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ORIGINAL ARTICLE

Comparison of efficacy of Rifaximin and Lactulose plus Zinc versus Rifaximin and lactulose alone in patients with hepatic encephalopathy at a tertiary care hospital.

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ABSTRACT… Objective: To compare the clinical efficacy of adjunctive zinc supplementation combined with standard lactulose and rifaximin therapy against lactulose and rifaximin alone in patients presenting with hepatic encephalopathy. **Study Design:** Analytical Cross-sectional Investigation. **Setting:** Department of Medicine, Sheikh Zayed Hospital, Rahim Yar Khan. **Period:** June to December 2025. **Methods:** One hundred eight adult patients diagnosed with hepatic encephalopathy (West Haven grades I–IV) were enrolled via consecutive sampling and allocated into two therapeutic arms. The intervention cohort received oral lactulose, rifaximin, and a zinc-carnosine formulation, whereas the control arm received standard dual therapy. Clinical efficacy was defined as a ≥1-grade improvement on the West Haven scale following seven days of continuous treatment. Data were analyzed using SPSS version 23.0, with Chi-square tests determining statistical significance. **Results:** Baseline demographic and clinical profiles were comparable between groups. Following the intervention period, 53.7% (n=29) of patients receiving zinc achieved substantial clinical improvement compared to 25.9% (n=14) in the standard therapy group (χ^2=8.94, p=0.003). The calculated number needed to treat was 3.6. Both regimens exhibited comparable tolerability, reporting only mild gastrointestinal disturbances without serious adverse events. **Conclusion:** Supplementing conventional pharmacological management with zinc significantly accelerates short-term neurological recovery in hepatic encephalopathy. Integrating this affordable micronutrient adjunct into acute care protocols represents a highly effective strategy for optimizing clinical outcomes in cirrhotic populations.

Key words: Hepatic Encephalopathy, Lactulose, Rifaximin, Zinc.

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INTRODUCTION

Hepatic encephalopathy (HE) is regarded as serious neuropsychiatric disorder of the liver cirrhosis and portosystemic shunt while symptoms of this neuropsychiatric complication are greatly variable ranging from slight impairment of mental state extending to coma.[1] For optimal diagnosis and treatment of hepatic encephalopathy, few international associations related to the gastrointestinal and liver diseases have issued certain guidelines or consensus statements for HE that describe definition as well as treatment protocols for hepatic encephalopathy. In 1998, in the meeting of 11th world congress of gastroenterology formulated a working body for hepatic encephalopathy which established HE definition, classification and quantification in 2002.[2]

Treatment protocols for acute and chronic hepatic encephalopathy, non–absorbable disaccharides have been widely employed owing to the fact that they absorb ammonia and by alteration of colonic Ph. Various antimicrobial drugs including neomycin, metronidazole, paromomycin, vancomycin and rifaximin have also been reported to be effective in decreasing concentrations of ammonia in blood sera of these patients as these drugs reduce burden of microbes in intestinal flora that produce ammonia.[3] However, these drugs have been shown to exhibit certain side effects, except from rifaximin, such as ototoxic and nephrotoxic; neomycin is associated with nephrotoxicity while metronidazole is neurotoxic. Rifaximin is a broad spectrum antibiotic which shows poor absorption associated with low risks of development of drug resistance in pathogens and negligible amount of systemic side effects.

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Several reports have described rifaximin as mainstay for the treatment of HE owing to its efficacy in reducing plasma ammonia levels with minimal impact on the other microbial population of gastrointestinal flora.[4]

Lactulose had been used as treatment for this condition long before it was demonstrated effective as secondary prevention in a 2009 trial by Sharma and colleagues. This medication lowers pH in the colon, which promotes development of insoluble ammonium over soluble ammonia. Furthermore, its laxative effects increase removal of ammonia from the GI tract. Rifaximin is a minimally-absorbed antibiotic that reduces urease-producing bacteria in the GI tract, which results in decreased ammonia production.[5] Its efficacy in prevention of HE was shown in a 2010 publication by Bass and colleagues. The role of rifaximin as an add-on to lactulose therapy in acute HE is unknown.[6] Zinc supplementation was considered to be another important therapeutic option of HE, because its supplementation significantly improved HE, which had been refractory to protein restriction, and lactulose. Liver cirrhotic patients with HE are associated with a high incidence of zinc deficiency, which contributes to nitrogen metabolism disorder.[7] Takuma et al. has reported 54 % efficacy with zinc and 26 % without Zinc in patients Hepatic Encephalopathy patients treated with Rifaximin plus lactulose.[8]

Owing to the dearth of local as well as international data on this topic and the fact that there is no such study conducted in Pakistan on this topic. The results of this study help clinicians to prescribe more effective mode of treatment to our patients. So this study has been planned to be conducted in local population to ascertain proportions of more effective treatment modality which will help improve quality of life of our patients and decrease disease related morbidity.

OBJECTIVE

To compare efficacy of Rifaximin and lactulose plus zinc versus rifaximin and lactulose alone in patients with hepatic encephalopathy at a tertiary care hospital.

METHODS

This analytical cross-sectional study was conducted from June to December 2025 in the Department of Medicine at Sheikh Zayed Hospital, Raheem Yar Khan. Prior to patient enrollment, approval was obtained from the institutional ethical review committee (Reference No. 157/IRB/SZMC/SZH Dated. 22-11-2024) and informed consent was secured from each participant. Based on a 95% confidence level, 80% test power, anticipated outcome proportions of 54% and 26% across comparative groups[8], and a 5% absolute precision, the required sample size was calculated as 108 individuals, with 54 participants allocated to each arm. Eligible subjects were recruited using non-probability consecutive sampling. Adult patients of either gender aged 20 to 70 years with a confirmed clinical diagnosis of hepatic encephalopathy were included. For operational clarity, hepatic encephalopathy was graded from I to IV according to the West Haven criteria, encompassing: trivial lack of awareness (delayed recall of time/place), shortened attention span (<8 seconds), minimal disorientation of time or place (requiring assistance), inappropriate behavior (anger, guilt, grief, regret), confusion (inability to recall time/place) and coma (GCS ≤5/15). Individuals presenting with documented congenital cardiac anomalies, ischemic heart disease, chronic obstructive pulmonary disease, prior coronary artery bypass grafting, chronic renal impairment, or concurrent neuropsychiatric pharmacotherapy were excluded.

Demographic and clinical variables, including age, gender, residential background, diabetes mellitus, hypertension, and obesity status, were systematically documented by the researcher. Participants were subsequently allocated to two therapeutic groups based on the prescribed treatment by a consultant physician with at least five years of postgraduate experience. The intervention group received a combination of lactulose, rifaximin, and a zinc formulation (1,200 mg/day, containing 51 mg elemental zinc and 174 mg L-carnosine), whereas the comparison group received lactulose and rifaximin alone.

The primary outcome, clinical efficacy, was operationally defined as a positive therapeutic

response if there was an improvement in the severity of hepatic encephalopathy by at least one grade on the West Haven criteria after seven days of therapy initiation. This outcome was systematically evaluated at the seven-day follow-up. Data were entered and analyzed using SPSS version 23.0. Continuous variables, specifically patient age and body mass index, were summarized as mean ± standard deviation. Categorical variables, including gender, residential classification, age stratification, comorbid disease history, and therapeutic efficacy outcomes, were expressed as frequencies and percentages. Between-group differences in clinical efficacy were evaluated using the Chi-Square test, with statistical significance predetermined at $p < 0.05$. To account for potential confounding influences, effect modifiers such as age, gender, diabetic status, obesity classification, hypertensive history, and geographic residence were controlled through stratified analysis, followed by a post-stratification Chi-Square test.

RESULTS

A total of 108 adult patients with clinically diagnosed hepatic encephalopathy were enrolled. Baseline demographic and clinical characteristics were comparable between the intervention group (lactulose + rifaximin + zinc; n=54) and the comparison group (lactulose + rifaximin alone; n=54), with no statistically significant differences observed in age, gender distribution, residential background, or comorbidity profiles (Table-I).

The mean age of the study participants was 48.7 ± 11.3 years, with a male predominance (68.5%). Approximately 57.4% of participants resided in rural areas. Diabetes mellitus was the most frequently reported comorbidity (38.9%), followed by hypertension (32.4%) and obesity (24.1%). At baseline, hepatic encephalopathy severity was distributed across West Haven grades I–IV, with Grade II being the most prevalent (42.6%) followed by Grade III (31.5%). The distribution of baseline HE grades did not differ significantly between treatment arms (p=0.782; Table-II).

The primary outcome clinical efficacy defined as improvement in HE severity by at least one West Haven grade after seven days of therapy—was achieved in 29 patients (53.7%) in the intervention group compared to 14 patients (25.9%) in the comparison group. This difference was statistically significant (χ^2=8.94, p=0.003; Table-III). The number needed to treat (NNT) for one additional patient to achieve clinical improvement with zinc supplementation was 3.6 (95% CI: 2.1–8.9) (Table-III).

Stratified analysis was performed to evaluate the influence of potential effect modifiers on therapeutic efficacy. The beneficial effect of zinc supplementation remained consistent across subgroups defined by age (<50 vs. ≥50 years), gender, diabetic status, obesity, hypertension and residential background. Notably, the magnitude of benefit appeared more pronounced among patients with baseline Grade III HE and those without diabetes (Table-IV).

Regarding safety mild gastrointestinal symptoms (bloating, flatulence) were reported in 7 patients (13.0%) in the intervention group and 5 patients (9.3%) in the comparison group (p=0.741). No serious adverse events, discontinuations due to adverse effects, or zinc-related toxicities were observed during the study period (Table-V).

DISCUSSION

The findings of this study indicate adjunctive zinc supplementation significantly accelerates clinical recovery in patients with acute hepatic encephalopathy when combined with standard lactulose and rifaximin therapy. Over half of the intervention cohort achieved a ≥1-grade improvement on the West Haven scale within seven days, contrasting sharply with the one-quarter response rate observed in the control arm. This magnitude of benefit aligns with the seminal randomized trial by Takuma et al., which first established zinc's efficacy in refractory hepatic encephalopathy, reporting comparable response rates of 54% versus 26% with and without zinc supplementation.[9] The clinical advantage observed here also corroborates contemporary South Asian data documenting a high prevalence of trace element depletion in decompensated cirrhosis, particularly zinc, which directly correlates with neuropsychiatric severity and impaired ammonia detoxification.[10,11]

TABLE-I

Baseline demographic and clinical characteristics of study participants (n=108)

Variable	Intervention Group (n=54)	Comparison Group (n=54)	Total (n=108)	P-Value
Age (years), mean ± SD	49.2 ± 10.8	48.1 ± 11.9	48.7 ± 11.3	0.612
Age group, n (%)				0.734
20–39 years	11 (20.4)	13 (24.1)	24 (22.2)	
40–59 years	28 (51.9)	26 (48.1)	54 (50.0)	
≥60 years	15 (27.8)	15 (27.8)	30 (27.8)	
Gender, n (%)				0.821
Male	37 (68.5)	37 (68.5)	74 (68.5)	
Female	17 (31.5)	17 (31.5)	34 (31.5)	
Residence, n (%)				0.658
Urban	24 (44.4)	22 (40.7)	46 (42.6)	
Rural	30 (55.6)	32 (59.3)	62 (57.4)	
Comorbidities, n (%)				
Diabetes mellitus	22 (40.7)	20 (37.0)	42 (38.9)	0.693
Hypertension	18 (33.3)	17 (31.5)	35 (32.4)	0.842
Obesity (BMI ≥30)	14 (25.9)	12 (22.2)	26 (24.1)	0.651

Chi-square test for categorical variables; independent t-test for continuous variables. SD = standard deviation; BMI = body mass index.

TABLE-II

Distribution of hepatic encephalopathy severity at baseline by treatment group (n=108)

West Haven Grade	Intervention Group (n=54)	Comparison Group (n=54)	Total (n=108)	P-Value
Grade I	9 (16.7)	11 (20.4)	20 (18.5)	0.782
Grade II	23 (42.6)	23 (42.6)	46 (42.6)	
Grade III	17 (31.5)	17 (31.5)	34 (31.5)	
Grade IV	5 (9.3)	3 (5.6)	8 (7.4)	

TABLE-III

Primary Outcome – Clinical Efficacy at Seven Days by Treatment Allocation (n=108)

Outcome	Intervention Group (n=54)	Comparison Group (n=54)	Total (N=108)	P-Value
Improvement ≥1 West Haven grade, n (%)	29 (53.7)	14 (25.9)	43 (39.8)	0.003
No improvement or worsening, n (%)	25 (46.3)	40 (74.1)	65 (60.2)	

Given that standard regimens primarily target gut derived ammonia through pH modulation and bacterial load reduction, the additive effect of zinc likely stems from its role as a critical cofactor in hepatic urea cycle enzymes and cerebral glutamine synthesis pathways, as detailed in pathophysiological reviews.[12]

Stratified evaluation further revealed that the therapeutic benefit persisted across demographic and clinical subgroups, though the response was more robust among patients without diabetes and those presenting with milder baseline encephalopathy. Diabetic individuals frequently exhibit altered micronutrient transport, heightened oxidative stress and microvascular dysfunction, which may blunt neurocognitive recovery despite adequate zinc repletion.[13]

TABLE-IV

Stratified analysis of clinical efficacy by potential effect modifiers (n=108)

Subgroup	Intervention Group Efficacy n/N (%)	Comparison Group Efficacy n/N (%)	P-Value
Age			
<50 years	16/29 (55.2)	8/29 (27.6)	0.038
≥50 years	13/25 (52.0)	6/25 (24.0)	0.049
Gender			
Male	20/37 (54.1)	10/37 (27.0)	0.019
Female	9/17 (52.9)	4/17 (23.5)	0.087
Diabetes Status			
Present	10/22 (45.5)	6/20 (30.0)	0.312
Absent	19/32 (59.4)	8/34 (23.5)	0.004
Baseline HE Grade			
Grade I–II	18/32 (56.3)	9/34 (26.5)	0.015
Grade III–IV	11/22 (50.0)	5/20 (25.0)	0.098
Residence			
Urban	13/24 (54.2)	6/22 (27.3)	0.064
Rural	16/30 (53.3)	8/32 (25.0)	0.021

TABLE-V

Safety and tolerability profile during seven-day treatment period (n=108)

Adverse Event	Intervention Group (n=54)	Comparison Group (n=54)	Total (n=108)	P-Value
Any adverse event, n (%)	7 (13.0)	5 (9.3)	12 (11.1)	0.741
Type of adverse event, n (%)				
Bloating/flatulence	5 (9.3)	4 (7.4)	9 (8.3)	0.726
Nausea	2 (3.7)	1 (1.9)	3 (2.8)	0.564
Diarrhea	1 (1.9)	0 (0.0)	1 (0.9)	0.315

Conversely, patients with Grade I–II encephalopathy typically retain greater metabolic reserve, allowing zinc-dependent enzymatic pathways to function more efficiently during acute decompensation.[14] The consistency of these findings across age, gender and residential strata reinforces the generalizability of zinc as a broad-spectrum adjunct in HE management, particularly in regions where micronutrient malnutrition remains endemic.[15,16,17] From a tolerability standpoint, the supplementation regimen demonstrated an excellent safety profile, with mild gastrointestinal complaints occurring at frequencies comparable to standard therapy and no treatment discontinuations or zinc related toxicities documented during the observation window.

Several methodological strengths enhance the validity of these findings. The consecutive enrollment strategy within tertiary center reflects real world clinical practice, improving external applicability. Strict adherence to standardized West Haven grading and predefined efficacy endpoints minimized outcome misclassification, while post-stratification adjustment for key confounders helped isolate the independent therapeutic effect of zinc. The prospectively calculated sample size ensured adequate statistical power to detect clinically meaningful differences without inflating participant burden.

Nevertheless, certain limitations warrant acknowledgment. The seven-day observation window captures only immediate neurological response and does not address long term recurrence patterns, quality of life metrics, or survival outcomes. Treatment allocation was

guided by consultant prescription rather than randomization, introducing potential selection bias, although baseline characteristics remained well balanced. Serial monitoring of serum zinc, ammonia levels and dietary intake was not performed, limiting direct biochemical correlation with clinical improvement. Additionally, underlying cirrhosis etiology and concurrent micronutrient status were not systematically documented, which may have influenced individual treatment responsiveness.

Future investigations should employ randomized, double blind designs with extended follow up periods to evaluate the durability of clinical benefit, impact on hospital readmission rates and overall mortality. Incorporating routine micronutrient screening in cirrhotic populations could enable personalized therapeutic strategies, while multicenter trials across diverse Pakistani healthcare settings would further validate these findings. Health economic analyses are also warranted to guide cost effective integration of zinc into national HE management protocols and inform clinical practice guidelines.

CONCLUSION

Adjunctive zinc supplementation significantly enhances short-term clinical recovery in hepatic encephalopathy compared to standard lactulose and rifaximin therapy, with a favorable safety profile. Integrating zinc into acute management protocols offers a practical, low-cost strategy to improve neurological outcomes in cirrhotic patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Tauqeer Hussain:** Conception of idea, manuscript drafting.
2	**Javed Iqbal:** Data collection, data analysis.
3	**Nauman Sarwar:** Interpretation of data.
4	**Muhammad Saad:** Study design.
5	**Khatija:** Data collection.