the study, was thoroughly explained to the patients or their families.

- **Study Tools:**
  Candidates admitted to the ICU were subjected to a screening procedure to exclude renal failure due to causes other than HRS.
  Screening included:
  1. Comprehensive history taking, including the duration of illness.
  2. Thorough clinical examination, including:
     - Vital signs assessment
     - Mean blood pressure estimation
     - Abdominal and liver examination

- **Laboratory Measurements:** Blood samples were collected, with a portion drawn into EDTA tubes for complete blood count (CBC) analysis using the Sysmex automated hematology analyzer SF-300 (Sysmex Corporation, Japan). The remaining blood was allowed to clot at room temperature, and serum was separated by centrifugation for 10 minutes at 3000 rpm. The serum was then used for various biochemical investigations, including:

  - **Liver Function Tests:** SGOT, SGPT, Serum albumin
  - **Renal Function Tests:**
    - Urine output
    - Glomerular Filtration Rate (GFR)
    - Serum urea and creatinine
    - Serum sodium

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Treatment Protocol:

All patients were divided into two groups:

Group I: Terlipressin Treatment

This group included 20 patients with Type I hepatorenal syndrome who received terlipressin. The treatment regimen was as follows:

- Initial Dosage: Terlipressin was administered at a dose of 0.5 mg to 1 mg every 6 hours. If there was no improvement in serum creatinine or mean arterial blood pressure, the dose was increased to 1-2 mg every 6 hours for two days, along with 20% albumin.
- Administration Method: During the first three days, terlipressin (1 mg) was given either as an intravenous bolus every 4 hours or as a short-period infusion (15–30 minutes) in 50 patients.
- Dosage Adjustment: If, after the first three days, serum creatinine decreased by at least 25% of the pretreatment values, the dose remained unchanged. If serum creatinine did not decrease by at least 25%, the dose was increased up to a maximum of 2 mg every 4 hours.
- Treatment Duration: Terlipressin was continued until serum creatinine decreased below 1.5 mg/dL and urine output increased above 500 mL/day. There was no fixed maximum treatment duration.
- Albumin Administration: Patients received 40 g of albumin during the first 24 hours, followed by 20 g/day.
- Antibiotic Treatment: Patients with bacterial infections were treated with broad-spectrum antibiotics, including second- and third-generation cephalosporins and carbapenems, based on culture and susceptibility results. Prophylactic antibiotics were not administered during treatment.

Group II: Norepinephrine Treatment

This group included 20 patients with Type I hepatorenal syndrome who received norepinephrine. The treatment regimen was as follows:

- Initial Dosage: Norepinephrine was initiated at 1 mg/hour by continuous infusion, gradually increasing up to a maximum of 4 mg/hour to achieve a mean arterial pressure (MAP) of at least 12 mmHg or a 12-hour urine output of at least 400 mL.
- Albumin Administration: Patients additionally received daily intravenous infusions of 20% albumin (20–40 g/day) until the end of the study period.
- Diuretics: No diuretics were used during the study period.

Primary Outcome Measures:

1. Mean arterial blood pressure
2. Serum creatinine
3. Serum lactate

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This protocol ensures the structured administration and monitoring of terlipressin and norepinephrine in patients with Type I hepatorenal syndrome, providing a basis for assessing the efficacy and safety of these treatments.

Statistical Analysis:

All data were recorded, analyzed, and statistically compared between the two groups to identify any significant differences.

The collected data were reviewed; coded, tabulated and fed to a PC using a reliable software program. Data were presented and suitable analysis was done according to the type of data obtained for each parameter. In the current study, statistical analyses of data were carried out by using the SPSS version 23. The Shapiro –Wilks test was used to test the normal distribution of the variables. Numerical data were expressed as Mean ± SD or Median and Range. Categorical data were summarized as percentages. The Significance for the difference between groups was determined by using two-tailed Student's t test and one way ANOVA (analysis of variance) and Post hoc tests or for quantitative data as appropriate. Also Qualitative variables were assessed by chisquared $\chi 2$test. Correlations between different parameters were done using spearman's and Pearson's correlation coefficient and the area under the curve (AUC) greater than 0.5 was considered to be statistically significant. The probability (P) values of ≤0.05 were considered statistically significant indicated, while P> 0.05 was considered statistically not significant and indicated NS.

Results:

This study included 40 patients diagnosed with Type I hepatorenal syndrome, who were admitted to Smt. SMS Multispeciality Hospital, Chandkheda, Ahmedabad. All patients had either acute or chronic liver disease in addition to Type I hepatorenal syndrome.

They were randomly assigned into two treatment groups:
Group I: consisting of 20 patients who received terlipressin
Group II: comprising 20 patients who were treated with norepinephrine.

The Baseline Characteristics of the studied cases at the time of enrollment in the study:

Parameter	Group {I}	Group {II}	p-value
Age (years)			0.678
Range	50–65	45-67	
Mean ± SD	55.3 ± 5.20	54.1 ± 6.70	

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Gender			0.745
Male/Female	10/10	11/9	
Percentage of Male (%)	50%	55%	

Table show that the mean age of patients in both groups I and II was 55.3±5.20, and 54.1±6.70 years respectively. There was no statistically significant difference between both studied groups regarding to age (P=0.678). Also, studied patients showed a high percentage of males in both studied groups but without statistically significant different between different groups (P>0.05)

Stage of AKI:

Acute kidney injury (AKI)	**Group I [N=20]**	**Group II [N=20]**	**P-value**
Stage II			
N	14	10	
%	70%	50%	0.367
Stage III			
N	6	10	
%	30%	50%	

Of 20 patients received terlipressin, 14 (70%) had AKI stage II, and 6 (30%) has AKI stage III.
AKI stage II and III were equally distributed among patients who received norepinephrine.

Medical history:

Hypertension	**Group I [N=20]**	**Group II [N=20]**	**P-value**
No			
N	11	8	
%	55%	40%	0.749
Yes			
N	9	12	
%	45%	60%	

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In this study, 45% (9/20) of patients in the terlipressin group and 40% (8/20) of those in the norepinephrine group were suffering from hypertension. There was no statistically significant difference between number of cases with hypertension in both studied groups (P>0.05) (Table 3).

Condition	Outcome	Group I (N=20)	Group II (N=20)	P-value
Pneumonia	No	15 (75%)	17 (85%)	0.950
Pneumonia	Yes	5 (25%)	3 (15%)	
UTI (Urinary Tract Infection)	No	17 (85%)	18 (90%)	0.950
UTI (Urinary Tract Infection)	Yes	3 (15%)	2 (10%)	
SBP (Spontaneous Bacterial Peritonitis)	No	15 (75%)	17 (85%)	0.950
SBP (Spontaneous Bacterial Peritonitis)	Yes	5 (25%)	3 (15%)	

In Group I, the incidence of Pneumonia was 5 out of 20 participants, accounting for 25% of the group. Similarly, the group had 3 cases of Urinary Tract Infection (UTI), representing 15%, and 5 cases of Spontaneous Bacterial Peritonitis (SBP), also 25%. On the other hand, Group II reported 3 cases of Pneumonia, making up 15% of the group, 2 cases of UTI, which is 10%, and 3 cases of SBP, equating to 15%. Overall, the number of cases and their respective percentages for each condition showed some variation between the two groups, but these differences were not statistically significant as indicated by the consistent P-value of 0.950. There was no difference between two studied groups regarding number of case with pneumonia, SBP, and UTI.

Hematological Parameters for Different Studied Groups:

Parameter	Group I (Mean ± SD)	Range	Group II (Mean ± SD)	Range2	P-value
RBCs (10^12/L)	3.85 ± 0.30	2.96 - 5.33	3.60 ± 0.65	2.53 - 4.83	0.380
Hemoglobin (g/dL)	10.50 ± 1.77	6.9 - 12.8	10.25 ± 1.83	7.1 - 13.3	0.785
Platelets (10^9/L)	138 ± 61	41 - 252	159 ± 100	27 - 515	0.399
WBCs (10^9/L)	12.15 ± 4.80	3.7 - 22.68	12.85 ± 6.18	6.1 - 33.1	0.680

The results of this study showed that the mean value ± SD for the red blood cells (RBCs) count was 3.85±0.30, 3.60± 0.65 (10^6/µL), the hemoglobin (10.50± 1.77, 10.25 ± 1.83)(g/dL), the platelets count (138 ± 61, 159 ± 100), and the white blood cells (WBCs)

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count (12.15 ± 4.80, 12.85 ± 6.18) (10^3/µL) in terlipressin norepinephrine group respectively, (Table 6). These results revealed that there was no significant difference between the two studied groups regarding the mean value of RBCs (P=0.380), the hemoglobin (P=0.785), the platelets count (P=0.399), and WBCs (P=0.680).

Comparison between Studied groups regarding liver function tests & INR:

Parameter	Group I Mean ± SD	Group I Range	Group II Mean ± SD	Group II Range	P-value
ALT (U/L)	113.5 ± 16.30	51 - 141	91.1 ± 15.41	33 - 71	0.263
AST (U/L)	52 ± 29.03	16 - 179	112 ± 30.61	28 - 196	0.757
Serum albumin (g/dL)	4.15 ± 0.17	1.7 – 3.2	1.96 ± 0.48	1.2 – 2.7	0.164
Total bilirubin (mg/dL)	8.49 ± 5.5	1.15 - 18	14.63 ± 9.39	8.93 - 18.5	0.051
INR	1.85 ± 0.62	1.15 - 3.3	1.85 ± 0.57	0.95 - 2.5	0.788

The examination of routine liver function tests across different cohorts did not reveal any statistically significant variations. Notably, both groups exhibited elevated ALT levels, with the terlipressin group showing an average of 113.5 ± 16.30 U/L and the norepinephrine group 91.1 ± 15.41 U/L, both above the normal range. The study found no significant disparity in ALT levels between the groups (P=0.263). AST levels, which correlate with the progression of chronic liver disease, averaged 52 ± 29.03 U/L for the terlipressin group and 112 ± 30.61 U/L for the norepinephrine group. However, there was no significant difference in AST levels between the groups at the start of the study (P=0.757).

Additionally, serum albumin, total bilirubin, and INR levels were significantly linked to the severity of chronic liver disease. At the study's outset, the mean serum albumin levels were comparable between the groups, recorded at 4.15 ± 0.17 g/dL for the terlipressin group and 1.96 ± 0.48 g/dL for the norepinephrine group (P=0.164). A statistically significant difference was observed in the mean total bilirubin levels between the groups (P<0.05), indicating a notable distinction. In contrast, comparisons of INR values between the terlipressin and norepinephrine groups did not show a significant difference (P>0.05).

Kidney function and hemodynamic variables in both studied Groups before therapy:

Parameters	Group I (N=20) Mean ± SD	Range	Group II (N=20) Mean ± SD	Range 2	P-value
Creatinine (mg/dL)	3.28 ± 1.16	1.7-5.6	3.12 ± 1.09	2.0-4.5	0.8
Urea (mg/dL)	108.9 ± 65.33	24-214	125.9 ± 44.5	31-205	0.701

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Serum Na (mmol/L)	118.7 ± 10.27	108-134	121.7 ± 8.69	110-133	0.390
Urine output (mL/24 h)	445 ± 218.9	110-890	507.5 ± 243.54	160-1050	0.297
Mean Arterial Pressure (mm Hg)	82.6 ± 7.98	65-92	84.9 ± 8.19	69-99	0.418

At the study's commencement, kidney function and mean arterial pressure (MAP) were analogous across both cohorts. No discernible disparity was noted in kidney function at baseline between the groups (P>0.05). The terlipressin group's initial mean creatinine level was 3.28 mg/dL, while the norepinephrine group's was 3.12 mg/dL, indicating no significant difference (p-value = 0.8). Additionally, the terlipressin group's mean urea level prior to treatment was 108.9 ± 65.33 mg/dL, compared to 125.9 ± 44.5 mg/dL in the norepinephrine group, with no significant difference in serum urea levels between the groups (p-value = 0.701).

Furthermore, the mean serum sodium (Na) level before treatment initiation was 118.7 ± 10.27 mmol/L in the terlipressin group and 121.7 ± 8.69 mmol/L in the norepinephrine group, without a significant difference (P=0.390). The average urine output at enrollment was 445 ± 218.9 mL/24 h for the terlipressin group and 507.5 ± 243.54 mL/24 h for the norepinephrine group. The initial mean arterial pressure was also comparable, recorded at 82.6 ± 7.98 mm Hg for the terlipressin group and 84.9 ± 8.19 mm Hg for the norepinephrine group. No significant difference was observed in urine output and MAP when comparing patients in the terlipressin group to those in the norepinephrine group (P >0.05).

1) Serum Creatinine Levels:

- **Group I (Terlipressin)**: Started at **3.28 ± 1.16 mg/dL**, decreased to **1.10 ± 0.85 mg/dL** at the end.
- **Group II (Noradrenaline)**: Started at **3.12 ± 1.09 mg/dL**, decreased to **1.35 ± 0.22 mg/dL** at the end.
- **P-value**: No significant difference between groups over time (P=0.271 to 0.91).

Table: Comparison between different groups regarding creatinine levels at different time points following drug administration:

Creatinine (Time After Treatment)	Group I (N=20) Mean ± SD	Group II (N=20) Mean ± SD	P-value
Start	3.28 ± 1.16	3.12 ± 1.09	0.91
3 days	2.85 ± 1.30	3.55 ± 1.40	0.295
5 days	2.65 ± 1.60	2.90 ± 1.50	0.830

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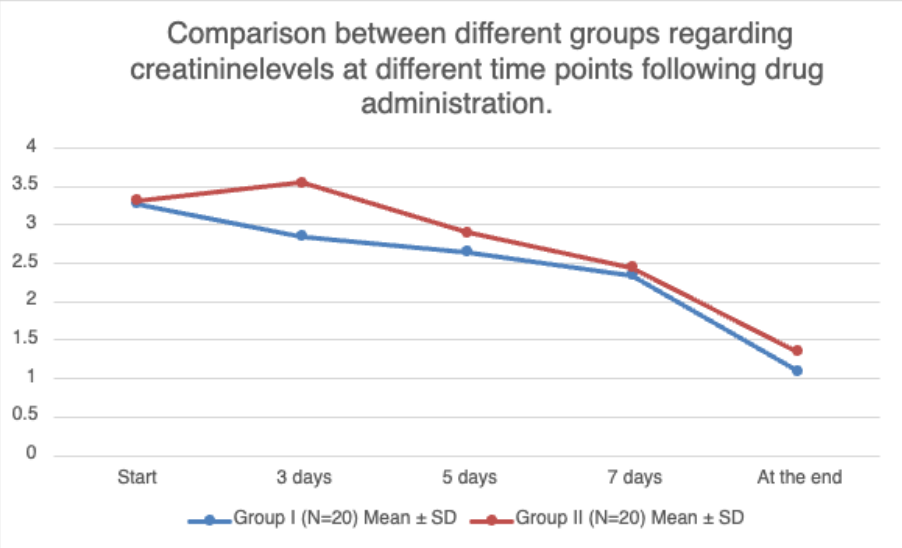
7 days	2.35 ± 1.55	2.45 ± 1.50	0.855
At the end	1.10 ± 0.85	1.35 ± 0.22	0.271



2) Urine Output:

- **Group I**: Increased from **445 ± 218.9 mL/24h** to **896.36 ± 164.45 mL/24h**.
- **Group II**: Increased from **507.5 ± 243.54 mL/24h** to **854.44 ± 148.84 mL/24h**.
- **P-value**: No significant difference between groups (P=0.267 to 0.861).

Table: Comparison between different groups regarding urine output levels at different time points following drug administration:

Time After Treatment	Group I (N=20) Mean ± SD	Group II (N=20) Mean ± SD	P-value
Start	445 ± 218.9	507.5 ± 243.54	0.267
3 days	515.26 ± 240.31	531.88 ± 210.53	0.861
5 days	547.5 ± 325.32	610 ± 252.26	0.536
7 days	626.67 ± 294.13	704.44 ± 246.78	0.589
At the end	896.36 ± 164.45	854.44 ± 148.84	0.592

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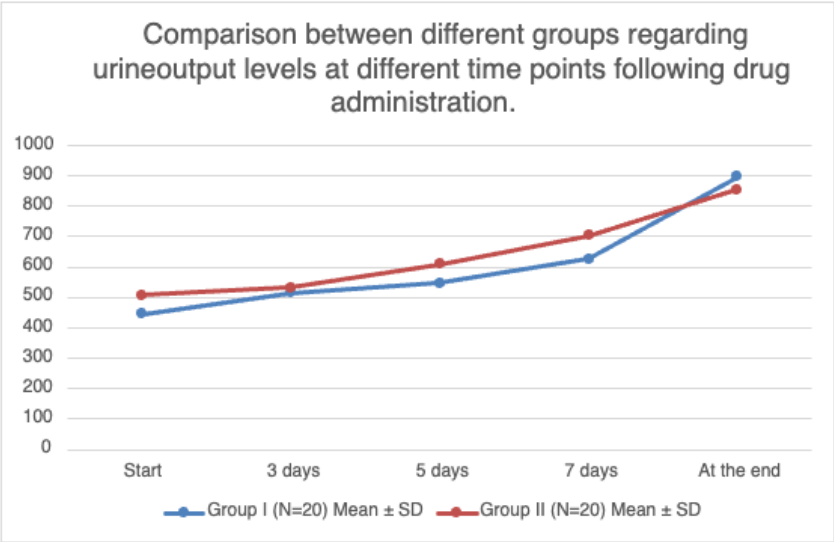
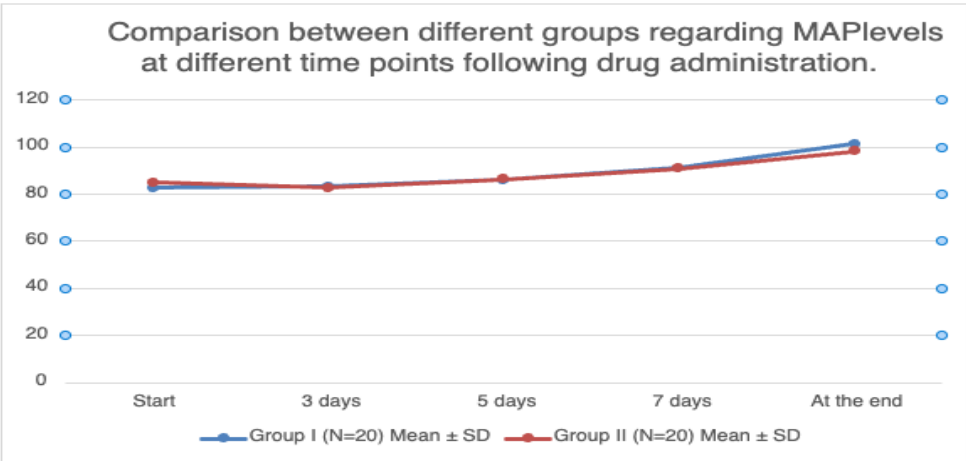


3) Mean Arterial Pressure (MAP):

- **Group I**: Increased from **82.6 ± 7.98 mmHg** to **101.3 ± 7.48 mmHg**.
- **Group II**: Increased from **84.9 ± 8.19 mmHg** to **98.3 ± 6.26 mmHg**.
- **P-value**: No significant difference between groups (P=0.390 to 0.981)

Table: Comparison between different groups regarding MAP levels at different time points following drug administration:

Time After Treatment	Group I (N=20) Mean ± SD	Group II (N=20) Mean ± SD	P-value
Start	82.6 ± 7.98	84.9 ± 8.19	0.439
3 days	83.2 ± 10.27	82.7 ± 9.09	0.981
5 days	86.2 ± 14.77	86.3 ± 10.14	0.968
7 days	91.1 ± 12.38	91.0 ± 12.6	0.945
At the end	101.3 ± 7.48	98.3 ± 6.26	0.390



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Discussion of Baseline Characteristics and Outcomes Baseline Characteristics:

- **Age and Gender:**

  The mean ages for Groups I and II were 55.3 ± 5.20 and 54.1 ± 6.70 years, respectively, with no significant difference (p=0.678).
  Gender distribution was also similar, with Group I having 10 males and 10 females, and Group II having 11 males and 9 females (p=0.745).
  The similarity in age and gender distribution ensures that the outcomes are not biased by demographic differences.

- **Stage of Acute Kidney Injury (AKI):**

  In Group I, 70% of patients were in Stage II and 30% in Stage III.
  In Group II, 50% were in Stage II and 50% in Stage III.
  The distribution of AKI stages was not significantly different between the groups (p=0.367).
  This indicates that the severity of AKI was comparable between the two groups at the start of the study.

- **Medical History**
  Hypertension:

  Hypertension was present in 45% of patients in Group I and 60% in Group II (p=0.749).
  The prevalence of hypertension was similar between the groups, suggesting comparable cardiovascular risk profiles.

- **Incidence of Infections**
  Pneumonia, UTI, SBP:

  Group I had incidences of pneumonia, UTI, and SBP at 25%, 15%, and 25%, respectively.
  Group II had incidences of 15%, 10%, and 15%, respectively.
  There were no significant differences in the incidence of these infections between the groups (p=0.950).
  This similarity indicates that both groups had a comparable risk of infections during the study period.

- **Hematological Parameters**
  RBCs, Hemoglobin, Platelets, and WBCs:

  No significant differences were found in these parameters between the groups, with p-values of 0.380, 0.785, 0.399, and 0.680, respectively.

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The lack of significant differences in hematological parameters suggests that neither treatment adversely affected the patients' blood profiles.

- **Liver Function Tests and INR**
  ALT, AST, Serum Albumin, Total Bilirubin, and INR:

  ALT, AST, serum albumin, and INR levels were not significantly different between the groups (p-values of 0.263, 0.757, 0.164, and 0.788, respectively).
  There was a trend towards a significant difference in total bilirubin levels (p=0.051).
  While liver function tests were mostly similar, the trend in bilirubin levels suggests a potential area for further investigation.

- **Kidney Function and Hemodynamic Variables**
  Creatinine and Urea:

  Initial creatinine levels were 3.28 ± 1.16 mg/dL in Group I and 3.12 ± 1.09 mg/dL in Group II (p=0.8).
  Initial urea levels were 108.9 ± 65.33 mg/dL in Group I and 125.9 ± 44.5 mg/dL in Group II (p=0.701).

- **Serum Na and Urine Output:**

  Serum Na levels were 118.7 ± 10.27 mmol/L in Group I and 121.7 ± 8.69 mmol/L in Group II (p=0.390).
  Urine output was 445 ± 218.9 mL/24 h in Group I and 507.5 ± 243.54 mL/24 h in Group II (p=0.297).

- **Mean Arterial Pressure (MAP):**

  MAP was 82.6 ± 7.98 mm Hg in Group I and 84.9 ± 8.19 mm Hg in Group II (p=0.418).
  These similar baseline values for kidney function and hemodynamic parameters ensure that the comparison of treatment effects is valid.

- **Treatment Outcomes**

  1. **Serum Creatinine Levels Over Time:**

  Both groups showed a significant reduction in serum creatinine levels from baseline to the end of the study, with no significant differences at any time point (p-values ranging from 0.271 to 0.91).
  This indicates that both treatments were equally effective in improving kidney function.

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2. Urine Output Over Time:

Both groups showed a significant increase in urine output, with no significant differences at any time point (p-values ranging from 0.267 to 0.861).
The increased urine output reflects improved kidney function in both groups.

3. Mean Arterial Pressure (MAP) Over Time:

MAP increased in both groups from baseline to the end, with no significant differences at any time point (p-values ranging from 0.390 to 0.981).
The improvement in MAP indicates that both treatments effectively stabilized hemodynamic status.

Conclusion:

The analysis of the tables and charts demonstrates that there were no significant differences between the terlipressin and norepinephrine groups across a range of baseline characteristics, medical histories, hematological parameters, liver function tests, kidney function, and hemodynamic variables. Both treatments showed similar efficacy in improving kidney function and stabilizing hemodynamic status without significant adverse effects. These findings support the use of either terlipressin or norepinephrine in managing AKI secondary to chronic liver disease, providing flexibility in clinical decision-making.

Discussion:

This is one of the few studies that compare the effects and safety of norepinephrine and terlipressin when used in the treatment of type 1 HRS. As evident from this study, norepinephrine proved to be non-inferior to terlipressin in treatment of type 1 HRS. In addition, norepinephrine was safe and far more economical than terlipressin.

The ideal treatment for HRS would be a drug that selectively dilates renal vessels without affecting other vascular beds, especially the splanchnic circulation. No drug with such selectivity exists. Thus, drugs with other, proven splanchnic vasoconstrictor activity have been used in patients with HRS. On this basis, renin acting vasoconstrictor agents, vasopressin analogues, and a newer alpha-adrenergic agent, midodrine, have been reported to improve renal function and reverse HRS. Ornipressin is a potent vasopressin analogue, approved for parenteral use only, due to severe ischemic complications related to its use. Terlipressin is a newly synthesized vasopressin analogue, with a general increase in the therapeutic index and fewer reported side effects. The vasopressin effects are mediated by activation of V receptors on vascular smooth muscle cells, which increase the intracellular calcium and increase release of tissue plasminogen activator. In patients with portal hypertension, this drug causes vasoconstriction in both systemic and splanchnic circulation and has been shown to reduce portal inflow, reduce portal-systemic shunting and reduce intrahepatic resistance, therefore reducing the intrahepatic resistance to portal inflow. Several controlled prospective studies and few meta-analyses supported the terlipressin efficacy in the treatment of HRS by improving the impaired renal function and medium survival time. However, due to the high cost and its unavailability, terlipressin is less practical for prolonged use in several countries.

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Norepinephrine is a powerful splanchnic alpha-adrenergic receptor agonist that leads to intense vasoconstriction and results in increasing effective arterial blood volume and thereby improving renal perfusion and glomerular filtration and leads to reversal of HRS. The renal vasodilatory effect of norepinephrine has been documented as well in the healthy dogs at clinically used dosages of norepinephrine (0.2–0.4 μg/kg/min), which further improves the renal perfusion and helps in HRS reversal. A pilot study by Duvoux et al. reported an HRS-1 reversal in 83% of 12 patients with norepinephrine. Subsequent randomized controlled trials, which included both type 1 and type 2 HRS patients, have reported almost similar efficacy rates with norepinephrine and terlipressin, and an overall average rate of HRS reversal for type 1 HRS of close to 55% in these trials. The findings of the present study were in concurrence with those of these studies. Other studies have reported a higher response rate for type 2 HRS, i.e., 74% in the study by Ghosh et al., and 77% in the study by Alessandria et al. The 30-day mortality rate was around 50% in the previous studies compared with 65% in those which only included type 1 HRS. Our study observed lower mortality rates in both the groups. A recent systematic review and meta-analysis of all studies comparing norepinephrine with terlipressin in the treatment of HRS concluded that norepinephrine is a viable alternative to terlipressin. Both norepinephrine and terlipressin have a safe adverse event profile; its dose titration easily fixes non-serious cardiovascular events (mostly episodes of segment ST depression), and diarrhea and abdominal pain, although common, are self-limiting and decrease with dose titration. In our study, one patient had to stop terlipressin because of persistent diarrhea. Because of the significantly lower cost of norepinephrine, it is preferable, particularly in developing countries. Because terlipressin has to be administered as an intravenous bolus in a peripheral vein, it has its disadvantage, whereas norepinephrine has to be administered by continuous intravenous infusion through a central venous catheter, usually in an intensive care unit setting.

Our study is quite the same as the previous studies. Its limitations are the same, due to small sample size being a great challenge for most of the previous investigators, since a large number of patients with this condition could not be recruited in a single center. Most published studies have enrolled around 40 patients. Plasma renin and aldosterone were not measured in our study.

Therefore, both norepinephrine and terlipressin have equal response rates in treatment for type 1 HRS. Norepinephrine, however, is associated with fewer adverse events and is much cheaper than terlipressin, but because norepinephrine is always not readily available, its usefulness in the developing world is curtailed. Norepinephrine should, therefore, be recommended as an alternative to terlipressin in the treatment of HRS, especially in developing countries and where terlipressin is considered very expensive. Larger, multi-center clinical trials comparing norepinephrine with terlipressin in treatment for HRS will conclusively establish the fact related to a firm conclusion on this subject.

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