Original Article

Impact of Zinc Deficiency on Grade of Hepatic Encephalopathy: A Clinical Study at Ghurki Trust Teaching Hospital, Lahore

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ABSTRACT

Introduction: Zinc is an important cofactor in ammonia metabolism in the liver and in the regulation of cognitive functions. Deficiency of this trace mineral is common in patients with advanced hepatic disease, and has been blamed for hepatic encephalopathy (HE) degeneration. The current study determined the effect of 12 weeks of oral zinc supplementation on serum zinc concentrations in patients with liver cirrhosis.

Methods: This single-center, prospective, pre-post interventional study was conducted at Ghurki Trust Teaching Hospital, Lahore, from July to December 2025. A total of 240 cirrhotic individuals (Child-Pugh class B-C) were recruited for this study. The patients received oral zinc sulfate (50 mg) twice daily up to 12 weeks and underwent follow-up to assess improvement in zinc levels and the grade of hepatic encephalopathy. Serum zinc levels were measured by atomic absorption spectroscopy at baseline and after 12 weeks of supplementation.

Results: The study participants had significantly lower serum zinc levels (mean, 37 ± 10 µg/dL) and higher plasma ammonia levels (mean, 85 ± 20 mmol/L) at baseline. Among them, 20.8% (n=50) had West Haven grades III, and 20.8% (n = 50) had grade IV, while the rest fell into grades I-II. There was a significant elevation in mean serum zinc levels (78 + 15 µg/dL; p<0.001), accompanied by a reduction in mean ammonia levels (60 + 18 µmol/L; p<0.001) after Zinc supplementation. There was a significant increase in the proportion of the participants with no or minimal HE (grade I) from 12.5% to 41.7% (p<0.01). On the contrary, the number of participants with severe HE (grade IV) decreased from 20.8 to 8.3 percent.

Conclusion: Zinc supplementation in cirrhosis significantly reduces ammonia concentrations and is associated with an overall improvement in HE grading.

Keywords: Zinc deficiency; Hepatic encephalopathy; Cirrhosis; Serum ammonia; West Haven grade

INTRODUCTION

Chronic liver disease is a major global health burden that accounts for a serious morbidity and mortality burden in a variety of different populations. Hepatic encephalopathy (HE), which is a common and disabling complication of cirrhosis, occurs in 30-40% of patients with cirrhosis over the course of their disease. The clinical spectrum of HE is wide ranging between mild cognitive lapses and frank coma, and severity is classically graded using the West Haven classification (grades I-IV).[1,2]

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However, in the pathophysiology of HE, hyperammonemia is a key driver. Impaired hepatic function reduces urea cycle function and leads to ammonia depletion. Increased plasma ammonia crosses the blood-brain barrier with ease, causing the swelling of astrocytes, which disrupts neurotransmissions and leads to the breakdown of cerebral functions.[3,4] Zinc, an essential trace element that acts as an essential cofactor in many hepatic enzymes of ammonia detoxification, is most important among them, being ornithine transcarbamylase (OTC) in the urea cycle.[5] In the case of cirrhosis, an association of several factors, such as hypoalbuminemia, malnutrition, impaired intestinal absorption, increased urinary losses, chronic inflammation, and cholestasis, predisposes to zinc deficiency.[5] Consequently, deficiency of zinc is very common in cirrhotic populations with reported rates of between 50% and 80%, especially in the late stages of liver disease.[6] Both experimental and clinical findings show that zinc deficiency causes a deficiency in ammonia metabolism by lowering the activity of OTC and thereby aggravates hyperammonemia and is implicated in the development and progression of HE.[7]

A growing body of observational research has supported a strong correlation between low serum zinc levels and increased severity of HE. For example, Kumar et al

reported that an overwhelming majority of cirrhotic patients with overt HE are deficient in zinc, with serum concentrations being inversely correlated with Child-Pugh class and West Haven grade.[8] Similarly, Deep et al. reported significantly low serum zinc concentration in patients with decompensated cirrhosis when compared to controls and found a strong negative correlation between zinc concentration and HE severity.[9] On the other hand, zinc repletion has shown clinical benefit in patients with HE. A systematic review and meta-analysis of randomized controlled trials showed a significant benefit in the psychometric performance of individuals with mild HE following zinc supplementation in combination with standard lactulose therapy, despite only a moderate decrease in serum ammonia levels.[10,11] A prospective randomized double-blind trial in patients with minimal HE showed that 12 weeks of zinc supplementation (45 mg/day) led to significant improvements in neurocognitive test results and quality-of-life indices.[6] Further clinical investigations lend credence to the usefulness of oral zinc therapy in improving HE- related outcomes, and this is especially true in patients with a known deficiency in zinc.[7] Acute zinc deficiency is present in those with alcoholism, renal failure, hepatitis, and sexually transmitted viral hepatitis.[12] The importance of zinc in these cases can be explained by its ability to stimulate essential metabolic pathways such as the renin-angiotensin system and mitochondrial oxidative phosphorylation.[13]

Despite this growing body of evidence, relatively few studies of zinc supplementation in the form of prospective interventional studies have quantified the effect of supplemental zinc on changes in HE severity using standardized clinical grading systems. The present 12-week interventional study, done at Ghurki Trust Teaching Hospital, Lahore, evaluates 240 patients with advanced liver disease and assesses the change in serum zinc levels, serum ammonia, and West Haven HE grade pre-supplementation and post-supplementation of zinc. We hypothesize that correction of zinc deficiency will cause an increase in serum zinc concentrations, attenuate hyperammonemia, and result in measurable improvements in HE severity. By correlating biochemical changes to outcome as part of clinical practice in this study, an effort is made to further clarify the importance of zinc supplementation in the management of hepatic encephalopathy, consistent with prior data and current clinical recommendations.[10-13]

PATIENTS AND METHODS

This single-center study was carried out at Ghurki Trust Teaching Hospital, Lahore, from July to December 2025. Ghurki Trust Teaching Hospital in Lahore is a tertiary-level liver clinic. Ethical clearance was obtained from Ghurki Trust Teaching Hospital, Lahore (Ref. No. 2025/08/R-59 dated August 13, 2025) before starting the study. The study group consisted of adult patients with liver cirrhosis of any etiology with concomitant signs and symptoms of overt hepatic encephalopathy (West Haven grades I - III). Confirmation of cirrhosis was based on clinical, laboratory, and imaging criteria. Exclusion criteria were grade IV hepatic encephalopathy (coma), acute alcohol intoxication, ongoing gastrointestinal hemorrhage, sepsis, renal failure with the need for dialysis, a diagnosis of Wilson's disease or hemochromatosis, acute zinc supplementation, and patient refusal of participation. All participants continued to receive the standard care, which included lactulose with or without rifaximin as clinically indicated.

The study was powered based on preliminary data and existing literature to enroll a total of 240 participants to detect a minimal clinically meaningful increase of 15 µg/dL of serum Zinc concentration (SD 30) with 90% power and a two-tailed alpha level of 0.05.[8]

At the baseline stages, each patient had undergone a detailed clinical examination, including West Haven's grading of hepatic encephalopathy (I = trivial lack of awareness, II = confusion, and III = stupor). Those forms are baseline laboratory studies such as serum zinc using atomic absorption spectroscopy (manufacturer, analyzer model, reference range, fasting/non-fasting sample, location?) (<60 µg/dL imbalance, <60 µg/dL insufficiency, 60-80 µg/dL, and venous ammonia using an enzymatic test. Child-Pugh and MELD scores were determined. Nutritional status was recorded using body mass index and mid-arm circumference. All participants were provided with 50 mg (elemental zinc) of oral zinc sulfate tablets twice daily with meals for 12 weeks. Adherence was strengthened at the time of each clinic visit, and no concomitant therapies to treat hepatic encephalopathy were changed.

The patients were then reassessed after 6 and 12 weeks. Changes in (1) serum Zinc concentration, (2) venous ammonia concentrations, and (3) the West Haven hepatic encephalopathy grade at 12 weeks compared to baseline were the primary endpoints. Secondary outcomes were the change in a neuropsychiatric test of number connection and the incidence of any adverse events. The diagnosis of hepatic encephalopathy grade was made by two hepatologists who were blinded to the zinc status. All the biochemical tests were performed in the same certified laboratory using standardized methodologies.

Data were analyzed by using Student's paired t-test for continuous variables and the chi-square test for categorical variables. Means and standard deviations were presented for normally distributed data. A p-value of less than 0.05 was considered a statistically significant effect. Statistical analyses were done using Stata v. 15.1 (StataCorp).

RESULTS

A total of 240 patients with advanced chronic liver disease and hepatic encephalopathy were included and completed the 12-week study period. The mean age of the participants was 54+12 (n = 13,817) years, with males predominating (158 men; 65.8%). The most common etiology of cirrhosis was chronic hepatitis C infection 48%, followed by hepatitis B 20%, alcohol-related liver disease 15%, non-alcoholic fatty liver disease (NAFLD, 10%), and other causes (autoimmune and cryptogenic cirrhosis, 7%). Disease severity was high at baseline, with 81% of patients being Child-Pugh class B or C, reflecting decompensated liver disease. The mean Model for End-stage Liver Disease (MELD) score was 16 (4), which was consistent with moderate-to-severe hepatic dysfunction. Baseline nutritional status was poor as indicated by a mean serum albumin level of 2.8 + 0.6 g/dL. Zinc deficiency was very common at enrollment. The average baseline serum concentration of zinc was 37 (10) µg/dL (range of 20-58 µg/dL). Overall, zinc levels in the patients amounted to 92% serum zinc concentrations <60 µg/dL, and all patients had serum zinc concentrations <80 µg/dL, confirming universal zinc insufficiency in this group of patients. Baseline venous ammonia levels were quite high, with a mean ammonia level of 85 + 20 (normal range <50 µmol/L) (Table 1).

Following 12 weeks of oral zinc supplementation, a marked, statistically significant improvement was observed in biochemical parameters associated with hepatic encephalopathy. Mean serum zinc concentration increased from 37 ± 10 µg/dL at baseline to 78 ± 15 µg/dL at week 12 ($p < 0.001$). Correspondingly, mean venous ammonia levels decreased significantly from 85 ± 20 µmol/L to 60 ± 18 µmol/L ($p < 0.001$), indicating improved ammonia detoxification.

Table 1: Baseline Demographic and Clinical Characteristics (n = 240)

Characteristics	Frequency
Age (years), mean ± SD	54 ± 12
Male gender, n (%)	158 (65.8)
Etiology of cirrhosis, n (%)	
Hepatitis C	115 (48)
Hepatitis B	48 (20)
Alcohol-related	36 (15)
NAFLD	24 (10)
Other	17 (7)
Child–Pugh class B/C	194 (81)
MELD score, mean ± SD	16 ± 4
Serum albumin (g/dL), mean ± SD	2.8 ± 0.6
Serum zinc (µg/dL), mean ± SD	37 ± 10
Serum ammonia (µmol/L), mean ± SD	85 ± 20

The proportion of patients with clinically significant hyperammonemia (>75 µmol/L) declined from 58% at baseline to 18% after supplementation, representing a relative reduction of nearly 70%. Both changes were highly significant in paired t-testing, underscoring the biochemical efficacy of zinc therapy (Table 2).

At baseline, HE severity was predominantly moderate to severe. Specifically, 30 patients (12.5%) were classified as West Haven grade I, 90 (37.5%) as grade II, 70 (29.2%) as grade III, and 50 (20.8%) as grade IV. Following zinc supplementation, there was a substantial shift toward milder disease categories.

At week 12, 100 patients (41.7%) were classified as grade I, 80 (33.3%) as grade II, 40 (16.7%) as grade III, and only 20 patients (8.3%) remained grade IV. Overall, 58% of patients improved by at least one HE grade, and 45% transitioned from severe HE (grades III–IV) to mild or moderate disease (grades I–II). This redistribution of HE grades was statistically significant (χ^2 test, $p<0.01$), indicating a clinically meaningful improvement associated with zinc therapy (Figure 1).

Table 2: Effect of Zinc Supplementation on Biochemical Parameters

Parameter	Baseline (mean ± SD)	Week 12 (mean ± SD)	p-value
Serum zinc (µg/dL)	37 ± 10	78 ± 15	<0.001
Serum ammonia (µmol/L)	85 ± 20	60 ± 18	<0.001

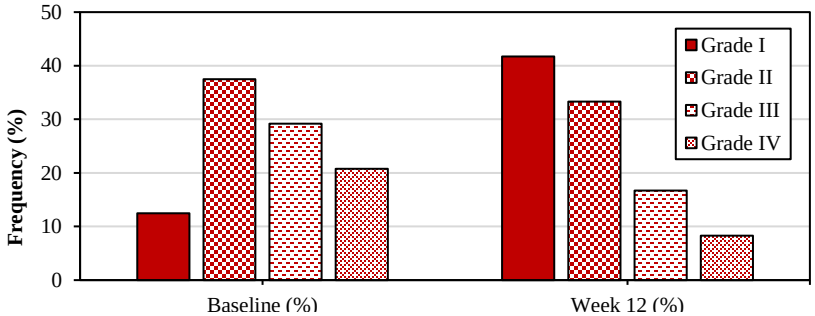

Figure 1: Distribution of West Haven HE grades before and after zinc supplementation. Zinc therapy resulted in a marked increase in mild HE (grade I) and a significant reduction in severe HE (grades III–IV).

DISCUSSION

In a cohort of 240 patients who had advanced cirrhosis, correction of zinc deficiency caused a significant increase in serum zinc concentrations, as well as a marked reduction in both plasma neurotoxicity (ammonia levels) and severity of hepatic encephalopathy (HE). These biochemical and clinical findings are very consistent with previous studies. Zinc is an essential cofactor in the urea cycle, so when zinc is deficient, production of ornithine transcarbamylase and glutamine synthetase is reduced, leading to precipitation of hyperammonemia. In accordance with this mechanistic premise, we documented the strong inverse relationship between zinc and ammonia: a 29.4% decrease in mean ammonia concentrations was seen with this increase in zinc levels. This finding is in agreement with a recent study in which decreased plasma ammonia was reported in zinc-electrolyzed HE patients.[14] Likewise, recently, a randomized controlled trial of 12 weeks of 45 mg/day zinc supplementation in patients with mild HE showed a trend towards a reduced ammonia (from 89 to 73 µmol/L, p=0.058) with improvements in cognition.[8] Our clinical outcomes build on the available literature. Deep et al. also found an inverse correlation between zinc status and West Haven gradation. Our interventional data support the opposite trend: zinc repletion reallocates patients to lower HE grades (I - II, Figure. The proportion of patients with severe (III - IV) HE dropped from 50 percent to 25 percent.[9] These grade improvements hold good sound for history: a seminal 1984 Lancet trial has shown that short-term zinc acetate significantly improved HE at the cost of placebo (before the time frame of our current investigation).[15] Recent systematic reviews have focused on cognitive endpoints; consulting the work of Shen et al. (2019), which documented an impact of adjuvant therapies: Zinc and lactulose improved psychometric test scores among patients with mild HE; however, with little impact on overall mortality or extensive clinical outcomes.[10] Our data offer quantitative rigor to HE grade as an outcome measure. By week 12, total serum zinc concentrations had normalized in the majority of participants, exhibiting not only sufficient compliance but also excellent bioavailability. Concurrently with a significant decrease in reading speed (at least in a few tasks), positive effects on functional assessment were observed: the times relating to the number connection test decreased significantly. These findings add more weight to the idea of the neuromodulatory functions of zinc. Zinc has both antioxidant and anti-inflammatory properties, and its deficiency can induce neurological dysfunction within the central nervous system.[16] In our cohort, however, no appreciable benefit was noticed in survival or ascites during the 12 weeks (secondary outcomes not displayed) - this is similar to the meta-analysis by Dhanda et al., which detected no benefit in mortality from zinc in the pre-mortality period in cirrhosis.[11] Nevertheless, the effect of zinc on the quality of life and cognitive function is still obvious. These findings have real-world clinical implications. Present guidelines for treating cirrhosis focus on optimization of nutritional status; however, routine assessment of zinc status is rare. Our results therefore suggest that clinicians include screening for zinc deficiency for patients with HE and consider zinc supplementation. The observed increase in patients assigned to grade I (41.7%) suggests that many patients may progress from overt to minimal HE, and this may have a possible attenuation effect on hospitalization rates (overt HE admissions were not directly captured in this analysis). Moreover, the lack of any serious adverse events confirms that this is a safe dose to administer zinc in cirrhotic patients, as reported previously.

Limitations of our study include the lack of a placebo-controlled arm of the study and a single-center study. Moreover, the cerebrospinal fluid concentrations of zinc and the ammonia metabolism were not studied in detail. Nevertheless, the pre-post design and substantial sample size provide strong evidence of the observed effects. A potential area for future studies would be comparisons of the effects of zinc with other agents that reduce ammonia or examining long-term outcomes.

CONCLUSION

This prospective clinical study shows that the supplementation of zinc in advanced patients with cirrhosis results in important biochemical and clinical benefits. The severity of the HE was lower, manifested by a lower proportion of patients with high West Haven grades. These findings, which are supported by modern clinical studies and mechanistic reviews, emphasize the important role of zinc in the pathophysiology of HE. For this reason, routine evaluation of zinc deficiency and adequate repletion should be added to the management paradigm for hepatic encephalopathy.

Author Contributions

HA: Conceptualization, Formal analysis, Writing – original draft.
SZ: Supervision, Writing – review & editing.
SZ: Methodology, Formal analysis.
MHNK: Investigation, Data curation, Validation. Had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.
AM: Investigation, Patient follow-up, Writing – review & editing.
AM: Writing – review & editing.

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