META-ANALYSIS

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Prophylactic Lactulose Therapy in Patients with Cirrhosis and Upper Gastrointestinal Bleeding: A Meta-analysis of Randomized Trials

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ABSTRACT

Background & Aims: Lactulose is the first-line drug for both treatment and secondary prophylaxis for overt hepatic encephalopathy (HE). The use of lactulose for the primary prophylaxis of HE in patients with cirrhosis and acute upper gastrointestinal bleeding (AUGIB) has been debated. Hence, we conducted this meta-analysis to assess the role of lactulose in HE prophylaxis in patients with cirrhosis and AUGIB.
Methods: A comprehensive search of literature from inception to December 2022 was performed of three databases for randomized studies comparing lactulose and placebo in patients with cirrhosis and AUGIB. Risk ratios (RR) with 95% confidence intervals were calculated for all the dichotomous outcomes.
Results: A total of five studies were included in the final analysis, out of which three studies had a low risk of bias, and two had a moderate risk of bias. Lactulose therapy was associated with a significantly lower risk of OHE compared to placebo, with a RR of 0.38 (0.23-0.62) and a number needed to treat of 6. There was no difference in the risk of mortality between the groups, with a RR of 0.71 (0.29-1.76). The pooled incidence rates of overall adverse events (AEs) and diarrhea with the use of lactulose therapy were 53.2% (42.2- 64.2) and 34.7% (17.7-51.7), but a majority did not require drug discontinuation. The certainty of the evidence was moderate to low.
Conclusions: Prophylactic lactulose reduces the incidence of HE after AUGIB but has no effect on mortality. Diarrhea and abdominal discomfort are common AEs but do not need drug discontinuation.

Key words: variceal bleeding – gastrointestinal bleeding – cirrhosis - hepatic encephalopathy – lactulose.

Abbreviations: ACLF: acute on chronic liver failure; AE: adverse event; AUGIB: acute upper gastrointestinal bleeding; CI: confidence interval; HE: hepatic encephalopathy; GI: gastrointestinal; MD: mean difference RR: risk ratio.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is one of the commonest precipitating factors for hepatic encephalopathy (HE) [1]. The incidence of HE after AUGIB is variable, ranging from 10-39%, and is associated with increased mortality [1, 2]. Although gastrointestinal (GI) bleeding serves as the precipitant, the development of HE is generally multifactorial, influenced by the degree of liver dysfunction, systemic inflammation, and infections [3]. Generation of toxic substances from the breakdown of blood in the GI tract leading to hyperammonaemia has been proposed as one of the key mechanisms responsible for the precipitation of HE. Consequently, the rapid removal of blood from the GI tract using cathartics has been recommended to prevent HE in patients with cirrhosis and AUGIB [3].

Lactulose is the first-line drug for both treatment and prophylaxis for overt HE across guidelines. [4, 5]. However, the evidence for using lactulose to prevent HE in GI bleeding is limited. While certain studies have indicated a benefit [6, 7] conflicting data from a recent randomized trial also exist [2]. The possible conflict in the literature stems from the multifactorial nature of HE pathogenesis, wherein AUGIB may be one of the drivers. In this context, we aimed to systematically review the literature on the role of lactulose for prophylaxis of HE in patients with GI bleeding and to analyse the data to establish the benefits of lactulose prophylaxis in this setting.

METHODS

Information Sources and Search Strategy

A comprehensive search of all relevant studies was conducted using the databases of MEDLINE, EMBASE, and Scopus from inception to December 2022. The keywords used were Cirrhosis AND [(Gastrointestinal OR Variceal) AND Bleed*] AND Encephalopathy AND (Prophylaxis OR Lactulose). Manual searching of reference lists of the included studies was also undertaken to ensure that no potentially relevant items were overlooked. The study methodology was designed and executed to adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [8].

Study Selection

The PICO criteria used for included comparative studies were: (a) patients – patients with cirrhosis and acute variceal bleeding; (b) intervention – lactulose therapy; (c) comparison – to establish the benefits of lactulose prophylaxis compared to placebo. (d) outcomes – overt hepatic encephalopathy, mortality, adverse events (AE), and duration of hospitalization. In accordance with the selection criteria above, the titles and abstracts of all studies were independently reviewed by two authors. Any disagreements were resolved by a third reviewer. The exclusion criteria used were non-comparative studies, case series, and studies that do not report original data, including reviews, editorials, or opinions.

Definition of Outcomes

The primary outcome of overt HE was defined by the development of HE of grade II or more as per the West Haven criteria, within 5 days of admission. The secondary outcomes were in-hospital mortality, and AE associated with lactulose.

Data Extraction and Risk of Bias Assessment

Two independent reviewers performed the data extraction, and a third reviewer resolved any disagreement. Data were collected under the following headings: study author and year, country of study, study design, number of patients, age and gender distribution, details of liver disease, clinical outcome, mortality, and AEs. After data extraction, the same two reviewers performed a risk of bias (quality) assessment using the Cochrane risk-of-bias tool for randomized controlled trials [9].

Statistical Analysis

Risk ratios (RR) with 95% confidence intervals (CI) were calculated for all the dichotomous outcomes. Continuous variables were analysed using mean difference (MD). A Cochran's Q test and I^2 statistics were used to determine the heterogeneity between the studies. A p-value of Q test < 0.1 or the I^2 value > 30% was considered significant. A fixed-effect model was used in the absence of significant heterogeneity, while a random-effect model was used in the presence of significant heterogeneity. Visual inspection of funnel plots along with Egger's test was used for publication bias assessment. The sensitivity analysis was performed using a leave-one-out meta-analysis. RevMan software (version 5.4.1, Cochrane Collaboration) and STATA software (version 17, StataCorp., College Station, TX) were used for statistical analysis.

RESULTS

Study Characteristics and Risk of Bias Assessment

A total of 1,271 records were identified with the predefined search strategy, out of which five studies were included in the meta-analysis. Fig. 1 shows the flowchart for the study selection and inclusion. Based upon our search and selection criteria, five randomized trials were identified, of which four originated from Asia [2, 6-8] and one from South America [9]. The characteristics of the individual studies are shown in Table I. All the trials compared lactulose against a placebo, with three trials being double-blind [2, 8, 9] and two as open-label [6, 7]. The etiology of liver disease was specified in three studies, with alcohol being the predominant etiology in two [7, 9] and hepatitis B in one [6]. Majority of the patients belonged to Child-Pugh class A/B. Variceal bleeding was the predominant type of AUGIB in all studies. Fig. 2 shows the traffic-light plot for risk of bias assessment. Three studies had low risk of bias, and two had moderate risk of bias.

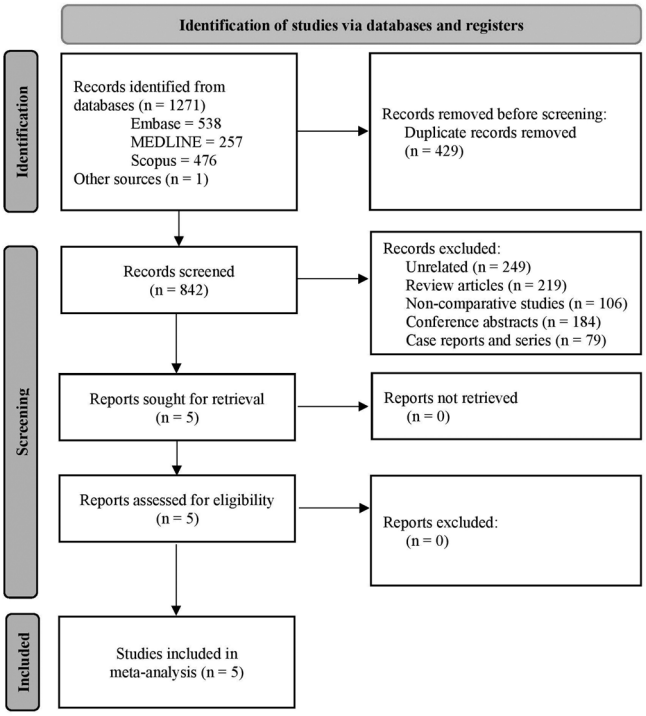

Fig. 1. PRISMA flowchart for study identification, screening, and inclusion process.

Incidence of Overt Hepatic Encephalopathy

All five studies (n=368) compared the incidence of overt HE with or without lactulose therapy. Lactulose therapy was associated with a significantly lower risk of overt HE compared to placebo with a RR of 0.38 (95%CI: 0.23–0.62; I^2=0%) (Table II, Fig. 3A). The number needed to treat for lactulose in the prevention of overt HE in AUGIB in cirrhosis was 6.

Table I. Baseline characteristics of the studies included in the meta-analysis

Author, year, reference	Country	Indication	Intervention	Number of patients	Age, in years	Male/ Female	Child-Pugh A/B/C, MELD score	Source of bleed
Sharma 2011, [7]	India	Liver cirrhosis and acute gastrointestinal bleeding with hematemesis and/or melena within 24 hrs. of presentation	Lactulose (30 mL, 3-4 times/day, then adjusted to 2-3 stools/day)	35	41.6±12.9	30/5	- 16.7±5.7	EV: 92%, GV: 8%
			No lactulose	35	37.2±16.0	28/7	- 15.8±3.8	EV: 88%, GV: 12%
Wen 2013, [6]	China	Liver cirrhosis and gastrointestinal bleeding within 72 hrs. of presentation	Lactulose (10–30 ml 2–3 times/day, then adjusted to 2-3 stools/day)	63	53.0±13.3	44/19	38/20/5 -	Variceal: 63.5%, non-variceal: 36.5%
			No lactulose	65	50.4±10.2	47/18	33/26/6 -	Variceal: 66.1%, non-variceal: 33.9%
Tijera 2018, [9]	Mexico	Patients with cirrhosis admitted with acute variceal bleeding	Lactulose (30 ml every 8 hours, then adjusted to 2-3 stools/day)	22	50.1±11.3	14/8	7/10/5 -	EV: 86.4%, GV: 13.6%
			No lactulose)	22	49.3±9.5	17/5	5/15/2 -	EV: 90.9%,GV: 9.1%
Rattanasupara 2018, [2]	Thailand	Liver cirrhosis and gastrointestinal bleeding within 72 hrs. of presentation	Lactulose (30 ml, 2-3 times/day, then adjusted to 2-3 stools/day)	24	51.9±14.7	19/5	3/18/3, 15.0 ± 4.7	Variceal: 79.2%, non-variceal: 20.8%
			No lactulose	22	49.7±14.2	19/3	6/7/9, 15.6 ± 6.4	Variceal: 90.9%, non-variceal: 9.1%
Khan 2022, [8]	Pakistan	Patients with cirrhosis admitted with acute upper gastrointestinal bleeding	Lactulose (30 ml, 2-3 times/day, then adjusted to 2-3 stools/day)	40	44.4±15.4	21/19	-	-
			No lactulose	40	38.7±18.6	24/16	-	-

EV: Eesophageal varices; GV: gastric varices.

Mortality

All five studies (n=368) compared the incidence of death, with or without lactulose therapy. There was no difference in the risk of mortality between the groups with a RR of 0.71 (95%CI: 0.29–1.76; I^2=0%) (Fig. 3B).

Adverse Events with Lactulose

The incidence of diarrhea varied from 3.8% to 54.5% in the included studies. The study by Khan et al. [8] being a significant outlier, was excluded from final analysis of diarrhea incidence.

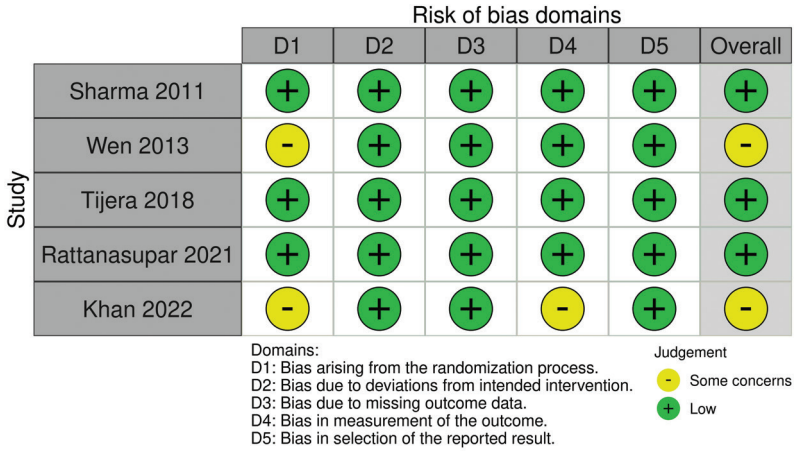

Fig. 2. Risk of bias assessment for the included studies using the Cochrane risk-of-bias tool for randomized controlled trials.

Table II. Outcome of the studies included in the meta-analysis

Author, year	Intervention	Number of patients	Overt hepatic encephalopathy	Death	Length of hospitalization, in days	Adverse events
Sharma 2011, [7]	Lactulose	35	5	3	7.8±1.9	Diarrhea: 26%, bloating 11%, distaste: 15%, No AE required stopping treatment
	No lactulose	35	14	6	8.7±1.7	-
Wen 2013, [6]	Lactulose	63	1	0	-	2 withdrawn due to abdominal distension and diarrhea
	No lactulose	65	8	1	-	-
Tijera 2018, [9]	Lactulose	22	6	1	-	Diarrhea: 54.5%, bloating and abdominal discomfort: 45.5%
	No lactulose	22	12	0	-	-
Rattanasupara 2021, [2]	Lactulose	24	4	1	5.3±0.4	Diarrhea: 25%, bloating 20.8%, distaste: 17%
	No lactulose	22	5	0	5.7±1.2	-
Khan 2022, [8]	Lactulose	40	2	1	-	Diarrhea: 3.8%, bloating: 6.2%
	No lactulose	40	8	2	-	-

The pooled incidence rates of overall AEs and diarrhea with the use of lactulose therapy were 53.2% (95%CI: 42.2–64.2; I^2= 0%) and 34.7% (95%CI: 17.7–51.7; I^2=63.3%).

Duration of Hospitalization

Only two studies compared the difference in duration of hospitalization between the two groups. Hence, a meta-analysis could not be conducted. There was no significant difference in the duration of hospitalization between the lactulose and placebo groups in the study by Sharma et al. [7] (7.8±1.9 days vs. 8.7±1.7 days) and Rattanasupara et al. [2] (5.3±0.4 days vs. 5.7±1.2 days).

Publication Bias, Sensitivity Analysis, and Certainty of the Evidence

Due to limited studies, publication bias could not be assessed. Sensitivity analysis using leave-one-out analysis did not significantly change the relative effect for overt HE and mortality. Table III shows the summary of findings with the certainty of the evidence for the present analysis.

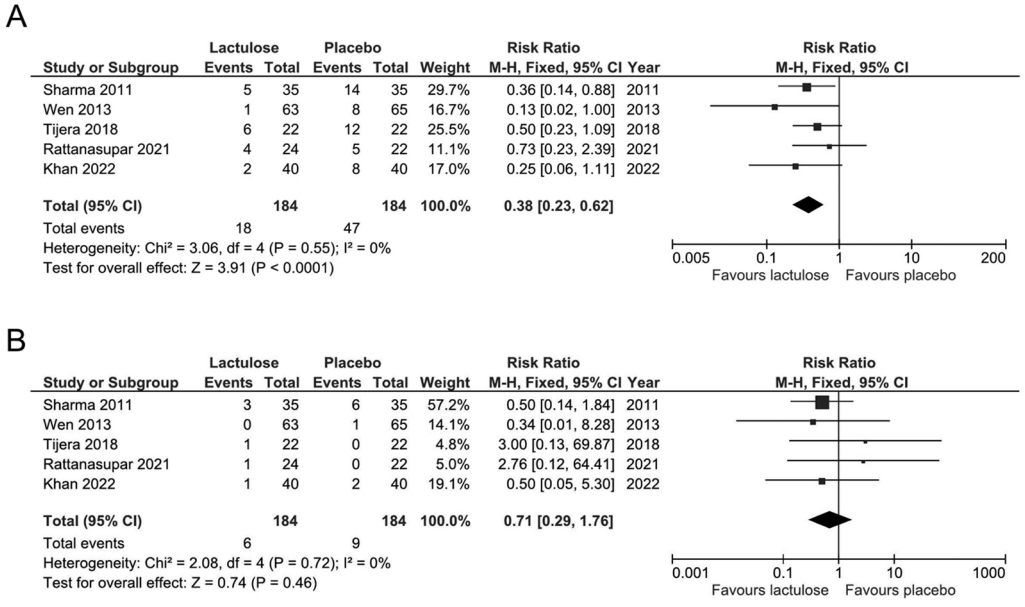

Fig. 3. Forest plot comparing the (A) risk of overt hepatic encephalopathy and (B) mortality between patients with cirrhosis and upper gastrointestinal bleeding receiving lactulose and placebo.

Table III. Summary of findings with a grade of evidence

Population: Upper gastrointestinal bleeding in patients with cirrhosis
Intervention: Lactulose
Comparison: Placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of patients (Studies)	Certainty assessment				Overall certainty of the evidence
	Risk with placebo	Risk with lactulose			Risk of bias	Inconsistency	Indirectness	Imprecision	
Overt hepatic encephalopathy	255 per 1,000	158 fewer per 1,000 (196 fewer to 97 fewer)	0.38 (0.23 – 0.62)	368 (5 studies)	-	-	-	+	Moderate ■■■□
Mortality	50 per 1,000	15 fewer per 1,000 (36 fewer to 38 more)	0.71 (0.29 – 1.76)	368 (5 studies)	-	+	-	+	Low ■■□□

CI: confidence interval.

DISCUSSION

Hepatic encephalopathy portends poor prognosis in patients with AUGIB and is associated with increased mortality [7, 10]. Presence of toxic substances generated from blood proteins leading to exaggerated ammonia genesis has been proposed as the principal pathophysiological mechanism for the precipitation of HE in the setting of AUGIB [11]. Consequently, the rationale for prophylactic therapy revolves around rapidly eliminating toxic substances from the gut to prevent HE. Lactulose acts both by reducing ammonia absorption as well as catharsis and therefore has been used in the prevention of HE in the setting of AUGIB [11]. A previous systematic review by Aires et al. [12] had included only two studies [6, 7] which showed a decrease of approximately 20% (range 10 to 28%) in the absolute risk HE with lactulose prophylaxis. However, following the review by Aires et al. [12] further studies with conflicting results [2] have been reported. The efficacy of lactulose in this setting is substantiated in this systematic review showing a definitive reduction in the pooled HE incidence with prophylactic use of lactulose in AUGIB.

Overall, our review yielded five randomized trials that evaluated the effect of lactulose for the prevention of overt HE in the setting of AUGIB. All the trials [6-9] except for one [2] reported a significantly lower incidence of precipitated HE, translating into a RR of 0.38 (0.23-0.62). For the outlier study by Rattanasupar et al. [2] it is important to note that the study protocol allowed for the use of an additional rescue laxative with lactulose in cases of inadequate bowel movement, which might have influenced the results. Furthermore, liver disease severity is a key factor associated with HE precipitation after AUGIB. Overall, all the studies primarily included patients with Child-Pugh class A and B with a relatively smaller number of Child-Pugh class C patients. It would have been important to analyze such subgroup data, which, however, has not been stratified in the studies. Additionally, the studies by Rattanasupar et al. [2] and Wen et al. [6] included patients with both variceal and non-variceal AUGIB. However, no studies have individually examined any differential impact of lactulose depending on variceal or non-variceal bleeding.

With respect to mortality, there were no significant differences with the use of lactulose for prophylaxis versus placebo with RR of 0.71 (0.29–1.76). However, the overall mortality events were low across studies, with only six events in the lactulose group and nine events in those without. Given that the study population is primarily Child-Pugh A/B, mortality expectedly would not be a determining endpoint for such trials. Hence, it would be important to assess the impact of lactulose in Child-Pugh C patients with advanced cirrhosis and patients with acute on chronic liver failure (ACLF).

One of the concerns with the use of lactulose was adverse events. Overall, the pooled incidence was more than 50%, diarrhea being the most common (34.7%), followed by bloating and abdominal distention. None of the studies reported adverse events requiring therapy withdrawal except for Wen et al. [6] where two patients had to be taken off lactulose. Interestingly, the most recent study from Pakistan reported an extremely low incidence (3.8%) of diarrhea which is inconsistent with the overall literature. In the context of adverse events due to lactulose, there is a single trial comparing lactulose with rifaximin for HE prophylaxis in AUGIB [13]. The study showed no difference between lactulose and rifaximin in preventing HE (10/60 events vs. 9/60 events; p=1). However, adverse events were lesser with rifaximin in comparison to lactulose (5% vs. 26%). Although not a part of the current meta-analysis, this study raises questions on the exact mechanistic basis of HE prophylaxis in AUGIB and mandates future prospective trials further to explore the role of rifaximin in this setting.

Our systematic review has some key limitations, which include a lack of stratification and subgroup analysis according to the primary etiology of liver cirrhosis and type of AUGIB due to a lack of data. The overall number of mortality events was low, which precludes definitive conclusions with regard to mortality and calls for future trials designed specifically looking at Child-Pugh class C and patients with ACLF. The use of antibiotics and type of vasoconstrictor (terlipressin, octreotide, somatostatin) are also important determinants of outcomes in variceal AUGIB which could not be analyzed separately due to lack of data. Lastly, the presence of portosystemic shunts is an additional factor in the development of overt HE, which was looked at only in one of the studies [2].

CONCLUSIONS

Precipitated HE after AUGIB is an important determinant of morbidity and mortality. Lactulose prophylaxis reduces the incidence of HE after AUGIB but does not influence the mortality. Diarrhea and abdominal discomfort are common adverse events but do not translate to a significant need for drug discontinuation. Future clinical trials predominantly involving cohorts of advanced cirrhosis and ACLF are warranted for evidence generation.

Conflicts of interest: None to declare.

Authors' contribution: S.G. and A.R. conceived the study. S.G., A.S. and K.K. collected the data. S.G., A.S. and K.K. performed the analysis and interpreted data. S.G. and A.S. drafted the manuscript. S.G., A.S., K.K., M.K. and A.R. revised the manuscript. SG, KK: supervised the study. All the authors approved the final version of the manuscript.

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