Original Article

Effectiveness of Combination of Zinc and Lactulose Versus Lactulose Alone to Decrease Recurrence of Hepatic Encephalopathy in Patients With Hepatic Cirrhosis

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Objective: To determine the effectiveness of combination of Zinc and lactulose with lactulose alone to decrease recurrence of hepatic encephalopathy in patients with hepatic cirrhosis.

Methods: This Randomized Controlled Trial was conducted in South Medical Ward , Mayo Hospital, Lahore from 1st July, 2016 to 30th June, 2017. One hundred and two patients of both sexes were selected using simple random sampling technique. Patients were divided into 2 groups. Group A received Zinc in addition to lactulose and other standard treatment for hepatic encephalopathy whereas Group B received lactulose and standard treatment. Patients were then followed up every 4 weeks for six months or early in case of development of any complication.

Results: Out of a total of 102 patients, 73(71.6%) were males and 29 (28.4%) were females. Mean age of the patients was 51.43±6.63. Out of the 51 patients enrolled in Group A, 16 (15.7%) developed recurrent hepatic encephalopathy whereas 37 (36.3%) of 51 patients in Group B developed recurrence during the follow up period. Oral zinc supplementation was significantly associated with reduction in recurrence of hepatic encephalopathy and showed statistical significance ($p < 0.0001$).

Conclusions: Oral zinc supplementation in addition to standard therapy for hepatic encephalopathy leads to a decrease in its recurrence when compared with standard therapy alone.

Keywords: hepatic encephalopathy, cirrhosis, zinc supplementatione.

Introduction

Hepatic cirrhosis is described as the disruption of the hepatic parenchymal framework and regenerative nodules formation. Chronic hepatic inflammation and cholestasis are the two main pathological phenomenon that can lead to this. Chronic HCV infection, Acute liver disease (ALD) and Non- alcoholic fatty liver disease (NAFLD) are the major causative factors.[1]

Hepatic encephalopathy (HE), variceal bleeding, hepatocellular carcinoma (HCC), hepatopulmonary syndrome and hepatorenal syndrome (HRS) are the main sequelae and complications of liver cirrhosis.

Hepatic encephalopathy is a brain dysfunction with combination of neurological and psychiatric changes.[2] Pathophysiology of HE is multifactorial and it is assumed that it could be due to increased intestinal bacterial products synthesis and absorption or raised serum ammonia (NH3) levels.[3] Hepatic encephalopathy occurs in almost 50% of the patients of hepatic cirrhosis at some stage of the disease process which if left untreated has a survival rate of only 23 % at 3 years.[4,5] Treatment includes restriction of protein intake, lactulose, rifaximin, probiotics, branched chain amino acids (BCAA), sodium benzoate etc. Zinc is also given to patients for treatment of hepatic encephalopathy. HE alongwith other complications of cirrhosis carry a poor prognosis and lead to an increased mortality.[6,7]

Mostly patients of liver cirrhosis with hepatic encephalopathy have low serum zinc level.[8] Low serum zinc levels in advanced cirrhotic patients are considered due to protein-restricted diet, intestinal malabsorption and excessive urinary losses. Zinc increases the production of hepatic ornithine transcarbamylase (OTC) which converts ammonia to urea and also improves activity of skeletal muscle glutamine synthetase which prevents hyperammonemia.[9]

Lactulose creates acidic environment in the gut which helps in conversion of soluble ammonia to insoluble ammonium ion which results in decreased systemic absorption from the gut.[10]

A study was published in 2010 by Takuma and his colleagues regarding Zinc as treatment option in HE. Forty patients were given Piperazinc 225mg daily with standard therapy and 39 patients were given standard therapy including protein restricted diet, lactulose and branched chain amino acids. Twenty one patients taking piperazinc and 10 patients receiving only standard therapy improved their hepatic

encephalopathy grades, Child Pugh score and blood ammonia level.[9] Mousa et al. in 2014 studied the effect of Zinc with antioxidant in carpenters with Minimal hepatic encephalopathy (MHE). Sixty selected individuals were randomly given Zinc , vitamin E and Vitamin A once daily with lactulose for three months duration. They found a significant response in neuropsychometric tests at the end of treatment duration.[11] A study was carried out in Japan showing the role of Zinc supplements in reduction of hepatic encephalopathy recurrence [8] but limited data is available in Asia regarding this supplementation. Furthermore, previous studies were conducted on a relatively smaller patient population [8,10] and cause of hepatic cirrhosis was not predominantly viral hepatitis. In our Pakistani population, the main cause of viral cirrhosis is HBV and HCV, therefore, the rationale of this study is to determine the effect of zinc supplementation with standard therapy in our local population.

Methods

This Randomized controlled trial was conducted in South Medical Ward, King Edward Medical University, Mayo Hospital, Lahore from 1st July, 2016 to 30th June, 2017. A sample size of 102 patients was taken using 5% level of significance, 90% power of test with expected percentage of Zinc with standard treatment as 54% and in the control group as 26%. 8 Simple random sampling technique was applied in selecting the patients. Patients of either sex between the age group of 13-60 years were selected for the study. Furthermore, those patients who have had at least one episode of hepatic encephalopathy and were discharged after treatment, patients of cirrhosis regardless of etiology ascertained on ultrasonography (coarse texture, increased portal vein diameter, splenomegaly, ascites) and those with serum Zinc level of <70 ug/dl (Normal value: 70-127ug/dl) were included in the study. Patients with fulminant hepatic failure assessed by serum ALT/AST levels, altered sensorium due to metabolic disorders assessed by blood sugar levels, serum urea, creatinine, sodium(Na+) and potassium (K+) levels, neurological disease assessed by focal neurological deficit on physical examination and haemodynamically unstable patients screened on physical examination were excluded from the trial. Also patients who gave history of zinc allergy and upper gastrointestinal bleeding were also excluded from the study. After getting approval from the Board of Studies (BOS) and Institutional Review Board (IRB) of King Edward Medical University, 102 patients conforming to the inclusion criteria were selected for the study. Informed consent was taken from the patients' first degree relatives. Patients were divided into 2 groups of 51 patients each using computer generated method. Patients' demographic data was obtained. Hepatic encephalopathy grade was assessed by hepatic encephalopathy scoring algorithm (HESA). Baseline serum Zinc levels, LFTs, RFTs, serum electrolytes and abdominal ultrasound were also done. Group A patients were given Zinc Sulphate 20mg three times daily alongwith lactulose 30 ml once daily whereas patients in Group B were given lactulose alone 30ml daily orally. Apart from this, a standard treatment regimen was followed in all the study subjects. All these patients were then followed up every 4 weeks for another 6 months after discharge from the hospital, or earlier if the patient developed altered sensorium. On every visit, history regarding Hepatic encephalopathy grade, compliance, current medications and adverse effects was taken. Serum Zinc levels were repeated at the end of 6 month study period. If episode of altered sensorium occurred, then history, examination and investigations were carried out to rule out any cause other than hepatic encephalopathy. The data was analyzed using computer software SPSS version 17.0. Quantitative variables like age, grade of hepatic encephalopathy and hospital stay were presented as mean ±standard deviation (Mean±SD). Qualitative variables like sex were presented as frequencies and percentages. Comparison of the two groups was done by applying chi-square test. P value less than or equal to 0.05 was considered significant.

Results

Out of a total of 102 patients included in the study, 73 (71.6 %) were males and 29 (28.4 %) were females . Twenty six (25.5%) patients fell in the age group of 30 to 45 years and 76 (74.5%) patients in the 46 to 60 years group. Mean age of the patients was found to be 51.43 ± 6.63 years. Only 3 patients were infected with HBV and 89 patients with HCV infection and the rest had both HBV and HCV infection. In Group A, 16 (15.7%) patients developed recurrence of HE and 35 (34.3%) patients did not develop HE during the six month follow up period. Whereas in Group B, 37 (36.3%) patients developed recurrence of HE and 14(13.7%) remained free of HE during the follow up. Comparisons between gender, group and recurrence of HE are given in Table 1, 2 and 3. Oral Zinc supplementation was significantly associated with

reduction in recurrence of hepatic encephalopathy and showed a statistical significant difference between the two groups ($p < 0.0001$).

Table-1: Comparison of gender among groups group* gender Cross tabulation.

			Gender		
			Male	Female	Total
Group	Zinc + Lactose (Group A)	Count	38	13	51
		% Total	73.3%	12.7%	50.0%
	Zinc + Lactose (Group B)	Count	33	18	51
		% Total	32.4%	17.6%	50.0%
Total		Count	71	31	102
		% of Total	69.6%	30.4%	100.0%

Table-2: Comparison of causes among groups * gender Cross tabulation.

			Causes			
			HCV+	HBV+	HBV & HCV+	Total
Group	Zinc + Lactose (Group A)	Count	46	0	5	51
		% Total	45.1%	0.0%	4.9%	50.0%
	Zinc + Lactose (Group B)	Count	44	2	5	51
		% Total	43.1%	2.0%	4.9%	50.0%
Total		Count	90	2	10	102
		% of Total	88.2%	2.0%	9.8%	100.0%

Table-3: Comparison of recurrence among groups * gender Cross tabulation.

			Recurrence		
			Yes	No	Total
Group	Zinc + Lactose (Group A)	Count	16	35	51
		% Total	15.7%	34.3%	50.0%
	Zinc + Lactose (Group B)	Count	37	14	51
		% Total	36.3%	13.7%	50.0%
Total		Count	53	49	102
		% of Total	52.0%	48.0%	100.0%

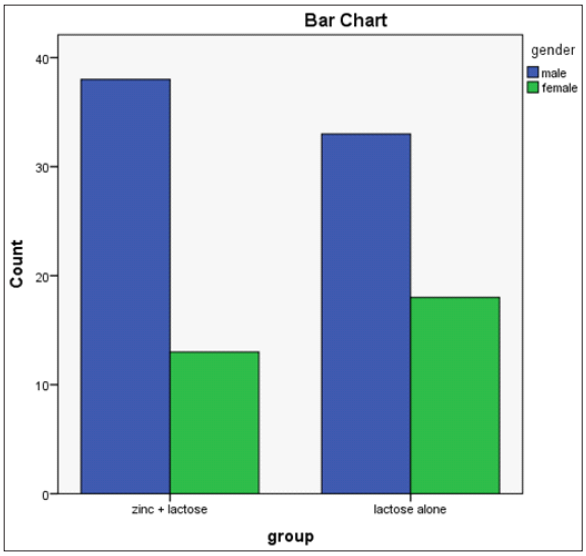

Fig-1: Gender distribution.

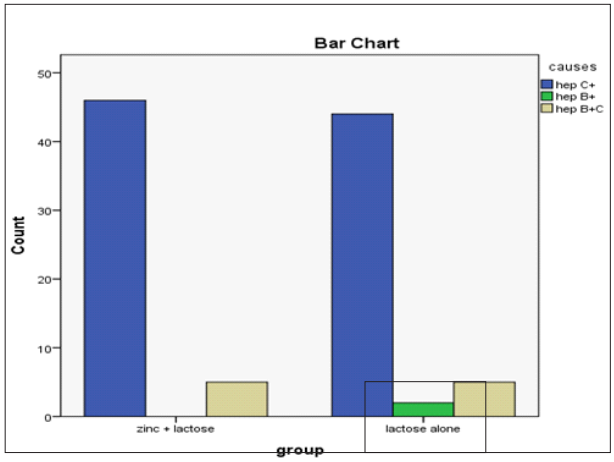

Fig-2: Causes distribution.

Discussion

Hepatic encephalopathy (HE) incorporates a wide range of reversible neuropsychiatric deficits developing in cirrhotic patients who present with symptoms of mild to severe cognitive abnormalities e.g., sleep disturbance, sudden altered behavior, changed mentation or coma. The mechanisms behind brain abnormalities in HE are yet to be known, however it is proposed that ammonia synthesized by gut flora plays a significant role[12]. There is a dearth of evidence backed by large, well-controlled clinical trials in favor of specific treatment options currently in use for patients with Minimal HE. However the existing evidence suggests some advantage of lactulose in the treatment of Minimal HE. Treatment of patients with Overt HE is mainly based on dietary protein restriction, lactulose, rifaximin, BCCAs (branched chain amino acids), probiotics, sodium benzoate and Zinc are given to patients for treatment of hepatic encephalopathy.[7] Mostly patients of liver cirrhosis with hepatic encephalopathy have low serum Zinc level.[8] It is mainly due to a protein-restricted diet, intestinal malabsorption, and excessive urinary losses. A study was published in 2010 by Takuma and his colleagues carried out a study in 2010 on a small group of HE patients and showed that in the group that received zinc in addition to the standard treatment of HE, there was a significant improvement in the grades of hepatic encephalopathy, Child Pugh score and blood ammonia level.[9] The results of this study were comparable with the results of our study.

Mousa et al. in 2014 studied the effect of Zinc with antioxidant on Minimal hepatic encephalopathy (MHE) in which 60 individuals were selected and were randomly given Zinc gluconate, vitamin E and Vitamin A daily with lactulose for three months

Duration. They found a significant response in neuropsychometric tests at the end of treatment duration.[11] Chavez-Tapia NC et al., also studied the role of zinc supplements in HE and showed the improvement in number connection test (NCT) whereas no significant effect was observed on health-related quality of life.[13]

A robust protective effect of antioxidants and Zinc against HE was observed by Mousa and his colleagues in a randomized controlled trial conducted in Mansoura, Egypt in 2016.[14] The results of the above-mentioned studies favour the addition of zinc to the standard therapy given to patients of HE in terms of earlier improvement in their grades.

Conclusion

Oral Zinc supplementation in addition to the standard treatment of HE reduces the rate of recurrence of HE in patients with cirrhosis so zinc should be added as a regular supplement in the treatment of such patients.

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