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ORIGINAL ARTICLE

Comparison of Terlipressin Plus Human Albumin with Norepineprine Plus Human Albumen in Hepatorenal Renal Syndrome

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ABSTRACT

Aim: to evaluate the efficacy of norepinephrine plus albuman versus terlipressin plus albumin in the management of patients with type 1 HRS.

Study Design: Randomized prospective study.

Place and duration: medical unit of Nishter Hospital Multan from 10th June 2019 to 9th June 2020.

Methodology: This study included 80 patients with type 1 HRS. Patients were randomized into two groups to receive norepinephrine plus albumin or terlipressin plus albumin. Renal functions such as serum creatinine, creatinine clearance and urine output were observed in both the groups, for baseline and after 15 days. The outcomes assessed were as follows: reversal of HRS, kidney functions, survival rate at day 30. SPSS version 23 was used for data analysis.

Results: Renal analysis of terlipressin and norepinephrine was noted as 17.5% and 30%, respectively. Child-pugh score and APACHE II score of terlipressin group was 10.73±2.01 and 22.94±10.05. Child-pugh score and APACHE II score of norepinephrine group was 9.03±2.25 and 25.39±9.87. **Conclusion**: Norepinephrine in combination with albumin is as effective as terlipressin in combination with albumin when used for the management of hepatorenal syndrome (HRS) type 1. But easy availability and cheap rate of norepinephrine makes it alternative of terlipressin.

Keywords: norepinephrine, hepatorenal syndrome, terlipressin, patient outcome.

INTRODUCTION

Hepatorenal syndrome is a potentially reversible condition characterized by failure of renal function at last stage of liver illness[1]. International Ascites Club classified HRS as type I and II. HRS type I is associated with rapid renal failure or double production of serum creatinine from normal values (less than 2.5 mg/do)[2]. It can be defined as fast decrease (less than 20mg/dl) in creatinine clearance from last two weeks. In this type of HRS mortality rate is much higher[3]. On another hand a slow progression of serum creatinine or renal failure is labeled as HRS type 2.

Main cause of HRS is abnormal circulation to hepatorenal system which is associated with vasodilatation of splenic vessels[4]. Many drugs are in practice as vasoconstrictors, one of them is terlipressin which is a prodrug[5,6]. Release of terlipressin is completed in several hours that avoided the side effects of previous drugs like ornipressin. Terlipressin reduce the interhepatic resistance by dilating the interhepatic vessels[7].

Some studies conducted on combination of terlipressin with albuman in treatment of hepatorenal syndrome and its benefits were reported[8,9]. Norepinephrine is another potent vasoconstrictor which is easily available and economical. It is also considered as alternative of terlipressin in type 1 HRS treatment[10]. Aim of this study is to compare the terlipressin and albumin combination with norepinephrine and albumin combination in management of HRS type 1.

METHODOLOGY

This randomized prospective study was conducted at medical unit of Nishter Hospital Multan from 10th June 2019 to 9th June 2020 in one year duration. Study was started after ethical approval from hospital ethical board. Sample size was calculated by using online software Openepi.com using statistics, confidence level 95%, and power of study 80%, mean creatinine production in terlipressin group 3 ± 1.1 and in norepinephrine group 3.4 ± 0.9. Non probability consecutive sampling was used as sampling technique. Written informed consent was obtained from patients and all patients were divided into two equal groups (group T and group N) by lottery method. Patients in group T were treated terlipressin and human albumin and patients in group N were treated with Norepinephrine and albuman.

Patients admitted from OPD and emergency department with diagnosed liver cirrhosis complicated with type 1 hepatorenal syndrome were included in the study. Patients having septic shock, multinodular hepatocellular carcinoma, peripheral vascular disease, coronary heart disease, respiratory failure, previous myocardial infarction and sensitivity to study drugs were excluded from the study. HRS was diagnosed according to International Ascites Club criteria as rapid progressive renal failure. Double fold increase in serum creatinine from normal values within 2 weeks. Patients diagnose with HRS 1 one time were treated at the same line of protocols. Bilateral IV lines were maintained and human albumin started at 1g/kg body weight at very initial day and then increased 40g/day. Norepinephrine was also started with intravenous infusion

in group N. Similarly in group T terlipressin was started after start of albumin 20%. Terlipressin was started at dose of 3mg/24hours intravenously. If no responseobtained dose increases to 6mg/24hour but in our study dose was not increased in any patients. It can be increased to 12 mg/dl if response was not achieved. Child pug score and APACH II were also calculated. Child-Pugh score was used to estimate the risk of operative mortality in patients with bleeding esophageal varices. APACHE II score is a general measure of disease severity based on current physiologic measurements, age & previous health conditions.

Norepinephrine was started at the dose of 0.5mg/h initially in infusion form, if response was not achieved dose was increased step wise 0.5mg/h to maximum dose 3mg/h. mean arterial pressure was kept 90 mmHg and norepinephrine dose was titrated accordingly. Both drugs terlipressin and norepinephrine with albuman were continued till 24 hours for reversal of HRS and to prevent the recurrence medication stopped gradually. Routine laboratory investigations including the liver function, complete blood profile, coagulation profile, serum albumin levels, serum electrolyte levels and kidney functions were recorded as baseline. Renal function tests were investigated till reversal. Urine output in 24 hours and fluid balance was compared in both groups. SPSS version 23 was used for data analysis, frequency percentages were calculated for categorical data and mean SD were calculated for numerical data. Tests of significance were applied and p value ≤ 0.05 was taken as significant.

RESULTS

Table 1: Demographic characteristics and comorbidities of both the groups

Variable	T n=40 (50%)	N n=40 (50%)	P-value
Age (years)	40.25±6.51	41.81±6.59	0.292
Gender			
Male	n=27 (67.5%)	n=26 (65%)	0.813
Female	n=13 (32.5%)	n=14 (35%)	
Weight (kg)	73.19±8.07	70.03±8.36	0.089
Child–Pugh Score	10.73±2.01	9.03±2.25	0.035
APACHE II Score	22.94±10.05	25.39±9.87	0.273
Liver Disease			
Hepatitis C virus	n=30 (75%)	n=31 (77.5%)	0.793
Hepatitis B virus	n=13 (32.5%)	n=10 (25%)	0.459
Hepatocellular carcinoma	n=9 (22.5%)	n=9 (22.5%)	1.00
Primary biliary cirrhosis	n=3 (7.5%)	n=7 (17.5%)	0.176
Alcoholic hepatitis	n=4 (10%)	n=8 (20%)	0.210
Hepatic encephalopathy (%)	n=13 (32.5%)	n=9 (22.5%)	0.317
Ascites (%)	n=27 (67.5%)	n=26 (65%)	0.813
Mechanical ventilation (%)	n=4 (10%)	n=1 (2.5%)	0.166
Diabetes mellitus (%)	n=13 (32.5%)	n=7 (17.5%)	0.121

Liver functions, kidney functions and hemodynamic characteristics of both the groups were shown in table. II. All the difference were statistically insignificant. (Table. II). Renal functions such as serum creatinine, creatinine clearance and urine output were observed in both the groups, for baseline and after 15 days. Renal analysis of terlipressin and norepinephrine was noted as n=7 (17.5%) and n=12 (30%), respectively. (Table. III).

Table 2: Baseline Investigations of both gorups

Variable	T n=40 (50%)	N n=40 (50%)	P-value
Liver functions			
Total serum bilirubin (mg/dl)	14.39±5.65	15.29±7.28	0.541
AST (U/l)	116.84±71.38	125.12±61.95	0.579
ALT (U/l)	66.26±30.46	72.52±30.18	0.359
Serum albumin (g/dl)	2.51±0.63	2.53±0.61	0.888
INR	1.96±1.23	2.19±1.17	0.388
Prothrombin concentration (%)	45.84±6.76	44.85±6.01	0.492
Kidney functions			
Serum creatinine (mg/dl)	4.36±1.31	4.46±1.25	0.735
Creatinine clearance (ml/min)	15.26±6.04	15.72±5.93	0.735
Serum sodium (mmol/l)	129.59±8.22	127.71±6.79	0.243
Serum potassium (mEq/l)	2.29±2.33	3.74±2.27	0.066
Urinary sodium (mmol/l)	8.83±7.79	10.21±7.69	0.432
Urine output (ml/24 h)	406.12±62.84	429.14±56.24	0.088
Hemodynamic characteristics			
Mean arterial pressure	77.67±10.75	79.06±9.29	0.542
Central venous pressure	11.57±7.73	10.95±6.81	0.705

Table 3: Effect of the intervention on the renal function of all participants of both groups

Variable	Terlipressin+ Albuman n=40 (50%)	Norepinephrine+ Albuman n=40 (50%)	P-value
Serum creatinine (mg/day)			
Baseline	5.14±2.27	5.31±2.23	0.739
15 days	3.47±1.05	3.84±0.94	0.106
Paired samples t test P-value	0.000	0.000	
Creatinine clearance (ml/min)			
Baseline	15.55±5.94	15.67±4.86	0.927
15 days	32.33±7.25	34.38±7.83	0.227
Paired samples t test P-value	0.000	0.000	
Urine output (ml/24 h)			
Baseline	446.88±231.44	381.52±210.67	0.190
15 days	942.41±313.35	841.47±300.78	0.989
Paired samples t test P-value	0.000	0.000	

Renal functions in responders in terlipressin plus albumin and norepinephrine plus albumin group were shown

in table. IV. The differences were statistically significant within the group for baseline and after 15 days, after applying the paired samples t test. P-value ≤0.05 considered as significant. (Table. IV).

Table 4: Renal functions in responders of both the groups

Variable	Terlipressin+ Albuman n=21	Norepineph-rine+ Albuman n=19	P-value
Serum creatinine (mg/day)			
Baseline	4.42±1.98	3.79±2.56	0.739
15 days	1.26±0.65	1.21±0.39	0.106
Paired samples t test P-value	0.000	0.000	
Creatinine clearance (ml/min)			
Baseline	14.07±8.26	15.81±6.18	0.927
15 days	66.14±12.62	68.05±8.02	0.227
Paired samples t test P-value	0.000	0.000	
Urine output (ml/24 h)			
Baseline	330.84±78.50	293.11±75.69	0.190
15 days	1148.04±196.95	1192.13±136.61	0.989
Paired samples t test P-value	0.000	0.000	

DISCUSSION

Assuming that terlipressin and norepinephrine are associated with better management of hepatorenal syndrome, but efficacy of both drugs is not known. Thus, in our study we compared outcomes after use of both drugs to fulfil the deficiency in literature regarding decision of treatment of HRS.

Our results reveals that norepinephrine in combination with albumin is as effective as terlipressin with albumin. A study was conducted by Singh et al[11] on comparison of terlipressin and norepinephrine with human albuman in treatment of HRS type 1 and reported that norepinephrine with albuman is more effective as compare to terlipressin. In this study HRS was recovered in was recovered in 39.1% of patients in terlipressin group and 43.4% in norepinephrine group. In anotherstudy Sharma et al[12] concluded that both terlipressin and norepinephrine are equally effective when used for the reversal of HRS type 1. But in some outcomes norepinephrine is more efficacious than terlipressin.

Alessandria et al[13] conducted a unblinded pilot study on comparison of terlipressin plus albuman and norepinephrine plus albuman. Treatment was continued for two weeks or till the time of reversal of HRS and observed a significant improvement in circulation and renal functions. Findings of previous studies and reversal of HRS type 1 after administration of vasoconstrictive drugs can be explained. Leung et al[14] explained this study status in his report, he also concluded that both drugs are equally effective when used for the adjustment of HRS type 1.

Another similar study was conducted by Nguyen-Tat et al[15] in 2019 and concluded that terlipressin is quite better for treatment of Type 1 HRS patients who are listed for transplantation and waiting for long time. But the sample size of his study was small, studies with larger sample size are required to justify this drug results. Badawy et al[16] completed a similar study in 2013 and observedthat norepinephrine and terlipressin are equally effective for management of HRS type 1. Kidney function and liver function both found improved in his trial.

Duvoux et al[17] concluded in his study that reversal of HRS type 1 in norepinephrine was 83% which was a large proportion as compare to any other study proportion of HRS results. Both HRS and renal functions are found improved. Ghosh et al[18] also completed a study in 2013 on combination of terlipressin with albuman with norepinephrine with albuman and observed more side effects in terlipressin group, most common adverse events were arrhythmias, abdominal cramps and cyanosis.

A randomized clinical was completed by Gluud et al[19] on terlipressin and other vasoconstrictors and concluded that terlipressin is much better than any other vasoconstrictor. Similarly in 2017 Goyal et al[20] observed that terlipressin is better management option than other vasoconstrictors for treatment of HRS type 1. Placebo with terlipressin was also observed but good and excellent results were obtained regarding terlipressin.

CONCLUSION

Results of our study reveals that norepinephrine in combination with albumin is as effective as terlipressin in combination with albumin when used for the management of hepatorenal syndrome (HRS) type 1. But easy availability and cheap rate of norepinephrine makes it a better option than terlipressin.

Limitations: Study was conducted on smaller sample size that limits the aspects of conclusion regarding efficacy of terlipressin and norepinephrine in treatment of HRS type I. The treatment was not blinded and hence any bias cannot be excluded.

Conflict of interest: Authors declare no conflict of interest.

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