OPEN

Comparative Effectiveness and Safety of Polyethylene Glycol Electrolyte Solution Versus Lactulose for Treatment of Hepatic Encephalopathy

A Systematic Review and Meta-analysis

Mengting Li, MD,† Zhijie Zhang, MD,† Qiao Chen, MD,†*
*Xiaoling Zhou, PhD,† Diankui Shui, PhD,† and Jiean Huang, PhD**

Background: Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome associated with liver failure and/or portal systemic shunting. Polyethylene glycol (PEG) electrolyte solution is a commonly used for catharsis of gut, which has been demonstrated to relieve HE in a number of randomized controlled trials. The aim of this paper was to evaluate the comparative efficacy and safety of PEG with lactulose for current HE treatment.

Methods: PEG electrolyte solution versus lactulose of HE was deeply studied by conducting a systematic search in electronic databases and other sources until December 31, 2020. The PRISMA statement recommended the use of meta-analysis with 95% confidence interval (CI), relative risk (RR), and weighted mean deviation (WMD) as the estimated effect size. A sensitivity analysis was performed comprehensively to present the risk of bias and the source of heterogeneity.

Results: A total of 434 patients were involved in 7 randomized studies. It is found that there was a significant advantage of PEG therapy in the increase of clinical efficacy (RR = 1.46; 95% CI: 1.26-1.68; $P = 0.000$; $I^2 = 0.0\%$) and the decrease of hospital stay (WMD = −1.78; 95% CI: −2.72 to 0.85; $P = 0.000$; $I^2 = 90.1\%$). There was no significant difference in the incidence of adverse events (RR = 0.75; 95% CI: 0.48-1.19; $P = 0.222 > 0.05$; $I^2 = 7.2\%$) and the level of serum ammonia (WMD = 9.02; 95% CI: −14.39 to 32.43; $P = 0.45 > 0.05$; $I^2 = 84.9\%$) after 24 hours between the 2 groups.

Conclusions: The results prove that PEG has a beneficial effect on the treatment of HE. Compared with lactulose, PEG can lead to more rapid HE resolution during the first 24 hours and shorten the length of stay without increasing the rate of adverse effects.

Key Words: polyethylene glycol electrolyte solution, PEG, lactulose, HE, meta-analysis

(*J Clin Gastroenterol* 2022;56:41–48)

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that can complicate acute or chronic liver failure. The main characteristic is the change of mental state, involving a wide range of neuropsychiatric symptoms from a slight change in brain function to a deep coma.[1] Although the pathogenesis of HE is not yet fully understood, it is generally believed that gut-derived neurotoxin ammonia plays a key role.[2] Elevated serum ammonia can be observed in ~60% to 80% of HE patients, indicating that serum ammonia mainly comes from the gut.[3,4] Ammonia can easily pass through the blood-brain barrier and lead to cirrhotic patients with altered mental status.[5]

Lactulose has been recommended as a guide to HE for decades,[6] which is able to reduce the intestinal production and absorption of ammonia generated by catharsis and intestinal microbial metabolism.[7–9] Although lactulose is the standard therapy for gut catharsis in HE patients, polyethylene glycol (PEG) electrolyte solution can also relieve constipation and reduce the absorption of ammonia. PEG has been found to be effective and safe in several randomized controlled trials (RCTs) comparing PEG with lactulose. PEG can be considered an alternative treatment for lactulose in acute HE, but it should be reserved for patients with poor response to lactulose in chronic encephalopathy. A number of new randomized clinical trials about the efficacy of PEG have been published since 2014. And these small-scale studies have shown that PEG may become an additional choice for the treatment of patients with HE. Thus, this study aims to determine the efficacy and safety of PEG compared with lactulose for HE therapy by conducting a comprehensive systematic review and meta-analysis of published clinical research. Also, it systematically evaluates the beneficial and harmful effects of PEG versus lactulose in HE treatment and was registered in the International Prospective Register of Systematic Reviews (ID: CRD42021245648).

METHODS

Search

RCTs on the comparison of PEG and lactulose used for HE treatment were searched in Cochrane Central

From the *Department of Gastroenterology, The Second Affiliated Hospital of Guangxi Medical University, Nanning; and †Department of Gastroenterology, Liuzhou Traditional Chinese Medical Hospital, Liuzhou, China.

M.L. and Q.C.: performed the data search. M.L. and D.S.: collected and analyzed the data. M.L.: wrote the first draft. J.H., X.Z., and Z.Z.: revised the manuscript. J.H.: is the guarantor.

Supported by a project of Liuzhou Science and Technology (2021CBC0130), Guangxi Zhuang Autonomous Region (C.N.).

The authors declare that they have nothing to disclose.

Address correspondence to: Jiean Huang, PhD, Department of Gastroenterology, The Second Affiliated Hospital of Guangxi Medical University, 166 Daxue East Road, Nannning 530007, Guangxi, China (e-mail: hjagxmu@163.com).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jcge.com.

DOI: 10.1097/MCG.0000000000001621

Register of Controlled Trials, Web of Science (WOS), PubMed, Embase, and Medline until December 31, 2020, The detailed search terms are listed in the Supplementary File 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A784). It was not limited to the publication status but limited to English as the language of publication. To obtain more potential studies, HE, PEG, lactulose, and RCT 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.

Selection

All the randomized trials comparing PEG with lactulose for the treatment of HE were included regardless of publication status. Included patients (above 18 y old) had minimal, chronic, or acute HE. The primary outcome was at least 1 scale improvement of the Hepatic Encephalopathy Scoring Algorithm (HESA), while the secondary outcomes were adverse events, length of stay (LOS), and serum ammonia concentration. The exclusion criteria included: (1) patients with congenital liver disease or in pregnancy; (2) studies with no designated comparator or intervention; (3) studies only comparing different doses of the same medication.

Data Abstraction

The primary outcome measure was to improve 1 or more in HESA within 24 hours. The secondary outcome measures were the LOS, adverse events, and serum ammonia concentration. All the results were evaluated at the end of treatment and maximum follow-up.

Trial Features

The first author's name, publication year, country, experiment design, age, gender, etiology of cirrhosis, HESA score, serum ammonia level, time of evaluation were all extracted. Data on all patients were obtained regardless of follow-up or compliance. Please contact the primary investigators if any missing data.

Quality Assessment

Cochrane Risk of Bias Tool was used to evaluate the methodological quality of studies. For each eligible trial, articles were judged to have an unclear, low, or high risk of bias in the domains, such as allocation concealment, random sequence generation, selective reporting, incomplete outcome data, binding of outcome assessment, and other sources of bias. The overall risk of bias for a trial would be seen as relatively high if at least 1 domain was evaluated as having a high risk of bias.

Statistical Analysis

For continuous variables, the mean difference with 95% confidence intervals (CIs) would be applied to compare groups if measured on the same scale. If not, they were represented as the standardized mean difference. The Inverse-Variance fixed-effect model was used to summarize the results, and if heterogeneity was present, the D+L random effect model would be used for outcomes. For dichotomous variables, the relative risk (RR) was considered with 95% CIs. The Mantel-Haenszel fixed-effect model was used to collect the results, and if heterogeneity was present, the random effect model would be used for outcomes. The heterogeneity among studies was assessed by analyzing both χ^2 and I^2 statistics. Significant heterogeneity was obtained using χ^2 statistics of P-value <0.1, and different levels of heterogeneity were observed using I^2 statistics based on 75% to 100% considerable, 50% to 90% substantial, 30% to 60% moderate, and 0% to 40%

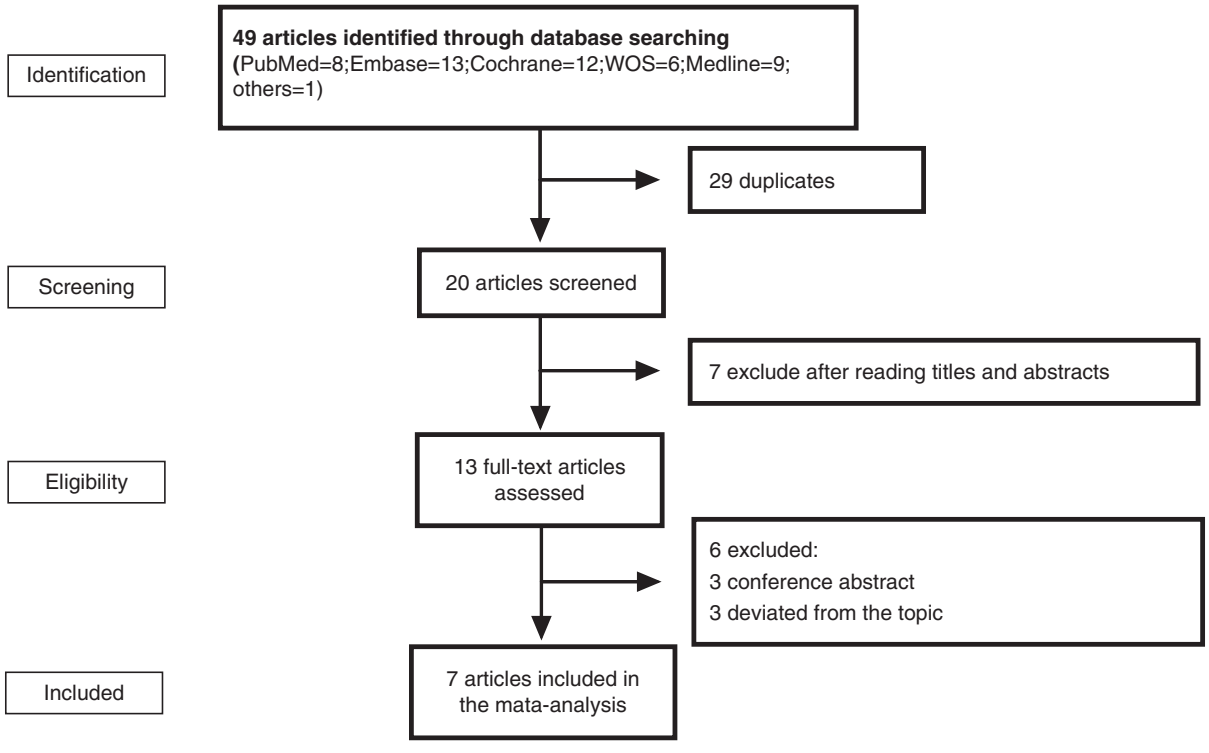

FIGURE 1. Flowchart of the literature screening. WOS indicates Web of Science.

TABLE 1. Characteristics of Studies in the Meta-analysis

References	Trial Design	N (M/F)	Age (Mean ± SD) (y)	Etiology of Cirrhosis (V/A/Other)	HESA Score (1/2/3/4)	Time of Evaluation (h)
Ahmed et al[10]	Randomized	P: 29 (27/2) L: 31 (26/5)	P: 43.38 ± 10.28 L: 43.5 ± 10.62	ND	P: 0/20/9/0 L: 0/17/14/0	24
Bajwa et al[12]	Randomized	P: 47 (28/19) L: 47 (28/19)	P: 39.51 ± 13.27 L: 40.45 ± 14.10	ND	ND	24
Ismail et al[13]	Randomized	P: 20 L: 20	ND	ND	ND	24
Naderian et al[14]	Randomized	P: 21 (16:5) L: 19 (18:1)	P: 53.57 ± 11.61 L: 59.63 ± 9.24	P: 11/1/10 L: 10/1/8	P: 0/9/12/0 L: 0/11/8/0	24
Rahimi et al[11]	Randomized	P: 25 (16/9) L: 25 (10/15)	P: 56 ± 7 L: 56 ± 11	P: 9/10/6 L10/9/5	P: 0/6/3/14 L: 0/6/6/13	24
Raja et al[15]	Randomized	P: 25 (20/5) L: 25 (19/6)	P: 62.12 ± 5.93 L: 60.48 ± 8.45	P: 3/18/4 L: 4/17/4	P: 0/9/13/3 L: 0/7/16/2	24
Shehata et al[16]	Randomized	P: 50 (22/28) L: 50 (30/20)	P: 56.42 ± 8.6 L: 54.5 ± 11.8	ND	P: 13/19/15/3 L: 10/23/12/5	24

A indicates alcoholic liver disease; F, female; HESA, Hepatic Encephalopathy Scoring Algorithm; L, lactulose; M, male; ND, not determined; P, polyethylene glycol; V, viral liver disease.

unimportant. Analyses and diagrams were performed in Stata (version 15.1) and PRISM Graph Pad (version 8.4.3) software.

RESULTS

Search Results

Figure 1 shows the search results in full detail. A total of 49 articles were identified in the initial search algorithm, and there were still 20 studies after removing 29 duplicates. In addition, 7 studies were also canceled for not meeting eligibility criteria after screening titles and abstracts. Then, the remaining 13 articles were retrieved for full-text reviewing. Of these, 1 was excluded for not reporting the primary outcome data; 3 were excluded for conference abstracts of 2 included articles[10,11]; another 3 deviated from the topic. Ultimately, a total of 7 trials that assessed PEG versus lactulose was included in this study.[10–16] One of the trials was published as an abstract.[13] The remaining were published as full articles. All the trials were designed in parallel groups and described as randomized. The generation of allocation sequences was adequately described; treatment allocation was fully hidden in 6 trials[10–12,14–16]; single blinding was reported in 5 trials[10,11,14–16] ; assessment of blinded outcomes was conducted in 2 trials.[10,14] The 6 trials were classified as high quality.[10–12,14–16]

Research Features

Table 1 shows the features of eligible studies. A total of 7 trials with 432 patients (63% of men) were included to assess PEG versus lactulose.[10–16] All patients suffered from minimal, chronic, or acute HE and cirrhosis; the average age was between 40 and 60 years old. Parallel RCTs were performed in all studies. Five studies[10,11,14–16] reported the HESA score at baseline. All included patients had cirrhosis, and 3 studies[11,14,15] reported the etiology of cirrhosis. As for intervention, the daily mean doses of PEG ranged from 2 to 4 L (1 sachet of PEG dissolved in 1L water), and each 1 sachet of PEG (137.5 g) contained 118 g of PEG, 11.36 g of anhydrous sodium sulfate, 3.37 g of sodium bicarbonate, 2.93 g of sodium chloride, and 1.48 g of potassium chloride. In the lactulose group, patients were treated with 30 to 60 mL lactulose 3 times a day. There was no follow-up after the treatment. The evaluation time of efficacy was 24 hours.

Quality Evaluation

Cochrane Risk of Bias Tool was used to assess the quality. In general, the risk of bias was high for participants who were not blinded due to huge differences in dosage and taste between PEG and lactulose, but it was unclear or low for most items. It was difficult to achieve participants blind to trial. The risk of bias for the included studies is shown in Figure 2.

Synthesis of Results

Primary Outcomes: Improvement Rate in HESA Score

Five studies with a total of 288 patients compared PEG (n = 143) with lactulose (n = 145) in the early 24 hours of treatment.[10,11,13,14,16] Based on the Mantel-Haenszel fixed mode, the use of PEG increased HESA score more significantly than that of lactulose within 24 hours (RR = 1.46, 95% CI: 1.26-1.68; $P = 0.000$; Fig. 3, Supplementary File 2: Fig. S2A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784). Neither publication bias (Egger test $P = 0.077 > 0.05$; Supplementary File 2: Figs. S2B, S2C, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) nor significant heterogeneity ($\chi^2 = 3.73$, $P = 0.444$, $I^2 = 0.0\%$; Supplementary File 2: Fig. S2A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) were found in the 5 studies.

Secondary Outcomes

Adverse Effects. Patients who received PEG (n = 215) or lactulose (n = 217) were compared, and all the adverse events were summarized.[10–16] The combined effect of the fixed-effect model was RR = 0.75 (95% CI: 0.48-1.19; $P = 0.222 > 0.05$; Fig. 4, Supplementary File 3: Fig. S3A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784), and there was no statistical significance, suggesting that the rate of adverse effects was similar between the 2 groups. Neither significant heterogeneity ($\chi^2 = 3.23$, $P = 0.357$, $I^2 = 7.2\%$; Supplementary File 3: Fig. S3A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) nor publication bias (Egger test $P = 0.345 > 0.05$; Supplementary File 3: Figs. S3B, S3C, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) were observed in the 7 studies.

LOS. Six studies with a total of 392 patients compared PEG (n = 195) with lactulose (n = 197) in the LOS.[10–12,14–16] The results showed that the LOS in the PEG group was (WMD = −1.78, 95% CI: −2.72 to −0.85; $P = 0.000$; Fig. 5,

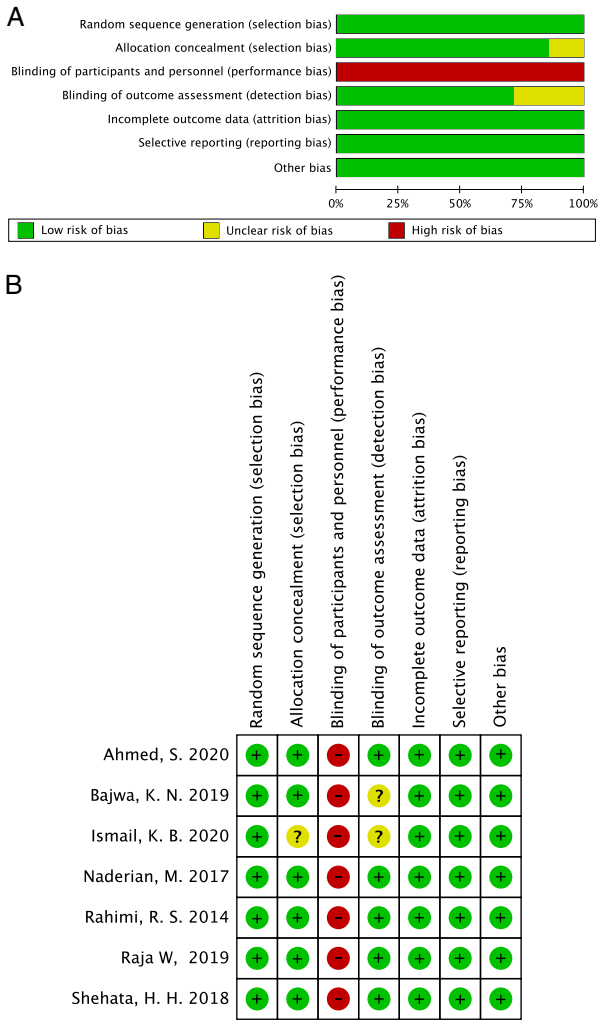

FIGURE 2. Risk of bias of bias assessment for the included studies. A, A graphic view for the risk of bias. B, A summary for the risk of bias.

Supplementary File 4: Fig. S4A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) shorter than that in the lactulose group with significant heterogeneity ($\chi^2 = 50.74$, $P < 0.05$, $I^2 = 90.1\%$; Supplementary File 4: Fig. S4A, Supplemental Digital Content 1, http://links.lww.com/JCG/A784). The funnel plot was drawn to mean that there was no publication bias (Egger test $P = 0.914 > 0.05$; Supplementary File 4: Figs. S4B, S4C, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) in the 6 studies.

Serum Ammonia Concentration. Before the meta-analysis, it is necessary to ensure that the baseline period of the 2 groups is consistent, so that meta-analysis can be performed subsequently.

Three studies with a total of 148 patients compared PEG (n = 73) with lactulose (n = 75) in the levels of serum ammonia concentration.[10,11,14] The results showed that the ammonia concentration of the baseline was consistent (WMD = 6.851, 95% CI: −2.72 to 16.424; $P = 0.161$; Supplementary File 5: Figs. S5A, S5B, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) with insignificant heterogeneity ($\chi^2 = 3.09$, $P = 0.214$, $I^2 = 35.2\%$).

Compared with lactulose, there was no significant difference (WMD = 9.02, 95% CI: −14.39 to 32.43; $P = 0.45$; Fig. 6, Supplementary File 5: Fig. S5C, Supplemental Digital Content 1, http://links.lww.com/JCG/A784) in serum ammonia levels of patients treated with PEG with certain heterogeneity ($\chi^2 = 13.20$, $P = 0.001$, $I^2 = 84.9\%$). Due to the small number of included studies (n < 5), the funnel plot was not further drawn for bias analysis.

Sensitivity Analysis

To ensure the quality of study design, a sensitivity analysis of both primary and secondary outcomes was performed to discuss heterogeneity. Based on the Cochrane Collaboration's risk assessment tool, the consistency of findings was determined by excluding studies that were considered at higher risk of bias, and there was no statistically significant change in all the comparisons performed (Supplementary File 4: Fig. S4D, Supplemental Digital Content 1, http://links.lww.com/JCG/A784).

DISCUSSION

The definite mechanism that causes HE remains unknown. Treatment of patients with overt HE basically depends on nutritional support, reduction of inflammation, correction of nutritional deficiencies, regulation of neurotransmission, modulation of fecal flora, decrease of blood ammonia, and elimination of potential induction factors.[17] A great number of studies have shown that ammonia production plays a role in the gastrointestinal (GI) tract and an imperfect liver leads to impaired ammonia elimination.[18,19] Therefore, the use of antibiotics and colon cleaners to reduce the number of GI bacteria plays a therapeutic role in HE. The underlying cause of HE is separated from such a therapeutic strategy. No matter electrolyte disorder or GI bleeding is an induction factor, HE can be possibly resolved by the administration of cleansing agents. PEG and lactulose are both osmotic laxatives used in the treatment of HE.

In this meta-analysis, for the first time, the efficacy of PEG was reviewed compared with lactulose on HESA improvement, adverse effects, hospital stay, and serum ammonia concentration. It was found that PEG was superior to lactulose in the treatment of an acute episode of HE, which could deliver clinical improvement in HESA score and reduce the LOS without increasing the incidence of adverse events. However, there was no significant difference between the 2 groups in serum ammonia levels.

PEG is a nonabsorbable, nondigestible macromolecule that is not metabolized by colonic microflora, and it can be commonly used for colonoscopy preparation, causing osmotic diarrhea through osmotic and volumetric expansion in the colon.[20] Although the use of nonabsorbable disaccharides for HE therapy has not yet been supported or refuted by sufficient evidence,[18] lactulose has been always used for the catharsis of the gut mainly through creating an acidic environment in the gut which helps in the conversion of soluble ammonia (NH_3) to insoluble ammonium ion (NH_4^+), thereby resulting in decreased systemic absorption from the gut.[21] Compared with lactulose, PEG was found to be more effective in catharsis or relieving constipation.[22] Similar results were found in this study, suggesting that bowel cleansing with PEG is an immediate, effective, rapid, and safe therapeutic strategy for patients with acute HE. This is because PEG electrolyte solution is a more powerful cathartic agent than

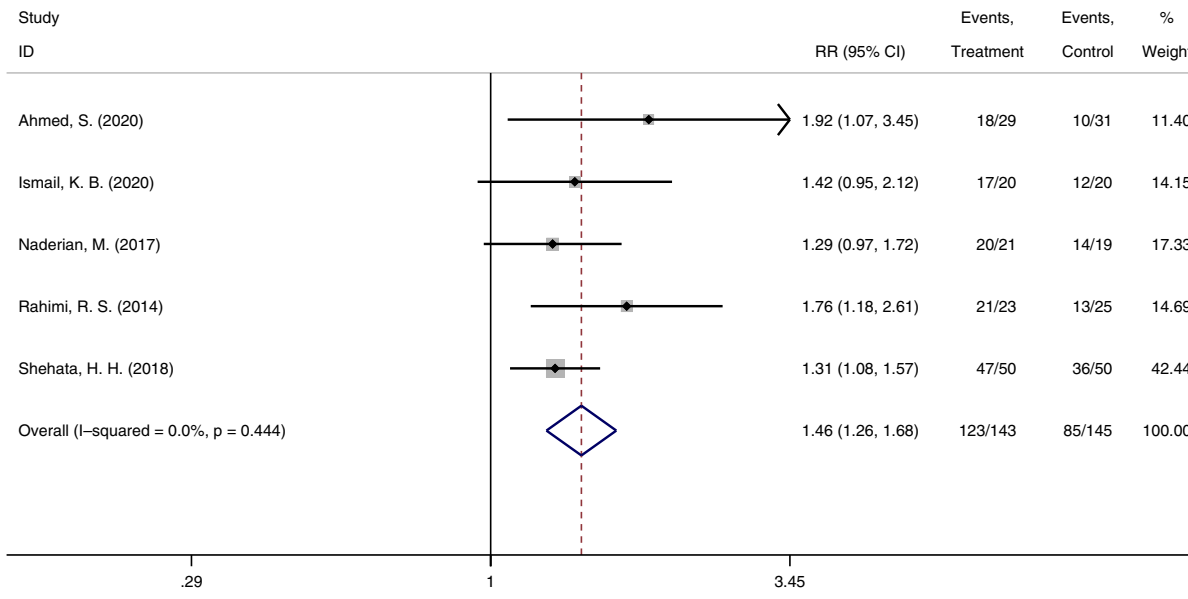

FIGURE 3. Forest plot illustrating the comparison of the clinical efficacy of polyethylene glycol with lactulose (fixed-effects analysis). CI indicates confidence interval; RR, relative risk. full color online

lactulose and may prevent electrolyte disturbance to help promote the improvement of encephalopathy. The fixed-effect model was used in this study, and the results showed there was not enough intertrial heterogeneity, which strengthened the outcomes. In addition, all the above-mentioned studies targeted patients with a history of cirrhosis rather than reversible hepatic dysfunction (like the alcoholic or viral hepatitis). Coupled with the continued beneficial effects of each trial and the short duration of the research, evidence was further reinforced that the efficacy of HE treatment could be attributed to the use of individual agents rather than an accidental discovery.

The results of this study provide substantial evidence for the efficacy of PEG in the treatment of HE with shorter hospitalization. The reason may be that the early resolution of HE not only contributes to timely and effective intestinal nutrition, which plays an important role in patient recovery but also enables health care professionals to focus on managing the factors that cause metabolic encephalopathy and identifying other possible causes.[15] Significant heterogeneity was observed in the meta-analysis of hospital stay, and conservative results were obtained using the random effect model. Uncorrected triggers for HE were excluded from all the trials included in the review. Nevertheless,

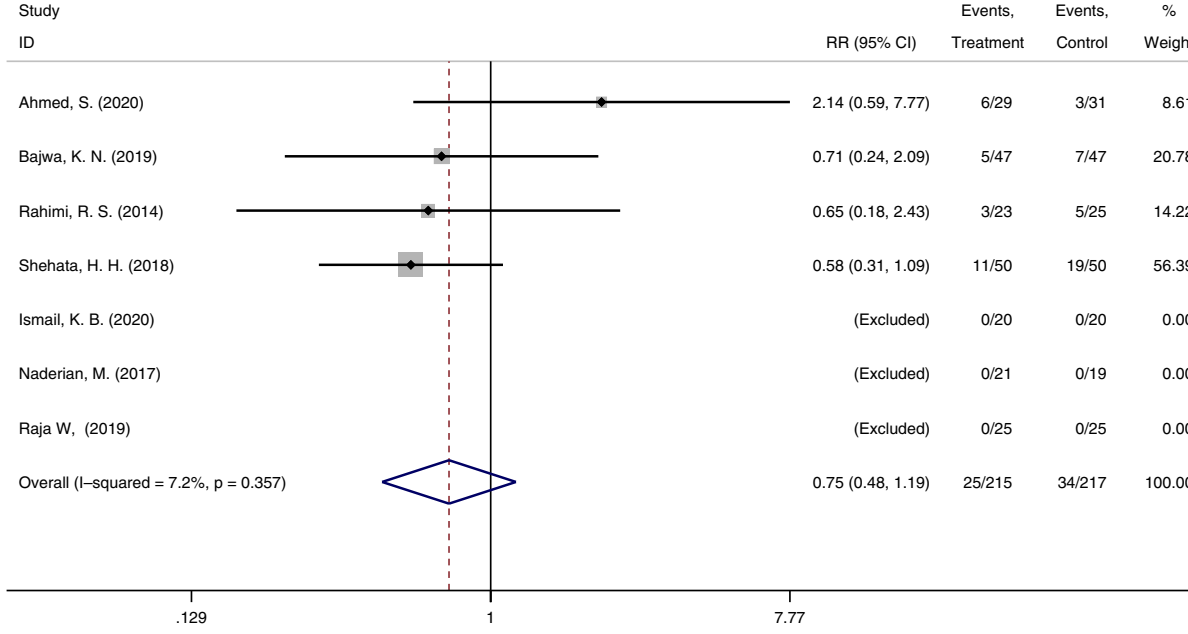

FIGURE 4. Forest plot illustrating adverse events experienced by patients treated with polyethylene glycol versus lactulose (fixed-effects analysis). CI indicates confidence interval; RR, relative risk. full color online

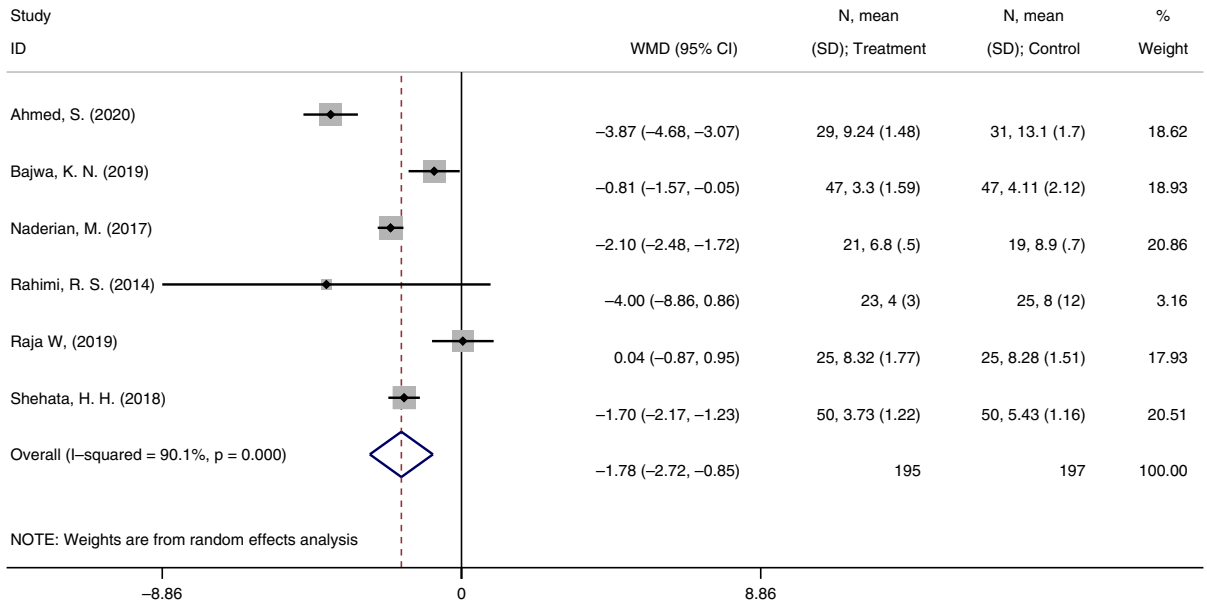

FIGURE 5. Forest plot illustrating the comparison of hospital stays of polyethylene glycol with lactulose (random-effects analysis). CI indicates confidence interval; WMD, weighted mean difference. full color online

relevant data were not acquired from individual patients to ascertain whether the LOS varied depending on the grade or etiology of liver disease or other comorbidities in each population. Importantly, these aspects would be most likely to generate the heterogeneity observed in the studies.

None of the patients included in this study had any serious adverse reactions, which is consistent with a Cochrane systematic review of PEG verse lactulose in the treatment of chronic constipation.[22] No difference in the incidence of adverse events between PEG and lactulose was observed after collecting valid studies. The meta-analysis of adverse events had no significant heterogeneity in the pooled studies. Adverse reactions mainly include diarrhea, bloating, nausea, etc. More bloating symptoms appeared in the lactose group, while more diarrhea symptoms appeared in the PEG group. Lactose produces short-chain fatty acids with the help of the metabolism by the colon flora, and its cooperation with hydrogen, methane, carbon dioxide and other significant gases contributes to the production of laxative effects. However, PEG has an osmotic activity with no need of being metabolized by the colonic flora or increasing the production of colonic gases.[23] In this study, neither treatment caused any serious electrolyte disorders, with no significant difference in serum sodium and potassium between the 2 groups after 24 hours of treatment. Therefore, the use of PEG does not increase the incidence of adverse events compared with lactulose.

It is known that ammonia plays a significant role in the pathogenesis of HE.[24,25] Only 3 trials compared serum ammonia concentration between the 2 groups. In this study,

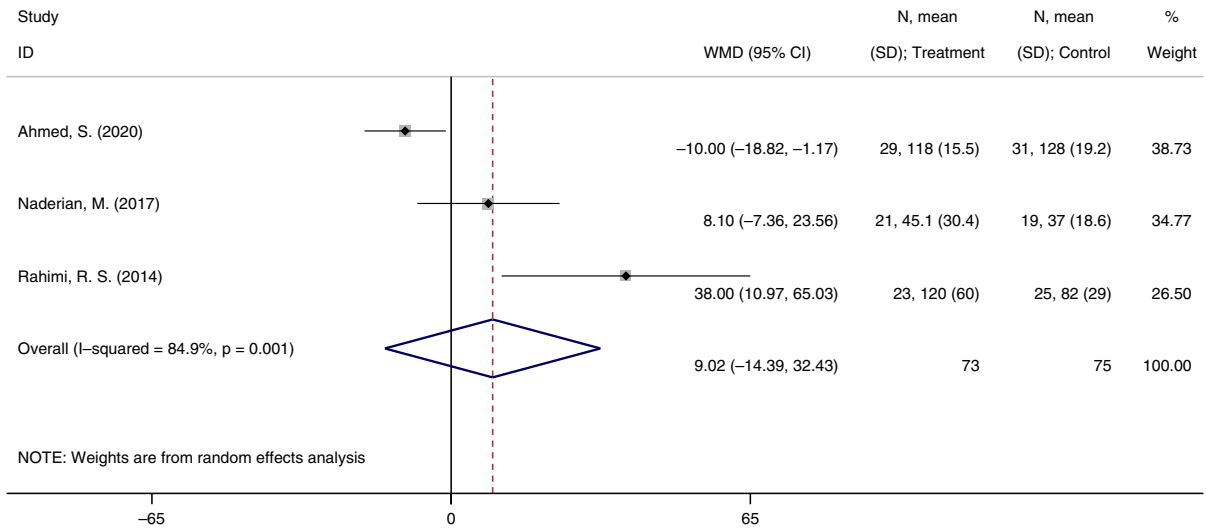

FIGURE 6. Forest plot illustrating serum ammonia concentration of patients treated with polyethylene glycol versus lactulose at 24 hours (random-effects analysis). CI indicates confidence interval; WMD, weighted mean difference. full color online

serum ammonia concentration increased from the baseline in all patients after 24 hours of treatment. However, aggregate data confirmed that PEG had no significant effect on the serum ammonia concentration after 24 hours of treatment compared with lactulose. Ammonia levels were not associated with better improvement in HESA grades. One reasonable explanation for this inconsistency is that the method and timing of testing used as biological samples to determine serum ammonia fail to distinguish between NH_4^+ ion and NH_3. NH_3 exists in the form of gas with pH-dependent equilibrium, which is the form implicated in HE-related neurotoxicity.[26] In contrast, NH_4^+ ion is independent of the pathogenesis of HE, which is the predominant form (98%) of ammonia at physiological pH.[27] It is worth noting that PEG may cause a mild metabolic acidosis,[21] leading to an increase in NH_4^+ ion levels and a decrease in NH_3. These chemical changes can explain the rapid improvement of PEG in mental status without significantly altering ammonia levels. Another explanation could be that PEG does not just work through ammonia. The fast-acting laxative leads to changes in the gut microbiome and a reduction in other gut-derived toxins or neuroinflammation contributing to the resolution of HE. Since PEG is a highly effective laxative, the potential clinical improvement of HE may be more clinically significant than the actual decline in ammonia levels.[10] Publication bias and sensitivity analysis were not conducted due to only 3 studies include in the analysis. As such, this conclusion should be explained with caution and require more high-quality, multicenter RCTs validation.

There are several limitations that should be noted in this study. First, this meta-analysis is limited by the small number and poor quality of included trials. Second, significant heterogeneity still exists in the outcomes of studies, and the source of heterogeneity may include age, gender, culture, and many other corresponding factors. In addition, only the follow-up in the short term was conducted in these included studies. In the future, more prospective studies should be undertaken with the follow-up in the long term.

Also, there are a number of advantages in the study. A wide range of literature research was carried out, providing updated information about the efficacy of PEG in the treatment of HE. The inclusion or exclusion of studies and the extraction of data were independently conducted with the help of 2 reviewers, which can be regarded as more accurate. Moreover, potential studies were not excluded because of publication year or status, and the external validity of the results was increased due to the fact that the trials included were conducted in different settings or even several countries. Here is another advantage that not only the efficacy and side effects of both treatments were assessed, but also other significant clinical results were included, such as serum ammonia concentration and hospital stay. In addition, the funnel plot was also included to investigate substantial publication bias, though a rigorous search strategy was used to reduce the introduction of potential publication bias.

HE is considered to be a severe sequela of chronic liver disease, which has prominent medical costs, morbidity, and mortality. It is reported that HE in America has a total of 22,931 patients hospitalized, with a total of $64,108 per case and an average stay of 8.5 days.[28] Compared with lactulose, PEG preparations are inexpensive, commonly used, and widely available. The treatment of overt HE with PEG may lead to shorter LOS, which depends on the cause of HE. In the PEG group, it is found that HE resolution is significantly faster with shorter lengths of hospital stay. This is more likely to bring about a reduction in the total direct and indirect costs of illness caused by HE.

CONCLUSIONS

In summary, this study shows that PEG is able to improve the clinical efficacy of HE within 24 hours better than lactulose and does not increase side effects. Due to its effectiveness and safety, PEG should be considered as a first-line treatment for patients who are intolerant of lactulose and as second-line therapy for HE patients with lactulose treatment failure.

REFERENCES

1. American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;61:642–659.
2. Patel VC, White H, Støy S, et al. Clinical science workshop: targeting the gut-liver-brain axis. *Metab Brain Dis*. 2016;31:1327–1337.
3. Nusrat S, Khan MS, Fazili J, et al. Cirrhosis and its complications: evidence based treatment. *World J Gastroenterol*. 2014;20:5442–5460.
4. Sheasgreen C, Lu L, Patel A. Pathophysiology, diagnosis, and management of hepatic encephalopathy. *Inflammopharmacology*. 2014;22:319–326.
5. Gabduzda GJ, Hall PW III. Relation of potassium depletion to renal ammonium metabolism and hepatic coma. *Medicine (Baltimore)*. 1966;45:481–490.
6. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database Syst Rev*. 2004:CD003044.
7. Weber FL Jr, Banwell JG, Fresard KM, et al. Nitrogen in fecal bacterial, fiber, and soluble fractions of patients with cirrhosis: effects of lactulose and lactulose plus neomycin. *J Lab Clin Med*. 1987;110:259–263.
8. Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. *Nature*. 2014;513:59–64.
9. Bajaj JS, Gillevet PM, Patel NR, et al. A longitudinal systems biology analysis of lactulose withdrawal in hepatic encephalopathy. *Metab Brain Dis*. 2012;27:205–215.
10. Ahmed S, Premkumar M, Dhiman RK, et al. Combined PEG3350 plus lactulose results in early resolution of hepatic encephalopathy and improved 28-day survival in acute-on-chronic liver failure. *J Clin Gastroenterol*. 2020. [Epub ahead of print].
11. Rahimi RS, Singal AG, Cuthbert JA, et al. Lactulose vs polyethylene glycol 3350—electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. *JAMA Intern Med*. 2014;174:1727–1733.
12. Bajwa KN, Aziz B, Nazar T. Comparison of the effectiveness and safety profile of polyethylene glycol-electrolyte solution with lactulose in patients of overt hepatic encephalopathy. *Pak J Med Health Sci*. 2019;13:411–414.
13. Ismail KB, Khedher S, Khaled A, et al. Lactulose vs. polyethylene glycol electrolyte solution for treatment of hepatic encephalopathy. *Ann Intensive Care*. 2020;10:126.
14. Naderian M, Akbari H, Saeedi M, et al. 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;9:12–19.
15. Raja W, Jan R, Sebastian B, et al. To compare the effect of polyethylene glycol vs. lactulose in the treatment ofovert hepatic encephalopathy. *J Hepatol Gastroint Dis*. 2019;5:166.
16. Shehata HH, Elfert AA, Abdin AA, et al. Randomized controlled trial of polyethylene glycol versus lactulose for the treatment of overt hepatic encephalopathy. *Eur J Gastroenterol Hepatol*. 2018;30:1476–1481.

17. Frederick RT. Current concepts in the pathophysiology and management of hepatic encephalopathy. *Gastroenterol Hepatol (N Y)*. 2011;7:222–233.
18. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ*. 2004;328:1046.
19. Sturgeon JP, Shawcross DL. Recent insights into the pathogenesis of hepatic encephalopathy and treatments. *Expert Rev Gastroenterol Hepatol*. 2014;8:83–100.
20. Dipalma JA, Cleveland MV, McGowan J, et al. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol*. 2007;102:1436–1441.
21. Sharma BC, Sharma P, Lunia MK, et al. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013;108:1458–1463.
22. Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev*. 2010;7:CD007570.
23. Attar A, Lémann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut*. 1999;44:226–230.
24. Häussinger D, Schliess F. Pathogenetic mechanisms of hepatic encephalopathy. *Gut*. 2008;57:1156–1165.
25. Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med*. 2003;114:188–193.
26. Kramer L, Tribl B, Gendo A, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. *Hepatology*. 2000;31:30–34.
27. Dhiman RK, Rana B, Agrawal S, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology*. 2014;147:1327.e3–1337.e3.
28. Stepanova M, Mishra A, Venkatesan C, et al. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clin Gastroenterol Hepatol*. 2012;10:1034.e1–1041.e1.