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Efficacy Comparison of Nitazoxanide Combined with Lactulose versus Lactulose Monotherapy in Managing Overt Hepatic Encephalopathy

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Abstract

Objective: To evaluate the efficacy of combining Nitazoxanide with lactulose compared to lactulose alone in the treatment of overt hepatic encephalopathy.

Methods: This Comparative Cross-sectional Study was conducted at the department of Gastroenterology and Hepatology, Pakistan Institute of Medical Sciences, Islamabad from July 2019 to December 2019. In this study, 150 cirrhotic patients with overt hepatic encephalopathy were randomized into two groups: one receiving Nitazoxanide plus Lactulose (Group A) and the other receiving Lactulose alone (Group B). Patient demographics, aetiology of cirrhosis, MELD score, and efficacy of treatment were assessed. Statistical analysis was conducted to compare outcomes between the two groups.

Results: A total of 150 patients, with a mean age of 44.08 ± 11.31 years were enrolled. Hepatitis C was the predominant aetiology in 81 patients (54%). The mean MELD score was 23.24 in Group A and 22.36 in Group B. Upon admission, 20 patients (13.3%) presented with grade 2 hepatic encephalopathy (HE), while 70 patients (46.6%) had grade 4 HE. The duration of hospital stay showed statistical significance in both groups ($p < 0.001$). Furthermore, a significant difference in drug efficacy was observed between the two groups ($p < 0.005$).

Conclusion: In conclusion, our study suggests that combining Nitazoxanide with Lactulose yields superior efficacy compared to Lactulose alone in managing overt hepatic encephalopathy among cirrhotic patients.

Keywords: Comparison, Efficacy, Hepatic encephalopathy, Lactulose, Management, Nitazoxanide, Treatment.

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1. Introduction

Overt hepatic encephalopathy manifests as a spectrum of neuropsychiatric symptoms ranging from subtle alterations in cognition, attention, and motor function to severe manifestations such as confusion, coma, and even death.[1] It predominantly affects patients with advanced liver disease, particularly those with cirrhosis, where compromised hepatic function leads to the accumulation of neurotoxic substances such as ammonia and mercaptans in the bloodstream.[2,3] The presence of neurotoxins, combined with compromised hepatic clearance of neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate, leads to the disturbance of neurotransmission and synaptic function within the central nervous system (CNS), ultimately resulting in the onset of clinical symptoms associated with hepatic encephalopathy.[4]

According to epidemiological data, the prevalence of hepatic encephalopathy in cirrhotic patients ranges from approximately 30% in compensated cirrhosis to over 70% in patients with decompensated cirrhosis.[5] The pathophysiology of overt hepatic encephalopathy revolves around the concept of ammonia neurotoxicity. In the setting of liver dysfunction, impaired ammonia metabolism leads to the accumulation of ammonia in the bloodstream, crossing the blood-brain barrier and entering the central nervous system (CNS). Within the CNS, excess ammonia interferes with neurotransmission and synaptic function, disrupting the balance between excitatory and inhibitory neurotransmitters.[6] The impact of hyperammonemia on the brain is profound. It enhances the synthesis and release of glutamate, an excitatory neurotransmitter while impairing the conversion of glutamate to glutamine, leading to excitotoxicity and neuronal injury. Additionally, the reduction of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) further worsens the imbalance, ultimately contributing to the development of neuropsychiatric symptoms characteristic of hepatic encephalopathy. This highlights the critical importance of addressing hyperammonemia to prevent these detrimental effects on brain function.[7]

The West Haven Criteria is widely recognized for categorizing the severity of hepatic encephalopathy into different stages based on the level of cognitive impairment and consciousness. Nitazoxanide, an antiparasitic agent, has emerged as a promising adjunctive therapy for overt hepatic encephalopathy (OHE) due to its anti-inflammatory and neuroprotective properties.[8] Clinical studies have

indicated that Nitazoxanide, when combined with standard therapy such as lactulose, has the potential to decrease ammonia levels and alleviate symptoms of OHE. This suggests that Nitazoxanide could be an effective treatment option for improving cognitive function in OHE patients.[9] Lactulose, a non-absorbable disaccharide, remains the cornerstone of OHE management due to its ability to lower colonic pH, reduce ammonia absorption, and induce catharsis. Combining lactulose with Nitazoxanide may offer synergistic effects, enhancing therapeutic efficacy in managing OHE. However, further research is needed to elucidate the optimal dosing regimens, safety profile, and long-term outcomes of this combination therapy in OHE patients.[10]

The current study aims to investigate the potential efficacy of combining Nitazoxanide with lactulose for treating overt hepatic encephalopathy (OHE) to improve patient outcomes. Nitazoxanide, an antimicrobial agent, may enhance the treatment of OHE due to its broad-spectrum activity against gut pathogens and ability to reduce ammonia production. Given the role of intestinal dysbiosis in OHE, Nitazoxanide's antimicrobial action may complement lactulose's ammonia-reducing effects. This study evaluates whether this combination therapy offers superior efficacy compared to lactulose monotherapy, potentially influencing future treatment guidelines.

2. Materials & Methods

After approval from the hospital's ethical review board (ERB), this comparative cross-sectional study was conducted at the Department of Gastroenterology and Hepatology, Pakistan Institute of Medical Sciences from July 2019 to December 2019. Informed consent was obtained from all participants. The sample size calculated using the WHO sample size calculator, with a power of 80% and a significance level of 5%, revealed 75 patients needed per group, totalling 150 patients. Anticipated efficacy proportions were set at 76% for the NTZ+LAC Group and 54% for the other LAC monotherapy group.16 The sampling technique employed in this study was non-probability consecutive sampling. Female and Male patients aged 18 to 80 years with Liver Cirrhosis and Hepatic Encephalopathy according to West Haven criteria were included in the study.

Pateints with Creatinine > 1.5mg/dl at admission, active alcohol intake < 4 weeks before the present episode, Hepatocellular carcinoma & Degenerative CNS disease or major psychiatric illness were excluded from the study.

Eligible participants were randomly assigned to one of two study arms: A combination therapy group (Nitazoxanide + lactulose) or a Control group (lactulose alone). Randomization was performed using computer-generated randomization sequences, and allocation concealment was ensured. Despite this, the distribution of subjects across the two arms was not uniform, which will be addressed with statistical adjustments during data analysis. Participants in the combination therapy group received Nitazoxanide (one 500 mg tablet twice daily) in addition to standard therapy with lactulose (30–60 ml three times a day) along with antibiotics such as rifampin, as well as other treatments like PPIs and diuretics. To rule out the confounding effects of these treatments, we will monitor and document all concurrent medications and use statistical methods to adjust for their impact during data analysis. Participants in the control group received standard therapy with lactulose alone (30–60 ml/three times a day). The duration of treatment was a total of 7 days, and treatment adherence was monitored closely. The primary outcome measure was the efficacy in both groups. Efficacy was labelled if there was a significant improvement in hepatic encephalopathy symptoms, such as reduced confusion, improved cognitive function, and decreased severity of asterixis, with a reduction in symptoms of ≥50%. Mortality was labelled as the occurrence of death among patients during the study period.

Data was analysed using SPSS 22. The mean and standard deviation of quantitative variables like age, hospital stay, and days for recovery were shown by descriptive statistics, while frequency and percentages showed qualitative variables like Child Class, gender, efficacy, and encephalopathy grades. Quantitative variables were compared using independent samples t-tests, whereas qualitative variables used chi-square testing. A p-value under 0.05 was significant.

3. Results

Table 1 compares gender and age distribution between the NTZ+LAC and LAC groups. In the NTZ+LAC group, 78.66% were male and 21.33% female, while the LAC group had 40% male and 60% female participants. The total male percentage across both groups was 59.3%, and females was 40.6%. The mean age of participants in the NTZ+LAC group was 44.27 ± 11.31 years. The distribution of Child-Pugh Class and Encephalopathy Grade was similar between the NTZ+LAC and LAC groups. For Encephalopathy Grade, the distribution across grades 2, 3, and 4 was also

similar (p = 0.346), with a higher proportion of patients in grades 3 and 4 in both groups in Table 2.

Table 1: Comparison of Gender and Age Distribution between NTZ+LAC and LAC Groups

Variable	Type	NTZ+LAC Group	LAC Group	Total
Gender	Male	59(78.66%)	30(40%)	89 (59.3%)
	Female	16(21.33%)	45(60%)	61 (40.6%)
Age	Mean ±SD	44.27±11.31 years		-

Table 2: Comparison of Encephalopathy Grade between NTZ+LAC and LAC Groups

Variables	Categories of Variables			P-Value
Encephalopathy Grade	EG 2	EG 3	EG 4	0.346
NTZ+LAC	13(17.3%)	28(37.3%)	34(45.3%)	
LAC	7(9.3%)	32(42.6%)	36(48%)	
Total	20 (13.3%)	60 (40%)	68 (45.3%)	

In Table 3 in Group A, the mean MELD score was 24.24±2.5, while in Group B, it was slightly higher at 24.76±2.1. The range of MELD scores in Group A ranged from 28 to 14, whereas in Group B, it ranged from 28 to 12. Additionally, the mean hospital stay in Group A was 2.34±1.11 days, whereas in Group B, it was slightly longer at 2.42±1.7 days.

Table 3: Comparison of Mean MELD Score, Range of MELD Score, and Mean Hospital Stay between Group A and Group B

Variables	Group A	Group B
Mean MELD Score	24.24±2.5	24.76±2.1
Range of MELD Score	28─14	28─12
Mean Hospital Stay (Days)	2.34±1.11	2.42±1.7

Table 4: Comparison of Efficacy of Drugs between Group A (NTZ+LAC) and Group B (LAC) & mortality rates

Variables	Type	Group A	Group B	Total	P-value
Efficacy of Drugs	Yes	57 (76%)	41 (54%)	75 (100.0%)	0.006
	No	18 (24%)	34 (46%)	75 (100.0%)	
Mortality Rate	Yes	3 (2%)	4 (2.6%)	7 (4.6%)	0.576

In Group A (NTZ+LAC), 76% of patients experienced positive outcomes, while in Group B (LAC), 54% of patients reported positive results. The difference in efficacy between the two groups was statistically significant, with a p-value of 0.006. Group A (NTZ+LAC) had a mortality rate of 2%, and Group B (LAC) had a rate of 2.6%. The p-value for mortality was 0.576, suggesting that there was no significant difference in mortality rates between the groups.

4. Discussion

Hepatic encephalopathy is a neuropsychiatric complication of liver dysfunction, characterized by cognitive impairment and altered consciousness. The combination therapy of Nitazoxanide with Lactulose has shown promise in managing overt hepatic encephalopathy, potentially improving cognitive function, and reducing ammonia levels. However, Lactulose alone remains a cornerstone treatment for hepatic encephalopathy, acting as a non-absorbable disaccharide to promote ammonia excretion and alleviate symptoms.[11,12]

In our study, we observed a similar trend in gender distribution, with a higher proportion of males enrolled in the NTZ+LAC group compared to the LAC group, while more females were distributed in the LAC group. This finding aligns with Elrakaybi et al. (2015), who also reported a predominance of males in the Nitazoxanide group compared to the monotherapy group. However, the median age of patients in our study was lower in the NTZ+LAC group (44.27 years) compared to the Nitazoxanide group in Elrakaybi et al., indicating potential differences in patient demographics across studies.[13]

In our study, we observed significant differences in the aetiology of cirrhosis between patients receiving NTZ+LAC and those receiving LAC alone, echoing findings from Ali et al. (2014). Specifically, a higher proportion of patients in the NTZ+LAC group had Hepatitis B (36%) compared to the LAC group (28%), while a higher percentage of patients in the LAC group had Hepatitis C (61.3%) compared to the NTZ+LAC group (46.6%). Furthermore, our study and Ali et al. (2014) both investigated the range and mean MELD scores in patients with hepatic encephalopathy. While our study reported slightly higher mean MELD scores in both treatment groups (24.24±2.5 in Group A and 24.76±2.1 in Group B), Ali et al. found comparable

mean MELD scores but noted differences in the distribution of MELD score ranges. [14]

Our study's findings reveal notable differences between Group A (NTZ+LAC) and Group B (LAC) in the management of hepatic encephalopathy (HE). Specifically, the mean MELD score was slightly lower in Group A (24.24±2.5) compared to Group B (24.76±2.1), indicating a potential variation in disease severity between the treatment groups. This observation is consistent with the study by Abd-Elsalam et al. (2019), where the NTZ group demonstrated a more significant improvement in cognitive function, as evidenced by a decrease in CHESS scores.[15] .[18,19,20]

In our study, 76% of patients receiving Nitazoxanide plus Lactulose experienced positive outcomes, significantly higher than the 54% in the Lactulose-only group. This finding is consistent with research by Sharma et al., which demonstrated that Nitazoxanide significantly improved outcomes in patients with hepatic encephalopathy when used in combination with other therapies.[16] Similarly, Khalaf et al. found that the addition of Nitazoxanide improved therapeutic outcomes compared to Lactulose alone in hepatic conditions.[17] Despite these improvements, mortality rates in our study were comparable between the groups 2% in the NTZ+LAC group vs. 2.6% in the LAC group, $p = 0.576$), which is consistent with findings from Sanyal et al, who observed similar mortality rates across different treatment regimens for hepatic encephalopathy. The overall mortality rate of 4.6% in our study reflects broader literature trends, indicating that while Nitazoxanide plus Lactulose improves symptoms, it does not significantly alter mortality rates.[18]

One limitation of our study is the lack of long-term follow-up data, which could provide insights into the sustainability of treatment effects. Additionally, the study's single-center design may limit the generalizability of the findings to broader populations.

5. Conclusion

Based on our study findings, it is evident that the combination of Nitazoxanide and Lactulose offers significantly greater efficacy in managing overt hepatic encephalopathy among cirrhotic patients when compared to the use of Lactulose alone.

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Contributions:
T.H.J, A.A, S.A, S.S, Z.R, A.I - Conception of study
T.H.J, A.A, S.A, S.S, Z.R, A.I - Experimentation/Study Conduction
T.H.J, A.A, S.A, S.S, Z.R, A.I - Analysis/Interpretation/Discussion
T.H.J, A.A, S.A, S.S, Z.R, A.I - Manuscript Writing
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