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Original Article

Noradrenaline and Albumin for Type 1 Hepatorenal Syndrome: A Prospective Study from Eastern Nepal

Rabin Sharma*, Bickram Pradhan, Denis Peeyush, Manish Subedi and Sadhana Sah
Division of Gastroenterology, Department of Internal Medicine,BPKIHS, Dharan, Nepal
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Abstract

Background

Hepatorenal Syndrome (HRS) is a serious complication of liver cirrhosis with critically poor prognosis with treatment currently based on vasopressors. We aimed to study the safety and effects of Intravenous Noradrenaline in patients with Type 1 HRS and also to define factors predictive of a response.

Materials and Methods

It was a prospective observational study conducted in a tertiary care hospital in Eastern Nepal enrolling patients withType 1 HRSfrom 2014 to 2015. All patients received Noradrenaline (0.5-3 mg/hr, intravenously) and albumin (1 g/kg followed by 20–40 g/day). Primary outcome was improvement of renal function.

Results

60 Type 1 HRS patients were enrolled in the study -37 males (61.7%) and 23 females (38.3%), mean age 58.18±9.33 years. The therapy was well tolerated as only 6.7% of patients withdrew treatment. Reversal of HRS was observed in 38 patients (63.3%) with the mean duration of 6.39±1.33 days. Of the baseline variables, higher urine output, higher mean arterial pressure and lower serum creatininewere predictive of response. Multivariate analysis showed Mean arterial pressure to be an independent variable of response (adjusted odds ratio 0.588, 95% CI- 0.393-0.880, P>0.05). Finally mean arterial pressure had a negative correlation with serum creatinine and a positive correlation with Urine output.

Conclusion

Noradrenaline and albumin are safe and effective in improving renal function in patients with Type 1 HRS.There is a need for studies with larger sample size to correlate improvement in renal function with overall survival.

Key words: *Nepal, Noradrenaline, Type 1 Hepatorenal Syndrome*

Introduction

Cirrhosis is a worldwide problem that is associated with a substantial economic burden. Hepatorenal Syndrome (HRS) is a complication of decompensated liver cirrhosis carrying relatively poor prognosis. The disease is secondary to severe renal vasoconstriction as a result of changes in splanchnic and general circulations complicated by perturbations in systemic and renal vasoconstrictors and vasodilators [1]. International club of ascites has defined Type 1 HRS asa rapidly progressive renal failure with the

Corresponding Author: **Dr. Rabin Sharma, MD | E-mail: docrabinsharma@gmail.com*

rise in serum creatinine value to more than 2.5 mg/dl in less than 2 weeks[2]. Type 2 HRS presents with insidious onset refractory ascites with moderate and more stable impairment of renal function. The definition of acute kidney injury in cirrhosis is constantly evolving. The international club of ascites (ICA) organized a consensus development meeting in Dec 2012 and proposed a new definition of AKI in cirrhosis [3]. Currently the treatment of Type 1 HRS is based on vasopressors as a bridge to liver transplantation. Terlipressin (along with albumin) has been a widely studied vasopressor in the treatment of Type 1 HRS, the benefit of which has been supported by many randomized controlled trials and metaanalysis [4-14]. Similarly, other treatment options include octreotide, midodrine and noradrenaline (NA) along with albumin which have been studied in few trials. Terlipressin is available in developing countries like Nepal but is expensive and not easily available. Moreover, noradrenaline being cheap and easily available becomes the preferred treatment of choice, though the cost of albumin remains high. Published papers on the treatment of Type 1 HRS with noradrenaline in Nepal are virtually nonexistent. Our aim was to study the safety and effects of Intravenous Noradrenaline in patients with Type 1 Hepatorenal Syndrome (HRS) and also to define factors predictive of a response and to correlate hemodynamic changes to changes in renal function in Type 1 HRS.

Material and Methods

Design of the study

It was a prospective observational study in a tertiary center of eastern Nepal, enrolling all consecutive adult patients (age>18) who met the criteria of type 1 HRS from November 2014 to November2015. The study was conducted in Medical wards and Intensive care units (ICU) under division of Gastroenterology, Department of Internal medicine.

Patients

Sixty patients of type 1 HRS were enrolled in the study. Criteria for inclusion in the study were: decompensated cirrhosis with ascites and type 1 HRS. The diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic findings [15]. Decompensation was defined as the presence of ascites, variceal bleeding, encephalopathy or icterus [16]. Type 1 HRS was diagnosed by using the criteria of the International Ascites Club [2]. Exclusion criteria were congestive cardiac failure, respiratory failure, coronary disease, or peripheral artery disease. The study was approved by the Institutional Review Board and written informed consent was taken from the patients or their relatives.

Treatment and Interventions

On suspicion of Type 1 HRS, patients were enrolled in the study. The patients were either admitted for 15 days or asked to follow up after discharge on Day 15 of therapy. After enrollment patient's urine output and arterial blood pressure (by using a noninvasive technique) were measured every 4 hours. All patients received Human Albumin infusion (1g/kg/day) for 48 hours to rule out the existence of renal failure because of volume depletion. Albumin being expensive, all patients and relatives were appropriately counseled regarding the grave nature of the disease and the emphasis was made on the role of drugs like albumin to which they were willing to afford. We managed to procure poor patients funds to provide IV Albumin for patients who could not afford. Response to volume expansion was assessed after 48 hours. Patients who failed to achieve daily urine output more than 600 ml and /improvement in the serum creatinine level were considered to have Type 1 HRS.

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

These patients received a continuous infusion of NA at an initial dose of 0.5 mg/h, designed to achieve an increase in the MAP of at least 10 mmHg or an increase in 4-hour urine output to more than 200 ml. Upon failure of achieving these goals the NA infusion was increased every 4 hours in steps of 0.5 mg/hr up to the maximum dose of 3mg/hr. Efficacy was assessed on serum creatinine measured daily. A 30% decrease in serum creatinine being considered a positive response to NA.

NA was administered either until HRS reversal (serum creatinine below 1.5 mg/dl and or creatinine clearance >40 ml/min), or for a maximum of 15 days. NA dose was subsequently tapered to 0 over 3 days [17]. Patients also received Human Albumin infusion 20 g per day till the duration of the vasopressor therapy. Patients were excluded from the study if they developed any adverse effects secondary to the treatment (Noradrenaline or Albumin).

Statistical Analysis

Collected data was entered in MS Excel 2007 and converted to SPSS 11.5 version for statistical analysis. For descriptive statistics percentage, mean ± SD, Median (IQR) was calculated and also graphical and tabular presentations were made. For inferential statistics χ^2-test, paired t test and Pearson's correlation coefficient were applied to find out the significant difference between day wise reading and other related variables at 95% CI, where p=0.05. For multivariate analysis if variable was significant at <0.05 then that variable was considered for multivariate analysis. For multivariate analysis binary, logistic regression was applied to determine baseline patient characteristics that would be predictive of HRS reversal (defined as serum creatinine on treatment ≤1.5 mg/dl).

Results

Patient characteristics

60 Type 1 HRS patients were enrolled in the study -37 males (61.7%) and 23 females (38.3%), mean age 58.18±9.33 years. Alcohol was the most common cause of cirrhosis (86.7%). Precipitating factor for Type 1 HRS could not be identified in any of the subjects. The baseline characteristics are shown in table I.

Response to Noradrenaline and Albumin

Of the 60 patients, 38 patients (63.33%) responded to treatment (defined by serum creatinine <1.5 mg/dl) while 18 patients (30%) did not respond to treatment. The average number of days required for reversal of HRS (Patients who responded to treatment) was 6.39±1.33 days. Treatment was stopped in 4 patients (6.7%) due to side effects encountered. All of the treatment induced side effects were attributed to I.V. Noradrenaline. Of the 4 patients 3 patients experienced central chest pain which got relieved after the NA infusion was stopped. There was no any obvious electrocardiographic abnormality detected in these patients but the therapy was not reinitiated in these patients again. Similarly, one patient experienced shortness of breath during the therapy which was relieved after cessation of NA therapy. The treatment was not reinitiated in the patient again. All the patients tolerated Human Albumin without experiencing any known adverse reaction to the compound. Four patients (6.7%) died during the course of treatment probably due to the natural course of the disease. They were also considered as non-responders and included in that group for the purpose of simplicity.

Factors predictive of response

Of the baseline variables, higher urine output (responders780.26±316.40 ml/24 hours vs non-responders 536.6±313.27 ml/24 hours, p value<0.05), higher mean arterial pressure (responders71.84±2.42 mmHg vs non-responders 61.44±5.80

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

mmHg, p= <.001) and lower serum creatinine mg/dl (responders3.21±.57 mg/dl vs non responders4.19±.70 mg/dl, p<.001) were predictive of response. Multivariate analysis showed Mean arterial pressure to be an independent variable of response (adjusted odds ratio 0.588, 95% CI- 0.393-0.880, P>0.05). The findings of multivariate analysis are shown in table II. We also assessed the changes in the clinical and laboratory parameters in responders and non responders. The decrease in serum creatinine and increase in mean arterial pressure was significant in both the groups. The findings are shown in table III.

Correlation of hemodynamic changes to changes in renal function in Type 1 HRS.

We went further to analyze the various hemodynamic alterations achieved by therapy with noradrenaline and the parallel changes in the renal function. We selected the values of mean arterial pressure (mmHg), serum creatinine (mg/dl) and urine output (ml/24h) at day0, day 7 and day 15 and performed a correlation study between the parameters (MAP vs Creatinine and MAP vs Urine Output). With the higher values of MAP, corresponding serum creatinine valueswere significantly lower on Day 0, Day 7 and Day 15 (r= -0.675,p= <0.001, r=-0.874, p=<0.001 and r=-0.888, p=<0.001, respectively). Mean arterial pressure had a negative correlation with serum creatinine. Similarly with the higher values ofMAP, corresponding urine output values were significantly higher on Day 0, Day 7 and Day 15 (r= -0.529,p= <0.001,r=0.818,p=<0.001 and r=0.772,p=<0.001, respectively). Mean arterial pressure had a positive correlation with urine output. The findings of the correlationsbetween MAP, serum creatinine and urine output on day 0 and day 15 are depicted in fig 1 and fig 2, respectively.

Tables

Table I. Demographic, Clinical and Laboratory data of All Patients with Cirrhosis and Type 1 HRS at the Time of Inclusion in the Study

Demographic Characteristics	All (n=60)
Age (Years) (Mean±SD)	58.18±9.33
Gender Male Female	37 (61.7%) 23 (38.3%)
CAUSE OF CIRRHOSIS Alcohol Hepatitis B Hepatitis C Others/Cryptogenic	 52 (86.7%) 4 (6.7%) 0 (0%) 4 (6.7%)
SBP	7(11.7%)
Biochemical Investigations	
Bilirubin (mg/dl) (Mean±SD)	2.52±.40
Albumin (g/dl) (Mean±SD)	2.8±.07
CTP A B C	0 (0%) 6(10%) 54(90%)
MELD (Mean±SD)	32.7±5.283
Prothrombin Time (Secs) (Mean±SD)	29.3±7.41
Sodium (mmol/L) (Mean±SD)	124.75±6.75
Creatinine (mg/dl)(Mean±SD)	3.6±0.80
Urine output (ml/24 hrs)(Mean±SD)	680.33±331
MAP (mmHg) (Mean±SD)	67.92±6.38

NOTE. Values are mean±SD.
CTP-Child Turcotte Pugh Score;MELD- Model for end stage liver disease;MAP-Mean arterial pressure.

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

Table II. Multivariate logistic regression analysis of factors affecting response to vasopressor therapy (Among those P value <0.05 in univariate analysis)

Variables	Adjusted Odds Ratio	95% C.I.forEXP(B)		P value
		Lower	Upper	
Age	1.143	0.961	1.358	0.13
Gender	0.401	0.019	8.434	0.56
Creatinine	2.896	0.57	14.716	0.20
Urine Output	1.000	0.997	1.004	0.89
Prothrombin Time	1.068	0.669	1.705	0.78
Albumin	0.000	0.000	761.369	0.25
MAP *	0.588	0.393	0.880	0.010

NOTE. None of the parameters except MAP were predictive of response.
* p<0.05
MAP- Mean arterial pressure

Table III. Change in parameters with therapy in the Responder and Non Responder group.

Parameter	Responders n=38		P value (Day 0 vs Day 15)	Non-Responders n=18		P value (Day 0 vs Day 15)
	Day 0	Day 15		Day 0	Day 15	
Creatinine * (mg/dl)	3.371 ±0.48	1.18 ±.13	<0.001	4.460 ±.63	2.77 ±.46	<0.001
Albumin (g/dl)	2.821 ±0.08	2.77 ±.06	.003	2.78 ±.079	2.800 ±.08	.443
Biirubin (mg/dl)	2.47 ±0.42	2.46 ±.42	.183	2.68 ±.28	2.66 ±.28	.168
Sodium (mmol/l)	126.11 ±6.21	126.21 ±5.47	0.839	124.10 ±4.98	125.50 ±4.53	0.338
PT (secs)	30.58 ±6.94	30.63 ±6.96	0.661	26.70 ±8.00	26.90 ±7.92	0.343
MAP * (mmHg)	71.84 ±2.42	86.68 ±2.24	<0.001	59.00 ±4.16	64.30 ±4.16	<0.001
Urine output (ml/24 hrs)	741.58 ±311.86	1458.95 ±318.64	<0.001	365.00 ±181.06	442.00 ±137.99	.052

NOTE. Values are mean ± SD.

Discussion

The results of this prospective observational study showed that noradrenaline with albumin are effective and safe in the treatment of Type 1 HRS. Overall reversal of type 1 HRS was achieved in 63.33% of patients. The percentage of responders to treatment in our study is lesser compared to a similar study conducted by Duvoux et al. He enrolled 12 patients with type 1 HRS for therapy with noradrenalin and albumin. Of the 12 patients, 10(83%) patients responded to the treatment [17]. The therapy was well tolerated as only 4 patients (6.7%) withdrew from treatment. In a study done by Ghosh et al, one patient out of 23 experienced atypical chest pain during the treatment with normal cardiac investigations. No adverse effects related to the intravenous albumin infusion were seen [18]. Noradrenalin can be given safely for the treatment of Type 1 HRS though the common side effects of the drug should be monitored during the treatment, mainly chest pain and shortness of breath.

Univariate analysis showed lower creatinine, higher MAP and higher urine output at baseline were predictive of response. However on multivariate analysis only mean arterial pressure was the only independent predictor of response in our study. Studies in the past have also attempted to define the factors predictive of response. In the study conducted by Virendra Singh et al, 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 [19].

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

Figures

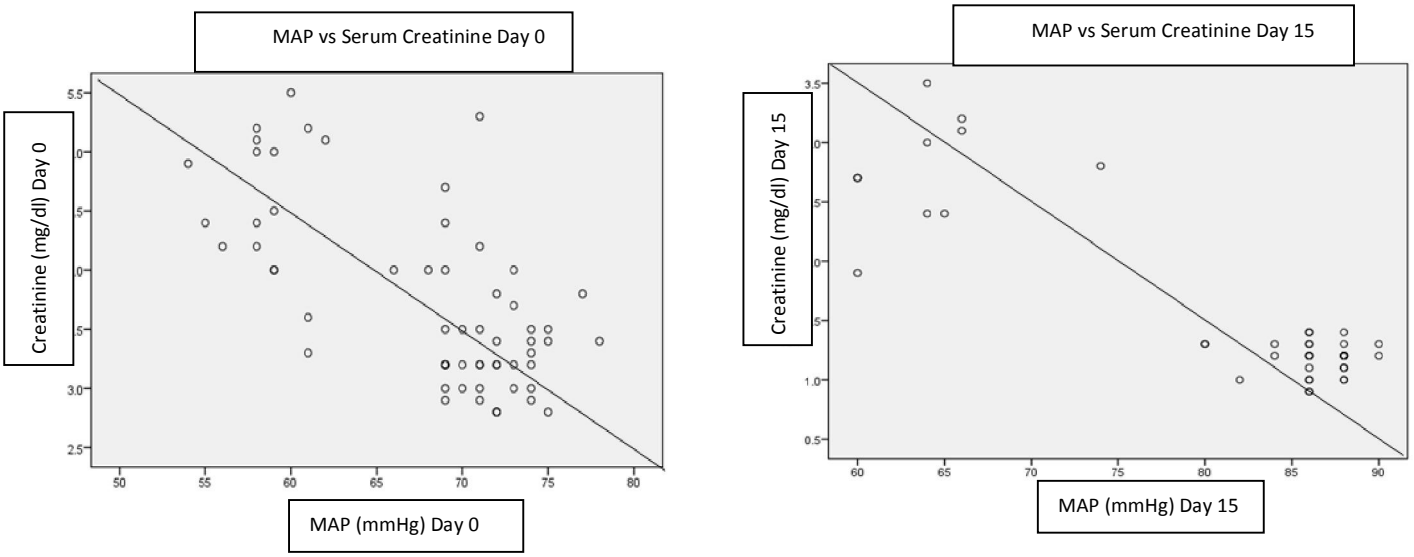

Fig.1. Changes in hemodynamics with renal function- MAP vs Serum Creatinine.
MAP-Mean arterial pressure

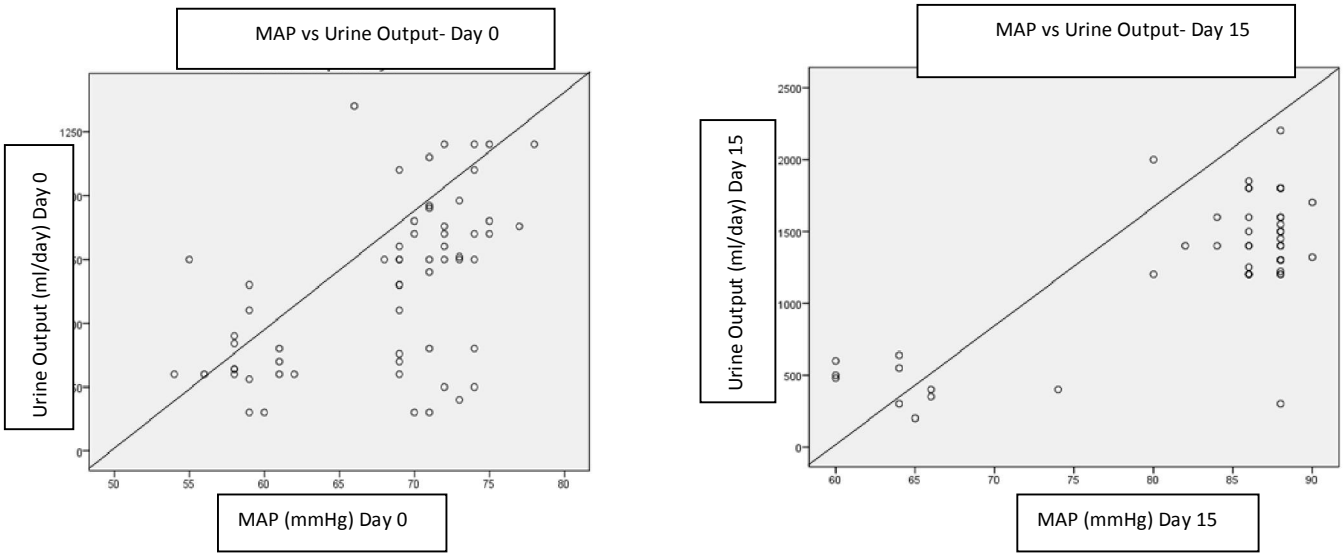

Fig.2. Changes in hemodynamics with renal function- MAP vs Urine Output.
MAP-Mean arterial pressure

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

In another study conducted by Marta Martin–Llahi et al the factors predictive of response to therapy were etiology of cirrhosis, baseline serum bilirubin, leukocyte count, serum creatinine and urine volume, and treatment assignment in both forms of hepatorenal syndrome. Upon conducting a multivariate analysis, the independent factors were baseline urine volume, serum creatinine and leukocyte count, and treatment assignment [20].

Use of vasoconstrictors hasbeen associated with increasing effective arterial volumewhich can be reflected by the various positive biochemical changes it produces during the therapy. In our study in the patients who responded to treatment serum creatinine decreased with therapy significantly. There was a positive response in MAP which significantly increased during the treatment along with the urine output. Serum creatinine decreased significantly with therapy in the non responder group too. But this was not able to achieve the primary end point (of serum creatinine <1.5 mg/dl).

Similarly even though the MAP increased significantly in the non responder group too, it was not enough to achieve the reversal of HRS. In the study conducted by Duvoux et al NA initiation was followed rapidly by a significant improvement in urine output, urinary sodium excretion, serum creatinine, creatinine clearance and MAP [17]. Since both noradrenaline and albumin were used as a therapy in all the patients in our study it would be difficult to differentiate the individual contribution of improvement in hemodynamic and laboratory parameters. A well designed randomized controlled trial comparing noradrenaline alone with noradrenaline and albumin in treatment of type 1 HRS is necessary. This becomes more important in developing countries if we could justify no added benefit of albumin over noradrenaline so that we could use only the later and significantly reduce the cost associated with albumin.

An outstanding observation made in this study was the strong association of improved hemodynamics with recovery of kidney function in Type 1 HRS. We correlated the Day 0, Day 7 and Day 15 values of MAP with serum creatinine and Urine output to see if there is any significant association. An increase in Mean Arterial Pressure (MAP) was strongly associated with the decrease in serum creatinine level and increase in urine output. Velez JC et al conducted a pooled analysis of clinical trials to explore across all tested vasoconstrictors to see the changes in hemodynamics and renal function with Vasopressor therapy. Velez JCQ et al found that an increase in MAP is positively associated with improved renal function and they considered a goal directed treatment of HRS [21].

There were limitations in our study. Since hemodynamic assessment was an important aspect of this present study we could only manage to monitor patients MAP (Mean Arterial Pressure). A proper assessment of the patients' volume status by central venous pressure measurement would have given us a better insight and titrate the dose of albumin accordingly. Similarly changes in systemic circulation (Cardiac output, Systemic vascular resistance) and Renin- aldosterone system (plasma active renin, aldosterone level) could not be monitored in this study due to technical reasons.

Another major limitation to this study was that it was a prospective observational study. We evaluated the patients at the end of the therapy or at day 15. Data regarding long term survival of these patients post therapy could not be analyzed given the design of the study. The probability of whether the patients who responded to therapy have a better long term survival as compared to the non

*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com

responders would further justify the role of Noradrenaline (Vasopressors) in the acute management of Type 1 HRS.

Current study shows that noradrenaline and albumin can achieve reversal of kidney injury in Type 1 HRS with a relatively excellent safety profile. Singh et al suggested that noradrenalin is as safe and effective as Terlipressin, but less expensive [19]. Noradrenaline is a potential cheap and safe option for Type 1 HRS in a developing nation like Nepal where poverty and burden of the disease is difficult to bear.

Conclusion

In conclusion noradrenaline is effective in reversal of kidney injury in Type 1 HRS (63% in our study). Albumin appears to be contributing in improvement of hemodynamics and renal function. Future studies with long term follow up are necessary to assess if reversal of HRS is predictive of survival.

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Corresponding Author: **Dr. Rabin Sharma, MD | E-mail: docrabinsharma@gmail.com*

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*Corresponding Author: **Dr. Rabin Sharma, MD** | E-mail: docrabinsharma@gmail.com