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An Overview of Polyethylene Glycol with Lactulose as Additional Therapy in the Treatment of Hepatic Encephalopathy

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Abstract

Background: Hepatic encephalopathy (HE) is a condition marked by compromised brain function resulting from liver dysfunction, often linked to acute liver failure or cirrhosis, with notable morbidity and mortality. Lactulose has been the conventional treatment, but polyethylene glycol (PEG) has garnered interest from several investigators.

Objective: To provide evidence-based recommendations on therapeutic decisions by a literature review of PEG as an add-on therapy in the Management of HE

Methods: We conducted a comprehensive search across five prominent databases, specifically Scopus, Web of Science, PubMed, Embase, and Cochrane Library. Moreover, additional records were identified through alternative channels, such as Google Scholar. Search through keywords based on the included systematic reviews and RCTs, and exclude non-randomized studies, conferences, and unpublished trials.

Results: According to the findings, polyethylene glycol (PEG) has a beneficial effect on managing hepatic encephalopathy (HE). Five randomized studies involving a total of 300 patients were conducted. In contrast to lactulose, the average HE Scoring Algorithm (HESA) Score at 24 hours (Mean difference) = -0.68, 95% CI (-1.05 to -0.31), $p < 0.001$) was substantially lower according to the pooled effect size. PEG therapy was found to have a substantial benefit in improving clinical efficacy and reducing hospital stays.

Conclusion: The results show that PEG is a successful treatment for HE. When PEG is used in place of lactulose, shorter stays are possible without raising the frequency of unfavourable events, and HE resolution can occur more quickly during the first twenty-four hours.

Keywords: Covert and Overt Hepatic Encephalopathy, Hepatic Encephalopathy, Lactulose, Polyethylene Glycol.

INTRODUCTION

The general term for brain damage resulting from portal-systemic shunting or inadequate liver function is hepatic encephalopathy (HE). This dysfunction manifests itself in a wide spectrum of neurological or psychiatric abnormalities, varying from mild subclinical alterations to a coma [1]. Brain edema, brain atrophy, reversible metabolic encephalopathy, or any combination of these conditions could be indicated. While the specific reasons behind brain dysfunction in cases of liver failure remain unidentified, certain factors are closely linked to the onset of this condition [2]. Hepatic encephalopathy can eventually progress to coma hepaticum or hepatic coma in its advanced stages, which can be fatal. Hepatic encephalopathy has a substantial negative influence on the quality of life, increasing morbidity and mortality and placing a financial strain on those who are affected [3,4]. Many other factors were linked to the adjusted risk of HE with a new onset. Medicare insurance was associated with comorbidities such as end-stage renal disease (ESRD) and disability, which had AHRs of 1.07 [5]. For new-onset HE, the accuracy of risk assessment using administrative data could be enhanced by utilizing medication use records. In a population that is predominantly older and has NAFLD and comorbidities, these data offer fresh perspectives on the risk of Hepatic Encephalopathy [6]. Factors such as older age, elevated bilirubin and creatinine levels, higher HE grades (III–IV versus I–II), previous HE and MHE occurrences, and a higher MELD score are associated with an increased risk of death in HE. In a study of 111 cirrhotic

patients, the survival rates for patients who developed grade 3 and grade 4 HE were 23% and 42%, respectively, at one and three years [7]. Patients with cirrhosis who have HE have a known effect on their prognosis. This subjectivity may have contributed to HE severity's exclusion from the original MELD scoring model, as concerns have been raised about the subjectivity that could influence HE severity grading. While various scoring systems exist for HE severity assessment, the West Haven Criteria are frequently employed [8]. Hepatic encephalopathy (HE) has three distinct types, according to the etiological basis and the World Health Congress of Gastroenterology's criteria: In advance, Type A brain dysfunction occurs in cases of acute liver failure, while Type B is associated with patients who have Porto-systemic bypass but no hepatocellular disease, and Type C arises in individuals with cirrhosis alongside either portal hypertension or systemic shunting [9]. The financial and socioeconomic burden of this illness is steadily rising as a result of the combined effects of growing treatment costs and the trend toward a more severe illness. Adopting these steps may reduce the incidence of chronic liver disease and delay the progression of the disease and its related complications until later stages. HE has been linked to changes in mental state that several theories have described. That being said, a theory suggests HE results from insufficient synthesis of substrates, which could be essential for mental processes. Ammonia, mainly produced by colonic bacteria and glutamine deamination in the small intestine, is a key factor in the pathogenesis of hepatic encephalopathy. Elevated ammonia levels can cross the

blood-brain barrier and cause neurotoxic effects, leading to the symptoms of this condition [10]. The variable neurological symptoms of episodic hepatic encephalopathy (HE) take many forms, as has been well described elsewhere. Numerous neurological anomalies were found, which prompted the creation of a nine-item Clinical Hepatic Encephalopathy Staging Scale [11]. Using principal component analysis, two factors that accounted for 77% of the variance were found for this scale. A new method for assessing hepatic encephalopathy (HE) called the HESA uses the benefits of objective markers of cognitive impairment in addition to clinical observation. This work represents one of the first attempts to develop and apply a multi-method, systematic approach to HE grading, offering a thorough evaluation tool that can be used for all severity levels [12]. Recent treatment, including lactulose, has been utilized for an extended period, demonstrating its ability to enhance cognitive function and overall quality of life for individuals with hepatic encephalopathy. Polyethylene glycol is an osmotic laxative, a non-absorbable substance administered alongside additional fluids. This process results in elevated water content within the intestines, causing distension and facilitating the passage of substantial amounts of stool [13]. Rifaximin, a synthetic rifamycin not absorbed by the body, exhibits in-vitro effectiveness against gram-negative bacteria in the intestinal region. It has been employed to treat traveler's diarrhea primarily caused by *E. coli* and prevent overt hepatic encephalopathy [14]. In contrast to non-absorbable disaccharides, antibiotics

were more effective in treating hepatic encephalopathy. The clinical significance of this discrepancy is still unknown, though. It is advised that in randomized trials focusing on hepatic encephalopathy, non-absorbable disaccharides not be used as a comparator [15].

Materials and methods

Clinical concerns about their safety and effectiveness compared to other treatment agents are the reason for their exclusion. We conducted a comprehensive search across five prominent databases: Scopus, Web of Science, PubMed, Embase, and Cochrane Library. Moreover, additional records were identified through alternative channels, such as Google Scholar. Keywords utilized in the literature search include the following "Hepatic Encephalopathy", "Lactulose", "Polyethylene Glycol", "Polyethylene glycol solution", and Overt Hepatic Encephalopathy. We obtained more potential studies on HE, PEG, lactulose, and RCT, which were selected as database-specific search terms, and all the reference sections of review articles and eligible studies on the topic were hand-searched as well. In the Included studies, the patients (above 18 years old) had minimal, chronic, or acute HE, and the primary outcome was HESA scale improvement and followed the length of hospital stay. The exclusion criteria were patients with congenital liver disease or in pregnancy, studies with no designated comparator or intervention. After screening the articles based on inclusion and exclusion, we identified twenty-nine articles for this study.

RESULT

According to the findings, lactulose uses osmotic activity to speed up colonic transit; however, in contrast to polyethylene glycol, lactulose causes longer transit times, particularly in the distal colon. Lactulose augments the frequency of diarrhea and does not diminish the mortality rate in individuals with minimal hepatic encephalopathy (MHE). Substantial heterogeneity was not detected across the studies, prompting the utilization of the fixed-effects model in the meta-analysis to enhance the robustness of the findings. The unabsorbed osmotic load of carbohydrates and short-chain fatty acids is the primary factor influencing stool weight and consistency. Hence, prolonged administration of lactulose may escalate the intensity and regularity of diarrhea, potentially leading to hypertonic dehydration accompanied by hypernatremia, and in turn, it has the potential to exacerbate the mental condition of the patient [16]. The application of polyethylene glycol (PEG) in managing hepatic encephalopathy (HE). In a particular study involving inpatients with HE, PEG was compared with lactulose. The study revealed that PEG led to elevated fecal ammonia excretion and greater improvement in HE compared to lactulose. Furthermore, the

PEG cohort experienced a shorter median time to resolve HE [17]. In ongoing investigations, Polyethylene Glycol (PEG) is being examined as a potential treatment for hepatic encephalopathy in individuals with cirrhosis, with preliminary studies indicating favorable outcomes. Clinical trials specifically involved a comparison between the efficacy of a combination of PEG solution and lactulose versus the use of lactulose alone in treating hepatic encephalopathy in cirrhotic patients [18]. RCTs were analyzed, comprising a total of 300 patients (PEG=150, lactulose=150). The pooled effect size demonstrated a significantly shorter time to resolution of HE in favour of the PEG group (MD=-1.45, 95% CI (-1.72 to -1.18), p<0.001. The pooled results were heterogeneous (I² =0%, p=0.32). Research is underway to explore the potential use of Polyethylene Glycol (PEG) in treating HE among cirrhotic patients, with initial studies indicating positive outcomes.

Clinical trial outcomes for lactulose and polyethylene glycol in the treatment of hepatic encephalopathy:

There are several research’s conducted most important research summarized in table 1

Table 1: summarize the all-clinical trial, which includes baseline characteristics of this studies

AUTHORS	HE GRADE	TRIAL DESIGN	DRUG	NO.OF SAMPLE	ROUTE OF ADMINIS RATION	TIME OF EVALUATION
Naderian , M. et al.[18]	Any grade	Randomized control	PEG	25	Oral /Rectal	24 h
			Lactulose	25	Oral /Rectal	

Rahimi et al [19].	Any grade	Randomized control	PEG	25	Orally or NGT	24 h
			Lactulose	25	Orally/rectally	
Shehata et al [20]	Any grade	Randomized control	PEG	50	Oral sachet	24 h
			Lactulose	50	Oral	
Raja et al [21].	Any grade	Randomized control	PEG	25	Oral /Rectal	24 h
			Lactulose	25	Oral /Rectal	
Ahmed et al [22].	Less than Grade 2	Randomized control	PEG	25	Oral/NGT	24 h
			Lactulose	25	Oral	

Five RCTs were analyzed, comprising a total of 300 patients (PEG=150, lactulose=150). The pooled effect size did not demonstrate a significant difference in length of hospital stay between both groups (MD=-1.00, 95% CI (-1.99 to -0.01), p=0.05). The pooled results were heterogeneous (I2 =78%, p=0.003). Compared to the exclusive use of lactulose, the combination of PEG-lactulose demonstrated more effective improvement in HESA scores within 24 hours. In the PEG-lactulose group, 20 patients experienced a reduction of at least 1 HESA score after 24 hours, surpassing the 14 patients in the lactulose group, with this variance proving statistically significant [13,18]. The main outcome measure involved a positive change of 1 or more in hepatic encephalopathy (HE) grade within 24 hours, as assessed through the hepatic encephalopathy scoring algorithm (HESA). The HESA scale ranges from 0 (indicating normal clinical and neuropsychological assessments) to 4 (indicating a state of coma). The average (standard deviation) HESA score at the 24-hour mark exhibited a decrease from

2.3 (0.9) to 1.6 (0.9) among individuals undergoing standard therapy. In contrast, it decreased from 2.3 (0.9) to 0.9 (1.0) in the groups treated with PEG (P = 0.002) [19]. When it comes to quickly curing hepatic encephalopathy (HE) in patients with cirrhosis, polyethylene glycol (PEG) seems to be a more effective treatment than standard lactulose. Although lactulose, the current standard treatment for HE resolution, is also considered safe and effective, PEG is thought to be much more efficient in terms of time saved during HE resolution and shorter hospital stays. Additionally, PEG led to early and sustained HE resolution with improved short-term survival, indicating that it is a safe and appropriate medication for ACLF patients experiencing acute HE [20,21].

DISCUSSION

Numerous research investigations have demonstrated that ammonia generation within the gastrointestinal (GI) tract is a contributing factor, and compromised liver function hampers the effective elimination of ammonia. Elevated concentrations of ammonia in the

bloodstream, coupled with systemic or neuroinflammatory processes, constitute the pivotal factors in the etiology of the ailment. Therapeutic interventions for Hepatic Encephalopathy (HE) presently center on diminishing blood ammonia levels, mitigating inflammation, or a combination of both. Existing treatment modalities fall short in addressing the entire spectrum of Hepatic Encephalopathy, with liver transplantation standing as the sole definitive recourse for individuals experiencing acute liver failure coupled with severe HE [22,23]. Lactulose and Rifaximin are traditionally used to induce gut catharsis by creating an acidic environment, converting soluble ammonia to insoluble ammonium ions. Polyethylene glycol (PEG) has proven more effective than lactulose in relieving constipation [24,25]. Another possible explanation is that PEG's effectiveness exceeds its effect on ammonia levels alone. The clinical improvement in Hepatic Encephalopathy (HE) may be more significant than the decrease in ammonia levels because PEG is a potent laxative [21,26]. When evaluating therapy for hepatic encephalopathy, it is crucial to factor in the overall costs of the disease, transcending mere treatment expenses. Despite having a higher daily cost compared to lactulose, rifaximin has demonstrated a decrease in hospitalization rates, a more favorable adverse-effect profile, and improved patient adherence. A study indicated that rifaximin yielded a cost savings of over \$3000 per patient per year compared to lactulose therapy [27]. Polyethylene glycol (PEG) is a cost-effective and commonly used treatment for constipation. It has now attracted

attention in the scientific community for its potential effectiveness in treating hepatic encephalopathy (HE). PEG has been shown to significantly reduce the Hepatic The Encephalopathy Scoring Algorithm (HESA) Score accelerates the resolution of Hepatic Encephalopathy (HE) faster than lactulose, suggested as the first-line treatment for individuals unable to tolerate lactulose and as a secondary option for those who do not respond to lactulose therapy for HE [28,29].

We concluded that PEG is beneficial in the treatment of Hepatic Encephalopathy (HE). Rapid resolution of HE within the first 24 hours of treatment and shorter hospital stays are attainable. When PEG is used instead of lactulose, this also leads to a quicker hospital discharge, all without increasing the frequency of side effects. For patients with cirrhosis experiencing hepatic encephalopathy, the combination of PEG and Lactulose is more effective than lactulose alone.

CONCLUSION

The results show that PEG is a successful treatment for HE. When PEG is used in place of lactulose, shorter stays are possible without raising the frequency of unfavourable events, and HE resolution can occur more quickly during the first twenty-four hours.

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Conflict of interest

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Both authors contributed equally in this research.

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