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Efficacy of Lactulose and Polyethylene Glycol in the Treatment of Hepatic Encephalopathy

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ABSTRACT

Background: Hepatic encephalopathy presents a significant clinical challenge in individuals with advanced liver dysfunction, manifesting as confusion, altered consciousness, and personality changes. This study aimed to compare the efficacy of lactulose and polyethylene glycol in managing Hepatic encephalopathy.

Methods: The study is conducted at Tribhuvan University Teaching Hospital in Nepal; the study enrolled 45 cirrhotic patients with altered mental status in each study group. Ethical approval and informed consent were obtained. The basic demographic and clinical data were collected, including laboratory investigation and precipitating factors for Hepatic encephalopathy. The severity of Hepatic encephalopathy was assessed using the West Haven Criteria.

Results: In this study there was significant difference between two groups in terms of mean time taken for complete resolution of hepatic encephalopathy, with mean of 2.98 ± 2.129 days in Polyethylene Glycol group compared to mean of 4.67 ± 3.076 days in Lactulose group, with a significant p-value of 0.004. There was also significant difference in length of hospital stay between two groups, with a mean hospital stay of 6.36 ± 3.654 days in Polyethylene Glycol group compared to 9.70 ±5.388 days in Lactulose group, with a significant p-value of 0.001.

Conclusions: In conclusion, polyethylene glycol showed promising results in the treatment of Hepatic encephalopathy compared to lactulose polyethylene glycol. demonstrated an improvement and quicker resolution of Hepatic encephalopathy symptoms, highlighting its potential as a cost effective and safe alternative for managing Hepatic encephalopathy in cirrhotic patients.

Keyboards: Hepatic encephalopathy; lactulose; polyethylene glycol.

INTRODUCTION

Hepatic encephalopathy (HE) is a serious complication of liver dysfunction, characterized by confusion, disorientation, and impaired consciousness, potentially progressing to coma and death.[1,2] HE is one of the dreadful complication of reversible or irreversible liver dysfunction, affecting 30 % to 45 % of cirrhotic patient.[3] Minimal Hepatic Encephalopathy (MHE) is also common, with 53% of cirrhotic patients experiencing it, and 84% of those with overt HE having a history of MHE.[4] The condition poses a significant burden on both patients and caregivers.[5,6] Elevated blood ammonia levels play a key role in HE's pathogenesis, as ammonia crosses the blood-brain barrier and is metabolized into glutamine, impairing brain function. Recent treatments focus on reducing ammonia levels.[7] Polyethylene glycol (PEG) has shown effectiveness in resolving HE, with clinical trials indicating it can reduce hospital stays compared to lactulose.[8-10] This study aims to compare the efficacy of PEG and lactulose in treating HE using the West Haven Criteria (WHC).

METHODS

A cross-sectional single centered study was conducted among people who visited with symptoms of hepatic encephalopathy and were admitted to Department of Gastroenterology at Tribhuvan University Teaching Hospital (TUTH) in Maharajgunj, Kathmandu, Nepal. TUTH is one of the largest health institutions in Nepal and is known to provide a wide variety of medical services. The research was performed in a qualitative cross-sectional study design.

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After a thorough review process, ethical approval was obtained from Institutional Review Board (IRB) of the Institute of Medicine (IOM; Approval number: 246(6-11)E2-078/079). All methods were carried out in accordance with declaration of Helsinki guidelines and regulation. Written informed consent was obtained from the participants.

All patient presenting to the emergency department and later admitted to department of Gastroenterology with known cirrhosis and altered mental status (AMS) were eligible. The study was done over the time period of 12 months and patient were randomly selected and randomly divided for the alternative treatment. Participant inclusion criteria were as follows: age between 18 to 80 years, a diagnosis of cirrhosis from any cause, presence of any grade of HE, and the availability of consent. Exclusion criteria were as follows: acute liver failure, AMS from causes other than HE, refusal of consent.

The basic demographic data were collected from the patient in both groups. The lab values were collected from the patient's test report. The precipitating factors were found by assessing the patient as well from the history and lab values. Similarly causes were noted by assessing the patient history and investigation. The west haven criteria grade was noted by assessing patients' history, physical examination and blood investigation. The Child Turcotte Pugh(CTP) and Model for end stage liver disease (MELD) score were also noted.

The WHC is used to assess and classify the severity of hepatic encephalopathy (HE). It is categorizing HE into four grade bases on the severity of symptoms and their impact on daily functioning (11). In our study WHC of participants were noted at the time of admission and 24 hours after the administration of lactulose or PEG. The value of WHC grade was compared in both groups.

For analyzing the data statistically, IBM Statistical package for the social sciences (SPSS) software, Version 26 (IBM Corp, Armonk, NY, USA) was used. Categorical study variables were expressed in terms of frequency and percentage. Continuous variables were expressed in terms of mean and standard deviation (SD).Pearson's Chi-square test was used to compare between two groups. P value of 0.05 or less was considered significant for used test.

RESULTS

The basic demographic data were similar between two groups. The study had 45 patients in treatment group and 45 patients in control group for comparison. Lactulose group consisted of 40% females and 60% males, while the PEG group had 31.1% females and 68.9% males. The mean age in the lactulose group was 48.29 ± 11.39 and PEG group, it was 51.29 ± 10.47.

We observed a significant difference in Albumin levels between the two groups. The mean Albumin level in Group 1 was 29.18 gm/L, compared to 27.42 gm/L in Group 2. This difference was statistically significant with a p value of 0.033. Other parameters such as Total Bilirubin (TB), Direct Bilirubin (DB), aspartate transaminase (AST), alanine transaminase (ALT), and others were also measured. However, these did not show a significant deviation between the two groups. A comprehensive overview of all the lab values is presented in Table 1.

Severity of cirrhosis according to MELD score and CTP score was also comparable between the two groups. The main cause of hepatic encephalopathy is alcohol, accounting for 51.1% and 40% in the lactulose and polyethylene glycol (PEG) groups, respectively. Non-alcoholic steatohepatitis (NASH) follows closely behind, with 22.2% and 20% in the lactulose and PEG groups, respectively. Other factors contribute to a smaller portion of cases presented in table 1. The most common precipitating factor was found to be hyponatremia in both groups accounting 46.7 % and 35.6 % in lactulose and PEG group respectively.

Patients on lactulose mostly had Grade 2 symptoms (40%), while those on PEG primarily had Grade 3 symptoms (33.3%). After 24 hours, the PEG group showed a better improvement rate in grade of hepatic encephalopathy (69.8% vs. 57.8% for lactulose), although the difference was not statistically significant (p-value = 2.408). The overall WHC grade of both groups are mentioned in table 2. Notably, a significant proportion of patients in both groups (42.2% on lactulose, 30.2% on PEG) experienced minimal improvement or no change. Overall, while treatment duration and complete resolution were similar between the groups, the PEG group showed a higher improvement rate given in table 3.

Table 1. Basic demographic and clinical information.

	Lactulose group	PEG group	P-Value
Age	48.29 ± 11.39	51.29 ± 10.47	
Sex, male	27 (60.0)	31 (68.9)	0.378
TB (µMol/L)	156.11 ± 148.92	125 ± 122.72	0.105
DB (µMol/L)	73.33 ± 81.21	57.67 ±68.85	0.068
TP (gm/L)	67.56 ± 11.54	68.64 ± 10.56	0.281
Albumin (gm/L)	29.18 ± 6.00	27.42 ± 6.21	0.033
AST (U/L)	94.20 ± 70.08	131.49 ± 114.68	0.089
ALT (U/L)	66.58 ± 73.88	65.58 ± 50.01	0.412
ALP (U/L)	140.40 ± 60.59	138.11 ± 94.59	0.132
GGT (U/L)	175.53 ± 119.52	221.13 ± 167.48	0.112
PT (sec)	26.64 ± 13.79	27.94 ± 16.22	0.625
INR (sec)	2.24 ± 1.12	2.28 ± 1.38	0.268
Hb (gm%)	10.08 ± 2.50	9.73 ± 2.22	0.145
TLC (/cmm)	21134.22 ± 59030.43	15104.00 ± 31903.65	0.315
Platelets (/cumm)	108993.42 ± 71524.51	115644.44 ± 76333.46	0.120
Na+ (mEq/L)	131.84 ± 6.37	130.11 ± 8.19	0.238
K+ (mEq/L)	4.33 ± 0.84	5.43 ± 6.82	0.608
Urea (mmol/L)	9.42 ± 8.92	10.01 ± 12.83	0.492
Creatinine (mmol/L)	127.24 ± 71.79	158.87 ± 190.49	0.254
	Precipitating factors		
Hyponatremia	21 (46.7)	16 (35.6)	0.284
Constipation	10 (22.2)	7 (15.6)	0.419
Hypokalemia	7 (15.6)	2 (4.4)	0.079
SBP	5 (11.1)	11 (24.4)	0.098
UTI	6 (13.3)	5 (11.1)	0.748
Pneumonia	3 (6.7)	9 (20.0)	0.063
Cellulitis	0 (0)	2 (4.4)	0.153
Dehydration	3 (6.7)	1 (2.2)	0.306
Mixed precipitants	27 (60.0)	18 (40.0)	0.058
Surgery	2 (4.4)	0 (0)	0.153
	Cause of cirrhosis		
Alcohol	23 (51.1)	18 (40.0)	
NASH	10 (22.2)	9 (20.0)	
Wilson	2 (4.4)	0 (0)	
Autoimmune	1 (2.2)	2 (4.4)	
Cryptogenic	2 (4.4)	9 (20.0)	0.306
Alcohol + HCV	1 (2.2)	3 (6.7)	
Alcohol + HBV	3 (6.7)	1 (2.2)	
HCV	2 (4.4)	2 (4.4)	
HBV	1 (2.2)	1 (2.2)	

TB: total bilirubin, DB: direct bilirubin, TP: total protein, AST: aspartate aminotransferase, ALT: alanine

aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, PT: prothrombin time, INR: international normalized ratio, TLC: total leukocyte count, SBP: spontaneous bacterial peritonitis, UTI: urinary tract infection, NASH: non-alcoholic steatohepatitis, HCV: hepatitis C virus, HBV: hepatitis B virus; PEG: polyethylene glycol

Table 2. West Haven criteria (WHC) of two group at admission and at 24 hours after treatment.

WHC	Grade	Group		P value
		Lactulose	PEG	
At admission	1	2 (4.4)	3 (6.7)	
	2	18 (40.0)	13 (28.9)	
	3	11 (24.4)	15 (33.3)	
	4	14 (31.1)	14 (31.1)	
At 24 hours	0	9 (20)	18 (40)	2.408
	1	9 (20)	6 (13.3)	
	2	9 (20)	8 (17.8)	
	3	9 (20)	6 (13.3)	
	4	9 (20)	7 (15.6)	

Table 3. Comparing the duration of illness between two groups.

Time (days)	Lactulose	PEG	P-value
Length of stay in hospital	5 ± 2.29	4.89 ± 1.91	0.803
Time of resolution of HE	2.78 ± 1.40	2.60 ± 1.47	0.558

HE: hepatic encephalopathy; PEG: polyethene glycol

DISCUSSION

The current treatment of HE primarily revolves around lactulose, a non-absorbable disaccharide, which serves as the first-line intervention. On the other hand, PEG is an osmotic laxative most commonly used for colon preparation before colonoscopy. Recently, PEG has emerged as a cost-effective and safe alternative for managing HE.

In our study, we found that PEG was effective than lactulose for hepatic encephalopathy (HE) in cirrhotic patients.Patients receiving PEG experienced shorter hospital stays and quicker resolution of, HE compared to those receiving lactulose. It aligns with findings from studies by Rahim et al.,[8] Shehata et al.,[12]Naderian et al.,[9]and Ahmed et al.[13]However, in Naderian et al, there is comparison of combination of lactulose and PEG with lactulose alone, where the combination showed greater effectiveness in treating, HE. Shorter hospital stays not only facilitate patients' return to daily activities sooner but also reduce the economic burden associated with HE, a condition affecting 30% to 45% of cirrhotic patients.[3] Additionally, quicker resolution of HE allows physicians more time to identify precipitating factors and underlying causes for targeted treatment interventions.

The exact mechanisms behind HE remains unclear. However, a widely accepted theory implicates hyperammonemia to cause HE.[14]Hyperammonemia occurs when the damaged liver fails to metabolize ammonia produced by gut bacteria. The ammonia or NH_3 (not NH_4^+) easily crosses blood brain barrier (BBB) and lead to encephalopathy in cirrhotic patients.[15](15). PEG is known to cause mild metabolic acidosis that eventually results in increase level of NH4+ and decrease NH3. Hence, there will be less NH_3 crossing across the BBB. This process explains the benefit of PEG that results in rapid improvement of AMS.[15,16] PEG has the advantage of not being absorbed, unlike lactulose, this means it doesn't contain the unabsorbed carbohydrates that usually lower stool pH and increase water loss.[17,18] Also, PEG helps remove more ammonia in stool compared to lactulose.[17]In a prior RCT, the blood ammonia level were measured between two groups, but the values did not show significance.[8,9] However, we have not measured the blood ammonia level.

In this study we have used West Haven Criteria (WHC) to evaluate the effectiveness of lactulose and PEG. This differs from previous studies that utilized the HESA score to find the improvement of HE following treatment.[8-9,12]As a result, direct comparison of improvement is not feasible. In our study 69.8% and 57.8% of participants in the PEG and lactulose group, respectively, demonstrated improvement, while 25.6% and 28.9% remain unchangedwithin a24-hour period.

Our study's limitation lies in the use of WHC instead of HESA. HESA, an adapted version of WHC, offers advantages by integrating both subjective and objective indicators to measure neuropsychiatric symptoms associated with HE.[19]It employs a multidimensional approach in HE diagnosis. Furthermore, being a single center cross sectional study, it would have been more reliable if it was done in larger sample population.

CONCLUSIONS

In this study, we evaluated treatment methods for HE. In comparing to lactulose, PEG showed better outcomes. PEG reduced the severity of encephalopathy within the first 24 hours, shortened hospital stay, and accelerated resolution of HE. Additionally, PEG is commonly used for bowel preparation and is easy to administer, suggesting its potential applicability to acute HE. Further research is warranted to enhance our understanding of PEG use.

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