Indian Journal of Gastroenterology (September 2018) 37(5):424–429
https://doi.org/10.1007/s12664-018-0876-3

ORIGINAL ARTICLE

Noradrenaline versus terlipressin in the management of type 1 hepatorenal syndrome: A randomized controlled study

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Received: 20 March 2018 / Accepted: 1 August 2018 / Published online: 3 September 2018

Abstract

Background Hepatorenal syndrome (HRS) occurs in decompensated liver disease and carries high mortality. Vasoconstrictors are the drug of choice. Terlipressin is widely used and is expensive. In this study, we compared noradrenaline and terlipressin in the management of type 1 HRS.

Methods Sixty consecutive patients with type 1 HRS were managed with noradrenaline (Group A, $n = 30$) or terlipressin (Group B, $n = 30$) with albumin in a randomized controlled trial at a tertiary center.

Results Reversal of type 1 HRS was achieved in 16 (53%) patients in group A and 17 (57%) in group B. There was statistically insignificant difference between the two groups in decreasing serum creatinine and increasing urine output ($p > 0.05$). On univariate analysis, Child-Turcotte-Pugh (CTP) score, serum sodium, serum urea, serum albumin, prothrombin time, International normalized ratio (INR), serum alanine aminotransferase (ALT), ascitic fluid protein, and history of bleeding were associated with response to treatment (noradrenaline/terlipressin). However, on multivariate analysis, only baseline CTP score, serum urea, serum albumin, and prothrombin time were independent predictors of response. All patients who responded were discharged alive with no mortality within 30 days.

Conclusions There is no difference in outcome of patients with type 1 HRS treated with noradrenaline or terlipressin. Thus, noradrenaline, which is cheaper, can be used instead of terlipressin (Clinical Trials Registry-India [CTRI] No. CTRI/2011/09/002032).

Keywords Cirrhosis · CTP score · International normalized ratio · Model for end-stage liver disease score

Introduction

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 [1]. At a model for end-stage liver disease (MELD) score of 18 or more, nearly 40% of patients are expected to develop HRS within a year [2]. The mechanism of the renal vasoconstriction that causes HRS is complex, since renal perfusion in decompensated cirrhosis correlates inversely with the activity of the renin-angiotensin and sympathetic nervous system [3–6]. Administration of vasoconstrictor agents (terlipressin, noradrenaline, or oral midodrine) and intravenous albumin infusion is the treatment of choice in patients with type 1 HRS [7, 8]. Numerous pilot studies have shown that this treatment induces reversal of HRS (decrease of serum creatinine < 1.5 mg/dL) in 40% to 60% of patients [9–18] and is associated with an increase in survival. A meta-analysis confirmed that terlipressin plus albumin may prolong short-term survival in patients with type 1 HRS [19]. Noradrenaline has also been shown to be effective and safe in the treatment of type 1 HRS. There are many controlled trials with a small number of patients which indicate that noradrenaline may be as effective as terlipressin [20–22]. The cost of terlipressin therapy is much more than noradrenaline [21, 22]. Furthermore, the relatively high cost of these drugs makes them less practical to use in many economically backward countries, especially over a prolonged duration. There is, therefore, a great need to evaluate

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alternative drugs for the management of HRS. Noradrenaline is widely available and is relatively inexpensive.

Methods

Eighty-eight consecutive patients of decompensated cirrhosis with oliguria and azotemia got admitted to the Department of Gastroenterology at Sher-I-Kashmir Institute of Medical Sciences. All patients received initial resuscitation with intravenous fluids, albumin, and other supportive care. Diuretics and beta blockers were stopped at admission. Patients were reassessed at 48 h; urine output and serum creatinine normalized in 10 patients, three had pneumonia, two had urosepsis and structural kidney disease, three died within 48 h, and 10 were reluctant for any aggressive treatment due to financial constraint. After excluding the above 28 patients, remaining 60 patients were included in the study. This study was approved by the Ethics committee of Sher-I-Kashmir Institute of Medical Sciences. Written informed consent was taken from all the patients. Diagnosis of type 1 HRS was based on the criteria of International Ascites Club [23, 24].

Inclusion criteria were cirrhosis with ascites; serum creatinine > 133 μmol/L (1.5 mg/dL); no improvement of serum creatinine (decrease to a level of ≤ 133 μmol/L) after at least 2 days of diuretic withdrawal and volume expansion with albumin; the dose of albumin used was 1 g/kg of body weight per day up to a maximum of 100 g/day for at least 2 days; absence of shock; no current or recent treatment with nephrotoxic drugs; absence of parenchyma kidney disease (as indicated by proteinuria > 500 mg/day, microhematuria as evidenced by > 50 red blood cells per high-power field, and/or abnormal renal ultrasonography). Patients with improvement in renal function after plasma volume expansion; evidence of sepsis excluding spontaneous bacterial peritonitis; coronary artery disease, obstructive cardiomyopathy; ventricular arrhythmia; or obliterative arterial disease were excluded.

Patients were randomized into two groups by a computer-generated randomization table. The patients from each group were given daily IV albumin 20–40 g/day until the end of the study period. Albumin administration was transiently stopped if central venous pressure increases above 18 cm of saline. All patients had an indwelling urinary catheter until recovery from the HRS for measurement of urine output. Patients in study groups were given either continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in mean arterial pressure (MAP) of at least 10 mmHg, or an increase in 4-h urine output to 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, or terlipressin as an IV bolus of 0.5 mg every 6 h; if a significant reduction in serum creatinine level (≥ 1 mg/dL) was not observed during each 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h to maximum of 8 mg per day. In patients with tense ascites, paracentesis was done along with an infusion of 8 g of albumin for each liter of ascitic fluid drained. Blood samples were taken before the initiation of therapy and at days 1, 3, 5, 7, and end of treatment to measure standard liver and renal function tests. Glomerular filtration rate was assessed by measuring creatinine at baseline, at the end of treatment. Mean arterial pressure was measured on daily basis.

Endpoints

The primary endpoint of this study was reversal of type 1 HRS, i.e. decrease in serum creatinine to a value of ≤ 1.5 mg/dL. The maximum duration of therapy with noradrenaline/terlipressin was 2 weeks. Secondary endpoints included survival at 30 days of therapy.

Statistical analysis

The sample size was calculated with a clinically significant difference of 0.5 and standard deviation (SD) of 1.1 for serum creatinine, with a power of 90% and significance level of 0.05% using a nomogram. The total sample size for the two groups came to be 55. The data were entered and analyzed using the SPSS 13 statistical package (SPSS Inc., Chicago, IL). The results were expressed as mean ± SD. Comparisons between groups were performed using Student's t test. A value of $p < 0.05$ was taken as significant. The results were analyzed at baseline, day 3, day 5, and at the end of treatment and finally at day 30 of the study. We enrolled 60 patients, 30 in each treatment group. The characteristics of responders and non-responders were analyzed irrespective of the treatment regimen given to them. Univariate and multivariate analyses were done to determine baseline predictors of response.

Results

There was no significant difference in the baseline clinical and laboratory profiles of patients receiving noradrenaline (Group A) or terlipressin (Group B) as shown in (Table 1). Creatinine clearance, urine output, and serum sodium increased while serum creatinine decreased significantly with noradrenaline (Group A) and terlipressin (Group B) from baseline values. On comparing MAP, serum creatinine and urine output at day 1, day 3, day 5, day 7, and end of treatment between noradrenaline (Group A) and terlipressin (Group B), there was a rapid and significant improvement in the surviving patients as compared to baseline values. While comparing two groups, there was statistically insignificant difference in these parameters in

Table 1 Baseline parameters of the patients treated with noradrenaline (Group A) and terlipressin (Group B)

Baseline Parameters	Noradrenaline (Group A)	Terlipressin (Group B)	*p*-value
Age (years)	51.5 ± 12.8 (25–70)	53.8 ± 8.6 (35–68)	0.418
Duration of CLD (months)	20.9 ± 19.3 (6–72)	23.4 ± 14.9 (6–48)	0.574
Child-Pugh score	12.0 ± 1.3 (9–14)	11.9 ± 1.4 (9–14)	0.782
MELD score	30.4 ± 9.2 (18–48)	29.1 ± 5.8 (17–39)	0.526
Serum sodium (mEq/L)	119.4 ± 9.2 (107–140)	118.5 ± 9.8 (104–135)	0.713
Urea (mg/dL)	94.3 ± 45.2 (14–200)	111.0 ± 46.8 (15–210)	0.165
Bilirubin (mg/dL)	13.8 ± 16.0 (0.4–54)	6.9 ± 12.4 (0.9–45)	0.067
Albumin (g/dL)	2.4 ± 0.49 (1.7–3.2)	2.7 ± 0.6 (1.7–3.9)	0.055
PT (seconds)	20.5 ± 6.3 (12–37)	21.3 ± 4.8 (14–30)	0.617
INR	2.1 ± 0.9 (1–4)	2.1 ± 0.6 (1.1–3)	0.787
Hb (g/dL)	9.6 ± 1.7 (7–15)	9.0 ± 2.2 (5.2–14)	0.234
TLC (thousand/mm^3)	6.7 ± 3.8 (2.6–18)	6.7 ± 3.2 (1.6–12)	0.994
Platelets (thousand/mm^3)	76.8 ± 33.9 (20–126)	71.6 ± 39.4 (30–196)	0.581
Ascitic fluid protein (g/L)	1.5 ± 0.5 (0.3–2)	1.6 ± 0.5 (0.8–2.6)	0.244
Creatinine (mg/dL)	3.3 ± 1.1 (1.9–5.6)	3.2 ± 0.9 (2.1–4.6)	0.668
Urine output (mL/day)	367.3 ± 175.6 (100–800)	587.0 ± 865.3 (100–350)	0.178
MAP (mmHg)	80.6 ± 10.2 (69–102)	81.3 ± 8.1 (66–96)	0.060

CLD chronic liver disease, *CTP* Child-Turcotte-Pugh score, *MELD* model for end-stage liver disease, *MAP* mean arterial pressure, *INR* international normalized ratio, *PT* prothrombin time, *Hb* hemoglobin, *TLC* total leukocyte count

patients receiving noradrenaline or terlipressin (Table 2). Overall, 33 patients (55%) responded with reversal of HRS, i. e. achieved primary endpoint and 27 patients (45%) did not respond to treatment. In group A, 16 (53%) responded and in group B 17 (57%) patients responded. Thus, both groups (noradrenaline and terlipressin) had similar (53% vs. 57%) response in reversal of HRS. In group A, 14 (47%) and in group B, 13 (43%) were non-responders. Noradrenaline was given at a median dose of 1.5 (range 1.0–3.0) mg/h for a median duration of 5 days (range 3–10) and the median dose of terlipressin was 3.3 (range 2.0–6.0) mg/day for a median duration of 5 days (range 4–8). Non-responders needed

Table 2 Comparison of outcome of treatment between the two groups (Group A and Group B)

Parameters	Noradrenaline (Group A)	Terlipressin (Group B)	*p*-value
Urea at the end of treatment (mg/dL)	79.0 ± 42.1 (39–198)	72.7 ± 31.7 (38–124)	0.513
Albumin at the end of treatment (mg/dL)	3.4 ± 0.5 (2.4–4.0)	3.6 ± 0.4 (2.7–4.2)	0.140
Sodium at the end of treatment (mEq/L)	132.6 ± 7.4 (121–145)	132.9 ± 4.7 (120–140)	0.857
Creatinine on day 1 (mg/dL)	3.3 ± 1.1 (1.9–5.6)	3.2 ± 0.9 (2.1–4.6)	0.668
Creatinine on day 3 (mg/dL)	3.2 ± 1.3 (1.7–6.9)	2.8 ± 1.0 (1.5–5.5)	0.202
Creatinine on day 5 (mg/dL)	2.6 ± 1.1 (1–4.8)	2.6 ± 1.3 (1.3–6.7)	0.859
Creatinine on day 7 (mg/dL)	2.4 ± 1.5 (1–6.5)	1.7 ± 1.0 (0.6–5)	0.061
Creatinine at the end of treatment (mg/dL)	2.3 ± 1.5 (1.0–6.5)	1.6 ± 1.1 (0.5–6.5)	0.766
Creatinine clearance at the end of treatment (mL/min)	34.1 ± 21.8 (6.2–79.9)	39.2 ± 28.0 (6.6–125.0)	0.416
Urine output (mL/day) on day 1	367.3 ± 175 (100–800)	587.0 ± 865.3 (100–3500)	0.178
Urine output (mL/day) on day 3	486.0 ± 187.9 (150–800)	515.0 ± 234.2 (200–1100)	0.599
Urine output (mL/day) on day 5	663.6 ± 337.2 (150–1500)	810.7 ± 375.0 (200–1500)	0.141
Urine output (mL/day) on day 7	807.1 ± 504.1 (100–1500)	1037.5 ± 472.1 (300–1700)	0.121
Urine output at the end of treatment (mL/day)	807.1 ± 504.1 (100–1500)	1037.5 ± 472.1 (300–1700)	0.121
MAP at the end of treatment (mmHg)	98.0 ± 7.8 (90–108)	106.7 ± 6.1 (100–112)	0.175

MAP mean arterial pressure

Table 3 Parameters predicting response on multivariate analysis in Group A and Group B

Variables	*p*-value
CTP score	0.002
Serum sodium	0.092
Serum urea	0.002
Serum albumin	0.003
PT	0.002
INR	0.034
Bleed	0.026

CTP Child-Turcotte-Pugh score, *PT* prothrombin time, *INR* international normalized ratio

increased doses and maximum dose of noradrenaline (3 mg/h) was given in three patients of (Group A), while two patients of (Group B) received terlipressin 8 mg/day. All these patients died in hospital without any response. All the 33 patients who responded to treatment were discharged alive from the hospital within mean duration of 6 days (range 4–11). While among non-responders no patient survived, 25 patients died during the hospital stay and two died at home within 10 days. In group A, all the 16 patients who responded to treatment were discharged from the hospital within mean duration of 6 days (range 4–11) while among non-responders all died within mean duration of 4.3 days (range 3–7). In group B, all the 17 patients who responded to treatment were discharged from the hospital within mean duration of 6 days (range 4–10), while among non-responders all died within mean duration of 5.3 days (range 3–7). Among survivors, no death occurred up to 30 days in both the groups (A and B). From 30 to 60 days after discharge, in group A only eight (50%) while in Group B, 13 (76%) patients survived. There was only one (6%) survival at 90 days in group A as compared to six (35%) in group B after discharge from the hospital. Two patients (6%) developed recurrence of HRS, one each from noradrenaline and terlipressin group. Responders (33 patients) and non-responders (27 patients), regardless of the group they belong, were compared with regard to baseline parameters to determine the predictors of response. On univariate analysis, Child-Pugh score, serum sodium, serum urea, serum albumin, prothrombin time, international normalized ratio (INR), aspartate aminotransferase (AST), ascitic fluid protein, and history of bleeding were associated with response to treatment (noradrenaline/terlipressin). However, on multivariate analysis, only baseline Child-Pugh score, serum urea, serum albumin, and prothrombin time (PT) were independent predictors of response (Table 3). The serum urea, serum creatinine, creatinine clearance, serum sodium, serum albumin, urine output, and mean arterial pressure at end of treatment improved significantly in responders than non-responders regardless of the

Table 4 Comparison of outcome of treatment in responders and non-responders (Group A and Group B)

Parameters	Responders (survivors)	Non-responders (died)	*p*-value
Urea at the end of treatment (mg/dL)	46.2 ± 4.7 (38–56)	112.1 ± 24.8 (88–198)	0.000
Serum sodium at discharge (mEq/L)	135.7 ± 4.3 (123–145)	129.3 ± 6.1(120–143)	0.000
Albumin at the end of treatment (g/dL)	3.8 ± 0.2 (3.4–4.2)	3.0 ± 0.3 (2.4–3.6)	0.000
Pulse at the end of treatment (beats/min)	94.1 ± 121.2 (66–769)	71.4 ± 4.0 (66–82)	0.335
Creatinine on day 1 (mg/dL)	3.4 ± 1.1 (2.1–5.6)	3.1 ± 0.9 (1.9–4.5)	0.285
Creatinine on day 3 (mg/dL)	2.6 ± 0.9 (1.5–4.9)	3.5 ± 1.3 (2.3–6.9)	0.003
Creatinine on day 5 (mg/dL)	2.0 ± 0.7 (1–4)	3.5 ± 1.3(1.9–6.7)	0.000
Creatinine on day 7 (mg/dL)	1.5 ± 0.59 (0.6–2.8)	3.8 ± 1.3 (2–6.5)	0.000
Creatinine at the end of treatment (mg/dL)	1.1 ± 0.2 (0.5–1.4)	3.7 ± 1.3 (1.9–6.7)	0.000
Creatinine clearance at the end of treatment (mL/min)	54.3 ± 20.6 (29.8–125.0)	15.3 ± 5.6 (6.2–27.4)	0.000
Urine output (mL/day) on day 1	366.7 ± 320.8 (100–1500)	378.9 ± 208.5 (150–350)	0.134
Urine output (mL/day) on day 3	593.9 ± 194.4 (300–1100)	386.3 ± 173.0 (150–800)	0.000
Urine output (mL/day) on day 5	953.0 ± 278.1 (500–1500)	392.0 ± 148.1 (150–650)	0.000
Urine output (mL/day) on day 7	1157.6 ± 363.8 (250–1700)	304.2 ± 119.6 (100–500)	0.000
Urine output (mL/day) at the end of treatment	1155.0 ± 423.0 (350–1700)	225.0 ± 28.9 (200–250)	0.000
MAP on day 1 (mmHg)	85.7 ± 10.6 (68–106)	84.7 ± 9.2 (70–98)	0.683
MAP on day 3 (mmHg)	93.5 ± 10.1 (68–110)	86.2 ± 9.8 (72–104)	0.006
MAP on day 5 (mmHg)	97.4 ± 8.9 (78–110)	90.1 ± 8.3 (78–110)	0.004
MAP on day 7 (mmHg)	101.0 ± 8.7 (78–110)	92.8 ± 6.9 (80–110)	0.004
MAP at the end of treatment (mmHg)	103.4 ± 7.8 (84–112)	93.0 ± 3.5 (90–96)	0.014

MAP mean arterial pressure

group they belong. There was statistically significant improvement in these parameters from baseline values in responders than non-responders (Table 4).

Cost of treatment

Total median dose of noradrenaline used per patient was 180 mg with cost of 4500 Indian National Rupees (INR) per patient (70 US dollars) while total median dose of terlipressin was 16.5 mg per patient with cost of 24,000 INR per patient (369 US dollars) with a statistically significant difference between two ($p < 0.05$). Time period was ≤ 2 weeks both for noradrenaline terlipressin.

Discussion

This randomized clinical trial shows that patients with type 1 HRS responded favorably to both terlipressin and noradrenaline treatment with significant improvement in renal function and systemic hemodynamics (MAP). The responding patients had survival benefit than non-responding patients; moreover, this is expected to delay liver transplantation allowing the patients and healthcare service to prepare for the transplantation. 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. Three earlier studies by Alessandria et al. [20], Sharma et al. [21], and Singh et al. [22] also showed that noradrenaline was as effective and safe as terlipressin in treatment of HRS. Although results shown by Alessandria et al. [20] are much better than our results, this could be probably explained by small study size and type of HRS used in their study. In our study, 33 patients (55%) responded with reversal of HRS and 27 patients (45%) did not respond to treatment; our results are in accordance to results of several other studies in which the frequency of reversal of HRS ranged between 40% and 60% [9–17, 21, 22, 25–27]. However, response rate was higher (> 70%) in some studies (two with noradrenaline and one with terlipressin) probably because these were nonrandomized, with small number of patients and one of these studies included type 2 HRS [10, 20, 28]. The dose and duration of noradrenaline and terlipressin in our study were less than the earlier studies [20–22]. Noradrenaline was much cheaper than terlipressin as shown in earlier studies [21, 22]. Our study showed that non-responders did not do well by reduction in the creatinine level even with higher dose of noradrenaline/terlipressin over a longer duration. So, we recommend that there is no benefit of increasing dosage and duration of treatment in patients with nonresponse. The treatment with either drug was well tolerated and safe without any significant side effect. Our results were, however, contradictory to the results of Gluud et al. who showed side effects in 20% of patients [19]. Thus, it is evident from our results that vasoconstrictor (noradrenaline/terlipressin) may prolong life and delay liver transplantation. Vasoconstrictors, by reversing HRS, not only have survival benefit prior to liver transplantation but are also have been shown to prolong post-transplant survival [29–32]. Noradrenaline was much cheaper than terlipressin but was equally effective as terlipressin in reversal of HRS [33–35]. Our study showed that noradrenaline may be effective, safe, and less expensive alternative for treating HRS.

HRS occurs frequently in patients with decompensated liver disease and carries a risk of high mortality. Without treatment, 80% of patients die within 2 to 3 weeks. Definitive treatment is liver transplantation, which is not available in every center. Vasoconstrictors are the drugs of choice for treating HRS and are found to improve survival by normalizing renal functions. Our randomized controlled trial showed that vasoconstrictors are effective in reversing HRS, have short-term beneficial effect on mortality, and thus may help to buy time to go for liver transplantation. Noradrenaline is effective, safe, and less costly alternative to terlipressin in managing patients with type 1 HRS.

Compliance with ethical standards

Conflict of interest RUS, HAD, SMS, MSA, GJ, and SAZ declare that they have no conflict of interest.

Informed consent Written informed consent was taken from all the subjects.

Ethics statement The authors declare that the study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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