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ORIGINAL ARTICLE

Comparison of Efficacy of Lactulose with and without Polyethylene Glycol in the Treatment of Patients with Hepatic Encephalopathy

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ABSTRACT

Objective: To compare the effectiveness of the combination of Lactulose and Polyethylene glycol (PEG) versus Lactulose alone in improving the grade of hepatic encephalopathy (HE) within 24 hours of hospital admission in patients with hepatic encephalopathy due to decompensated liver cirrhosis precipitated by constipation.

Study Design: Randomized controlled trial.

Place and Duration: The Department of Gastroenterology, Hepatology and GI Endoscopy, Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan from 07-05-2020 to 06-05-2021.

Methodology: One hundred and sixteen patients (58 in each group) of either gender aged 20-70 years having decompensated liver cirrhosis with HE grade 2 to 4 secondary to constipation were enrolled. Patients were randomly and equally divided into either Lactulose and PEG (Group-1) or Lactulose alone (Group-2) by lottery method. West Haven Criteria was used for labeling HE grades at the baseline and after 24 hours of treatment in both study groups. A one-grade improvement in HE after 24 hours of treatment from the baseline was considered as effectiveness of treatment.

Results: Treatment was found effective (at least one HE grade improvement) in 43 (74.1%) patients treated with PEG+Lactulose, while it was 32 (55.2%) in patients who were treated with Lactulose alone (p=0.033). When stratified for age and gender, PEG+Lactulose was significantly effective in improving HE grades in younger age group (p=0.007) and males (p=0.040).

Practical Implications: Combination treatment with PEG+Lactulose can be a preferred option for improvement in HE grades in comparison to treatment with lactulose alone

Conclusions: Combination treatment with PEG+Lactulose was found to be more effective in improving HE grades when compared to treatment with lactulose alone within 24 hours of hospital admission among patients who had decompensated liver cirrhosis precipitated by constipation.

Keywords: Constipation, decompensated liver disease, Hepatic encephalopathy, Lactulose, Polyethylene glycol.

INTRODUCTION

Liver cirrhosis is among the most common causes of mortality in several parts of the world, including the United States now days, and a huge financial budget has been allocated in order to find out its underlying etiology.[1,2] In developed countries, liver cirrhosis is the sixth leading cause of mortality and the 10th most common cause of death in different regions of the world.[3] Increasing trend of chronic hepatitis C and non-alcoholic steatohepatitis can lead to increase in the number of people that are suffering from liver cirrhosis and ultimately liver transplantation has to be considered as a treatment option in such population.[4] It has been reported that approximately 30-45% of patients show overt hepatic encephalopathy (HE) and 30-70% develop minimal HE as a consequence of liver cirrhosis.[1,2] Reduction in blood ammonia levels and management of aggravating factors are the major considerations for overt hepatic encephalopathy as ammonia possesses the ability to cross blood brain barrier and cause HE.[5,6] Some clinical trials reported lactulose as effective option in relieving symptoms while 70% of the patients of overt HE show improvement when treated with lactulose.[1]

Polyethylene glycol (PEG) is thought to be highly effective purgative that leads to immediate relief of constipation by facilitating the passage of the stool which is very necessary in overt HE and it also causes mild metabolic acidosis which leads to increase in NH_4^+ ion and decrease in NH_3 which possesses the ability to the cross blood brain barrier and cause HE.[7] Several other agents like sodium phenyl butyrate and sodium benzoate that are proposed to be the potential treatment for HE but are more expensive and less well studied than PEG.[1,4]

Some researchers have reported the efficacy of Polyethylene glycol (PEG) in improving grades of hepatic encephalopathy when administered in combination with lactulose. Naderian M, et al reported that 50% of the patients with HE who used lactulose alone and 80% of the patients who used lactulose with PEG have shown improvement in grade of HE after 24 hours.[1]

In this clinical trial, PEG solution with lactulose is compared with lactulose alone in the treatment of HE secondary to constipation in patients with liver cirrhosis as previous studies reveal that PEG and lactulose combination provides relief more rapidly from constipation to recover the patients suffering from HE.[1,2] The findings of this study were thought to help the physicians in offering better management options for improvement in HE grades in those patients.

METHODOLOGY

This randomized controlled trial was conducted at The Department of Gastroenterology, Hepatology and GI Endoscopy, Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan Institute of Medical Sciences, Islamabad, Pakistan from 07-05-2020 to 06-05-2021. A sample size of 116 (58 in each group) was calculated taking 95% confidence level, 90% test power, anticipated proportion of population-1 (Lactulose alone) P1 =73.68%[1] and anticipated proportion of population 2 (efficacy of PEG+Lactulose) P2=95.24%.[1] Non-probability consecutive sampling technique was employed. Inclusion criteria were patients of either gender aged 20-70 years and diagnosed patients of decompensated liver cirrhosis as per Child Turcotte Pugh (CTP) Class B or C. All patients who had HE grade 2 to 4 secondary to constipation as per West Haven criteria. Exclusion criteria were patients with HE having upper gastrointestinal bleed (established by bleed in the nasogastric tube or history of melanotic stools). Patients with infection (white blood cell count <4.5 x10^9/L or >11 x10^9/L) were also excluded. Patients with metabolic abnormalities [random blood sugar <70mg/dL, serum K+ <3.5 mEq/L, serum Na+ <125 mEq/L, BUN: creatinine ratio <10 (indicative of intrinsic renal disease)] were also excluded. Informed and written consents were acquired from all patients or their caregivers/guardians. Approval

from the "Institutional Ethical Committee" was obtained (No.F.1-1/2015/ERB/SZABMU/211).

At the time of enrollment, demographic and clinical information were recorded. The causes of liver cirrhosis were documented (as per medical record and history). Patients were randomly divided into 2 groups: Group-1 (PEG+Lactulose) and Group-2 (Lactulose alone) by lottery method. Group-1 were given 30 ml of Lactulose oral or via nasogastric tube, plus 280 grams of PEG in 4 liters of water orally or via nasogastric tube as a single dose within 4 hours. Lactulose group were given 30 ml of lactulose (at least 3 doses in 24 hours) orally or by a nasogastric tube. All the patients received otherwise routine care by the treating physician (which consisted of IV ceftriaxone, IV isotonic fluids). Serial physical examinations were performed between the time of enrollment and after 24 hours of treatment while relief of constipation was determined by performing diaper checks 3 hourly. We used West Haven criteria to evaluate the grade of HE.. Child Turcotte Pugh (CTP) class score was determined for all the patients. The main outcome was considered as the change in grade on West Haven criteria after 24 hours. The issue of compliance was easily addressed as the data was collected by study conducting doctor within 24 hours of admission with black and white scoring system and the study did not need long follow ups. Standard care and treatment was provided to all the study subjects and interventional group contained addition of another drug along with the standard treatment. Data was collected on a specially made proforma.

Data analysis was performed utilizing "Statistical Package for Social Sciences (SPSS)", version 28.0. Frequency and percentages were calculated for categorical data. Mean and standard deviation (SD) were estimated for quantitative variables. Efficacy in both the groups was compared by applying chi-square test. Potential confounders were stratified. Post stratification chi square test was applied taking p-value<0.05 as significant.

RESULTS

A total of one hundred and twenty-five subjects (n=125) were assessed for eligibility and out of these, one hundred and sixteen (n=116) were enrolled as per inclusion/exclusion criteria. Figure-1 is showing flow diagram explaining study setup.

There were 29 (50.0%) males and 29 (50.0%) females in Group-1 and 21 (36.2%) males and 37 (63.8%) females in Group-2. Mean age of patients in Group-1 was 53.1±11.36 years and 54.9±14.9 years in Group-2. Table-1 is showing comparison of baseline demographic and clinical characteristics in both study groups.

Comparison of laboratory parameters are shown in table-2 and it was found that laboratory studies were statistically similar among patients of both study groups (p>0.05).

Table-1: Comparison of baseline Demographic and Clinical Characteristics

Characteristics		PEG+Lactulose (n=58)	Lactulose alone (n=58)	P-Value
Gender	Male	29 (50.0%)	21 (36.2%)	0.510
	Female	29 (50.0%)	37 (63.8%)	
Age years	<60	39 (67.2%)	29 (50.0%)	
	≥60	19 (32.8%)	29 (50.0%)	
Causes of Liver Cirrhosis	HCV	53 (91.4%)	51 (87.9%)	
	HBV	1 (1.7%)	3 (5.2%)	
	Cryptogenic	4 (6.9%)	4 (6.9%)	
Ascites	No	15 (25.9%)	12 (20.7%)	
	Mild to Moderate	32 (55.2%)	33 (56.9%)	
	Severe	11 (19.0%)	13 (22.4%)	
CPT Classification	Class-B	81 (31.0%)	13 (22.4%)	
	Class-C	40 (69.0%)	45 (77.6%)	
Hepatic Encephalopathy Grading	II	32 (55.2%)	26 (44.8%)	
	III	16 (27.6%)	12 (20.7%)	
	IV	10 (17.2%)	20 (34.5%)	

Treatment was found significantly more effective in 43 (74.1%) patients who were treated with PEG+Lactulose while it was noted to be effective in 32 (55.2%) patients treated with lactulose group (figure-2). The statistical difference in terms of effectiveness was witnessed to significant favoring PEG+Lactulose group in comparison to Lactulose alone (p=0.033)

Table-2: Laboratory Parameters (Mean±SD) at baseline in both study groups

Laboratory Parameters	PEG+Lactulose (n=58)	Lactulose alone (n=58)	P-Value
Random blood sugar (mg/dl)	122.2±73.2	135.7±61.5	
White blood cell (x10^9/l)	8.2±2.1	7.9±1.9	
Serum Na+ (mEq/L)	131.1±4.1	133.7±5.6	
Serum K+ (mEq/L)	4.2±1.1	3.9±1.1	
BUN: Creatinine ratio	26.7±7.5	28.2±6.3	
Bilirubin (mg/dl)	3.3±4.8	3.6±4.1	
Albumin (g/dl)	3.3±3.9	2.7±0.7	
PT-Prolongation (sec)	3.8±2.5	4.9±3.9	

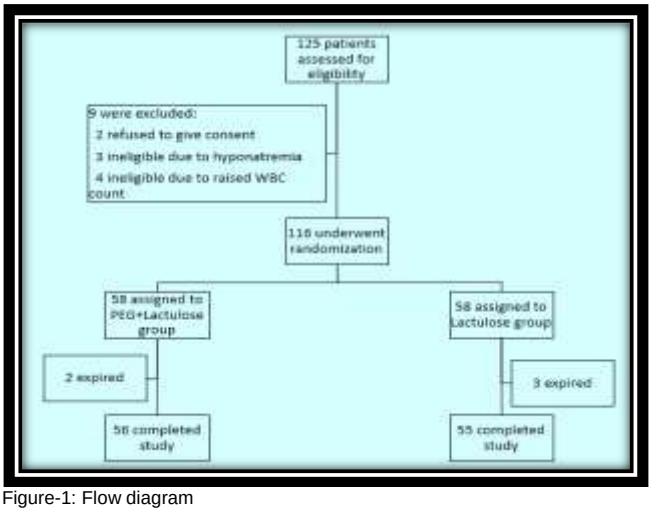

Figure-1: Flow diagram

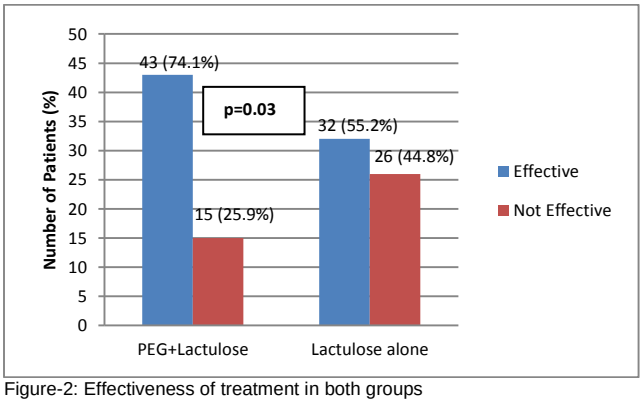

Figure-2: Effectiveness of treatment in both groups

Relatively younger age (p=0.007) and male gender (p=0.040) had significant association with effectiveness in improving HE grades (table-3).

Table-3: Stratification of Gender and Age with respect to Effectiveness of Treatment in both study groups

Study Variables		Effectiveness	PEG+Lactulose (n=58)	Lactulose alone (n=58)	P-value
Gender	Male	Yes	22 (75.9%)	10 (47.6%)	0.040
		No	7 (24.1%)	11 (52.4%)	
	Female	Yes	21 (72.4%)	22 (59.5%)	0.273
		No	8 (27.6%)	15 (40.5%)	
Age (years)	<60	Yes	31 (79.5%)	14 (48.3%)	0.007
		No	8 (20.5%)	23 (33.8%)	
	≥60	Yes	12 (63.2%)	18 (62.1%)	0.932
		No	7 (36.8%)	11 (37.9%)	

DISCUSSION

Polyethylene Glycol is a high-molecular weight, non absorbable polymer, formulated as solution that passes through the colon without net absorption or secretion. It has been used as a bowel

cleansing agent before colonoscopy. PEG preparations are associated with good cleansing efficacy and reasonable patient tolerance. Overall, PEG preparations are safe and generally do not cause fluid and electrolyte shifts.[8,9]

The findings of this study revealed that that treatment was found to be significantly more efficacious (at least one HE grade improvement) in 74.1% patients who were given PEG+Lactulose while the effectiveness was 55.2% in cases treated using Lactulose alone (p=0.033). Efficacy of treatment was significantly better with PEG+Lactulose when compared with Lactulose alone (P=0.033). Shehata HH et al in a quite similar research analyzed the effectiveness and safety of PEG in comparison with lactulose. They enrolled a total of one hundred patients diagnosed with HE and randomized them into two equal groups.[10] Group-I patients were given Lactulose while the group-II used PEG. Their results revealed that there were 72% of patients who demonstrated an improvement in one grade or more in HE after 24 hours therapy with lactulose, whereas in patients who were treated with PEG, the percentage of such patients was 94% (P<0.05). The time needed for resolution of HE and length of hospital stay were significantly lower in PEG group versus lactulose group (P<0.001). Shehata HH et al did not use PEG as add-on therapy to lactulose like we did in our study, nonetheless trends appearing in both the studies are similar.

Another research comparing PEG versus lactulose among cirrhotic patients admitted with HE revealed that after 24 hours, patients who were using PEG showed more improvement in their HE scoring algorithm (HESA) in comparison to those who were given lactulose (from a mean of 2.3 to 0.9 compared with 2.3 to 1.6). In addition, the median time to resolution of the hepatic encephalopathy was shorter with PEG (one versus two days).[11]

A recent meta-analysis found that PEG, in comparison to lactulose, can assist more rapid HE resolution within first 24-hours. Moreover, PEG can reduce overall length of hospitalization with minimum adverse effects among patients of HE with liver cirrhosis.[12] These findings further emphasize the evidence that we observed during the present study.

Current study has some strengths and the major one is in its innovative approach and randomized controlled design. We used an agent, which is widely available, cost effective and safe.[13,14] There are not many studies available on the use of PEG in patients with HE. The results are potentially generalizeable, however, we suggest more studies. Although we did not measure the time to improvement in the HE grades, yet we generally observed that along with improvement in HE grades, the group administered with PEG showed better rate of recovery, which resulted in earlier discharge of those patients as has been reported by others.[15-17] We suggest further studies to estimate the time to improvement in HE grades as this has potential implications towards reducing the economic burden to patients and their families and to the hospital as well.

There are certain limitations in the current study. Firstly, we conducted the trial in only one hospital and sample size is not large enough to generalize our study results. Secondly, we only used single dose of PEG and we suggest more studies using escalating to find out the optimum dose of PEG for the treatment of HE with minimal adverse effects. Finally, we only compared PEG plus lactulose with lactulose alone in the current study. We suggest superiority trials in future that compare PEG alone regimens with other traditional treatments being used for the treatment of HE

In summary, treatment of HE with PEG preparations are currently in experimental phase. The evidence is not sufficient and only few trials have been found in the literature reporting efficacy and tolerability of PEG preparations in the treatment of HE. Current randomized controlled trial demonstrated that combination treatment with PEG and lactulose was found more effective in improving hepatic encephalopathy grades when compared to treatment with lactulose alone. The treatment was safe and we did not come across any significant adverse effects. We strongly suggest future trials with larger sample size involving multiple centers to validate the efficacy of PEG preparations in the treatment of HE.

CONCLUSION

Combination treatment with Polyethylene glycol and lactulose was found more effective in improving hepatic encephalopathy grades when compared to treatment with lactulose alone within 24 hours of hospital admission among patients who had decompensated liver cirrhosis precipitated by constipation.

REFERENCES

1. Naderian M, Akbari H, Saeedi M, Sohrabpour AA. Polyethylene Glycol and Lactulose versus Lactulose Alone in the Treatment of Hepatic Encephalopathy in Patients with Cirrhosis: A Non-Inferiority Randomized Controlled Trial. Middle East J Dig Dis. 2017;9:12-9.
2. Rowe IA. Lessons from Epidemiology: The Burden of Liver Disease. Dig Dis. 2017;35(4):304-9.
3. Abubakar II, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
4. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatol. 2015;61(1):77-87.
5. De Micco MP, Clayton LB, Pilot J. Novel L polyethylene glycol-based bowel preparation NER1006 for overall and right-sided colon cleansing: a randomized controlled phase 3 trial versus trisulfate. Gastrointest Endosc. 2018;87:677-8
6. Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:394–402.
7. Suraweera D, Sundaram V, Saab S. Evaluation and Management of Hepatic Encephalopathy: Current Status and Future Directions. Gut Liver. 2016 Jul;10(4): 509–19.
8. Ferenci P. Hepatic encephalopathy. Gastroenterol Rep (Oxf). 2017 May; 5(2):138–47.
9. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350--electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. J Am Med Assoc Intern Med. 2014;174:1727-33.
10. Shehata HH, Elfert AA, Abdin AA, Soliman SM, Elkhouly RA, Hawash NI, et al. Randomized controlled trial of polyethylene glycol versus lactulose for the treatment of overt hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2018 Dec;30(12):1476-81.
11. Doran AE, Shah NL. Polyethylene glycol for hepatic encephalopathy: a new solution to purge an old problem? J Am Intern Med. 2014;174:1734-5.
12. Li M, Zhang Z, Chen Q, Zhou X, Shui D, Huang J. Comparative Effectiveness and Safety of Polyethylene Glycol Electrolyte Solution Versus Lactulose for Treatment of Hepatic Encephalopathy: A Systematic Review and Meta-analysis. J Clin Gastroenterol. 2022;56(1):41-48. doi:10.1097/MCG.0000000000001621
13. US Department of Health and Human Services. [Accessed August 1, 2014];Healthcare Cost and Utilization Project (HCUP) http://www.ahrq.gov/research/data/hcup/index.html.
14. Nusrat S, Khan MS, Fazili J, Madhoun MF. Cirrhosis and its complications: evidence based treatment. World J Gastroenterol 2014;20:5442-60.
15. Hoilat GJ, Ayas MF, Hoilat JN, et al. Polyethylene glycol versus lactulose in the treatment of hepatic encephalopathy: a systematic review and meta-analysis. BMJ Open Gastroenterol. 2021;8(1):e000648. doi:10.1136/bmjgast-2021-000648
16. Giri S. Polyethylene Glycol Versus Lactulose for Hepatic Encephalopathy: Do We Have a Clear Winner?. J Clin Gastroenterol. 2022;56(2):192. doi:10.1097/MCG.0000000000001654
17. Zacharias HD, Zacharias AP, Gluud LL, Morgan MY. Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis. Cochrane Database Syst Rev. 2019;6(6):CD012334. doi:10.1002/14651858.CD012334.pub2