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Hepatorenal Syndrome in Cirrhosis of Liver at Tertiary Care Centre of Nepal

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ABSTRACT

Introduction: Hepatorenal syndrome (HRS) is the development of renal failure in patients with severe liver disease. Acute renal dysfunction including HRS is commonly occurs in hospitalized patients with cirrhosis. It is observed that morbidity and mortality remain high once the syndrome is established. This syndrome is usually managed with different vasoconstrictors and albumin with variable outcome but ultimate treatment is the liver transplantation.

Methodology: This was a hospital based descriptive study carried out in Liver unit of Bir hospital. The cases were collected from (April, 2015 to March, 2016), admitted in Liver unit, Bir Hospital, Kathmandu, Nepal. One hundred and thirty eight cases were randomly selected from 450 patients admitted in the hospital. Patients of HRS were selected and treated with one of the treatment regime from 1. Albumin and Nor adrenaline group 2. Albumin and Dopamine group 3. Dopamine only 4. Terlipressin and Albumin groups. Patients with No HRS group were treated according to standard protocol of the institute.

Results: Among 138 patients, 107(67%) of them were male and 31(23%) were female. The mean age of study population was 49.99 years. Incidence of HRS was 24(17%). On treatment of HRS, 10(42%) were treated with Dopamine/Albumin, 3(13%) were treated with Nor adrenaline/Albumin, 7(29%) were treated with Terlipressin / Albumin and 4(17%) were treated with Dopamine. Twelve(50%) patients were complete responder, 9(37%) were non responder and 3(13%) were partial responder. Terlipressin had a better outcome. Mortality of patient was 31(22%) out of 138 in study populations, 6(25%) out of 24 patients in HRS and 25(22%) out of 114 in no HRS group (p=0.74).

Conclusion: Our study has higher incidence of HRS. Treatment with vasopressors like Nor Adrenaline or Terlipressin with Albumin were very effective regimes to revert HRS in cirrhosis. There was no significant difference in mortality between HRS and to no HRS group.

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Introduction

Cirrhosis is a diffuse process with fibrosis and nodule formation. It is the end result of the fibrogenesis that occurs with chronic liver injury. It is a histopathologically defined entity that is associated with a spectrum of characteristic clinical manifestations like Portal hypertension, Hypersplenism, Ascites, Spontaneous bacterial peritonitis, Hepatorenal syndrome type 1 and 2, Hepatic encephalopathy [1]. Hepatorenal syndrome (HRS) is the development of renal failure in patients with severe liver disease

in the absence of any identifiable renal pathology which is a functional rather than structural disturbance in renal function [2]. Affected patients usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, or (less often) metastatic tumors, but can also have fulminant hepatic failure from any cause [3]. Common causes of kidney injury are: sepsis or spontaneous bacterial peritonitis (46%), Prerenal acute kidney injury (32%), Hepatorenal syndrome (13%), Parenchymal renal disease such as glomerulonephritis (9%) [4].

Acute renal dysfunction occurs in 15% to 25% of hospitalized patients with cirrhosis [5]. Arterial vasodilatation in the splanchnic

circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in cirrhosis [6]. The annual frequency of HRS in cirrhotic patients with ascites is roughly 8% and, in some reports, as high as 40% [1]. Hepatorenal syndrome is a functional disorder, and therefore diagnostic laboratory and imaging studies are not available. The diagnosis of HRS requires a high index of clinical suspicion and exclusion of other potential causes of kidney injury. The diagnostic criteria for HRS as defined by the International Ascites Club Consensus Workshop in 2007 is usually used for diagnosis [7]. The patient who develops HRS has high rate of mortality and morbidity so early diagnosis and treatment is the key factor for better outcome. In treatment of HRS commonly used drugs are Terlipressin, Nor adrenaline and octreotide with albumin. Terlipressin, has also been examined as a treatment for hepatorenal syndrome in several randomized trials and, when available, is preferred therapy in patients who cannot receive norepinephrine (typically those not in an intensive care setting) [8]. The best data come from a trial that randomly assigned 49 patients to terlipressin (starting at 3 mg infused over 24 hours, titrated as needed to 12 mg over 24 hours) or midodrine plus octreotide (midodrine starting orally at 7.5 mg thrice daily and octreotide at 100 mcg subcutaneously thrice daily, increased as needed to 12.5 mg thrice daily and 200 mcg thrice daily, respectively); all patients also received intravenous albumin (1g/kg on day 1, and then 20 to 40 g/day thereafter). Both regime had better outcome [9]. Although the efficacy of terlipressin and norepinephrine were similar, adverse events were more common with terlipressin. In addition, the cost of terlipressin therapy is more than three times the cost of norepinephrine therapy [10]. Volume replacement, albumin infusion, dopamine, prostaglandins, ascites re-infusion, peritoneovenous and portocaval shunting have usually proved to be ineffective though dramatic recoveries from hepatorenal syndrome have also been reported [11]. Among the complications, ascites with HRS is one of the common complications, having poor outcome, with significant recurrence, the study of incidence, predictors and treatment outcome of HRS in cirrhosis should be done, still the limitation of resources is common problem in developing country like Nepal. Since there are a numbers of treatment regimes for HRS, one aim of the study was to determine the most effective and economical regime in our part. Albumin is expensive and may not afford by poor people. This study was focused on patients who were treated with nor adrenaline and albumin, albumin and dopamine, dopamine only or treated with any other alternate regime like terlipressin, midodrine. Since albumin is expensive and nor adrenaline needed ICU support, so we wanted to study the different regime which could be cost effective, easily available and more effective for treatment of HRS

Method

This study was a hospital based descriptive study conducted in the Department of Medicine, Liver unit, Bir Hospital, Nepal. One hundred thirty eight patients who fulfilled the inclusion and exclusion criteria attending the Hospital were chosen for the study. The study was conducted from April, 2015 to March, 2016. Patients of HRS were selected and treated with one of the treatment regime from 1. Albumin and Nor adrenaline group 2. Albumin and Dopamine group 3. Dopamine only and 4. Terlipressin and Albumin groups. Patients were selected in different groups after detail discussion regarding the nature of disease, its severity, types of treatment, total cost, affordability and its outcome with the patient and patient party. Patients with No HRS group were treated according to standard protocol of the institute.

Inclusion Criteria

All cases of cirrhosis of liver. For HRS, criteria's fulfilling for diagnosis of HRS [8].

Exclusion Criteria

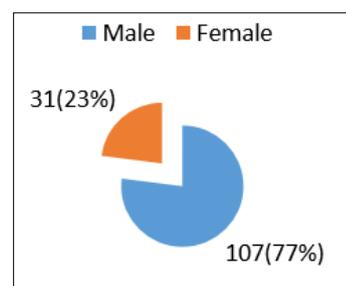
- A. Non cirrhotic cases
- B. All patients who refused to give consent
- C. For HRS, not fulfilling criteria

Calculation of Sample Size

The Sample was calculated with formula: $N = (Za)^2 (P) (Q) / d^2$, Where, N=required sample size, Za=Variate corresponding to desired reliability level (1.96 for 95% reliability), P=Estimated proportion in the population (10% for this study), Q=100-P (if P is in %) and d=Maximum tolerable error (5%) $N = 1.96^2 * 10 * 90 / 5^2 = 138$.

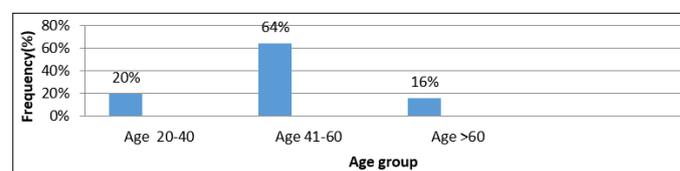
Result

During the study period of one year, a total of 138 participants were included in the study. The total numbers of male participants were 107(77%) and females were 31(23%).



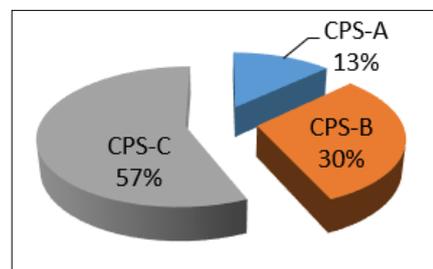
Pie Chart Showing Sex Wise Distribution of Study Population

The mean age of HRS group was 49.33 year and no HRS group was 50.02 (p=0.71). When the study population was subdivided according to various age groups, the maximum numbers of participants were in the age group of 41 to 60 years (88/64%). The least numbers of participants were in the age group above 60 years (22/16%). The age group between 21-40 was 28/20%.



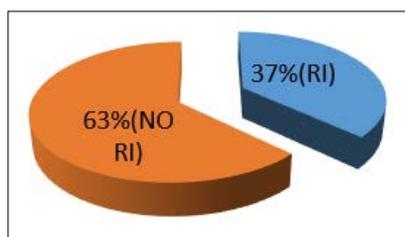
Bar Diagram showing various age Groups of the Study Population

We analyzed the severity of cirrhosis and classified the study population according to CPS score. Among them, CPS A-18(13%), CPS B-42(30%) and CPS C-78(57%) were there. Patients with CPS C were predominant in the study.



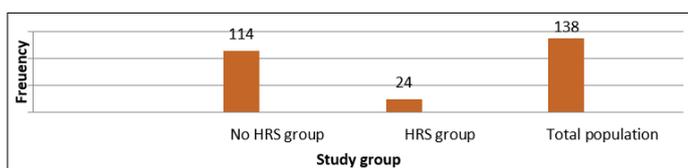
Pie Chart Showing CPS Status in Study Population

On Analysis of Renal Impairment, in our Study among 138 Patient, 51(37%) has Renal Impairment.



Pie Chart Showing Renal Impairment

Among the study population, we calculated the patients having HRS and no HRS. 24(17%) has HRS among the study population.



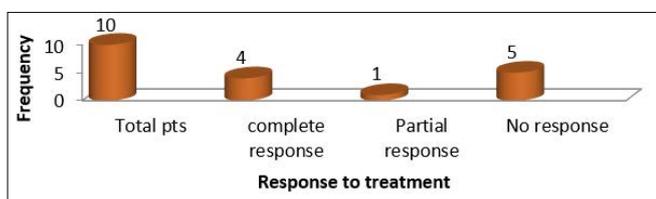
Bar Diagram Comparing Different Study Population

The study group analyzed the incidence of type I and type II HRS. Among 24 patients of HRS, 21 were type I and 3 were type II.



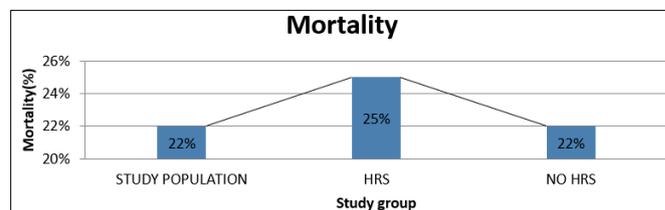
Pie Chart Comparing Types of HRS

On analysis of individual treatment regime, In Dopamine/Albumin group, 4(33%) patient were completely responsive, 1(8%) patient was partially responsive and 5(42%) patients are non-responsive to treatment.



Bar Diagram Representing Average Hospital Stay

On analysis of mortality, mortality of patient was 31(22%) out of 138 in study populations. Out of them, patient of HRS has mortality of 6(25%) out of 24 patients and 25(22%) out of 114 of no HRS group (p=74).



Bar Diagram Representing Mortality in Different Study Population

Discussion

On analysis of demographic output, during the study period of one year, a total of 138 participants were included in the study. The total number of male participants were 107(77%) and females were 31(23%) with male predominance. Male dominance may be due to high prevalence of the disease among males and easy approach of male in health centre. Similar result was there in a cross-sectional study done from July 2001 to March 2002 at Civil Hospital, Karachi where male were 61.7% and female were 38.3% (M:F=2.1:1) [12]. Regarding age wise distribution in the study population, the mean age of HRS group was 49.33 year and no HRS group was 50.02 with (p=0.71). When the study

population was subdivided according to various age groups, the maximum numbers of participants were in the age group of 41 to 60 years (88/64%). The least numbers of participants were in the age group above 60 years (22/16%). The age group between 21-40 was 28/20%. It was an interesting finding in our study, majority of patients were in age group of 41-60 yrs. It may be due to habit of early starting of drinking alcohol or due to genetic association. Productive age group was mostly affected which is a worse scenario for the development of a country. Similar result was seen in a study conducted by Heidemann et al. in 119 patients having average age of 56.50 yrs with HRS with cirrhosis [13]. We analyzed our study population according to CPS. Among them, CPS A-18(13%), CPS B-42(30%) and CPS C-78(57%) were there. Choi YJ et al. has done a study based on the medical records analysis of cirrhotic patients who were admitted to Konkuk University Hospital between 2006 and 2010 [14]. Six hundred forty three patients were admitted, of whom 190 (29.5%), 273 (42.5%), and 180 (28.0%) were Child-Pugh class A, B, and C, respectively. The higher number of our patients attended in hospital at advanced stage. It may be due to low economic status, low awareness regarding CLD and its clinical manifestations and use of complementary and alternative medicines which precipitates decompensation.

The renal impairment is common in cirrhotic patient admitted to the hospital. In our study among 138 patient, 51(37%) have renal impairment. Similar to our study, a descriptive, analytical study done by Qureshi MO et al in Shifa International Hospital, Islamabad, Pakistan, from May 2011 to March 2013 in a total of 523 patients with end stage liver disease. According to result, out of 523 patients, 261 (49.9%) had RF [15]. Patients who were enrolled in the study with the diagnosis of liver cirrhosis with various aetiologies, among 138 of them 24(17%) has HRS. The annual frequency of HRS in cirrhotic patients with ascites is roughly 8% and, in some reports, as high as 40% [5]. Still our incidence was in upper limit. It may be due to difference in sample size, economic status, awareness toward health and life style of the people. Our patients were presented in the hospital in advanced stage. Most of the patients in our study were in CPS C which was itself predictor of advanced cirrhosis. Male and female ratio looks in proportion (m: f=19:5) which is variable in different studies. Among them HRS I was 88% which was higher than the result of a study by Schepke M et al. which was 45.5% [16]. Such a high rate may be due to low survival after development of HRS in advanced cirrhosis.

On treatment analysis of HRS, 10(42%) was treated with Dopamine/Albumin, 3(13%) was treated with Noradrenalin (NA) /Albumin, 7(29%) was treated with Terlipressin /Albumin and 4(17%) was treated with Dopamine. Number of patients treated with Dopamine and Albumin was higher because of easy availability of albumin and dopamine. This regime can be used safely in general ward too. It is relatively safe in old age and can be used in cardiac patient. Terlipressin was not easily available when we were started our study. In the midway it was available and we treated 7 patients with it. It is little expensive having few side effects. Few patients did not tolerate this medicine. We studied 3 patients who was treated with NA/Albumin. This regime needed ICU, so most of the patients were not able to afford ICU and it was not easily available too. So the few patients were treated with this regime. In our study, 4 patients were treated with Dopamine which was not so effective therapy for treatment of HRS. Still we had used it because these patients were not able offered to other alternate treatment.

Among the treated patient, 12(50%) patient were complete responder, 9(37%) were non responder and 3(13%) were partial responder. Success rate of individual regime was analysed. Among them, Terlipressin/Albumin was most effective. Total 7 patients were treated with Terlipressin and Albumin. Among them, 6(86%) were completely responsive and 1(14%) was partially responsive. This regime looks very effective in our study. Still few patient developed abdominal pain and loose motion which decreased after reduction of dose. Average duration of treatment was 5 days. Similarly, Patients who were treated with Nor-adrenaline and Albumin, 2(67%) patients completely responded to treatment and 1(33%) patient did not responded. This regime also looked effective in HRS but the sample size was small. Complication was not noted in any of patient. Mean duration of treatment was 4 days. We have given treatment till the RFT became normal. An impressive result we got from treatment done with Albumin and Dopamine. In Dopamine/Albumin group, 4(33%) patient were completely responsive, 5(42%) patients are non-responsive and 1(8%) patient was partially responsive to treatment. The number of responders and partial responders were more than other studies. The complications were minimal and mean duration of treatment was 7 days who were responded to treatment. We advised for further study to evaluate the effectiveness of Albumin and Dopamine in treatment of HRS. Similarly, we treated 4 patients with Dopamine regime. Out of them 3(75%) were non responder and 1(25%) was partial responder. The mean duration of treatment was 5 day. There were no significant complications. This regime did not look effective in treatment of HRS still it increased urine output. So we did not advice to treat HRS patients with this regime. Range of treatment was 3-10 days. Among the patients who did not responded to the treatment, 2 cases under gone peritoneal dialysis and 1 case under gone haemodialysis. The renal impairment improved for few days and again deteriorate. So we did not advice for dialysis that are not responded to standard treatment of HRS. Similar to our study, a study was done by Licata A et al [17]. Regarding the clinical course and prognostic factors of hepatorenal syndrome. They have treated 28 patients (84.8%) with terlipressin plus albumin, 2 patients (6.1%) with dopamine and albumin, and 3 patients (9.1%) with albumin alone. The median duration of therapy was 7 days. At the end of treatment, a complete response was obtained in 3 cases (9.1%), one with type-1 and two with type-2 HRS, and partial response was obtained in 7 patients (21.2%), 4 with type-1 and 3 with type-2 HRS. The result of this study had shown that either Terlipressin or Dopamine with albumin were much effective. Our success rate was higher than them. Hiremanth SB, Kamdod MA have done a study in 89 patients. This study concluded that use of IVFs may be associated with better short-term survival benefits and favour HRS] reversal [18]. The positive response might be due to pre renal cause of ARF in that study where IVF worked. We analysed the recurrence rate of HRS. Out of 12 patient who completely responded to treatment, 2(13%) has recurrence of HRS. It was similar to a study done by Piano et al, the recurrence of type 1 hepatorenal syndrome has been described in up to 20% of responders to terlipressin and albumin after the discontinuation of the treatment [19]. Mortality of patient was 31(22%) out of 138 in study populations. Out of them, patient of HRS has mortality of 6(25%) out of 24 patients and 25(22%) out of 114 of no HRS group (p=0.74). Mortality of HRS group was slightly higher than no HRS group. Still the p value was not statistically significant. In a study, mortality was compared. Mortality was significantly higher in the patients with RF, when compared to the patients without RF (31% vs. 4.5%) [20].

Limitations

The limitation of the study was of short duration and the numbers of cases were small.

Conclusion

Our study has shown that the incidence of HRS is relatively high in our part of the world. The medical treatment with vasopressors like Nor-adrenaline, Terlipressin and dopamine with albumin were effective to revert renal impairment in cirrhosis with HRS.

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