Research Article

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Noradrenaline *vs.* terlipressin in the treatment of hepatorenal syndrome: A randomized study

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Background & Aims: Various vasoconstrictors are useful in the management of hepatorenal syndrome (HRS). Terlipressin is the drug of choice; however, it is expensive. In this study, we evaluated safety and efficacy of terlipressin and noradrenaline in the treatment of HRS.

Methods: Forty-six patients with HRS type 1 were managed with terlipressin (group A, N = 23) or noradrenaline (Group B, N = 23) with albumin in a randomized controlled trial at a tertiary center.

Results: HRS reversal could be achieved in 9 (39.1%) patients in group A and 10 (43.4%) patients in group B ($p = 0.764$). Univariate analysis showed baseline Child Turcotte Pugh score (CTP), model of end stage liver disease (MELD), urine output on day 1(D1), albumin, and mean arterial pressure (MAP) were associated with response. However, on multivariate analysis only CTP score was associated with response. Fourteen patients in group A and 12 in group B died at day 15 ($p > 0.05$). Noradrenaline was less expensive than terlipressin ($p < 0.05$). No major adverse effects were seen.

Conclusions: The results of this randomized study suggest that noradrenaline is as safe and effective as terlipressin, but less expensive in the treatment of HRS and baseline CTP score is predictive of response.

Introduction

Hepatorenal syndrome (HRS) is a functional impairment of the kidneys in decompensated cirrhosis, associated with high mortality [1,2]. Patients with HRS have marked circulatory dysfunction with splanchnic arterial vasodilatation resulting in severe renal vasoconstriction [3]. Several studies have evaluated the efficacy of various vasopressors in patients with post-paracentesis circulatory dysfunction [4–7], refractory ascites [8,9] and HRS [10–13]. Terlipressin is a drug of choice particularly in type 1 HRS [14–17]. However, terlipressin is not readily available in several countries and therapy is expensive. By contrast, noradrenaline, a catecholamine with predominantly alpha-adrenergic activity, is widely available and relatively inexpensive. Some recent studies showed reversal of HRS with noradrenaline [13,18]. Various studies have also predicted factors of response in patients with HRS [14,16,17,19,20]. We have planned to study the safety and efficacy of terlipressin and noradrenaline and predictive factors of response in type 1 HRS.

Materials and methods

A total of 60 consecutive patients with cirrhosis and HRS type 1, presenting at the hepatology department of a tertiary center between January 2009 and October 2011, were prospectively evaluated for inclusion in the study. Fourteen patients were excluded during the study due to various reasons (severe coronary artery disease in three, sepsis in nine, hepatocellular carcinoma in one and diabetic nephropathy in one patient). The study was approved by the Ethics committee of Postgraduate Institute of Medical Education and Research, Chandigarh. Written informed consent was asked. Diagnosis of HRS type 1 was based on the criteria of Salerno *et al.* [21].

Sample size

The sample size calculation was based on a previous study [16] with 95% confidence level and 80% power; we estimated that 22 patients in each group would provide the comparison between the two treatment groups. Assuming a drop-out rate of 10%, the study size should be 23 patients in each group. We enrolled 23 patients in each group.

Inclusion criteria were cirrhosis with ascites with serum creatinine levels $\geqslant$2.5 mg/dl; absence of shock , fluid losses and treatment with nephrotoxic drug; no improvement in renal function following diuretic withdrawal and plasma volume expansion; no ultrasound evidence of renal parenchymal disease or obstructive uropathy and absence of proteinuria more than 500 mg/24 h. Patients with history of coronary artery disease, cardiomyopathy, ventricular arrhythmia or obstructive arterial disease of limbs were excluded.

Patients were randomized to either terlipressin or noradrenaline group. A computer made the randomization code with 46 envelops, half for terlipressin (group A) and half for noradrenaline (group B). Patients and investigators were not blinded to the treatment assignments. Patients in either group received treatment with terlipressin or noradrenaline with 20 g albumin/day. Patients in group A received terlipressin as an intravenous bolus of 0.5 mg every 6 h. If a significant reduction in serum creatinine level ($\geqslant$1 mg/dl) was not observed during a 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days

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Table 1. Baseline clinical, biochemical and hormonal variables of patients in two study groups.

Variables	Terlipressin (n = 23)	Noradrenaline (n = 23)	*p* value
Age (yr)	51.4 (11.6)	48.3 (11.6)	0.328
Gender (M:F)	19 (82.6%):4 (17.3%)	19 (82.6%):4 (17.3%)	1
Etiology			
Alcohol	10 (43.4%)	12 (52.1%)	0.554
Others	13 (56.6%)	11 (47.8%)	
HCV	3 (13%)	2 (8.7)	
HCV + Alcohol	4 (17.4%)	3 (13%)	
HBV	1 (4.3%)	2 (8.7%)	
Autoimmune	2 (8.7%)	1 (4.3%)	
Cryptogenic	3 (13%)	3 (13%)	
Spontaneous bacterial peritonitis	7 (30.43%)	6 (26.08%)	0.743
Child-Pugh score	10.70 (2.01)	10.43 (1.72)	0.704
MELD score	26.39 (3.13)	24.65 (5.31)	0.294
Serum albumin (g/dl)	2.78 (0.40)	2.78 (0.20)	0.956
Serum bilirubin (mg/dl)	3.99 (2.58)	4.66 (5.72)	0.904
Serum sodium (mEq/L)	129.3 (4.8)	128.2 (5.3)	0.396
Blood urea (mg/dl)	94.08 (21.27)	92.95 (19.76)	0.838
Serum creatinine (mg/dl)	3.27 (0.71)	3.10 (0.66)	0.193
Urinary sodium (mEq/L)	46.95 (19.25)	46.74 (21.12)	0.794
Urine output/24 hours (ml)	651.5 (241.1)	638.7 (276.7)	0.668
Mean arterial pressure (mmHg)	64.7 (11.9)	65.2 (10.2)	0.733
Plasma renin activity (ng/ml/h)	36.73 ± 14.48	34.89 ± 10.91	0.709
Plasma aldosterone concentration (pg/ml)	1687.39 ± 743.3	1761.7 ± 613.1	0.505

Data are mean (SD) or number (%) of patients; MELD (model for end-stage liver disease).

Table 2. Change in parameters with therapy in two study groups.

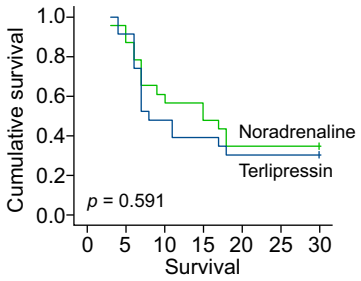
Parameter	Terlipressin group (A)			Noradrenaline group (B)		
	Baseline	Day 15	*p* value (baseline *vs.* day 15)	Baseline	Day 15	*p* value (baseline *vs.* day 15)
Serum creatinine (mg/dl)	3.263 ± 0.81	1.67 ± 0.92	0.002	2.82 ± 0.3	1.55 ± 0.5	0.000
Urinary sodium (mEq/L)	60.6 ± 22.3	72.4 ± 22.6	0.009	46.9 ± 23.5	73.4 ± 33.2	0.069
Urine output (ml/d)	672 ± 194	1084 ± 417	0.034	738 ± 323	1393 ± 529	0.004
Mean arterial pressure (mmHg)	63.2 ± 9.4	70.6 ± 11.2	0.021	70.4 ± 12.5	80.3 ± 5.9	0.036
Plasma renin activity (ng/ml/h)	38.68 ± 15.21	10.21 ± 3.60	0.001	35.23 ± 10.32	8.96 ± 2.21	0.000
Plasma aldosterone concentration (pg/ml)	1755.67 ± 873.44	668.89 ± 310.82	0.012	1757.27 ± 706.14	543.64 ± 269.34	0.001
Number of responders (%)	0	9 (39.1)		0	10 (43.4)[a]	
Cost of treatment for 15 days (€)		945			275[b]	

Data are mean ± SD; values between group A and group B at baseline and day 15 were not significantly different.
[a]$p = 0.764$ (group A *vs.* B).
[b]$p < 0.05$ (group A *vs.* B).

to a maximum of 2 mg every 6 h. Patients in group B received a continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase inMAP of at least 10 mmHg or an increase in 4-h urine output of more than 200 ml. When one of these goals was not achieved, the noradrenaline dose was increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. Albumin was withheld if central venous pressure (CVP) was more than 18 cm of saline. All patients were admitted for 15 days in hospital and followed-up up to 30 days. Clinical and biochemical parameters were assessed at baseline, and day 15. An arterial blood sample was collected after overnight fast and bed rest for at least 8 h in supine position for plasma renin activity and aldosterone concentration. Blood samples were taken from the radial artery, put into chilled ethylenediaminetetraacetic acid tubes, centrifuged at 2500 rpm for 10 min at −3 °C and stored at −80 °C. Plasma renin activity was measured by radioimmunoassay using gamma Coat- ^{125}I RIA plasma renin activity kit (Immunotech SA, France). Plasma aldosterone concentration was measured by radioimmunoassay using RIA aldosterone kit (Immunotech SA, France).

Outcome measures

The primary end point of the study was serum creatinine less than 1.5 mg. Secondary end points include death of patients or a maximum of 15 days of therapy.



Patients at risk	Day					
	5	10	15	20	25	30
Terlipressin group (n = 23)	20	11	9	7	7	7
Noradrenaline group (n = 23)	21	13	11	8	8	8

Fig. 1. Kaplan–Meier curve showing the cumulative probability of survival of patients treated with terlipressin and noradrenaline.

Statistical analysis

The results were expressed as mean ± standard deviation (SD) or median with range. Comparisons between groups were performed using Student's *t*-test or the Mann–Whitney U test. For categorical data, Chi-square test or Fisher's exact test was applied. The values for repeated sample analysis were analyzed using two-way repeated measures analysis of variance with Bonferroni adjustment for multiple comparisons. A value of $p < 0.05$ was taken as significant. The results were analyzed at baseline and day 15 of the study. The in-hospital mortality was shown by Kaplan–Meier survival curve.

Results

The baseline demographic profile, clinical and laboratory parameters were similar in patients receiving noradrenaline or terlipressin (Table 1). Table 2 shows the effect of noradrenaline in comparison with terlipressin on different parameters at baseline and day 15 of the study period. There was a significant decrease in serum creatinine from baseline in both groups ($p < 0.05$). Mean arterial pressures increased significantly in both groups at day 15 ($p < 0.05$). Urine output increased significantly in both groups at day 15 ($p < 0.05$). Plasma renin activity and aldosterone concentrations decreased significantly in both groups at day 15 ($p < 0.05$). Nine (39.1%) patients in group A and 10 (43.4%) in group B responded to therapy ($p = 0.764$). Twenty-seven (group A, 14; group B, 13) patients did not respond to treatment. At the end of 15 days of therapy, 9 (39.1%) patients in group A (seven responders and two non-responders) and 11 (47.8%) in group B (eight responders and three non-responders) survived ($p = 0.461$). Four of the patients who did not survive had reversal of HRS (group A, 2; group B, 2). All non-responders (group A, 2, group B, 3) died within 30 days of follow-up. There was no mortality between 15 and 30 days in responders. There was no relapse in responders in either group during the follow-up till 30 days. The main causes of death were sepsis (N = 14), liver failure (N = 6), acute tubular necrosis with metabolic acidosis (N = 2), gastrointestinal hemorrhage (N = 4) and multiorgan failure (N = 5). The survival curves shown by the Kaplan–Meier method (Fig. 1) and compared with the log-rank test were not different in both groups ($p = 0.591$) at 30 days. The mean duration of therapy in group A was 7.82 ± 3.12 days (range 4–15 days) and 9.3 ± 4.0 days (range 4–15 days) in group B. The cost of treatment with terlipressin with a median dose of 3 mg/day for 15 days was 975€. Noradrenaline with a median dose of 13.1 mg/day for 15 days was much more economical, costing only 275€ for the equal outcome ($p < 0.05$). However, costs of albumin and hospital admission were not taken into consideration while calculating the total cost in either group.

Urine output and urinary sodium increased significantly and there was a marked suppression of renin-angiotensin-aldosterone system in responders at day 15 (Table 3). There was also a trend towards an increase in MAP in these patients. There was no significant increase in urine output, urinary sodium and MAP in non-responders at day 15. There was also a marked suppression of renin-angiotensin-aldosterone system in non-responders at day 15 (Table 3).

Several variables obtained at baseline were analyzed for the predictive value of response to treatment. Univariate analysis (Table 4) showed baseline CTP score, MELD, urine output on D1, serum albumin and MAP were associated with response. However, in multivariate analysis only CTP score was associated with response (Table 5). Using CTP score for no response to treatment, a receiver operating characteristic curve (ROC) was made, which had an area under the curve of 0.808. Taking a cut-off of CTP score of $\geqslant 10$, the sensitivity, specificity, positive predictive value and negative predictive value were 85.18%, 68.42%, 79.31%, and 76.47%, respectively.

In the terlipressin group, four patients developed abdominal cramps and increased frequency of stools, one developed cyanosis of the toe and another developed transient ventricular extrasystole. These adverse events were self-limiting. In the noradrenaline group, two patients experienced atypical chest pain with normal electrocardiogram, troponin and creatine

Table 3. Change in parameters according to response in study group.

Parameter	Responders			Non-responders		
	Basal	Day 15	*p* value (basal *vs.* day 15)	Basal	Day 15	*p* value (basal *vs.* day 15)
Urinary sodium (mEq/L)	54.8 ± 22.6	85.0 ± 21.9	0.025	46.4 ± 25.2	57.8 ± 32.4	0.47
Urine output (ml/d)	754.4 ± 344.5	1290.0 ± 254.6	0.000	670.0 ± 197.7	1282.8 ± 759.4	0.08
Mean arterial pressure (mmHg)	67.1 ± 10.3	77.5 ± 5.3	0.10	68.8 ± 14.3	76.0 ± 13.2	0.18
Plasma renin activity (ng/ml/h)	33.4 ± 10.4	9.2 ± 3.0	0.000	46.8 ± 14.0	10.3 ± 2.5	0.004
Plasma aldosterone concentration (pg/ml)	1637.3 ± 701.6	614.0 ± 276.4	0.000	2116.0 ± 913.3	558.0 ± 351.4	0.03

Data are mean ± SD.

Table 4. Univariate analysis of baseline variables according to response to treatment.

Variables	Responders (n = 19)	Non-responders (n = 27)	*p* value
Gender (M:F)	18:1	20:7	0.115
SBP	4 (21.0%)	9 (33.3%)	0.362
Age (yr)	46.0 ± 10.1	52.6 ± 11.9	0.051
Treatment group			0.764
Terlipressin	9 (47.3%)	14 (51.8%)	
Noradrenaline	10 (52.6%)	13 (48.1%)	
Serum bilirubin (mg/dl)	4.8 ± 6.4	4.0 ± 2.2	0.219
Serum albumin (g/dl)	2.8 ± 0.2	2.7 ± 0.3	0.009
Child-Pugh score	9.4 ± 1.3	11.3 ± 1.7	0.000
MELD	24.4 ± 5.0	26.3 ± 3.8	0.020
Serum sodium (mEq/L)	130 ± 5.78	127.9 ± 4.49	0.214
Blood urea (mg/dl)	92.8 ± 25.8	94.0 ± 15.8	0.504
Serum creatinine (mg/dl)	3.08 ± 0.6	3.27 ± 0.7	0.394
Urine output/24 hours (ml)	768.9 ± 285.9	557.9 ± 195.8	0.009
Urinary sodium (mEq/L)	53.6 ± 22.5	41.8 ± 16.6	0.102
MAP (mmHg)	69.3 ± 9.3	61.9 ± 11.2	0.011
Plasma renin activity (ng/ml/hr)	34.66 ± 12.63	36.62 ± 12.94	0.746
Plasma aldosterone concentration (pg/ml)	1654.74 ± 726.01	1773.70 ± 645.83	0.496

Data are mean ± SD; MELD, model for end-stage liver disease); MAP, mean arterial pressure.

Table 5. Multivariate analysis (including variables with *p* value <0.05 in univariate analysis).

	p value	95% CI for non-responders	
		Lower bound	Upper bound
Serum albumin	0.868	-0.542	0.640
Child-Pugh score	0.024	-0.263	-0.019
MELD	0.262	-0.018	0.065
Urine output	0.122	0.000	0.001
MAP	0.491	-0.025	0.012

MELD, model for end-stage liver disease; MAP, mean arterial pressure; ROC of CTP for no response to treatment: 0.808 at cut-off ⩾10, sensitivity 85.18%, specificity 68.42%, positive predictive value 79.31%, and negative predictive value 76.47%.

phosphokinase (CPK). No adverse effects related to the intravenous albumin infusion were observed.

Discussion

Vasoconstrictors have demonstrated promising results in patients with HRS by causing splanchnic vasoconstriction and increasing effective arterial blood volume [10–13]. In the current study, we evaluated the role of terlipressin and noradrenaline with albumin in the management of type 1 HRS in patients with cirrhosis. Thirty-nine percent of patients in the terlipressin group and 43% in the noradrenaline group, in our study, responded to treatment. Similarly, previous studies, including a recent meta-analysis, showed reversal of type 1 HRS in 34–55% of patients [14,16,17,22,23]. There was no relapse in responders in either group during the follow-up till 30 days. Sanyal *et al.* [17] and Nazar *et al.* [19] reported a relapse rate of 5.3% and 27.7%, respectively among responders in HRS type 1. In our study, the mean dose of terlipressin received was 3.13 ± 0.73 mg/day and the mean duration of treatment was 7.82 ± 3.12 days. Earlier studies have reported a variable response with a wide range of terlipressin doses per day for different treatment durations [14,16,24].

In our study, patients in group B received 0.5–3 mg/h of noradrenaline (mean dose 0.59 ± 0.14 mg/h) for a mean duration of 9.3 ± 4.0 days. Sharma *et al.* [16] used a mean dose of noradrenaline of 1.0 ± 0.5 mg/h (range 0.5–3.0 mg/h) and it was administered for a mean duration of 7.8 ± 2.8 days (range 4–15 days). In the present study, HRS reversal was seen in 43% (10 out of 23) of patients, which is similar to the terlipressin group. There is a limited number of studies on noradrenaline in HRS, with variable results. Duvoux *et al.* [13] reported reversal of type 1 HRS in 10/12 (83%) patients after a median of 7 days treatment. Sharma *et al.* [16] showed a 40% response in type 1 HRS patients with noradrenaline. Alessandria *et al.* [18] reported reversal of HRS type 1 in 75% of patients with noradrenaline.

The results of the current study confirm previous observations indicating that response to treatment is associated with an improvement of circulatory function as evidenced by a significant increase in urine output, urinary sodium (p <0.05), marked suppression of renin-angiotensin-aldosterone system and a trend towards increase in MAP (p = 0.10) in responders on day 15, in patients with HRS. On the contrary, there was no significant increase in urine output, urinary sodium and MAP in non-responders despite the marked suppression of the renin-angiotensin-aldosterone system. Suppression of the renin-angiotensin-aldosterone system without any clinical improvement in non-responders may be due to the slow response apart from other reasons as increased levels of vasodilator cytokines [25],

increased bacterial products or latent infections [26], and presence of concomitant adrenal insufficiency [27].

Short term mortality was the same in both groups in this study. At the end of 15 days of therapy, 9 (39.1%) patients in group A (seven responders and two non-responders) and 11 (47.8%) in group B (eight responders and three non-responders) survived. Four of the patients who did not survive had reversal of HRS (group A-2; group B, 2). All non-responders (group A, 2; group B, 3) died within 30 days of follow-up. In another study, at the end of the 15-day period, 55% of patients in the terlipressin group and 45% in the noradrenaline group survived [16]. Nazar *et al.* [19] showed that the probability of survival at 3 months after developing HRS was significantly greater in patients who responded to terlipressin compared with non-responders. In a study comparing noradrenaline and terlipressin therapies in HRS, the majority (82%) of patients with complete response to therapy underwent liver transplant, while four of the five patients with no response to treatment died (80%) [18]. A recent meta analysis showed that overall, vasoconstrictor drugs used alone or with albumin reduced mortality compared with no intervention or albumin [28].

In the present study, baseline predictive factors of response to terlipressin/noradrenaline and albumin in patients with type 1 HRS were also assessed. Univariate analysis showed baseline CTP score, MELD, urine output on D1, serum albumin and MAP were associated with response. However, in multivariate analysis, only CTP score was associated with response. Various predictive factors of response or survival (baseline Child-Pugh and MELD scores, serum bilirubin, serum creatinine, mean arterial pressure, urine volume, leukocyte count, plasma renin activity, presence of alcoholic hepatitis and treatment with terlipressin and albumin) have been reported in previous studies in patients with HRS [14–17,19,20,29]. In the present study, CTP score on day 1 as predictor of response can be explained by the fact that high CTP score on day 1 is associated with more splanchnic vasodilatation and renal vasoconstriction. On the other hand, MELD score that depends on serum creatinine which may be spuriously low with low muscle mass in advanced cirrhosis, did not predict response in our study.

The adverse effect profile in both groups was the same, with no major side effects or drug withdrawal or modification of doses. However, the majority of the studies showed frequent side effects after treatment with terlipressin, as cardiovascular or ischemic complications, which have been reported in an average of 10–15% of patients treated, and required drug modification in at least 10–12% of patients [12]. Noradrenaline in HRS proved safe in previous studies too [13,16,18].

We also performed the cost calculation showing a major advantage of noradrenaline over terlipressin in the cost-effective analysis. The cost of treatment was 945€ and 275€ in the terlipressin and noradrenaline group respectively (p <0.05). However, the total cost of treatment did not include the cost of albumin and hospital expenses in the calculation and analysis. Sharma *et al.* [16] and Alessandria *et al.* [18] also reported noradrenaline therapy to be less expensive in comparison to terlipressin.

In conclusion, the results of this randomized study suggest that noradrenaline may be as effective and safe as terlipressin in the reversal of type 1 HRS in cirrhotics, but at a fraction of the cost; and baseline CTP score is predictor of response. However, more studies are warranted to establish this drug as an alternate therapy.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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