

Role of Zinc in Patients Presenting with Recurrent Hepatic Encephalopathy in Medical Unit of Tertiarycare Hospital Lahore

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Abstract

Objective: To observe the effects of zinc replacement on hepatic encephalopathy. To reduce hospital admission and health burden by reducing episodes of recurrent hepatic encephalopathy.

Methods: This study was carried out on 160 patients presenting with hepatic encephalopathy in medical ward of services hospital Lahore. The aim of the study was to assess the role of zinc in the improvement of encephalopathy.

Results: The mean age of patients in group A was 55.78 and that in group B was 56.88 years. There was significant difference in mean value of hepatic encephalopathy grade in both groups A and B after 3 months of follow up (p-value 0.027) indicating zinc is beneficial in treatment of hepatic encephalopathy.

Conclusion: Our study showed that zinc replacement improved outcome in patients with Hepatic encephalopathy.

Key words: Hepatic encephalopathy, zinc supplementation, chronic liver disease.

Introduction

Cirrhosis is a diffuse hepatic process characterized by inflammation and regeneration leading to fibrosis.¹⁻² The complications of cirrhosis include HTN, ascites, hepato renal syndrome and HE. HE is a spectrum of neuro-psychiatric abnormalities in patients with liver dysfunction.³ The development of HE is explained by the effects of neurotoxic substances which occur in the setting of cirrhosis and portal hypertension.⁴ The development of HE negatively impacts patient's survival. The encephalopathy leading to hospitalization is associated with a survival probability of 42% at one (01) year and 25% at three (03) years.⁵ Approximately 30% of patients dying of end-stage liver disease experience HE approaching brain edema.⁶

The economic burden of HE is substantial. After ascites and GI bleed, hepatic encephalopathy is the 2nd most common reason for hospital admission. Hepatic encephalopathy is also the most common, possibly preventable cause of readmission.⁷ This results in a negative impact on employment and finances of patients and their caregivers.⁹⁻¹¹

Overt HE occurs in 30% to 50% of cirrhotic patients and tends to 10% to 50% of patients with TIPS.²⁴⁻²⁶ The prevalence varies between 30% to 84%.³²⁻³⁴ As the level of ammonia (NH₃) is increased in blood, the most common strategy is to reduce ammonia production or increase its metabolism outside the brain. To increase ammonia metabolism, one can administer L-Ornithine and L-aspartate which enhance ammonia incorporation to amino acid glutamine in skeletal muscles. An earlier approach to decrease protein intake in diet led to decreased muscle mass, so this is no longer recommended now.¹²⁻¹⁴

Maintaining muscle mass is important because a chemical reaction that removes ammonia by incorporating it into glutamine can occur in the skeletal muscles.¹⁵

Zinc deficiency is common in cirrhosis and results in altered nitrogen metabolism.³ The recommended

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dietary allowance is 8 mg/day for women and 11 mg/day for men. The low serum zinc level in cirrhotic patients is due to decrease intake, decrease absorption, decrease bio availability and increase loss (because of metabolism).²

In study of Stamoulis et al in 2007, the prevalence of low serum zinc in cirrhotic patients was 65.3%.⁴

Because low serum zinc level precipitates HE, so zinc supplementation is considered a potential therapeutic option. The oral zinc replacement improved performance on number connection test (NCT), but no evidence about other clinical and biochemical outcomes available.

In one randomized trial average HE grade was 1.3+0.9 with the placebo while 0.9+0.9 with zinc supplementation (N=39, P<0.05) and NCT was 70.6+29.7 seconds with the placebo while 63.6+22 with the zinc.⁶

Literature has reported that zinc supplementation is better than no zinc. There is only one local study available which showed improvement in HE by zinc supplementation.

Objective

The objective of this study is to assess the beneficial effect of zinc supplements in the treatment of hepatic encephalopathy so the burden of recurrent admission could be reduced.

Methods

In this study 160 patients presenting with the Hepatic encephalopathy were included. Half of them (80) patients were given standard treatment for Hepatic encephalopathy i.e. Refixamin, Lactulose and branched chain amino acids were given, while the other half of patients were given standard treatment along with zinc supplements. Number connection test was carried out to assess the effect of treatment and time noted in seconds.

Inclusion Criteria: All the patients presenting with Hepatic encephalopathy were included in the study.

Exclusion Criteria:

1. Patients with organic brain disease like stroke, encephalitis, meningitis.

2. Patients with other causes of encephalopathy like uraemic encephalopathy in advanced renal failure, hypoglycaemia and severe electrolyte imbalance.

Study Design: Randomized controlled trial 160 patients with the hepatic encephalopathy were admitted through emergency and OPD over a period of 6 months. They are kept randomly in Group: A and B. Group A includes those on a standard therapy while the Group B includes standard therapy along with the zinc supplement. NCT was done during stay in the hospital at the discharge. Patients were advised to visit monthly for the follow up and NCT and recorded on the Performa.

Setting: medical unit-II of Services Hospital Lahore

Sampling Technique: Non probability consecutive sampling.

Data Analysis: SPSS 20

Results

Table 1: Percentage Distribution of Standard Treatment Group and Zinc Supplementation Treatment Group across NCT

NCT	Treatment Group		Total
	Standard Only	Standard +Zinc Supplementation	
<30	11 (13.8%)	15(18.8%)	26(16.3%)
31-50	19(23.8%)	32(40.0%)	51(31.9%)
51-80	34(42.5%)	21(26.3%)	55(34.4%)
81-120	13(16.3%)	11(13.8%)	24(15%)
Force End	3(3.8%)	1(1.3%)	4(2.5%)
Total	80(100%)	80(100%)	160(100%)

Figure-1 Multiple Bar Chart showing Percentage Distribution of Standard Treatment Group and Zinc Supplementation Treatment Group across NCT

Majority of patients (18.8%+40%=58.8%) who were given zinc supplementation along with standard treatment have low level of NCT (<50) as compared to those who were given only standard treatment.

Table 2: Comparison of NCT Across Standard Treatment and Zinc Supplementation Treatment Using Mann – Whitney U Test.

Treatment Type	Mean Rank of NCT	Mann-Whitney U	P-value
Standard Treatment	88.26		0.027
Zinc Supplementation	72.74	2579.5	

Table 3: Comparison of NCT across Standard Treatment and Zinc Treatment Using Mann-Whitney U Test (Stratified for Gender and Age)

		n	Mean Rank of NCT on Standard Therapy	Mean Rank of NCT Zinc Supp. & Standard Therapy	Mann-Whitney U	P-value
Gender	Male	106	58.71	48.29	1128.5	0.069
	Female	54	30.09	24.91	294.5	0.206
Age	35-45	20	11.53	7.40	22.0	0.197
	46-55	48	28	22	210.0	0.126
	>55	92	49.50	43.63	922.5	0.273

Majority of patients (34.4%) have NCT 51-80 irrespective of treatment groups.

Average rank for zinc supplementation is lower as compared to standard that indicates that there is improvement in the NCT for adding Zinc supplementation along with standard treatment. Difference in the NCT is significant among the two groups (p-value=0.027).

Table 4: Comparison of NCT for Treatment with Zinc Supplementation Using Mann-Whitney U Test across Gender and Age.

		n	Mean Rank of NCT	Test	P-value
Gender	Male	53	41.54	Mann-Whitney U Test=660.5	0.557
	Female	27	38.46		
Age	35-45	5	35.30	Kruskal Wallis Test=3.502	0.174
	46-55	28	34.91		
	>55	47	44.38		

Mean rank for zinc supplementation group has thoroughly lower value for various categories of gender and age as compared to standard treatment group. P-value for zinc supplementation and standard treatment is not significantly different for all categories of gender and age.

Effect of zinc supplementation on NCT is not significantly different among male and female (p-value=0.557). Similarly it has not significantly different effect on NCT for three age groups (p-value=0.174).

Discussion

It has been shown that zinc which is a trace metal is deficient in patients with chronic liver disease and is involved in metabolic abnormalities primarily pertaining to ammonia which can be alleviated by zinc replacement⁴. Zinc is an important, cheap and readily available mineral having many effects in HCV related

cirrhotic patients. HE is characterized at the neurophysiological level by disturbed corticocortical and corticomuscular coupling causing primary gliopathy.¹⁶ Ammonia is a key pathophysiological factor in HE.¹⁷ Zinc supplementation has shown to reduce ammonia levels in experimental animals and humans through hepatic urea synthesis stimulation and glutamine synthesis in skeletal muscles.¹⁸ Several reports describe zinc supplementation improving psychometric performance with a reduction in blood ammonia level in HE patients.³ In addition, combinations of zinc and conventional therapies such as a protein-restricted diet including BCAA preparation or lactic acid have been reported as effective therapies for HE. Hayashi et al.¹⁹ reported that combination treatment with BCAA and zinc supplement decreased blood ammonia level more than BCAA treatment alone in cirrhotic patients during the study period.

According to a recent meta-analysis three studies reported data on number connection test; all three showed an improvement in performance in the zinc group compared to placebo or standard therapy. This improvement suggests a beneficial effect of oral zinc in encephalopathy patients. These findings were also similar to the findings of our study as we found improved performance on the patients of encephalopathy patients with the use of zinc.²⁰⁻²² According to Takuma et al, in their study, zinc supplementation in addition to standard treatment clearly demonstrated improved liver function and HE in decompensated liver cirrhosis.⁶ Although the studies show improvement in HE but in Pakistan, limited data was available. One study at Allied Hospital Faisalabad compared the HE outcome during hospital stay of one week between standard treatment and with zinc along standard treatment which showed improvement.²³⁻²⁴ While another study at the same hospital showed improvement in HCV viral load when treated with

zinc.²⁵ In our study we have given zinc for three month period and assessed the improvement via NCT. In our study 160 patients were participated including 80 in each group. Those replaced with the zinc show improvement in NCT with p value of 0.027.

In gender distribution males show more response to therapy as compared to females but the difference is not significant. This might be because of more number of males in the study. Our females do it early according to NCT rank.

Age wise patients with the age of 46-55 years show more response followed by age 35-45 years and more than 55 years respectively. Although this difference is not significant with the p value 0.174 but it do exist.

Recommendations

As many studies show improvement with the zinc replacement along with the standard therapy, so keeping in view the health burden of decompensated liver disease one of which is HE results into repeated admissions. So zinc supplementation seems to be effective treatment for HE along with standard therapy to treat it. However more follow up studies should be conducted at other hospitals as well, so the large data could be analyzed and treatment be implemented.

List of Abbreviations

CLD: chronic liver disease

BCAA: Branched chain amino asides

HE: Hepatic encephalopathy

NCT: Number connection tests

Authors Contribution

AK: Main Author

AK: Statistical Analysis

SS: Write-up of Paper

NA: Helped in write-up

KT: Computerized write-up and editing

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