Original Article

Comparison of the Standard Therapy versus Add-On Zinc Therapy for the Management of Hepatic Encephalopathy

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ABSTRACT

Objective: The objective of this study is to compare the frequency of decrease in number of hepatic encephalopathy episodes with patients receiving standard versus add on zinc therapy.

Study Design: randomized controlled study

Place and Duration of Study: This study was conducted at the department of Gastroenterology, Aziz Fatima Medical and Dental college, Faisalabad for a period of six months from July, 2020 to December, 2020.

Materials and Methods: Total 90 patients meeting inclusion and exclusion criteria were studied in 6 months period from July to December 2020. HE was diagnosed with use of west haven criteria. Patients were divided in two groups. On group received standard treatment including lactulose, rifaximin and protein restricted diet (control group) and other group received add on zinc therapy 40 mg daily in addition to standard treatment (Zinc group) and were followed for 3 months and number of HE episodes were noted.

Results: In control group, decrease in episodes of hepatic encephalopathy was observed in 33.33% while decrease in episodes of hepatic encephalopathy was observed in 57.78%. By using chi-square test it found that decrease in number of HE was significantly higher in zinc therapy group having p-value = 0.017. By stratification of age, it was found that there was significant association found in decrease in HE episodes and study group in less than 45 years of age having p-value = 0.018 but there was no significant association between decrease in HE episodes and study group in greater than 45 years of age having p-value = 0.430.

Conclusion: Decrease in episodes of hepatic encephalopathy was observed significantly higher in zinc therapy group. Significant association was found in decrease in HE episodes and study group in less than 45 years of age, males and number of HE episodes in previous three months.

Key Words: Liver Cirrhosis, hepatic encephalopathy, Zinc Therapy.

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INTRODUCTION

In our part of the world cirrhosis of liver is a common cause of mortality and the viral hepatitis being the most common etiological factor. Hepatic encephalopathy (HE) is one of its complications[1].

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Hepatic encephalopathy is a state of disordered central nervous system function resulting from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and porto-systemic shunting[1]. The clinical scale ranges from day-night reversal and mild intellectual impairment to coma[1]. Hepatic encephalopathy is present in up to 70% of all patients with cirrhosis, including patients with abnormalities demonstrable only by psychometric testing[2,3]. Hepatic encephalopathy leads to death in 2.2% of cirrhotic patients during hospital stay[4]. Hepatic encephalopathy portends a worse survival for patients compared to similar patients without HE[5]. The inpatient incidence of HE is approximately 23,000/year[5]. 1-year mortality for patients with severe HE in intensive care unit (ICU) is 54%, with requirement for inotropic support[6].

The pathogenesis of hepatic encephalopathy is not completely understood but ammonia is considered to play a key role[7]. Hepatic encephalopathy is a result of several complex factors rather than a single

mechanism[4]. Etiology of hepatic encephalopathy is thought to be due to biochemical changes in the brain function as it is reversible and does not cause pathological changes in brain[8]. In advanced cirrhosis, ammonia reaches the systemic circulation via Porto-systemic shunting and the failure of the liver to metabolize ammonia. This contributes to the increased occurrence of motor dysfunction and the extra-pyramidal symptoms[7].

Most cases of hepatic encephalopathy are precipitated by infection, gastrointestinal bleeding, electrolyte imbalance, medications or other culprits[5]. Synthetic disaccharides such as lactulose and lactitol have been used as the main agents to treat hepatic encephalopathy in advanced cirrhosis[7]. Neomycin is a poorly absorbed aminoglycoside used to decrease gut bacteria-derived ammonia. Rifaximin can be added in patients not responding to lactulose[5].

Zinc deficiency is common in cirrhotics[5]. In a recent clinical trial, the zinc deficiency prevalence was 96% in patients with a median MELD score of 12[7]. Zinc is a co-enzyme in urea cycle. Ammonia conversion to urea is halted by zinc deficiency[5]. Treatment with zinc has been found to enhance the formation of urea from ammonia and amino acids[9]. The causes of low serum zinc levels in advanced cirrhotic patients are thought to be poor dietary intake via protein-restricted diet, impaired intestinal absorption and excessive urinary losses[7]. Zinc is relatively well tolerated with a rare side effect of dyspepsia[5].

The most recent study from Takuma et al. in 2010[7] randomized patients with cirrhosis and hepatic encephalopathy Grade I-II refractory to standard treatment to receive zinc treatment (n=39) in addition to lactulose and branch chain amino acids (BCAA) versus no zinc (n=40) with BCAA and lactulose. Patients were followed for 6 months to determine the effect on quality of life and hepatic encephalopathy. Hepatic encephalopathy improved in 21(54%) vs. 10 (26%) in the zinc vs. no zinc respectively, with 16 (41%) zinc-treated patients improving to HE grade zero. The role of zinc deficiency has been documented in cirrhotic patients in the development of hepatic encephalopathy. Previous studies have reported the benefit of using zinc supplements in patients with end stage liver disease in reducing the severity of hepatic encephalopathy. However, its role in patients with cirrhosis having hepatic encephalopathy has not been documented in patients in Pakistan as per my knowledge.

MATERIALS AND METHODS

This randomized controlled trial was carried out in department of Gastroenterology, Aziz Fatima Medical and Dental college, Faisalabad. All patients admitted or attended in SIH with HE meeting the inclusion and exclusion criteria were included in study after written informed consent by the guardian of the patient. Total 90 patients were studies which were randomly divided into two groups with 45 participants in each group i-e control group and zinc therapy group. Total duration of study was 6 months from July to December 2020.

Inclusion criteria:

i. Patients with liver cirrhosis diagnosed by radiological findings
ii. Age from 18 to 70 years.
iii. Six or more than six HE episodes in previous three months.
iv. HE of any grade.

Exclusion criteria:

i. Use of antibiotics & drugs having psychometric effect (benzodiazepines, antiepileptic's, psychotropic drugs, or narcotics)
ii. History of shunt surgery.
iii. Organic neurological diseases such as subdural hematoma, Wernicke's disease, encephalitis and drug intoxications.

This study was carried out in department of Gastroenterology, Aziz Fatima Medical and Dental college, Faisalabad. Liver cirrhosis was confirmed by ultrasonographic findings. History and clinical examination were carried out when patients were screened for enrollment. Previous history and recent episode of HE was assessed clinically with use of West Haven Criteria. The study included initial visit, enrollment and treatment phase during hospital stay and as outpatient department (OPD) visit. After taking informed consent eligible patients were selected and divided into two groups by using lottery method. One group received standard treatment including lactulose, rifaximin and protein restricted diet (control group) and other group received add on zinc therapy 40 mg daily in addition to the standard treatment (zinc group). Treatment was continued in both groups for three months. Both groups were followed for three months and the number of hepatic encephalopathy episodes were noted. All enrolled patients and their care-givers were educated about the potential side effects of the drugs.

Data Analysis: Data was analyzed using SPSS version 20. Chi-square test was applied to compare frequency of HE episodes between two groups. Qualitative variables like gender & decrease in hepatic encephalopathy episodes were measured as percentage & frequency. Quantitative variables like age & number of hepatic encephalopathy episodes were measured as mean and standard deviation. Effect modifiers like age, gender & previous number of HE episodes were controlled by stratification. Post stratification Chi-square test were applied

RESULTS

From 90 patients with liver cirrhosis the minimum age was found as 18 years and maximum was 70 years with mean and standard deviation of age as 39.31±18.185

years. The minimum and maximum HE episode in previous three months were found as 1 and 6 respectively having mean and standard deviation as 4.1±1.53 episodes. The minimum and maximum HE episode in last three months of study duration were found as 1 and 6 respectively with mean and standard deviation as 3.33±1.59 episodes. There were 53 (58.9%) male patients and 37 (41.1%) female patients. In control group, decrease in episodes of hepatic encephalopathy was observed in 15 patients (33.33%) while in Zinc group there were 26 patients (57.78%). By using chi-square test it found that decrease in number of HE was significantly higher in zinc therapy group having p-value = 0.017 (Table 1).

Table No.1: Comparison of Decrease in HE episodes in both groups

Group	Decrease HE episodes		Total	P-value
	Yes	No		
Control group	15	30	45	0.017
Zinc group	26	19	45	
Total	41	49	90	

Table No.2: Stratification of outcome in both groups with reference to age and gender

Characteristic	Total	Control group	Zinc group	P-Value
Decrease in HE episode <45 Years (Yes/No)	28/18	10/20	18/10	0.018
Decrease in HE episode >45 Years (Yes/No)	13/19	5/10	8/9	0.430
Decrease in HE episodes in males (Yes/No)	23/30	6/18	17/12	0.014
Decrease in HE episode in females (Yes/No)	18/19	9/12	9/7	0.317

Table 3: Stratification of outcome in both groups with reference to previous no. of HE episodes

Previous no. of HE episodes	Treatment Group	Decrease in HE episodes		Total	P-value
		No	Yes		
< 4 Episodes	Control group	11	6	17	0.251
	Zinc group	13	3	16	
≥ 4 Episodes	Control group	19	9	28	0.001
	Zinc group	6	23	29	
Total		49	41	90	

By stratification of age, it was found that there was significant association found in decrease in HE episodes and study group in less than 45 years of age having p-value = 0.018 but there was no significant association between decrease in HE episodes and study group in patients with age greater than 45 years having p-value = 0.430 (Table 2). By stratification of gender, it was found that there was significant association found in decrease in HE episodes and study group in males having p-value=0.014 but there was no significant association between decrease in HE episodes and study group in females with p-value = 0.317 (Table 2). By stratification of number of previous HE episodes it was found that there was no significant association in decrease in HE episodes and study group in less than 4 previous HE episodes having p-value = 0.251 whereas there was significant association between decrease in HE episodes and Zinc therapy group for more than 4 previous HE episodes having p-value 0.001 (Table 3).

DISCUSSION

The objective of the present research was to to compare the frequency of decrease in number of hepatic encephalopathy episodes with patients receiving standard versus add on zinc therapy. In this regard the present randomized control trial was conducted in department of Gastroenterology, Aziz Fatima Medical and Dental college, Faisalabad. This study revealed that zinc supplementation in addition to standard treatment clearly demonstrates improvement in hepatic encephalopathy episodes and its recurrence. Synthetic disaccharides are also effective in reducing blood ammonia levels by mainly inhibiting absorption of ammonia from intestine. This synergism of two agents (zinc and synthetic disaccharides) for reducing ammonia caused by different mechanisms seems to be effective in patients unresponsive to standard therapy. Several studies showed improvement in psychomotor performance with reduction in serum ammonia level in HE patients with zinc supplementation[10,11]

Previous studies[11-13] revealed significant improvement in patients with HE on zinc supplementation in addition to standard treatment that was consistent with our results. Hayashi et al[13] described that combined therapy with zinc and conventional therapy lowered blood ammonia level more than branch chain amino acids alone. They inferred from their result that zinc administration increased liver ability to metabolize ammonia.

Mean age in our study was 39.31 years whereas takuma et al[7] reported mean age of 66.5. In our study 58.9 % participants were male and 41.1 % were female. Comparison to it there were 50.63 % male and 49.4 % were female participants as previously reported[7]. In contrast to these results previous study[14] concluded that zinc supplementation failed to improve HE, the different outcomes between those studies and the present one are may be due to variable duration of zinc therapy or participants background.

Limitations of this study are that it was conducted in short period of time and was non-blinded. Although treatment bias unavoidable because our study was assessed by same person unaware of the assignment.

CONCLUSION

In conclusion, Zinc supplementation may be an effective treatment for the HE that also prevents its recurrence. However Double blinded randomized controlled trial in large population is necessary to make definitive conclusion.

Author's Contribution:

Concept & Design of Study:	Kashif Nawaz
Drafting:	Muhammad Rizwan, Awais Aslam
Data Analysis:	Atif Maqsood, Faizan Aslam, Muhammad Absar Alam
Revisiting Critically:	Kashif Nawaz, Muhammad Rizwan
Final Approval of version:	Kashif Nawaz

Conflict of Interest: The study has no conflict of interest to declare by any author.

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