TERLIPRESSIN VERSUS NOREPINEPHRIN IN MANAGEMENT OF TYPE 1 HEPATORENAL SYNDROME PATIENTS

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ABSTRACT:

Background: *Cirrhosis affects millions of people throughout the world. Patients with cirrhosis frequently develop renal failure. Hepatorenal syndrome (HRS) develops in decompensated liver disease and it is considered to be the most severe complication. It is the most frequent fatal complication of cirrhosis with nearly 50% of patients dying within 2 weeks of diagnosis.*

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

Patient & methods: *A prospective randomized controlled study. This study was held in Ain Shams University hospitals. 6 months from February to July 2019. 40 patients were divided equally into two groups (20 foreach group).*

Result: *This study comprised 40 patients with Type I hepatorenal syndrome admitted during the period of research from February 2019 to July 2019 to Ain Shams University hospitals. All patients have acute or chronic liver diseases with type I hepatorenal syndrome, and the patients were divided into two groups.*

Conclusion*: The results of this randomized comparative study suggest that norepinephrine and terlipressin had nearly similar response rates for the treatment of type 1 HRS. Therefore, norepinephrine is as effective as terlipressin in the management of patients with type 1 HRS. The lower cost and wider availability of norepinephrine make it a safe andeffective alternative to terlipressin.*

Recommendations: *The present study shows that norepinephrine is as effective as terlipressin in the management of patients with type 1 HRS in order to save costs and ICU beds. This study provides the basis for designing larger randomized controlled trials to confirm the present findings. Further studies should also aim to identify predictors of nonresponsiveness.*

Keywords; *Body mass index, Cystatin c and Haemoglobin.*

INTRODUCTION:

Cirrhosis affects millions of people throughout the world[(1)]**.** Patients with cirrhosis frequently develop renal failure. Hepatorenal syndrome (HRS) develops in decompensated liver disease and it is considered to be the most severe complication. It is the most frequent fatal complication of cirrhosis with nearly 50% of patients dying within 2 weeks of diagnosis[(2)]**.**

The annual prevalence of HRS among cirrhotic patients with ascites is roughly 8%,

but some reports mention a prevalence rate as high as 40%[3].

Advanced cirrhosis is a condition characterized by impaired liver function, portal hypertension, increased splanchnic blood volume, hyperdynamic state with increased cardiac output, systemic vasodilatation, a state of decreased central blood volume, and systemic inflammatory response. acute kidney injury (AKI) is one of the most severe complications of cirrhosis, occurring in up to 50% of hospitalized patients and has been associated with higher mortality, which increases with severity of AKI[4].

Hepatorenal syndrome is sub-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 itself as a slowly progressive functional renal failure associated with refractory ascites[5].

International Ascites Club consensus conference on hepatorenal syndrome defined diagnostic criteria that distinguish between two types of hepatrenal syndrome. Type 1 hepatorenal syndrome is defined as a rapid deterioration of renal function indicated by a two-fold increase of serum creatinine to values above 2.5 mg per dL (221 µmol per L), or a decrease of creatinine clearance to values below 20 mL per minute (0.33 mL per second)[6].

This from of hepatorenal syndrome usually is precipitated by spontaneous bacterial peritonitis and occurs in approximately 25 percent of patients with spontaneous bacterial peritonitis, even with the clearance of infection. The median survival duration of these patients is less than two weeks without treatment, and almost all patients die within 10 weeks after the onset of renal failure. Patients with type 2 hepatorenal syndrome exhibit moderately increased serum creatinine levels above 1.5 mg per dL (133 µmol per L) that remain stable over a longer period, and ascites that generally is resistant to diuretics. The median survival duration in these patients is three to six months[7].

Since morbidity and mortality remain high once HRS is established, the focus is currently on the prevention and early therapy of renal dysfunction in patients with cirrhosis. Emergent liver transplantation is currently the only proven treatment, but mortality among cirrhotic patients with renal dysfunction remains high because of the insufficient availability of donors. Furthermore, compared to transplant recipients without HRS, those with HRS have lower postoperative survival and increased risk of postoperative complications[3].

There are three classes of vasoconstrictors that have been studied in the management of HRS. The first group comprises vasopressin analogs, which include ornipressin and vasopressin, which bind to V1 receptors of vascular smooth muscle cells, leading to vasoconstrictions in systemic and splanchnic circulations. In addition, this group also includes terlipressin, which is a prodrug, the active metabolite of which is lysine vasopressin[8].

The second group comprises α-adrenergic receptor agonists, including norepinepherine and midodrine, which act by binding to α- 1-adrenergic receptors on vascular smooth muscle cells, leading to vasoconstriction. The third group includes octreotide, which is a somatostatin analogue and acts by inhibiting the release of glucagon and other vasodilator peptides, leading to vasoconstrictions in splanchnic, portal, and systemic circulations[8].

Terlipressin is gradually released over several hours, thereby avoiding many of the ischemic side effects of ornipressin and vasopressin without compromising its potency. Terlipressin dilates intrahepatic

vessels leading to a reduction in intrahepatic resistance and portal pressure, which may have a direct effect on the improvement of renal functions[9].

Terlipressin is costly and not universally available, and has side effects with abdominal cramps and diarrhea; moreover, it has not been sufficiently studied to determine the therapeutic protocol with the best efficacy/safety ratio[3].

Terlipressin and albumin is the standard of care for classical type-1 hepatorenal syndrome (HRS) not associated with active infections. However, there is no information on efficacy and safety of this treatment in patients with type-1 HRS associated with sepsis[10].

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.

PATIENTS AND METHODS

Type of the study:

A prospective randomized controlled study.

Study settings:

This study was held in Ain Shams University hospitals.

Study period:

6 months from February to July 2019.

Study population:

Inclusion criteria:

- Age group: (18-60 years of age)
- Patients with acute or chronic liver diseases
- Patients with Type I hepatorenal syndrome defined by ascites Club criteria rapidly progressive reduction in renal function, eg., doubling of SCr ≥ 2.5 mg/dL in less than 2 weeks and failure of renal function to improve following diuretic withdrawal and plasma volume expansion ***(Facciorusso, 2019).***

Exclusion criteria:

- Patients with Type II hepatorenal syndrome (a type of progressive kidney failure seen in people with severe liver damage caused by cirrhosis).
- Evidence of obstructive or parenchymal renal disease (e.g, acute tubular necrosis, glomerular disease, interstitial nephritis and urinary obstruction).
- Patients with comorbidities as severe congestive heart failure and patients with malignancies.

Sampling method: Random sample.

Sample size: 40 patients were divided equally into two groups (20 for each group).

Ethical considerations:

- The study was approved by the local ethics committee of intensive care Department and the Ethical Committee of Faculty of Medicine, Ain Shams University.
- An informed consent was taken from each individual or their families participated in the present study.
- The study protocol was explained to the patients or their families about the purpose of the study.

Study tools:

The candidate patients were admitted to the ICU were subjected to a screening procedure. During screening, all patients with renal failure due to causes other than HRS were excluded:

1. Thorough history taking including duration of illness.
2. Thorough Clinical examination:

All patients were exposed to clinical examination including:

- Assessment of vital signs.
- Mean blood pressure estimation.
- Abdominal examination and liver examination.

Laboratory measurements:

Blood samples were drawn; a portion of the blood was collected on EDTA tube for routine blood pictures (CBC) by Sysmex the automated hematology analyzer SF-300, which produced by Sysmex Corporation, Japan.

The other portion left to clot at room temperature. Serum was separated by centrifuging for 10 minutes at 3000 r.p.m, Sera were used immediately for other biochemical investigations.

- **Liver Function tests:** SGOT,SGPT, Serum albumin
- **Renal function tests:**
  - ✓ Urine output.
  - ✓ GFR
  - ✓ Serum Urea And Creatinine.
  - ✓ Serum Na

Treatment protocol:

All the patients were divided into two groups:

Group I: included 20 patients with type I hepatorenal syndrome who received terlipressin:

- Terlipressin were given to those patients and was started from 0.5 mg-1 mg /6hrs and if there was no improvement in serum creatinine or mean arterial blood pressure, the dose was increased to 1-2 mg/6 hrs for two days; in addition to albumin 20%.
- **During the first 3 days** of treatment, terlipressin (glypressin 1 mg; Ferring GmbH, Kiel, Germany) was administered at a dose of 0.5–1 mg every 4 h as an intravenous bolus in 50 patients and as a short-period infusion (15–30 min).
- If after the first 3 days, serum creatinine decreased at least 25 % of the pretreatment values, the dose remained unchanged. In patients whose serum creatinine did not decrease at least 25 % of the pretreatment values within the first 3 days, the dose was increased up to a maximum of2 mg/4 h.
- Terlipressin was given until serum creatinine decreased below
- 1.5 mg/dl and urine output increased above 500 ml/day.
- We did not use a fixed maximum time period for terlipressin treatment.
- Patients received 40 g of albumin during the first 24 h, followed by 20 g/day. Patients with proven bacterial infection were treated with wide-spectrum antibiotics including second- and third-generation cephalosporins and carbapenems according to culture and antimicrobial susceptibility results.
- Prophylactic antibiotic therapy was not given during thetreatment.

Group II: will include 20 patients with type I hepatorenal syndrome who will receive norepinephin:

Patients with suspected HRS will be started on noradrenaline at an initial dose of 1 mg/hour by continuous infusion. This will be gradually increased up to a maximum dose of 4 mg/hour in order to achieve a mean arterial pressure (MAP) of at least 12 mmHg or a 12-hour urine output of at least 400 mL. The patients additionally received daily intravenous infusions with 20% albumin (20–40 g/day) until the end of the study period. No diuretics will be used during the study period[(3)].

Primary outcome measures:

- Mean arterial blood pressure
- Serum creatinine
- Serum lactate
- **Statistical analysis:** all data will be recorded, analysed and statistically compared between both groups to identify any significant differences between them.

Statistical package:

The collected data was revised, coded, tabulated and introduced to a PC using a reliable software program. Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

In the present study, statistical analyses of data were carried out using SPSS version 23. Shapiro –Wilks test was used to test normal distribution of variables. Numerical data were expressed as mean ± standard deviation 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 chi-squared χ^2test.

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 comprised 40 patients with Type I hepatorenal syndrome admitted during the period of research from February 2019to July 2019 to Ain Shams University hospitals.

All patients have acute or chronic liver diseases with type I hepatorenal syndrome, and the patients were divided into two groups:

Group {I}: 20 patients with type I hepato-renal syndrome who received terlipressin.

Group {II}: 20 patients with type I hepato-renal syndrome who received norepinephrine.

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

Table (1) show that the mean age of patients in both groups I and II was 53.1±4.14, and 52.1±6.63 years respectively. There was no statistically significant difference between both studied groups regarding to age (P=0.571). Also, studied patients showed a high percentage of males in both studied groups but without statistically significant different between different groups (P>0.05) (Table 1).

Table (1): Demographic data of both studied group:

		Group {I} N=20	**Group {II} N=20**	**P-value**
Age (years)	Range	46–60	37-60	0.571
	Mean ± SD	53.1±4.14	52.1±6.63	
Gender	(Male/Female)	11/9	13/7	0.519
	Percentage of Male (%)	55%	65%	

Data expressed as mean± SD or Number (%)

Stage of AKI:

Of 20 patients received terlipressin, 13 (65%) had AKI stage II, and 7 (35%) has AKI stage III.

AKI stage II and III were equally distributed among patients who received norepinephrine (Table 2).

Table (2): Distribution of Acute kidney injury among both studiedgroups:

Acute kidneyinjury (AKI)		Group {I}N=20	Group {II} N=20	P-value
Stage II	N	13	10	0.337
	%	65%	50%	
Stage III	N	7	10	
	%	35%	50%	

Medical history:

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).

Table (3): Cases with hypertension in both studied groups:

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

In addition, cellulitis was detected in one case in the terlipressingroup (Table 4).

Table (4): Cases with cellulitis in both studied groups:

Cellulitis		Group {I}N=20	Group {II}N=20	P-value
No	N	19	20	1.000
	%	95%	100%	
Yes	N	1	0	
	%	5%	0%	

Bacterial-infection–associated HRS was noted in 15 (37.5%) of patients as pneumonia was observed in 4 (20%) of each group. Also, SBP was observed in 4 cases of those who received terlipressin and in 3 patients in norepinephrine.

In addition, UTI was detected in two cases (10%) in terlipressin group and 3 cases (15%) in norepinephrine group.

There was no difference between two studied groups regarding number of case with pneumonia, SBP, and UTI. (Table 5).

Table (5): Distribution of infection in both studied groups:

Pneumonia		Group {I}N=20	Group {II}N=20	P- value
No	N	16	16	1.000
	%	80%	80%	
Yes	N	4	4	
	%	20%	20%	
UTI				
No	N	18	17	1.000
	%	90%	85%	
Yes	N	2	3	
	%	10%	15%	
SBP				
No	N	16	17	1.000
	%	80%	85%	
Yes	N	4	3	
	%	20%	15%	

Hematological Parameters for Different StudiedGroups:

The results of this study showed that the mean value ± SD for the red blood cells (RBCs) count was 3.84±0.89, 3.62± 0.64)(10^6/µL), the hemoglobin (10.05± 1.78, 10.21 ± 1.82)(g/dL), the platelets count and the white blood cells (WBCs) count (137.7 ± 60.39, 160.37 ± 101.68), and (12.139 ± 4.79, 12.88 ± 6.19) (10^3/µL) in terlipressin norepinephrine group respectively, (Table 6).

These results revealed that there was no significant difference between two studied groups regarding the mean value of RBCs (P=0.378), the hemoglobin (P=0.783), the platelets count (P=0.397), and WBCs (P=0.675).

Table 6: Hematological Parameters for Different Studied Groups:

Groups Parameters		Group {I} N=20	Group {II}N=20	P-value
RBCs (10^6/µL)	Mean ±SD	3.83±0.89	3.62± 0.64	0.378
	Range	2.24 – 5.31	2.52 – 4.81	
Hemoglobin(g/dL)	Mean ±SD	10.05± 1.78	10.21 ± 1.82	0.783
	Range	6.8 - 12.7	7.2 – 13.4	
Plateletscount (10^3/µL)	Mean ±SD	137.7 ±60.39	160.37 ± 101.68	0.397
	Range	40 – 253	26 – 516	
WBCs (10^3/µL)	Mean ±SD	12.139 ±4.79	12.88 ± 6.19	0.675
	Range	3.6 - 22.67	6.2 – 33.2	

Abbreviations: RBCs, red blood cells; WBCs, white blood cells
- Mean ± SD = Mean ± standard deviation

Comparison between Studied groups regarding liver function tests &INR:

The variation in routine clinical investigations of liver function among different groups was not statistically significant. Both groups showed marked increase in ALT levels (103.6 ±71.36, and 81.05± 54.1) than its normal levels. The present study showed that there was no statistically significant difference between two studied groups regarding ALT levels (P=0.268) (Table 7).

Serum levels of AST was associated with the advances of chronic liver disease, the mean AST levels for terlipressin, and norepinephrine groups were 116.7± 114.83 and 107.3 ± 76.01, respectively, but mean AST levels were not found to differ between the two studied groups at the time of enrollment in the study (P = 0.762), (Table 7).

Furthermore, serum albumin, total bilirubin, and INR were significantly associated with the advance in chronic liver disease. The mean albumin levels were similar at the time of enrollment in the study between both studied groups. It was [2.17 ± 0.41 g/dl] in terlipressin group and [1.96 ± 0.48 g/dl] in patients who received norepinephrine (P=0.164), whereas there was statistically significant difference between the two studied groups regarding the mean levels of total bilirubin (P<0.001). However, no significant difference was observed when patients in terlipressin group were compared to those in norepinephrine group regading INR (P >0.05). (Table 7).

Table 7: Liver function tests &INR of Different Studied Groups:

Groups Parameters		Group {I}N=20	Group {II}N=20	P-value
ALT (U/L)	Mean ±SD	103.55 ±71.36,	81.05± 54.1	0.268
	Range	40 – 306	28 – 256	
AST (U/L)	Mean ±SD	116.7± 114.83	107.3 ± 76.01	0.762
	Range	40 - 522	27 – 326	
Serum albumin (g/dL)	Mean ±SD	2.16 ± 0.41	1.96 ± 0.48	0.164
	Range	1.7 – 3.2	1.2 – 2.7	
Total bilirubin (mg/dL)	Mean ±SD	8.54 ± 10.5	14.68 ± 4.39	0.056
	Range	1.2 - 23	8.98 – 23.5	
INR	Mean ±SD	1.9 ± 0.67	1.9 ± 0.52	0.793
	Range	1.2 – 3.8	1 – 3	

- Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; INR, International ratio. - *: P ≤ 0.05, **: P ≤0.01, ***: P ≤ 0.001.

The kidney function and hemodynamic MAP at the time of enrollment in the study were comparable in the two groups. Therewas no difference between the studied groups regarding kidney function at baseline (P>0.05).

The mean creatinine level (before starting treatment) in terlipressin group was 3.18 mg/dl while the mean creatinine level in norepinephrine group was 3.22 mg/dl; without significant difference between the two studied groups (p-value =0.9).

Furthermore, the mean urea level before starting treatment was 113.9± 60.33 mg/dl in terlipressin group while it was 120.9 ± 49.5 mg/dl in norepinephrine group. There was no significant difference inserum urea level between two studied groups (p-value =0.691).

Moreover, the mean serum NA level before starting treatment was 117.7± 11.27 in terlipressin group and 120.65 ± 9.69 in norepinephrine group; without significant difference (P=0.380).

The mean urine output at the time of enrollment in the study was 435 ± 228.9 and 517.5 ± 253.54 in terlipressin group and norepinephrine group; respectively.

Additionally, the mean arterial pressure was similar in both studied groups at the beginning of study. It was 81.6 ± 8.98 and

83.9 ± 9.19 in both terlipressin and norepinephrine groups; respectively.

No significant difference was observed in urine output and MAP when patients in terlipressin group were compared to those in norepinephrine group (P >0.05). (Table 8).

Table 8: Kidney function and hemodynamic variables in both studied Groups before therapy:

Groups Parameters		Group {I} N=20	Group {II} N=20	P-value
Creatinine(mg/dL)	Mean ±SD	3.18 ±1.26	3.22± 0.99	0.9
	Range	1.6 – 6	1.9 – 5.5	
Urea (mg/dl)	Mean ±SD	113.9± 60.33	120.9 ± 49.5	0.691
	Range	19 - 219	26 – 210	
Serum Na(mmole/l)	Mean ±SD	117.7± 11.27	120.7 ± 9.69	0.380
	Range	103-139	105-138	
Urine output(ml/24 h)	Mean ±SD	435 ± 228.9	517.5 ± 253.54	0.287
	Range	100 - 900	150 – 1100	
Mean Arterial Pressure (mm Hg)	Mean ±SD	81.6 ± 8.98	83.9 ± 9.19	0.428
	Range	64 - 93	68 – 100	

Changes in Creatinine levels, urine output, and MAP of all studied groups after therapy (9):

The mean creatinine level of groups I, and II following drug administration are shown in Table (8).

On comparing serum creatinine, urine output and MAP at day 1, day 3, day 5, day 7, and at the end of treatment between terlipressin (Group I) and noradrenaline (Group II), there was a progressive decrease in serum creatinine levels and progressive non-significant increase in urine output and MAP in both groups as compared to their baseline values. As, the mean values of creatinine, urine output, and MAP in both groups at the beginning of study were {3.18 ± 1.26 (mg/dL), 435 ± 228.89 (mL/24h) and 81.6±8.98 (mmHg)} vs. {3.22 ± 0.99 (mg/dL), 517.5 ± 253.5 (mL/24h), and 83.9 ± 9.19 (mmHg)} for group I, and II respectively (P=0.9, 0.287, and 0.428).

After 3 days of treatment, the mean serum creatinine lowered in terlipressin group than initial creatinine level {2.94±1.27 vs. 3.18 ±1.26 (mg/dL)}, but without significant difference (P = 0.16). While in noradrenaline group a slight increment in creatinine levels was detected after three days of treatment {3.43±1.4 vs. 3.22±0.99 (mg/dL)} (P=0.244). This is due to increase number of non-responder in this group; 4 patients died after 2 days and 5 patients showed no response to treatment.

Moreover, urine output and MAP were increased in both groups. There were {505.26 ± 240.31 (mL/24h) & 82.79±10.17 (mmHg)} in terlipressin group compared to {521.88 ±210.53 (ml/24h) & 82.38± 8.89(mmHg)} in norepinephrine group. There was no significant difference between 2 studied groups regarding urine output and MAP (P=0.831 & 0.9). Also, both parameters showed slight increase after 3 days than that detected at baseline. In terlipressin group urine output and MAP after 3 days were {505.26 ± 240.31 (ml/24h) & 82.79±10.17 (mmHg)} compared to {435± 228.89 (mL/24h), and 81.6±8.98 (mmHg)} at the beginning of study (P= 0.001 & P=0.254 respectively).

In addition, similar results were detected in patients who received norepinephrine as urine output and MAP after 3 days of treatment were {521.88

±210.53 (mL/24h) & 82.38± 8.89 (mmHg)} compared to {517.5± 253.5 (mL24h), and 83.9±9.19 (mmHg)} at the beginning of study (P=0.860 & P=0.423; respectively)

After 5 days, mean values of serum creatinine, urine output, and MAP were {2.74±1.57 (mg/dl), 537.5±325.3 (mL/24h), and 85.25±14.67 (mmHg)} in group I vs. {2.87±1.48 (mg/dl), 600±252.26 (mL/24h), and 85.33±10.04 (mmHg)} in group II with P values of 0.827, 0.586, and 0.987; respectively between the two studied groups.

After 5 days of treatment, patients in terlipressin group had mean creatinine level 2.74±1.57 (mg/dl) compared to 2.94±1.27 (mg/dL) after 3 days (P=0.721). In addition, mean creatinine level decreased in the norepinephrine group after 5 days to reach 2.87±1.48 (mg/dL) compared to 3.43±1.4 (mg/dl) after 3 days (P=0.899).

Furthermore, both drugs caused a non- significant increase inurine flow, and MAP in patients with AKI-HRS than that detected at 3 days but without significant difference (P=0.315 and 0.271) for group I and (P= 0.828 and 0.618) for group II.

After 7 days, mean creatinine levels, urine output, and MAP were 2.45±2.3 (mg/dL), 616.67±294.13 (mL/24h), and 90.182±12.28 (mmHg) in group I & 2.3±1.48 (mg/dL), 694.44± 246.78 (mL/24h), and 90±12.5 (mmHg) in group II; with P values of 0.854, 0.529, and 0.974 respectively between the two studied groups.

The terlipressin group recorded lower serum creatinine level after 7 days of treatment {2.45±2.3(mg/dL)} compared to that detected after 5 days {2.74±1.57(mg/dL)}, but without significant difference (P=0.787). Also, patients receiving norepinephrine showed similar response as creatinine levels were decreased after 7 days of treatment {2.3±1.48(mg/dL)} compared to that detected after 5 days {2.87±1.48(mg/dL)} with p-value =0.224.

In the terlipressin group, urine output rate increased from 537.5±325.3 to 616.67±294.13 (mL/24h) (P =0.212) and in the norepinephrine group from 600±252.26 to 694.44± 246.78 mL/24h (P=0.06).

Also, MAP elevated from 85.25±14.67 (mmHg) to 90.182±12.28 (mmHg) in the terlipressin group, P= 0.894 and from 85.33±10.04 (mmHg) to 90±12.5 (mmHg) in norepinephrine group (P=0.161).

Overall, out of 40 patients included in this study, 8 patients (40%) in group I and 11 (55%) of group II did not respond to treatment and died during the first week of study.

At the end of this study, 55% (11/20) of patients in the terlipressin group and 45% (9/20) of those in the norepinephrine group responded to vasoconstrictor therapy, and their HRS reverted.

The survival rates at the end of study were comparable in the two groups: 55% (11/20) in the terlipressin group versus 45% (9/20) inthe norepinephrine group.

In both groups, there was a progressive significant decrease in serum creatinine levels at the end of study than that detected after 7 days of treatment P=0.023 and 0.001 in group I and II; respectively.

Compared to norepinephrine group, terlipressin group achieved higher increase in urine/24h at the end of study from baseline. However, both drugs caused a significant increase in urine flow in patients with AKI-HRS from baseline.

In terlipressin group different in urine output at the end of study from that after one week of study was significant (P=0.024) Also, MAP show the same trend (P=0.009). Similar observation was also noticed in the norepinephrine group as urine output and MAP at the end of study showed

significant increase than that detected after one week of study (P=0.006 & P=0.032 for the two parameters respectively).

Table (9): Comparison between different groups regarding creatinine levels at different time points following drug administration:

Creatinine/time after treatment	Group {I}N=20	Group {II}N=20	P- value
Start	3.18 ±1.26	3.22±0.99	0.9
3 days	2.94±1.27	3.43±1.4	0.293
5 days	2.74±1.57	2.87±1.48	0.827
7 days	2.45±2.3	2.3±1.48	0.854
At the end	1.18± 0.2	1.29±0.21	0.269

-*P < 0.05: statistically significant

Table (10): Comparison between different groups regarding urine output levels at different time points following drug administration:

Urine output/time after treatment	Group {I}N=20	Group {II}N=20	P- value
Start	435 ±228.89	517.5±253.54	0.287
3 days	505.263±240.31	521.88±210.53	0.831
5 days	537.5±325.32	600±252.26	0.586
7 days	616.67±294.13	694.44±246.78	0.529
At the end	886.36±164.455	844.44±148.84	0.562

-*P < 0.05: statistically significant

Table (11): Comparison between different groups regarding MAP levels at different time points following drug administration:

MAP/time after treatment	Group {I}N=20	Group {II}N=20	P-value
Start	81.6 ±8.98	83.9±9.19	0.428
3 days	82.79±10.17	82.38±8.89	0.900
5 days	85.25±14.67	85.33±10.04	0.987
7 days	90.18±12.28	90±12.5	0.974
At the end	100.36± 7.38	97.33±6.16	0.339

-*P < 0.05: statistically significant

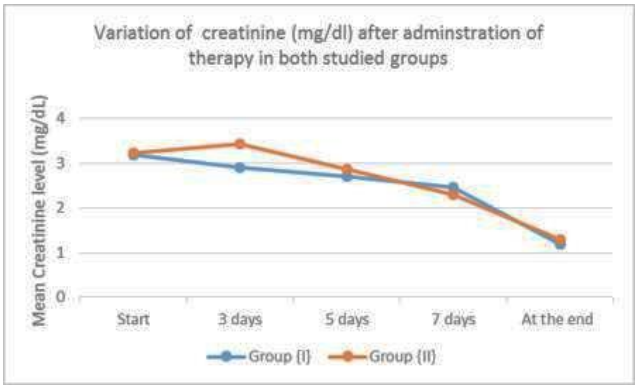

Figure (1): Comparison between different groups regarding creatinine levels at different time points following drug administration.

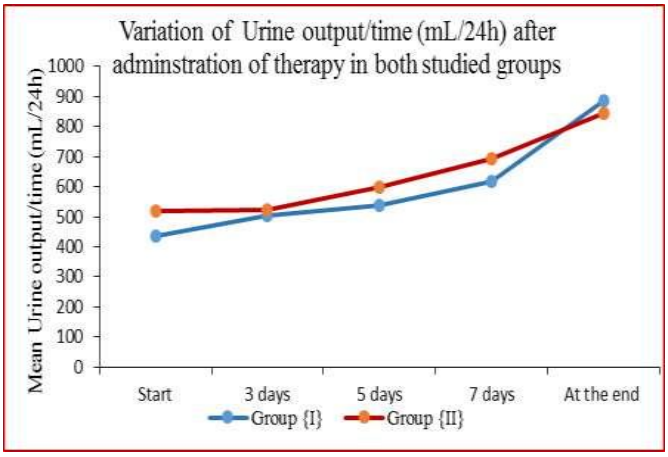

Figure (2): Comparison between different groups regarding urineoutput levels at different time points following drug administration.

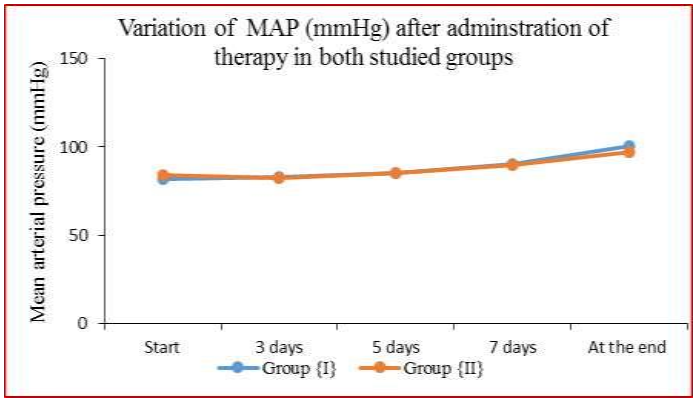

Figure (3): Comparison between different groups regarding MAPlevels at different time points following drug administration.

Outcome of the study:

At the end of study, there were 20 patients responded to treatment. In group I eleven (55%) while in group II, only 9 (45%) patients survived where the other 20 cases eleven (55%) in group II and 9 (45%) in group II. Responders (20 patients) were compared at end of treatment and were improved significantly compared than at the beginning of study.

Table 12: Renal functions in responders in terlipressin and norepinephrinegroups:

Groups Parameters		Group {I}N=11	Group {II}N=9	IntergroupP-value
Serum Creatinine (mg/dL)	Baseline	2.80 ±0.92	2.69± 0.62	0.745
	At the end	1.182±0.2	1.289 ± 0.215	0.269
Intra group P-value		<0.001**	<0.001**	
Urea (mg/dl)	Baseline	101.09 ± 62.07	113.3 ±37.8	0.611
	At the end	69.5± 25.47	73.89 ± 24.51	0.704
Intra group P-value		0.162	0.004**	
Serum Na (mmole/l)	Baseline	118.5± 11.6	120.1 ± 12.46	0.775
	At the end	134.36± 6.07	132.2± 6.49	0.457
Intra group P-value		<0.001**	0.01*	
Urine output	Baseline	490.9 ± 220	588.89 ± 255.9	0.369

(ml/24 h)	At the end	886.4 ± 164.5	844.4 ± 148.8	0.562
Intra group P-value		<0.001**	0.004**	
Serum albumin (g/dL)	Baseline	2.17 ± 0.39	2.03 ± 0.38	0.429
	At the end	3.1 ±0.44	3.2 ± 0.35	0.626
Intra group P-value		0.001**	<0.001**	
Mean Arterial Pressure (mm Hg)	Baseline	83.18 ± 9.2	84.11 ± 11.15	0.840
	At the end	100.36 ± 7.38	97.33 ± 6.16	0.339
Intra group P-value		<0.001**	0.002**	

Inter group P-value : P-value between both studied groups. Intra group P-value: P-value between lab data at baseline before therapy and at the end after therapy within each group.

DISCUSSION:

Renal failure is a frequent extrahepatic organ failure, and its presence is an independent prognostic marker for mortality ***(Arora et al., 2020)***[11]**.**

It is characterised by functional renal impairment due to vasoconstriction of the renal arteries and severe vasodilation of the splanchnic arteries, leading to decreased arterial blood volume and arterial pressure ***(Bui et al., 2020)***[12]**.**

Hepatorenal syndrome (HRS) is a potentially reversible clinical syndrome, which is characterized by functional renal failure in end-stage liver disease ***(Badawy et al., 2013)***[8]**.**

It has a deep impact on the survival of cirrhotics. Medical treatment for consists of using albumin and a vasoconstrictor ***(Mattoset al., 2016)***[13]**.**

Management of HRS is based on therapy with vasoconstrictors and albumin. Terlipressin is a drug of choice particularly in type 1 HRS. However, terlipressin is not readily available in several countries and the therapy is expensive. Noradrenaline, a catecholamine with predominantly alpha-adrenergic activity is widely available and is relatively inexpensive. Noradrenaline has shown encouraging results in circulatory dysfunction and type 1 HRS ***(Ghosh et al., 2013)***[14].

This study comprised 40 patients with Type I hepatorenal syndrome admitted during the period of research from February 2019 to July 2019 to Ain Shams University hospitals.

All patients have acute or chronic liver diseases with type I hepatorenal syndrome, and the patients were divided into two groups:

20 patients with type I hepato-renal syndrome who received terlipressin and 20 patients with type I hepato-renal syndrome who received norepinephrine.

Results of the current study revealed that mean age of patients in both groups I and II was 53.1±4.14, and 52.1±6.63 years respectively. There was no statistically significant difference between both studied groups regarding to age (P=0.571). Also, studied patients showed a high percentage of males in both studied groups (55%&65& respectively) but without statistically significant different between different groups (P>0.05).

Our results were in concordance with most prior results that end stage liver disease is more prevelant in middle and old age and in males ***(Badawy et al., 2013; Ghosh et al., 2013)***[8,14]**.**

Seetlani et al., 2016[15] reported that in their study the mean±SD age of patient was 48.23±7.87 years and 58% of the participants in their study were males.

In this study, There was no statistically significant difference between number of cases regarding presence of hypertension**,** cellulitis, pneumonia, SBP, and UTI in both studied groups (P>0.05)

Bacterial infections are common in cirrhosis, estimated tooccur in 25% to 46% of patients hospitalized with acute decompensation of cirrhosis ***(Wong, 2019)***[16]**.** Bacterial infections are the most common cause of renal failure, accounting for up to 46% of all cases in hospitalized patients with cirrhosis (***Martín-Llahí et al., 2011)***[17]**.**

Spontaneous bacterial peritonitis (SBP) and urinary tract infections were the most common precipitants for the development of renal failure in the North American study ***(Bajaj et al.; 2014)***[18] whereas SBP and respiratory infections were the most common precipitants in the CANONIC study ***(Moreau et al., 2013)***[19]**.**

The independent predictors of irreversible HRS were older age, Child-Pugh and Model for End stage Liver Disease (MELD) scores, high bilirubin levels, and nosocomial infection. The most important finding was the high prevalence of nosocomial infections associated with irreversible renal failure ***(Salerno and Monti, 2014)***[20]**.**

As regard the results of haematological parameters, the results of this study showed that the mean value ± SD for the red blood cells (RBCs) count was 3.84±0.89, 3.62± 0.64)(10^6/µL), the hemoglobin (10.05± 1.78, 10.21 ± 1.82)(g/dL), the platelets count and the white blood cells (WBCs) count (137.7 ± 60.39, 160.37 ± 101.68), and (12.139 ± 4.79, 12.88 ± 6.19) (10^3/µL) in terlipressin & norepinephrine group respectively, with no significant difference between two studied groups (P>0.05).

Chronic hepatitis C has been reported as one of the several causes that induce thrombocytopenia, even in chronic non-cirrhotic patients ***(Fouad, 2013, Osada et al., 2012)***[21,22].Thrombocytopenia in chronic liver disease may be explained, in addition to the sequestration of platelets, by myelosuppression caused by the etiological factors as viral infection, alcohol consumption, iron overload, and medications ***(Marks, 2013, Mitchell et al., 2016)***[23,24]**.**

Also, decreased activity of thrombopoietin (hematopoietic growth factor) as well as high levels of platelet-associated immunoglobulins (PAIgG), which are responsible for the high rate of platelets destruction in CLD patients, are other causes of thrombocytopenia ***(Mitchell et al., 2016)***[24]**.**

The variation in routine clinical investigations of liver function among different groups was not statistically significant. Both groups showed marked increase in ALT (103.6 ±71.36, and 81.05± 54.1), AST levels (116.7± 114.83 and 107.3 ± 76.01), bilirubin & INR levels than their normal levels and decrease in serum albumin levels [2.17 ± 0.41 g/dl&1.96 ± 0.48 g/dl] in group I &II respectively.

Regarding the aim of our work, at baseline there was nodifference between the studied groups regarding kidney function as it was all worse moreover urine output and MAP for all cases was decreased (P>0.05).The mean creatinine level (before starting treatment) was 3.18 mg/dl and3.22 mg/dl, the mean urea level was 113.9± 60.33 mg/dl & 120.9 ± 49.5 mg/dl, the mean serum NA level was 117.7± 11.27 and 120.65 ± 9.69, and the mean urine output was 435 ± 228.9 and 517.5 ± 253.54 in both groups; respectively. Moreover, the mean arterial pressure was similar in both studied groups at the beginning of study. It was 81.6 ± 8.98 and 83.9 ± 9.19in both terlipressin and norepinephrine groups; respectively.

After 3 days of treatment, the mean serum creatinine lowered in terlipressin group than initial creatinine level {2.94±1.27 vs. 3.18 ±1.26 (mg/dL)}, but without significant difference (P = 0.16). While in noradrenaline group a slight increment in creatinine levels was detected after three days of treatment {3.43±1.4 vs. 3.22±0.99 (mg/dL)} (P=0.244). This is due to increase number of non-responder in this group; 4 patients died after 2 days and 5 patients showed no response to treatment. Moreover, urine output and MAP were increased in both groups. There were {505.26 ± 240.31 (mL/24h) & 82.79±10.17 (mmHg)} in terlipressin group compared to {521.88 ±210.53 (ml/24h) & 82.38± 8.89(mmHg)} in norepinephrine group. There was no significant difference between 2 studied groups regarding urine output and MAP (P=0.831 & 0.9). Also, both parameters showed slight increase after 3 days than that detected at baseline. In terlipressin group urine output and MAP after 3 days were {505.26 ± 240.31 (ml/24h) & 82.79±10.17 (mmHg)} compared to {435± 228.89 (mL/24h), and 81.6±8.98 (mmHg)} at the beginning of study (P= 0.001 & P=0.254 respectively). In addition, similar results were detected in patients who received norepinephrine as urine output and MAP after 3 days of treatment were {521.88 ±210.53 (mL/24h) & 82.38± 8.89 (mmHg)} compared to {517.5± 253.5 (mL24h), and 83.9±9.19 (mmHg)} at the beginning of study (P=0.860 & P=0.423; respectively).

After 5 days, mean values of serum creatinine, urine output, and MAP were {2.74±1.57 (mg/dl), 537.5±325.3 (mL/24h), and 85.25±14.67 (mmHg)} in group I vs. {2.87±1.48 (mg/dl), 600±252.26 (mL/24h), and 85.33±10.04 (mmHg)} in group II with P values of 0.827, 0.586, and 0.987; respectively between the two studied groups. After 5 days of treatment, patients in terlipressin group had mean creatinine level 2.74±1.57 (mg/dl) compared to 2.94±1.27 (mg/dL) after 3 days (P=0.721). In addition, mean creatinine level decreased in the norepinephrine group after 5 days to reach 2.87±1.48 (mg/dL) compared to 3.43±1.4 (mg/dl) after 3 days (P=0.899) Furthermore, both drugs caused a non-significant increase in urine flow, and MAP in patients with AKI-HRS than that detected at 3 days but without significant difference (P=0.315 and 0.271) for group I and (P= 0.828 and 0.618) for group II.

After 7 days, mean creatinine levels, urine output, and MAP were 2.45±2.3 (mg/dL), 616.67±294.13 (mL/24h), and 90.182±12.28 (mmHg) in group I & 2.3±1.48 (mg/dL), 694.44± 246.78 (mL/24h), and 90±12.5 (mmHg) in group II; with P values of 0.854, 0.529, and 0.974 respectively between the two studied groups. The terlipressin group recorded lower serum creatinine level after 7 days of treatment {2.45±2.3(mg/dL)} compared to that detected after 5 days {2.74±1.57(mg/dL)}, but without significant difference (P=0.787). Also, patients receiving norepinephrine showed similar response as creatinine levels were decreased after 7 days of treatment {2.3±1.48(mg/dL)} compared to that detected after 5 days {2.87±1.48(mg/dL)} with p-value =0.224.In the terlipressin group, urine output rate increased from 537.5±325.3 to 616.67±294.13 (mL/24h) (P =0.212) and in the norepinephrine group from 600±252.26 to 694.44± 246.78 mL/24h (P=0.06).Also, MAP elevated from 85.25±14.67 (mmHg) to 90.182±12.28 (mmHg) in the terlipressin group, P= 0.894 and from 85.33±10.04 (mmHg) to 90±12.5 (mmHg) in norepinephrine group (P=0.161).

Overall, out of 40 patients included in this study, 8 patients (40%) in group I and 11 (55%) of group II did not respond to treatment and died during the first week of study. At the end of this study, 55% (11/20) of patients in the terlipressin group and

45% (9/20) of those in the norepinephrine group responded to vasoconstrictor therapy, and their HRS reverted. The survival rates at the end of study were comparable in the two groups: 55% (11/20) in the terlipressin group versus 45% (9/20) in the norepinephrine group.

Wang et al., 2018[25] meta-analysis found that the mortality ranged from 31.8% to 95%, with the overall rate of 61.7% in the terlipressin group and 62.0% in the norepinephrine group with no significant difference was found between the 2 groups (RR=1.05, 95%CI: 0.63–1.74, *P*=.86, *I*2=0%) ***().***

Goyal and his colluges 2016[26] reported that HRS reversal was seen in 47.6% (10/21) patients in group A, and 45% (9/20) patients in group B (p=1.00). In both groups, there was a significant decrease in serum creatinine from baseline (group A- 3.1±1.4 mg/dl to 2.2±1.3 mg/dl, p=0.028; group B- 3.4±1.6 mg/dl to 2.3±1.3 mg/dl, p=0.035). Both the groups showed a significant increase in mean arterial pressure (group A- 77.3±8.6 mmHg to 103.4±8.3 mmHg, p=0.0001; group B- 76.8±11.6 mmHg to 100±9.4 mmHg, p=0.0001). They reported that noradrenaline was associated with fewer adverse events and was significantly cheaper and as effective and safe as terlipressin in the treatment of HRS type 1***).***

Terlipressin is the most effective and widely used vasoconstrictor. It can not only reduce portal inflow and thereby decrease portal pressure, but also reduce the extent of the systemic vasodilatation, leading to a rise in the systemic arterial blood pressure, which in turn will improve the renal perfusion pressureand renal function ***(Mitchell et al., 2016)***[24]***.***

Moreover, our findings correlate with data from many studies that suggest that norepinephrine was as effective as terlipressin in reverting HRS and improving kidney functions. In a study by ***Singh et al. (2012)***[27] 46 patients with type 1 HRS were randomized to receive either terlipressin or norepinephrine with albumin. In this study, the authors reported that HRS reversal could be achieved in 39.1% of patients in the terlipressin group and 43.4% of patients in the norepinephrine group.

Sharma et al. (2008)[28] reported that patients in both groups had a significant improvement in kidney functions and that the incidences of HRS reversal were comparable.

Saif et al.[2] in their randomized trial found that noradrenaline led to reversal of HRS (complete response) in 53% of patients while terlipressin in (57%) patients. Thus, both the groups (noradrenaline and terlipressin) had similar (53% vs. 57%) response rate to reverse HRS.

In a recent study conducted via ***Arora and his co-workers*** in ***2020***[11] who compared noradrenaline and terlipressin, they found that terlipressin achieved greater day 4over noradrenaline (26.1% vs. 11.7%; P = 0.03) and day 7 (41.7% vs. 20%; P = 0.01) response. Reversal of HRS was also better with terlipressin (40% vs. 16.7%; P = 0.004), with a significant reduction in the requirement of renal replacement therapy (RRT; 56.6% vs. 80%; P = 0.006) and improved 28-day survival (48.3% vs. 20%; P = 0.001). They also reported that he terlipressin arm had lower mortality as compared to the noradrenaline group (51.7% vs. 80%; P = 0.002).

Therefore, Norepinephrine, an inexpensive α-adrenergic receptor agonist available worldwide, is a possible alternative treatment for HRS because its intense vasoconstriction action may increase the effective arterial blood volume.

Conclusion

The results of this randomized comparative study suggest that

norepinephrine and terlipressin had nearly similar response rates for the treatment of type 1 HRS. Therefore, norepinephrine is as effectiveas terlipressin in the management of patients with type 1 HRS. The lower cost and wider availability of norepinephrine make it a safe and effective alternative to terlipressin.

Recommendations:

- The present study shows that norepinephrine is as effective as terlipressin in the management of patients with type 1 HRS in order to save costs and ICU beds.
- This study provides the basis for designing larger randomized controlled trials to confirm the present findings.
- Further studies should also aim to identify predictors of no responsiveness, so that patients who are unlikely to respond to medical therapy with a particular vasoconstrictor could receive a different therapeutic agent or be preferentially indicated for liver transplantation.

Conflict of interest:

The authors declare that they have no conflict of interest.

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التيرليبريسين مقابل النورابينفرين فى علاج مرضى المتلازمة الكبدية الكلوية من النوع الأول

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الخلفية: يصيب تليف الكبد ملايين الأشخاص في جميع أنحاء العالم. المرضى الذين يعانون من تليف الكبد كثيرا ما يصابون بالفشل الكلوي. تتطور المتلازمة الكبدية الكلوية (HRS) في أمراض الكبد اللا تعويضية وتعتبر أكثر المضاعفات خطورة. إنه أكثر المضاعفات المميتة شيوعًا لتليف الكبد حيث يموت ما يقرب من 50 ٪ من المرضى في غضون أسبوعين من التشخيص.

هدف العمل: الهدف من الدراسة هو المقارنة بين تأثير تيرليبريسين والنورادرينالين في تدبير النوع الأول من المتلازمة الكبدية الكلوية.

المريض والطرق: دراسة عشوائية محكومة. أجريت هذه الدراسة في مستشفيات جامعة عين شمس. ستة أشهر من فبراير إلى يوليو 2019. تم تقسيم 40 مريضًا بالتساوي إلى مجموعتين (20 لكل مجموعة)

النتيجة: اشتملت هذه الدراسة على 40 مريضاً مصابين بالمتلازمة الكبدية الكلوية من النوع الأول تم إدخالهم خلال فترة البحث من فبراير 2019 إلى يوليو 2019 إلى مستشفيات جامعة عين شمس. جميع المرضى يعانون من أمراض الكبد الحادة أو المزمنة مع متلازمة الكبد من النوع الأول ، وتم تقسيم المرضى إلى مجموعتين.

الخلاصة: تشير نتائج هذه الدراسة المقارنة العشوائية إلى أن النورابينفرين وتيرليبريسين كان لهما معدلات استجابة متشابهة تقريبًا لعلاج HRS من النوع 1. لذلك ، فإن النوربينفرين فعال مثل تيرليبريسين في إدارة المرضى الذين يعانون من HRS من النوع 1. إن التكلفة المنخفضة والتوافر الأوسع للنورابينفرين يجعلانه بديلاً آمنًا وفعالًا لتيرليبريسين.

التوصيات: تُظهر الدراسة الحالية أن النوربينفرين فعال مثل تيرليبريسين في إدارة المرضى الذين يعانون من HRS من النوع 1 من أجل توفير التكاليف وأسرّة العناية المركزة. توفر هذه الدراسة الأساس لتصميم تجارب معشاة ذات شواهد أكبر لتأكيد النتائج الحالية. يجب أن تهدف الدراسات الإضافية أيضًا إلى تحديد مؤشرات عدم الاستجابة.