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ORIGINAL ARTICLE

Oral zinc supplementation in management of hepatic encephalopathy in patients with cirrhosis; A study conducted in developing country.

Riaz Hussain Awan[1], Ameet Jesrani[2], Latif Aziz Memon[3], Seema Nayab[4], Khadim Hussain Awan[5], Faqeer Muhammad Awan[6]

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ABSTRACT… Objective: To evaluate the effectiveness of oral zinc supplementation in cirrhotic patients with hepatic encephalopathy. **Study Design:** Retrospective Cohort study. **Setting:** Department of Gastroenterology, Liaquat University of Medical and Health Sciences, Jamshoro. **Period:** 15th February 2019 to 15th August 2019. **Material & Methods:** Adult patients of either gender suffering from hepatic cirrhosis and presenting with hepatic encephalopathy of any grade were included. Zinc acetate in a dose of 600 mg was given orally to the patients for two weeks duration. Standard lactulose treatment was also given alongside. Blood ammonia measurement was done at baseline and also after 2 weeks of treatment. Performance was assessed by utilization of number connection test (NCT) at week 1 and week 2 weeks post treatment. **Results:** Study included of 135 patients among which majority 95 (70.4%) of the patients were males. The mean age of the patients were 55.72 + 10.32 years. 40 (26.62%) patients were seen in Child Pugh class A, 65 (48.14%) were seen in Child Pugh class B and 30 (22.2%) were seen in Child Pugh class C. Serum ammonia levels were reduced in 110 (81.48%) patients and improved performance in NCT was seen in 90 (66.66%) patients. There was significant reduction of ammonia levels and significant improvement of NCT test in male patients (p value <0.05) and in Child Pugh class A and B patients (p value <0.05). **Conclusion:** In addition to standard therapy, inclusion of oral zinc acetate resulted in normalization of blood zinc and ammonia levels with improved performance in NCT and overall hepatic encephalopathy.

Key words: Chronic Liver Disease, Hepatic Cirrhosis, Hepatic Encephalopathy, Oral Zinc, Zinc Acetate.

INTRODUCTION

One of the major neuropsychiatric complications of hepatic cirrhosis is development of hepatic encephalopathy (HE).[1-3] It results in development of changes in personality, impairment of intellect and cognitive decline.[4,5] This complication usually develops as a result of increased ammonia levels. Ammonia is detoxified by liver and brain is vulnerable to increased ammonia levels. Gamma aminobutyric acid (GABA) is a substance produced by gastrointestinal (GI) tract for neuronal inhibition. Neuronal receptors of GABA have sites for binding of neurosteroids and some advocate the role of neurosteroids in development of hepatic encephalopathy.[6]

Ammonia metabolism is undertaken by liver and skeletal muscle. Metabolism of ammonia involves conversion of ammonia to urea within liver via enzyme ornithine transcarbamylase and conversion of ammonia to glutamic acid within skeletal muscle with enzyme glutamine synthetase.[7] Most patients with hepatic encephalopathy have hyperammonemia.[8] Ammonia reduction helps in resolution of hepatic encephalopathy. Standard management for hyperammonemia reduction includes lactulose and other disaccharides which are non-absorable.[9] However, despite this management, encephalopathy may persist in some of the patients.[10]

Zinc acts as a cofactor for enzymatic reactions performed within liver and skeletal muscles.

1. MBBS, FCPS, Assistant Professor Gastroenterology, Liaquat University of Medical and Health Sciences, Jamshoro.
2. MBBS, FCPS, Associate Professor Radiology Radiology, Sindh Institute of Urology and Transplantation, Karachi.
3. MBBS, FCPS, Consultant Gastroenterologist Gastroenterology, Liaquat National Hospital, Karachi.
4. MBBS, FCPS, Assistant Professor Radiology, Liaquat University of Medical and Health Sciences, Jamshoro.
5. MBBS, FCPS, Assistant Professor Urology, Baqai Hospital, Karachi.
6. MBBS, FCPS, Consultant Cardiologist, CMC Hospital, Larkana.

Correspondence Address:
Dr. Riaz Hussain Awan
Department of Gastroenterology
Liaquat University of Medical and Health Sciences, Jamshoro.
dr.awan.riaz@gmail.com

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Deficiency of zinc has been demonstrated in patients with hepatic cirrhosis.[11,12] According to a study, management of elevated ammonia by administration of zinc for three months effectively reduced its levels among hepatic cirrhotic patients.[13] Another study showed that administration of anti-oxidants and zinc served to improve minimal hepatic encephalopathy in hepatic cirrhosis patients.[14] As per our literature search, previous studies have been conducted in developed countries. This study would be a valuable addition to the already available literature and it determined outcome of oral zinc supplementation in patients with hepatic encephalopathy in a population of developing country.

MATERIAL & METHODS

A retrospective cohort study was conducted at Department of Gastroenterology of Liaquat University of Medical and Health Sciences, Jamshoro. Review of medical record from 15th February 2019 till 15th August 2019 was undertaken. Ethical Review Committee approval was obtained (LUMHS/REC/-891). A retrospective review of medical records of already diagnosed hepatic cirrhosis patients who developed hepatic encephalopathy and were treated with oral zinc acetate 600 mg per day for two weeks along with standard lactulose treatment. Hepatic encephalopathy was defined as presence of behavioral alteration, agitation or memory disturbance with or without development of coma. Both male and female patients of age 18 years and above having hepatic cirrhosis and presenting with hepatic encephalopathy of any grade were included. Patients were excluded if they had electrolyte imbalance, any neurological etiology of cognition impairment, spontaneous bacterial peritonitis, already took treatment for hepatic encephalopathy, and patients on medications that affect the psychomotor response such as benzodiazepines or antiepileptic drugs. Details related to zinc and ammonia in the blood were recorded from medical record at baseline and two weeks after treatment. Performance evaluation from records was also noted by number connection test (NCT) at two weeks post treatment. In number connection test, the numbers were arranged in an arbitrary sequence to be connected as quickly as possible by drawing a line between them. A healthy individual requires less than 30 seconds to complete NCT whereas a patient having hepatic encephalopathy requires more than 30 seconds to complete this test.

Data were entered and analyzed on Statistical package for social sciences (SPSS) version 18.0. Mean and standard deviation (SD) was calculated for quantitative variables like age. Frequency and percentage was evaluated for qualitative variables like gender, Child Pugh class, reduction in ammonia levels and improved performance in NCT. Effect modifiers such as age, gender and Child Pugh class were controlled through stratification. Post stratification chi square test was applied and p value of less than or equal to 0.05 was considered as significant.

RESULTS

Total of 135 patients were included in the study. Out of 135 patients, 95 (70.4%) were males and 40 (29.6%) were females. Mean age of the patients was 55.72 $\pm$ 10.32 years.

Child Pugh class A was found in 40 (26.92%), Child Pugh class B in 65 (48.14%) and Child Pugh class C in 30 (22.2%) patients.

Among 135 patients, total 110 (81.48%) patients showed reduction in blood levels of ammonia. Among 135 patients, total 90 (66.66%) patients showed improved performance of NCT.

There was significant reduction of ammonia levels in male patients (p value <0.05) (Table-I). There was significant improvement in NCT test in male patients (p value <0.05) (Table-II).

DISCUSSION

Hepatic encephalopathy is a grave complication that may eventually develop in cirrhotic patients. Hyperammonemia may be responsible for hepatic encephalopathy development and reduction in levels of ammonia improves this condition thereby improving health related quality of life (HRQoL).[15]

	Ammonia Level Reduced		Total	P-Value
	No	Yes		
Gender				
Female	13 (9.6%)	27 (20.0%)	40 (29.6%)	0.007*
Male	12 (8.9%)	83 (61.5%)	95 (70.4)	
Age, years				
≤50	10 (7.4%)	40 (29.6%)	50 (37.0%)	0.734*
>50	15 (11.1%)	70 (51.9%)	85 (63.0%)	
*Chi-square test applied				

Table-I. Comparison of ammonia level reduction with patient characteristics

	NCT Score Improved		Total	P-Value
	No	Yes		
Gender				
Female	20 (14.8%)	20 (14.8%)	40 (29.6%)	0.008*
Male	25 (18.5%)	70 (51.9%)	95 (70.4)	
Age, years				
≤50	18 (13.3%)	32 (23.7%)	50 (37.0%)	0.614*
>50	27 (20.0%)	58 (43.0%)	85 (63.0%)	
*Chi-square test applied				

Table-II. Comparison of Number Correction Test (NCT) score improvement with patient characteristics

Lactulose minimizes the ammonia absorption, however it does not detoxifies ammonia.[7,16] Zinc helps in ammonia metabolism by acting as a cofactor for enzymatic reactions in the liver and skeletal muscles.[17] Chronic liver damage leads to impairment in homeostasis of zinc thereby resulting in zinc deficiency.[18] Moreover, poor intake of nutrition, poor intestinal absorption and an increased loss in urine may all potentially serve to lower the zinc levels in patients suffering from advanced hepatic cirrhosis.[7] In the present study we assessed the effects of oral zinc supplementation in cirrhotic patients with hepatic encephalopathy. Oral zinc acetate was given alongside with standard lactulose treatment and response was assessed by measuring ammonia levels and performance in number connection test.

Our study results have shown that reduction in ammonia levels was observed in 81.48% patients. Another study conducted on 79 cirrhotic patients also demonstrated a reduction in blood ammonia levels.[19] The study utilized polaprezinc zinc of 225 mg/day along with standard management in the intervention group and comparison group was given standard management only. In our study 600 mg oral zinc acetate per day along with lactulose. A placebo controlled double blind trial conducted in Japan on liver cirrhosis patients utilized oral capsules of zinc acetate 150 mg/day and also demonstrated significant reduction in blood ammonia level.[13] Effectiveness of zinc has also been demonstrated in cases of minimal hepatic encephalopathy. A study on 58 cirrhotic patients with minimal hepatic encephalopathy demonstrated reduced level of ammonia in the blood after intake of 175 mg of zinc gluconate along with antioxidants.[14] The study also showed improvement in Child Pugh score, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.[14]

According to our study, a high percentage of 66.66% showed improved performance in number connection test. Another study showed improvement in NCT with zinc supplementation as compared to standard management. In the previous study, NCT was used in the form of number connection serially and figure connection. The results showed significant improvement in both NCT types.[19] Another study among patients with minimal hepatic encephalopathy demonstrated significant improvement in NCT, digit symbol test and block design test after three months of treatment with zinc and various

antioxidants.[14]

Zinc supplementation also results in improvement of various biochemical tests in cirrhotic patients. A study was conducted regarding the effect of low dose zinc supplementation in patients with non-alcoholic cirrhotic patients. Assessment of Child Pugh scores and biochemical tests were done.[20] In that study, 30 patients received low dose zinc and 30 patients received placebo in the form of starch. The study showed a significant reduction in Child Pugh score among patients receiving zinc supplementation.[20]

In another study, polaprezinc was given to patients suffering from chronic hepatitis C.[21] The study reported improvement in liver enzymes including ALT and AST. Improvement was also identified in the platelet count.[21] Moreover, in the group receiving zinc, there was a decline in incidence of hepatocellular carcinoma (HCC), the study results showed that zinc administration and platelet count were the factors contributing to a reduction in HCC incidence.[21]

A study was conducted on zinc supplementation effect on biochemical profile of patients suffering from chronic hepatitis C infection receiving combination of ribavirin and pegylated interferon alpha – 2b. The study results demonstrated a decrease in serum ALT in patients receiving zinc. Moreover, the study further showed complete disappearance of HCV RNA in all the patients receiving zinc after 48 week interval in comparison to control group.[22]

This study has certain limitations. We did not evaluate HRQoL of the patients. Studies utilizing short form 36 questionnaire have shown improvement of physical component scale (PCS).[19] Another limitation of this study was study design was not randomized controlled trial and control group was not available. However, this study was the first of its kind from developing country like Pakistan that evaluated the role of zinc in patients with hepatic encephalopathy. Moreover, further studies with a longer follow up duration and evaluation of HRQoL are recommended in our population to further validate the results of present study.

CONCLUSION

Our study has shown that oral supplementation of zinc acetate in addition to standard therapy resulted in improvement in blood levels of ammonia, number connection test and hepatic encephalopathy.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Riaz Hussain Awan	Contributed and conception and interpretation of data and gives its expert for manuscript designing.	
2	Ameet Jesrani	Contribution to conception and designing, acquisition and review of data.	
3	Latif Aziz Memon	Drafting of the article and shares expert research opinion and experience in finalizing the manuscript.	
4	Seema Nayab	Contribution and conception and interpretation of data and gives its expert for manuscript designing.	
5	Khadim Hussain Awan	Revision and corresponding author data collection and analysis.	
6	Faqeer Muhammad Awan	Contribution to conception and designing, acquisition and review of data.