COMPARISON OF EFFICACY ON NORADRENALINE AND TERLIPRESSIN IN HEPATORENAL SYNDROME IN THE PATIENTS OF DECOMPENSATED CIRRHOSIS – A RANDOMIZED CONTROLLED STUDY

Muhammad Siddique, Mansoor Ud Din Sajid*, Omar Ahsan**

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, *Rashid Latif Medical College Lahore Pakistan, **Foundation University Medical College Islamabad Pakistan

ABSTRACT

Objective: To compare the efficacy of noradrenaline and terlipressin in hepatorenal syndrome.
Study Design: Randomized controlled trial.
Place and Duration of Study: Combined Military Hospital Lahore, from May 2018 to Jan 2019.
Material and Methods: A randomized controlled trial was carried out at CMH Lahore. Patients admitted in hospital with diagnosis of hepatorenal syndrome were included in the study by non-probability convenient sampling. Detailed history and examination was carried out. PT/INR, Serum bilirubin, albumin, creatinine, sodium and urine output (ml/24 hour), were measured in all patients. Patient were screened by applying inclusion and exclusion criteria and randomized into terlipressin group and noradrenaline group and treated for one week as per study protocol. Serum creatinine level <133 µmol/L was considered reversal of hepatorenal syndrome. Data was collected on a predesigned form and entered in SPSS software for data analysis. Proportions were compared by applying chi square test and independent sample t test was applied for comparing means. For statistical significance *p*-value ≤0.05 was the standard.
Results: The study comprised of 40 patients. Both terlipressin and noradrenaline groups had 20 patients each. In terlipressin group 9 (45%) patients and in noradrenaline group 8 (40%) patients achieved the reversal of hepatorenal syndrome, respectively (*p*-value 0.5). Only 2 (10%) patient died in each group (*p*-value 0.698). Mortality was 2 (10%) in noradrenaline group and 2 (10%) in terlipressin group (*p*-value 0.698).
Conclusion: Terlipressin and noradrenaline are both effective and benign noninvasive treatment options for hepatorenal syndrome in the circumstances where liver transplant is not available. Noradrenaline and terlipressin have similar efficacy and safety profile.

Keywords: Hepatorenal syndrome, Noradrenaline, Terlipressin.

INTRODUCTION

Hepatorenal syndrome (HRS) is a well-recognized complication of decompensated chronic liver disease. Most of the studies report approximately 8-10% per year incidence at one year and almost 40% at 5 year[1]. HRS significantly contributes to the morbidity and mortality of chronic liver disease as the average survival for HRS type 1 is one month and for type 2 is around 6.7 months[1]. HRS is generally considered a functional failure in the absence of known causes of acute kidney injury. Current guidelines recommend treatment with albumin and terlipressin; However studies have reported a beneficial role of noradrenaline[2]. Terlipressin is relatively expensive and its availability is a problem as compared to noradrenaline. Terlipressin is not FDA approved and it is not freely available in countries like Pakistan. Cost of treatment with noradrenaline is significantly low as compared to terlipressin. Few studies have compared role of these two drugs in HRS. Considering the cost comparison, scarcity of data on subject and availability of these two drugs we planned a study to compare the effectiveness of noradrenaline and terlipressin in type 1 HRS.

Correspondence: Dr Mansoor Ud Din Sajid, Prof of Medicine, Rashid Latif Medical College Lahore Pakistan
Email: mansooruddinsajid@yahoo.com
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PATIENTS AND METHODS

Our study, a randomized controlled trial was carried out at Combined Military Hospital Lahore

from May 2018 to January 2019. Sample size was calculated by the formula

$$m \text{ (size per group)} = c \times \frac{\pi1(1-\pi1)+\pi2(1-\pi2)}{(\pi1-\pi2)^2}$$

for a dichotomous outcome with two sided 5% and 80% power. The study was formally approved by research review board of the relevant institute. Written consent was taken by all the patients or their next of kin. Patients admitted in hospital with diagnosis of hepatorenal syndrome were included in the study by non-probability consecutive sampling. Detailed history and examination was carried out and presence or absence of encephalopathy was documented. Ultrasound abdomen was done to document cirrhosis and presence of ascites. Serum Bilirubin, PT/INR, Serum Albumin, Blood Pressure, Urine Output (ml/24 hour), Serum Creatinine and Serum Sodium were measured in all patients.

Exclusion criteria was evidence of severe sepsis, pancreatitis, or shock, use of nephrotoxic drugs and evidence of peripheral vascular disease, ischemic heart disease, cardiomyopathy, cardiac arrhythmia. Inclusion criteria was the diagnosis of HRS according to International Club of Ascites (ICA-AKI) criteria, minimum 0.3 mg/dL (26 µmol/L) and/or ≥50% from baseline increase in serum creatinine, within 48 hours were defined as acute kidney injury, presence of cirrhosis and ascites, no improvement after 2 successive days of diuretic discontinuation and blood volume expansion with daily albumin infusion, no evidence of structural kidney disease on ultrasound examination and absence of proteinuria (> 500 mg/day) and no evidence of micro hematuria (> 50 red blood cells per high power field)[1,3,4].

Patients selected for study were treated for one week as per study protocol. Daily I Valbumin 1 gram per kg per day was administered in each group throughout the study period. In noradrenaline group, continuous infusion of noradrenaline was started at 0.5 mg/hour, to attain a minimum 10 mm Hg increase in mean arterial pressure (MAP) or more than 40 ml per hour urine output. If none of these objectives was accomplished, the noradrenaline dose was titrated up by 0.5 mg/hour after every 4 hours, not to exceed 3 mg/hour. In terlipressin group, intravenous bolus of terlipressin 1mg six hourly was initiated. After every 3 days terlipressin was increased to 2 mg every 6 hours if the target of more than 25% decrease in serum creatinine level was not achieved. Reversal of HRS was based on serum creatinine level <133 µmol/L. Block randomization was done by Principal investigator using online research randomizer. Principal investigator enrolled the patients and assigned the patients to terlipressin

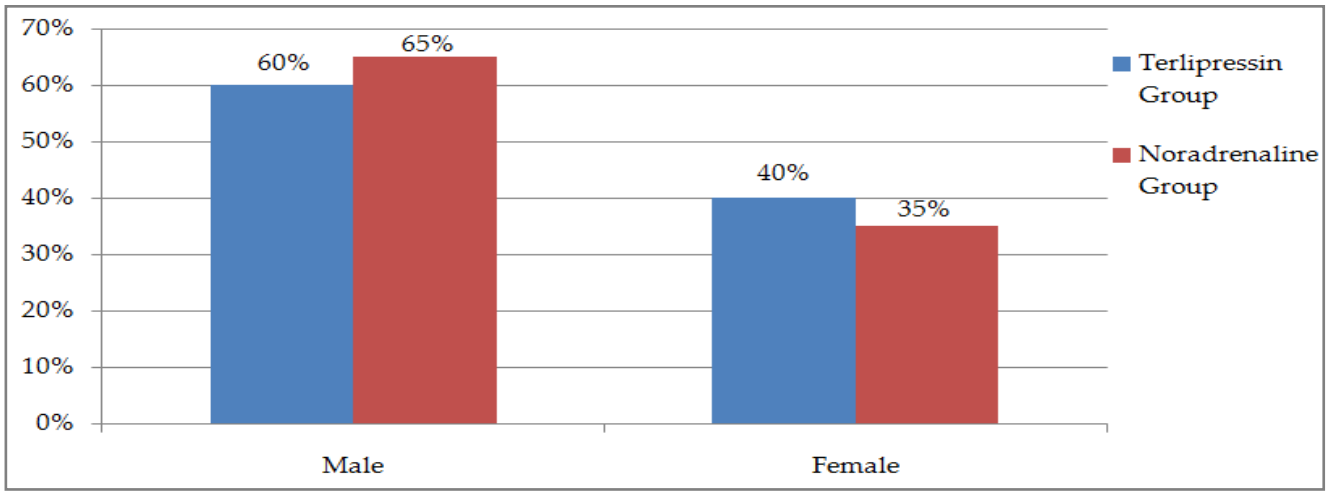

Figure: Comparison between male and female of terlipressin and noradrenaline group.

and noradrenaline groups according to generated random allocation sequence. Data was collected on a predesigned form and entered in SPSS software for data analysis. Proportions were compared by applying chi square test and independent sample t-test was applied for comparing means. For statistical significance *p*-value ≤0.05 was the standard.

RESULTS

The study comprised of 40 patients. Both terlipressin and noradrenaline groups had 20 patients each. Gender distribution in both groups is shown in the figure.

No adverse effects were observed significant enough to discontinue therapy with any of the two drugs. Noradrenaline was found less expensive as compared to terlipressin in our study.

DISCUSSION

Hepatorenal syndrome remains the foremost complications of decompensated chronic liver disease, and a major cause of morbidity and mortality. Renal circulatory dysfunction is thought to be the reason underlying the HRS. A rise in serum creatinine rather than a definite serum creatinine level is preferred by international club of ascites, for definition and diagnosis of HRS. We have used the same criteria in our study.

Table-I: Baseline characteristics of two groups.

	Terlipressin Group(20)	Noradrenaline Group(20)	*p*-value
Age	54.55 ± 10.56	54.60 ± 9.67	0.988
Serum Creatinine (µmol/L)	181.05 ± 33.58	188.1000 ± 31.47	0.497
Serum Sodium (mmol/L)	129.75 ± 5.46	132.85 ± 5.70	0.087
Serum bilirubin (mg/dl)	2.018 ± 0.438	2.27 ± 0.417	0.075
Serum Albumin	2.785 ± 0.41	2.66 ± 0.34	0.325
Urine output (ml/24 hour)	699 ± 267.77	676 ± 246.49	0.779
Mean arterial pressure (mm Hg)	73.45 ± 5.26	73.15 ± 4.84	0.852

Table-II: Comparison of parameters between two groups after treatment.

	Terlipressin Group(20)	Noradrenaline Group(20)	*p*-value
Serum Creatinine (µmol/L)	150 ± 35.32	152 ± 33.69	0.856
Serum Sodium (mmol/L)	136.20 ± 4.0	137.75 ± 4.15	0.242
Urine output (ml/24 hour	1775 ± 582.98	1896 ± 580.47	0.515
Mean Arterial pressure (mm Hg)	87.95 ± 7.01	87.45 ± 8.37	0.839

Age and biochemical profile of patients in both groups was not statistically different as described in table-I.

At the end of one week 2 (10%) patient died in each group (p>0.5). Mortality at one week was 2 (10%) in noradrenaline group and 2 (10%) in terlipressin group (p>0.5). In terlipressin group 9 (45%) patients and in noradrenaline group 8 (40%) patients achieved the reversal of hepatorenal syndrome, respectively however the difference was not significant (p>0.5). Other parameters improved similarly in both groups as shown in table-II.

Liver transplantation remains the ultimate curative treatment modality for HRS. Liver transplant facilities are not readily available and thus this treatment modality is not an option in most of the cases. Recent guidelines recommend terlipressin with albumin for treatment of HRS. Various clinical trials have reported efficacy of various drugs which can reverse the HRS. Noradrenaline, terlipressin, plasma volume expanders, dopamine, midodrine and octreotide have been reported to decrease serum creatinine and complete or partial recovery of HRS. Few invasive procedures like bio artificial liver support systems, transjugular intrahepatic portosystemic shunt and

hemodialysis are effective inimproving the renal profile but there is significantly high mortality by these interventions[3-5].

Various studies that compared the terlipressin and noradrenaline have reported a reversal of HRS in 39.1 to 73.9% with noradrenaline and 43.4 to 83% with Terlipressin. All the studies have described a reduction in serum creatinine, improved urine output and increased mean arterial pressure, serum sodium and urinary sodium, irrespective of treatment regimen. Most of the studies concluded that terlipressin was more expensive than noradrenaline[6-11]. The findings are consistent with that in our study. Our study has shown that terlipressin and noradrenaline have similar effectiveness in the management of HRS with the added advantage of noradrenaline being cost effective and easy availability. Reversal of hepatorenal syndrome in our study was low as compared to other studies and the reason is only one week duration of treatment while most of the studies treated the patients for two weeks. Similarly mortality was lower in our study perhaps, because of shorter duration of study.

Alessandria *et al* in 2007 in a prospective study reported a success rate of 70% with noradrenaline and 83% with terlipressin. There were no significant side effects of the two drugs. The results in this study are similar to our study but we did not achieve an extra ordinary reversal rate like this study. The study concluded noradrenaline as an economical and widely available option for management of HRS[6].

Sharma *et al* in 2008 compared the noradrenaline and terlipressin in a randomized controlled trial and found 50% response with both drugs and similar survival rate in both groups. He also inferred that noradrenaline was cost effective as compared to terlipressin[7]. Findings in this study are in complete agreement with our study.

Singh *et al* in 2012 achieved a 43.4% reversal with noradrenaline and 39.1% with terlipressin and a statistically significantly higher mortality with terlipressin[7]. Our study did not find a higher response with noradrenaline and insignificantly higher mortality with terlipressin but this study concluded the same that both noradrenaline and terlipressin are equally effective and safe while treatment with noradrenaline is cost effective as well.

Ghosh *et al* in 2013 compared terlipressin and noradrenaline and observed a 73.9% reversal of HRS in both groups however; Mortality was higher in noradrenaline group but it was not significant statistically. No significant adverse effects in any group. Treatment cost was lower with noradrenaline[10]. Our study demonstrated similar results with a difference in reversal rate that is lower in our study and we did not find any increased mortality with noradrenaline as observed in this study.

Goyal *et al* in 2016 conducted a prospective randomized trial comparing noradrenaline with terlipressin. He observed HRS reversal 47.6% with noradrenaline and 45% with terlipressin. He concluded that noradrenaline and terlipressin had same efficacy for treatment of HRS. Noradrenaline had fewer adverse events and was significantly cheaper than terlipressin. The results are in agreement with our study except for the higher response rate with noradrenaline[8].

Saif *et al* in 2018 in a randomized controlled trial demonstrated a 53% response with noradrenaline and 57% with terlipressin and 100% survival at 30 day in both groups[11]. Just like our study, the above study augmented the evidence that noradrenaline and terlipressin have similar efficacy and safety profile.

A recent study by Gupta *et al* in 2018 reported a 73% response rate with noradrenaline along with improvement in urine output, MAP, serum creatinine, creatinine clearance and serum sodium. No significant adverse events were reported in most of the patients. The findings in this study are consistent with our study except that we did not observe a very high rate of HRS reversal with both noradrenaline and terlipressin[12].

Other than end to end comparison of terlipressin and noradrenaline, these drugs were compared in meta-analysis and systemic reviews. Nanda *et al* in 2018 analyzed thirteen randomized controlled trial and concluded that terlipressin was more effective than placebo, midodrine oroctreotide. However, no significant difference was noted comparing terlipressin versus noradrenaline. HRS relapse and survival of patients was same in all groups. He concluded that terlipressin was the most effective medical therapy for treating HRS and noradrenaline was a suitable alternative[13].

Sridharan *et al* in 2018 analyzed 16 studies and mentioned that reversal of HRS was significantly better with noradrenaline and terlipressin. Cardiovascular side effects were higher with vasoactive drugs plus albumin than treatment with albumin alone. Mortality, incomplete HRS reversal, or side effects were similar for all interventions. He inferred that terlipressin was more effective in achieving complete HRS reversal[14].

Facciorusso *et al* in 2017 analyzed 13 randomized controlled trials. In every trial patients received albumin and supportive therapy. He found that terlipressin use was associated with decrease in short term mortality. For reversal of HRS terlipressin and noradrenaline were better than midodrine plus octreotide. He observed higher recurrence rate of HRS with noradrenaline as compared to terlipressin. A higher percentage of patients treated with terlipressin experienced adverse effects serious enough to discontinue therapy. He stressed the need for further trials of terlipressin to document its efficacy for treatment of hepatorenal syndrome[15].

In 2017 Israelsen *et al* studied 10 randomized clinical trials including 7 trials comparing terlipressin versus noradrenaline. He found a high risk of bias in trials reporting a mortality benefit or other better outcomes with terlipressin. He downgraded the evidence as very low quality on account of non-disclosure of funding source and improper reporting of adverse events. He described no significant difference in efficacy of terlipressin and other vasoactive drugs[16].

Mattos *et al* in 2016 in his meta-analysis on four studies (154 patients) found a similar efficacy with terlipressin or noradrenaline for HRS reversal and similar rates of survival. However he found that treatment cost with noradrenaline was higher. This finding is not consistent with our study as well as all other previous studies comparing terlipressin and noradrenaline[17].

A meta-analysis by Gifford *et al* in 2015 included 12 randomized clinical trials in his analysis and concluded that HRS reversal was higher with terlipressin and noradrenaline but the quality of evidence for noradrenaline was not convincing as the trials for noradrenaline were small and nonblinded. Terlipressin showed a reduction in mortality but the trials showing the mortality benefit had selection bias and terlipressin therapy was associated with higher incidence of adverse events[18].

Salerno *et al* in 2015 in a meta-analysis found a similar survival and HRS reversal rate with different vasoactive drugs. He concluded that baseline mean arterial pressure, baseline serum bilirubin, creatinine or albumin, vasoconstrictor dose or type, treatment duration, age of patients, or study design, size or time periodhad no effect on outcome and mortality[19].

Our study has a limitation of shorter study duration as compared to other studies, small sample size and lack of double blindness in study design. We did not examine the predictors of outcome and long term survival in our study.

CONCLUSION

Despite all the skepticism, it is prudent to conclude that terlipressin and noradrenaline are both effective and benign noninvasive treatment options for hepatorenal syndrome in the circumstances where liver transplant is not available. Noradrenaline and terlipressin have similar efficacy and safety profile with the noradrenaline being cost effective and relatively cheaper option. We recommend that further

unbiased randomized multi-center clinical trials with larger sample size are essential to reach a definite conclusion.

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CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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