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Comparison of polyethylene glycol 3350 electrolyte solution and lactulose in patients with overt hepatic encephalopathy: A retrospective study from a tertiary care hospital

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Abstract

Background: Hepatic encephalopathy (HE) is a brain dysfunction caused by liver failure and/or porto-systemic shunt and it manifests as a wide spectrum of neurological or psychiatric abnormalities. The aim of the study was to evaluate if polyethylene glycol (PEG) is more effective than lactulose in resolution of encephalopathy and determine if it decreases the hospital stay.

Material and methods: Retrospectively from hospital records we selected 80 patients with hepatic encephalopathy (HE) due to underlying cirrhosis of liver. Forty (40) patients were taken from the group who were treated with lactulose and based on age matching (± 2 years) and encephalopathy grade matching (±1 grade) 40 patients were selected from the group who were treated with PEG. Grading of HE was determined by using hepatic encephalopathy scoring algorithm (HESA) and West Haven (WH) criteria. Resolution of HE was defined as improvement in HESA/West Haven score to grade 0, patient discharge or 2 consecutive days when HESA grade remained at 1 after an initial improvement of at least 1 full grade.

Results: The mean age of PEG group was similar to lactulose group (58.2 ± 10.11 vs 58.70 ± 9.54 years; p = 0.829) with a male predominance in both groups. All patients were of Child Turcot Pugh (CTP) class C with a mean MELD score of 18.7±5.42 vs 18.9±4.75 in PEG group and lactulose group respectively (p = 0.827). The time taken for complete resolution of HE was also lesser in PEG group compared to lactulose group with a significant p value of <0.001.

Conclusions: PEG therapy significantly improved the overall grade of encephalopathy in first 24 hours and reduced days to complete resolution of hepatic encephalopathy.

Keywords: hepatic encephalopathy; cirrhosis; lactulose; polyethylene glycol.

Introduction

Hepatic encephalopathy is a diffuse disturbance of brain function caused by liver insufficiency and/or portosystemic shunt and it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alteration to coma [1]. The association between liver disease and mood disturbances was recognized, by the father of medicine, Hippocrates (460–371 BC). A clear improvement in the understanding of hepatic coma came from the experimental studies by Hann et al [2] who showed that dogs undergoing experimental portacaval shunt develop behavioural

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changes within 10–40 days after surgery. The symptoms include irritability, ataxia, convulsions and coma.

Hepatic encephalopathy (HE) is often serious sequelae of chronic liver disease with significant morbidity, mortality and healthcare costs. HE can be graded by severity using the West Haven criteria and can be divided into minimal HE (MHE) and overt HE (OHE). In the case of MHE, there may not be any obvious clinical changes. However these patients have abnormal psychometric tests and subtle changes in personality may be reported by caregivers [3]. As progression to OHE occur's, the patients will have greater disturbances in cognition leading to more drastic personality changes, irritability and disinhibition [4]. Sleep disturbances with excessive daytime sleepiness are another common manifestation in OHE [5]. Hepatic encephalopathy is not only associated with poor prognosis but also has significant detrimental effects on quality of life and a substantial burden to caregivers and healthcare systems. While the basis of HE is likely multi-factorial, increased systemic circulation of ammonia plays a pivotal role. Thus current management of HE focuses on reducing blood ammonia concentrations using non absorbable disaccharides and antibiotics. The present study was conducted to find out if the laxative polyethylene glycol 3350 electrolyte solution can treat hepatic encephalopathy better and/or more safely than lactulose.

The study was aimed to compare the effectiveness of polyethylene glycol (PEG) and lactulose in decreasing the grade of HE at 24 hours of treatment among patients of hepatic encephalopathy, and also to compare the time taken for complete resolution of HE among patients treated with PEG as compared to patients treated with lactulose.

Materials and methods

This present study was a retrospective study from hospital based data conducted in the Department of Gastroenterology, Sheri Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir. The hospital data used for the study was from September 2017 to August 2020. The study was approved by the institutional ethical committee of SKIMS, Srinagar.

A total of 230 cirrhotic patients with hepatic encephalopathy were admitted in the department from September 2017 to August 2020. Among them 40 patients were eligible for our study who were treated with lactulose. We matched them on one to one basis with 40 patients treated with PEG. The matching was based on age ± 2 years and encephalopathy grade ±1. Hence a total of 80 subjects were included in the study.

The reasons for exclusion were subjects with one or more of the following on presentation: Acute liver failure, structural brain lesions (as indicated by computed tomography imaging if available and confirmed by neurological examination), other causes of altered mental status (i.e. not meeting the definition of hepatic encephalopathy), suspected intestinal obstruction, recurrent vomiting, pregnancy, <18 years age, serum sodium <125 mEq/L, and uncontrolled infection with hemodynamic instability requiring vasopressors.

Potential causes of HE at the time of admission were evaluated. Grading of HE was defined by using hepatic encephalopathy scoring algorithm (HESA) and West Haven criteria [6]. Resolution of HE was defined as improvement in HESA / West Haven score to grade 0 or patient discharge or 2 consecutive days when HESA grade remained at 1 after an initial improvement in at least 1 full grade.

The lactulose group of patients had received lactulose 20-30 grams administered orally or by nasogastric tube (3 or more doses within 24 hours) or 200 grams by rectal tube, at the discretion of treating physician. The PEG group of patients had received 2 liters of polyethylene glycol 3350 electrolyte solution (PEG) administered orally or via nasogastric tube, again at the discretion of treating physician. PEG was administered in a single dose over 2 hours. Clinical variables including adverse events and HESA / West Haven scores were collected from the records and the outcome of the treatment.

Statistical analysis

Data was entered into Microsoft Excel spreadsheet. The said data was coded & exported to data editor of Statistical Package for Social Sciences (SPSS Ver. 23). Categorical variables were described as frequencies and percentages while as continuous variables as mean with standard deviation. Chi square test was used to analyze the relationship between two categorical variables & t-test to compare continuous variables. A p value of < 0.05 was considered as statistically significant.

Results

There was no significant difference between two groups in age and sex. The mean age of PEG group was similar to lactulose group (58.2 ± 10.11 vs 58.70 ± 9.54 years; $p = 0.829$) with majority of patients more than 55 years of age (72 % in PEG group and 75% in lactulose group), with a male predominance (65% in PEG group vs 62% in lactulose group). Majority of patients were from rural areas (87% in PEG group versus 75% in lactulose group). All patients were of Child-Turcotte-Pugh (CTP) class C with a mean MELD score of 18.7±5.42 versus 18.9±4.75

in PEG group and Lactulose group respectively with p value of 0.827. Etiological agents for cirrhosis in two groups were comparable (p value of 0.407) as shown in Table 1.

Table 1: Comparison based on etiology among two groups.

Etiology	*PEG group*		*Lactulose group*		*p value*
	No.	*% age*	*No.*	*% age*	
None	7	17.5	8	20	0.407
NASH	5	12.5	6	15	
Alcohol	1	2.5	1	2.5	
Hepatitis B	12	30	11	27.5	
Hepatitis C	13	32.5	14	35	
Wilson disease	1	2.5	0	0	
Autoimmune liver disease	1	2.5	0	0	

The two groups were comparable in underlying comorbidities (p value of 0.803). Most common comorbidity was hypertension and type 2 diabetes mellitus (35% in PEG group and 40% in lactulose group). The precipitating factors for hepatic encephalopathy were comparable between two groups (P value of 0.868). The common precipitating factor for hepatic encephalopathy was constipation in combination with other risk factors like sepsis, hypokalemia and variceal bleed. The two groups were comparable in baseline laboratory parameters like blood total leukocyte count, serum bilirubin, serum albumin, serum glucose, serum calcium, serum urea, serum creatinine, INR, serum sodium and serum potassium (with p value more than 0.05). The grade of encephalopathy between two groups at presentation was almost similar (p value 0.607). Majority of patients were in grade 3 encephalopathy (67.5% in PEG group versus 75% in lactulose group) Table 2.

Table 2: Showing grade of hepatic encephalopathy at presentation among two groups.

Hepatic encephalopathy grade	*PEG group*		*Lactulose group*		*p value*
	No.	*%age*	*No.*	*%age*	
Grade 2	8	20	5	12.5	0.607
Grade 3	27	67.5	30	75	
Grade 4	5	12.5	5	12.5	
Mean±SD encephalopathy grade	2.93±0.57		3.0±0.51		

The difference in Grade of hepatic encephalopathy after 24 hours of therapy between two groups was significant, the improvement being more in PEG group than in lactulose group with a p value of <0.001. The encephalopathy grade improved to mean of 1.55±0.81 in PEG group and 2.35±0.53 in lactulose group.

Table 3: Showing grade of hepatic encephalopathy at day 1 among two groups.

Hepatic encephalopathy Grade	*PEG group*		*Lactulose group*		*p value*
	No.	*% age*	*No.*	*% age*	
Grade 0	4	10	0	0	<0.001*
Grade 1	14	35	1	2.5	
Grade 2	18	45	24	60	
Grade 3	4	10	15	37.5	
Mean±SD	1.55±0.81		2.35±0.53		

In PEG group the mean West Haven Score / HESA score after 24 hours of therapy changed to 1.37±0.89 compared to mean change to 0.65±0.58 in lactulose group with a statistically significant P value of < 0.001 (Table 4).

19 of 40 patients in the PEG group (47%) had an incremental improvement of 1 HESA / WH grade; 18 (45%) improved by 2 grades at 24 hours; 3 of 40 patients had no improvement (7.5%). 4 (10%) patients had a score of 0 at 24 hours. In contrast, in the lactulose group 17 of 40 patients improved by 1 HESA/ WH grade at 24 hours (42%); 3 (7.5%) by 2 grades and 12 (30%) of 40 patients receiving lactulose had no improvement and none of the patients had a score of 0 at 24 hours.

Table 4: Outcome of two treatment groups.

	PEG group		*Lactulose group*		*P value*
	Mean	*SD*	*Mean*	*SD*	
Drop in West Haven Score/ HESA score at day 1	1.37	0.89	0.65	0.58	<0.001
Duration of hospital stay (Mean days)	8.28	1.22	8.35	1.17	>0.05
Mean days taken for complete resolution of hepatic encephalopathy	1.9	0.3	3.75	0.43	<0.001

However there was no significant difference in duration of hospital stay between the two groups with a mean hospital stay of 8.28±1.22 days for PEG group and mean hospital stay for lactulose group of 8.35±1.17 days. There was significant difference between two groups in time taken for complete resolution of hepatic

encephalopathy with 1.9±0.3 days in PEG group compared to 3.75 ±0.43 days in lactulose group with a significant p value of <0.001.

Both polyethylene glycol 3350 electrolyte solution and lactulose therapy were considered safe therapies with no definitive treatment related adverse events. 4 patients in lactulose group and 3 patients in PEG group had died. All of the patients who died had advanced liver disease (MELD>25 and CTP class C) with septicemia, developed multi-organ failure and died. None of the deaths was related to therapy (PEG/ Lactulose).

Discussion

The exact mechanism resulting in overt hepatic encephalopathy in patients with cirrhosis is not completely defined [7 - 9], although a number of possible factors have been proposed to play a role in the pathogenesis of hepatic encephalopathy, such as the production of central benzodiazepinic agents, endogenous opioids and false transmitters, ammonia being still viewed as a key contributor [10]. Numerous studies have indicated a central role of gastrointestinal bacteria [11, 12] and their importance is strongly suggested by the parallel responses observed with antibiotics and bowel cleaning. Thus the mainstay treatment for hepatic encephalopathy revolves around reducing the production and absorption of ammonia in the gut and to improve its excretion by drug therapy and diet modification.

Lactulose is currently recommended as the first line pharmacological treatment for hepatic encephalopathy by the practice guidelines proposed by the American College of Gastroenterology [13]. Lactulose (ß galactoside fructose) was introduced in the therapy of portosystemic encephalopathy by Bircher et al [14]. Classically it has been suggested that lactulose improves portosystemic encephalopathy due to its laxative properties. A complementary hypothesis is that lactulose may provide a carbohydrate source to facilitate ammonia utilization by the gut bacteria [15]. Laxative agents such as magnesium salts were used prior to the introduction of lactulose [16 - 18], suggesting that catharsis alone may be effective for the treatment of hepatic encephalopathy. However, since the first report of efficacy of lactulose in 1966 [19] and the consequent widespread adoption of the non-absorbable disaccharides for the treatment of hepatic encephalopathy, there have been few studies comparing their effect with cathartic methods [20]. Assuming that hepatocerebral intoxication is intimately related to the elevation of the blood and tissue ammonia levels, rational therapy should attempt to prevent excessive formation of the substances and to neutralize, remove or otherwise reduce it to a nontoxic form. To prevent excessive formation, elimination of the nitrogenous materials from the intestinal tract is of prime importance. One can accomplish this by cleansing the intestinal tract with laxatives and enemas [16].

PEG electrolyte solution is a mixture of non absorbable, non metabolized polymers of mean molecular weight of 3350 (±10%) that acts as pure osmotic agents [21]. PEG electrolyte solution have been widely used for bowel cleaning before colonoscopy or bowel surgery [22]. Even when large volumes are ingested, PEG induced diarrhea is associated with minimal electrolyte losses or gains [23]. PEG 3350 electrolyte solutions are thus safer than osmotic agents such as magnesium and sulphate or phosphate, especially in patients with impaired renal or cardiac function. Attar A. et al demonstrates that PEG electrolyte solution is more powerful laxative than lactulose [24]. Our study demonstrates that PEG 3350 electrolyte solution is more effective than lactulose in improvement of hepatic encephalopathy with mean drop in HESA score by 1.37 in PEG group as compared to only 0.65 drop in lactulose group at 24 hours of treatment, the results being consistent with the study conducted by Hoila et al [25].

The study included four trials with 229 patients for its systemic review and meta-analysis. It was observed that compared with lactulose, the pooled effect size showed a significantly lower average HE scoring Algorithm (HESA) score at 24 hours the mean difference being −0.68, 95% CI (−1.05 to −0.31) and a p value of <0.001). It was also demonstrated that higher proportion of patients with reduction of HESA Score by ≥1 grade at 24 hours (risk ratio (RR)=1.40, 95% CI (1.17 to 1.67), p<0.001) was seen with the PEG treatment. The study also demonstrated a higher proportion with a HESA Score of grade 0 at 24 hours (RR=4.33, 95% CI (2.27 to 8.28), p<0.0010) and a shorter time to resolution of HE group (MD=−1.45, 95% CI (−1.72 to −1.18), p<0.001) in favour of patients treated with PEG. Similar results were demonstrated in a meta analysis conducted by Bajwa et al [26], Raja et al [27] and Rahimi et al [28]. The difference in etiology for liver disease in our study group compared to Hoila et. al [25] was that alcohol was the most common etiological agent for liver cirrhosis found in the meta-analysis compared to 2.5 % of alcoholic etiology for liver cirrhosis in our study. Reason for this difference is that alcohol consumption is almost negligible in our society. Improvement in grade of encephalopathy in 24 hours after treatment with PEG was seen in our study and this was consistent with Hoila et al [25]. Reasons for this may be that PEG electrolyte solution is more powerful cathartic agent compared to

lactulose and PEG electrolyte solution might prevent dyselectrolytemia which may contribute to improvement in encephalopathy. Our study group had slightly higher CTP score (CTP score of 11.38±1.17 in PEG group versus CTP score of 11.38±1.17 in lactulose group), higher MELD score (MELD score of 18.7 ±5.42 in PEG group versus MELD score of 18.9 ± 4.75 in lactulose group) and higher TLC (TLC of 8.3±3.73 in PEG group versus TLC of 8.3±3.68 in lactulose group) at presentation compared to Rahimi et al study [28] in which CTP score was 10±1 in PEG group versus 10±2 in lactulose group, MELD score of 17±5 in PEG group versus 17±6 in lactulose group and TLC of 6.2 ±2.6 in PEG group versus TLC of 6.3±2.6 in lactulose group at presentation. Possible precipitating factors for hepatic encephalopathy in our study were hypokalemia, constipation, sepsis, variceal bleed but majority of our patients had multiple precipitating factors in combination (62.5% in PEG group versus 60% in lactulose group) compared with Romeiro et al [29], and Heredita et al [30] where risk factors were usually single and sepsis as precipitating factors was less.

As our study group had advanced age, high MELD and CTP score, high TLC count, multiple precipitating factors for hepatic encephalopathy in individual patients and many patients of sepsis, may be the reason for longer hospital stay (8.28±1.22) days of hospitalisation in PEG despite the more rapid resolution of hepatic encephalopathy compared with Rahimi et al study [28] in which hospital stay was 4±1 days of hospitalisation in PEG group versus 8±2 days of hospitalisation in lactulose group. The pooled effect size did not demonstrate a significant difference in terms of length of hospital stay between both groups in a metaanalysis conducted by Hoila et al [25] which was similar to our study. However, the quick improvement was also observed by Li et al in a systemic review and meta-analysis [31]. We could not properly explain why quick improvement in hepatic encephalopathy in PEG group did not convert into shorter hospital stay for PEG group patients, with possible reason may be treatment of other complications of cirrhosis like SBP, variceal bleed and treatment of precipitating factors like sepsis took long time to improve. An important consideration with the use of PEG is that, it causes a substantial catharsis and thus in theory may result in dehydration, electrolyte disturbances and even acid base abnormalities. However, it also contains electrolyte additives that help balance water and electrolyte loss across the gastrointestinal tract and is the most commonly used cathartic for patients requiring a colon preparation. Indeed it has been shown to be safe and effective in a wide variety of patients [32].

However by accelerating improvement in mentation, initial treatment with PEG will permit health care professionals to concentrate on managing the precipitating factors and identifying other causes of metabolic encephalopathy that may be present.

Limitations of the study

We recognize certain potential limitations of our study. First, serum ammonia levels were not measured in the patients in both groups, although ammonia levels did not correlate with better improvement in HESA grades in various other studies. Second, it is from a single center and thus may not be generalized to other centers. We believe that the results of this study should be generalized to most patients with acute HE. Also, further studies are needed to better understand whether the use of PEG could improve the quality of care and/ or reduce important quality metrics such as length of hospital stay.

Conclusion

The final conclusion of this study is that treatment with a single dose of PEG among patients of acute HE significantly improved the overall grade of encephalopathy in the first 24 hours and reduces days to HE resolution as compared to lactulose treatment, which is the current standard of care for acute HE in hospitalized patients.

Conflicts of interest

Authors declare no conflicts of interest.

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