Original Article

Clinical Efficacy of Mannitol Infusion in Chronic Liver Disease Patients Presenting with Hepatic Encephalopathy

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ABSTRACT

Objective: To assess the clinical efficacy of mannitol infusion in chronic liver disease patients presenting with hepatic encephalopathy.

Study Design: A randomized control trial study

Place and Duration of Study: This study was conducted at the Department of medicine Shalamar hospital, Lahore from January 2022 to January 2023.

Methods: In this randomized control trial 95 patients were selected from the male and female medical wards of Shalamar Hospital. A random assignment was made to place each patient in one of the two groups. Group B followed a regular treatment plan, whereas Group A added mannitol to their usual regimen. Following that, patients underwent daily evaluations, and the number of days they spent in the hospital as well as any improvements in their symptoms and overall health were noted. Serum electrolytes in groups A and B were also tested on days 1 and 3. SPSS 17 was used to arrange and analyze the data.

Results: Results indicated that 40 patients (88.9%) improved and were discharged, whereas 5 patients (11.1%) passed away while receiving therapy in group A. In comparison, among group B, 45 patients (90%) made improvements; nevertheless, 5 patients (10%) passed away during treatment. Mean Na^+ concentration in Group A on day 1 of treatment was 137.31mmol/L and on day 3 it was 135.42mmol/L whereas mean K^+ concentration in group A on day 1 was 4.0mmol/L and on day 3 it was 3.8.mmol/L. Mean Na^+ concentration in Group B on day 1 of treatment was 137.6mmol/L and on day 3 it was 136.0mmol/L whereas mean K^+ concentration in group B on day 1 was 4.1mmol/L and on day 3 it was 3.9mmol/L.

Conclusion: Our research revealed that although the use of Mannitol did not result in any changes to the overall course of the disease, it did improve the quality of life for patients and reduced the stay in hospital.

Key Words: Liver cirrhosis, Hepatic encephalopathy, Mannitol, Chronic liver disease.

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INTRODUCTION

Hepatic fibrosis and liver cirrhosis had been a big issue for humanity since ancient times. Early Egyptians had noticed the link between beer and ascites. Recently a large number of mummies were discovered with their Cirrhotic livers stored in special jars near their bodies. Man is still on war with chronic liver disease and its consequences.

Previously chronic viral hepatitis infections and alcohol hepatitis were two most common reasons for the development of chronic liver disease. But recently another front has been opened in developed countries in the shape of high prevalence of metabolic syndrome and obesity leading to Non-Alcoholic Fatty Liver Disease (NAFLD) culminating in liver cirrhosis. This shows that in future the burden of chronic liver disease and its complications is going to rise very high.[1]

In Pakistan about 7.6% population is suffering from chronic viral hepatitis. Among those suffering from viral hepatitis about 70% are HCV infection and 30% HBV infection .[2, 3] Alcoholic hepatitis and autoimmune hepatitis are among other major contributors of chronic liver disease in Pakistan.[1] Chronic liver disease leads to certain complications. Broadly these complications can be classified in three main groups. A) Decreased liver synthetic functions which causes coagulation disturbances, B) Portal hypertension which causes acsites and variceal bleeding, C) decreased detoxifing abilities of liver which causes Hepatic Encepthalopathy. 70% of cirrhotic patients have some signs of hepatic encephalopathy while 30-45% cirrhotic have overt encephalopathy. In Pakistan hepatic encephalopathy is

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the most common cause of hospitalization in patients of liver cirrhosis. Hepatic encephalopathy is defined as a neuropsychiatric syndrome characterized by changes in personality, intellect and consciousness. Raised intracranial pressure was noticed in patients of hepatic encephlaopathy by some authors in university of Nebraska in late 1990s. Cerebral Edema is thought to be caused by accumulation of neurotoxic substances in the brain i.e. serum ammonia, short chain fatty acids and Gamma Aminobutyric Acid (GABA) and others.[4, 5] Conventional treatment of hepatic encephalopathy includes suppression of production of neurotoxins by bacteria in bowel. Lactulose, gut cleansing antibiotics and L-Ornithine L-Aspartate are the most commonly used remedies to treat hepatic encephalopathy.[6] Use of Mannitol has been seen beneficial in treating hepatic encephalopathy in patients with Acute Fulminant Hepatic Failure in some trials.[7] However role of Mannitol in hepatic encephalopathy caused by chronic liver cirrhosis is not clear. This research was done to determine the clinical efficacy of mannitol infusion in chronic liver disease patients presenting with hepatic encephalopathy.

METHODS

In this randomized control trial 95 patients were selected from the male and female medical wards of Shalamar Hospital using non probability purposive sampling techniques. The male and female patients above 18 years of age, presenting in Shalamar Hospital with a diagnosis of Hepatic Encephalopathy caused by chronic liver disease were included in this study.

Patients with diagnosis of renal failure, hepato renal syndrome, gastrointestinal bleeding, acute on chronic hepatic failure and electrolyte imbalances were excluded from the study. One patient developed hypersensitivity reaction to mannitol and was also excluded from the study.

The data for this research was collected using a Performa. The Performa was designed using Child-Pugh score for the severity of chronic liver disease and West-Heaven classification system was used to classify the severity of hepatic encephalopathy. The patient presenting with the symptoms of hepatic encephalopathy were evaluated for the grade of encephalopathy and Child class on presentation using both clinical and defined lab criteria. Next, a random assignment was made to place each patient in one of the two groups. Group B followed a regular treatment plan, whereas Group A added mannitol to their usual regimen. Following that, patients underwent daily evaluations, and the number of days they spent in the hospital as well as any improvements in their symptoms and overall health were noted. In order to detect and compare any electrolyte imbalance brought on by our therapy, serum electrolytes in groups A and B were also tested on days 1 and 3.

Data analysis procedure: SPSS 17 was used to arrange and analyze the data. Demographic details of sample were analyzed using descriptive statistics. Statistical analysis of the data was done by Correlation testing and Independent sample t-test.

RESULTS

Totally, 95 patients were enrolled in this research after taking informed consent. Using random assignment, 45 patients were placed in group A, which received conventional treatment plus an intravenous Mannitol infusion of 100 ml. Group B, on the other hand, consisted of 50 individuals who did not get mannitol infusion. Amongst group A 12 patients (26.7%) were of child class B whereas 33 patients (73.3%) were of child class C. The mean stay in hospital was 5.17 days of these patients. Results indicated that 40 patients (88.9%) improved and were discharged, whereas 5 patients (11.1%) passed away while receiving therapy. In comparison, among group B 7 patients (14%) were of child class B and 43 patients (86%) were of child class C. Mean hospital stay of this group was 7.2 days. Throughout their hospital stay, 45 patients (90%) made improvements; nevertheless, 5 patients (10%) passed away during treatment. (Table 1) Mean Na^+ concentration in Group A on day 1 of treatment was 137.31mmol/L and on day 3 it was 135.42 mmol/L whereas mean K^+ concentration in group A on day 1 was 4.0mmol/L and on day 3 it was 3.8.mmol/L. Serum Na+ and K+ levels in group A differed by 1.89 mmol/L and 0.2 mmol/L, respectively, on day one and day three. Mean Na^+ concentration in Group B on day 1 of treatment was 137.6mmol/L and on day 3 it was 136.0mmol/L whereas mean K^+ concentration in group B on day 1 was 4.1mmol/L and on day 3 it was 3.9mmol/L. Serum Na+ and K+ levels in group B differed by 1.60 mmol/L and 0.2 mmol/L, respectively, on day one and day three. (Table 2)

Table No. 1: Comparison of group A and group B based on child class, improvement and mortality

Parameter		Group A	Group B
child class	Child Class B	12 (26.7%)	7 (14%)
	Child Class C	33 (73.3%)	43 (86%)
Mean hospital stay		5.17 days	7.2 days
Improvement		40 (88.9 %)	45 (90%)
Expiry		5 (11.1%)	5 (10%)

These results show that although there was no significant change in terms of outcome in both groups in hospital mortality being 11.1% in group A and 10% in group B during same hospital entry. But there was a significant improvement in terms of total days spent in hospital. Group A which includes the patients who received Mannitol during their treatment had to stay in

hospital for shorter duration than the group B which did not received Mannitol. There was an average difference of 2 days in both groups (Group A = 5.17 days, Group B = 7.22 days). In terms of electrolyte imbalance caused by treatment there was no major difference in group A and B on day 1 and day 3 of treatment and no clinical signs or symptoms of hypokalemia or hyponatremia were noted in any patient of both groups.

Table No. 2: Mean sodium and potassium concentration in both the group

Parameter		**Group A**	Group B
Mean Na^+ concentration	Day first	137.31mmol/L	137.6mmol/L
	Day three	135.42 mmol/L	136.0mmol/L
mean K^+ concentration	Day first	4.0mmol/L	4.1mmol/L
	Day three	3.8.mmol/L	3.9mmol/L

DISCUSSION

West Haven Classification System is used for grading of hepatic encephalopathy. Hepatic encephalopathy is graded from 0-4 grades according to its clinical presentation. Hepatic encephalopathy is treated according to the grade of hepatic encephalopathy at the time of presentation. The patients graded as minimal hepatic encephalopathy or grade I-II encephalopathy may be treated in outpatient settings and with the use of minimal drugs. While patients presenting in ER with deep grade III-IV encephalopathy may warrant more aggressive approach.[4] More deeper and more prolonged coma grades are associated with higher mortality and morbidity rates. Longer hospital stays are also associated with higher care giver burden and increased financial expenditures for health care system.[5]

Mainstay of treatment of hepatic encephalopathy is gut cleansing and decreasing ammonia producing bacteria in the gut by antibiotics.[6] Traditionally Lactulose has been used orally or in form of enemas to clear the gut and acidify the gut thus reducing ammonia producing coliform bacteria. Lactulose also promotes nonammoniagenic lactobacilli. Other then Lactulose, antibiotics mainly targeting ammonia producing bacteria in the gut are used.[8] Metronidazole, Rifaximin, quinolones, Neomycin sulphate and oral Vancomycin are used. Startrgies to increase ammonia clearance are also implicated. L-ornithine L-aspartate, L-carnitine and zinc are used for this propose.[9, 10]

In early 18th century Pavlov noticed the relation between portosystemic shunting and development of hepatic encephalopathy in dogs which was aggravated after they were fed meat. This was known as Meat Intoxication Syndrome. In 20th century Phillips and colleagues noticed behavior changes in patients with liver dysfunction. In 1990 role of ammonia in the development of hepatic encephalopathy was found. The effects of elevated ammonia has been a topic for discussion since long. It is postulated that in patients with chronic liver disease, low grade cerebral edema is present due to conversion of ammonia into glutamine in astrocytes, which promotes cerebral edema. This cerebral edema causes multitude of symptoms i.e. confusion, agitation and coma. [11, 7]

In 2001 Cordoba et al published their findings which showed that development of low grade cerebral edema is supported by MRI changes in the patients with hepatic encephalopathy. This was further supported by 2006 publication of D. Haussinger.[11] Keeping in view the development of cerebral edema as an important factor in pathogenesis of portosystemic encephalopathy, we used Mannitol infusions to revert the brain changes.[10] Our research revealed that although the use of Mannitol did not result in any changes to the overall course of the disease, it did improve the quality of life for patients and reduce the stay in hospital. Thus it reduced the cost of treatment for our patients. In our society where a large part of population belongs to lower middle class and the health care expenses are borne by the patient and their family, a decrease in hospital stay means decreased financial burden over them. Whereas the short hospital stay also means less crowded hospitals and improved efficiency of health care providers and hospitals. To verify our findings further large scale, multi centered randomized controlled trials are needed.

CONCLUSION

Our research revealed that although the use of Mannitol did not result in any changes to the overall course of the disease, it did improve the quality of life for patients and reduced the stay in hospital. These results have a direct impact on reducing the financial burden on the families and institutions that care for patients with cirrhosis and improving their quality of life.

Author's Contribution:

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Final Approval of version:	By all above authors

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