INTRODUCTION

Review question / Objective: To compare the clinical effects of rifaximin and non-absorbable disaccharide in hepatic encephalopathy, so as to provide basis for clinical treatment.

Condition being studied: Hepatic encephalopathy (HE) is a neuropsychiatric disease due to liver dysfunction or failure, or portsystemic bypass and characterized by alterations in cognition, personality, consciousness which may seriously affect the patient's quality of life. Due to the unclear pathogenesis, the treatment methods are relatively limited. Rifaximin was found to be a promising drug for Hepatic encephalopathy and was recommended to clinical application in many protocols. Although many studies have shown that the clinical effect of rifaximin in hepatic encephalopathy is better than that of non absorbable disaccharides such as lactulose, the actual clinical effect of rifaximin is still diverse. Therefore, comparing the efficacy of rifaximin and nonabsorbable disaccharide in hepatic encephalopathy is helpful to recommend more effective drugs and avoid unnecessary drug use.
unclear pathogenesis, the treatment methods are relatively limited. Rifaximin was found to be a promising drug for Hepatic encephalopathy and was recommended to clinical application in many protocols. Although many studies have shown that the clinical effect of rifaximin in hepatic encephalopathy is better than that of non absorbable disaccharides such as lactulose, the actual clinical effect of rifaximin is still diverse. Therefore, comparing the efficacy of rifaximin and nonabsorbable disaccharide in hepatic encephalopathy is helpful to recommend more effective drugs and avoid unnecessary drug use.

**METHODS**

**Participant or population:** Patients who were diagnosed with cirrhosis induced hepatic encephalopathy or minimal hepatic encephalopathy were included in this meta-analysis.

**Intervention:** Rifaximin therapy, regardless of drug dose and duration.

**Comparator:** Non-absorbable disaccharide (including lactulose and lactitol) therapy.

**Study designs to be included:** Randomized controlled trials which include rifaximin and non-absorbable disaccharide treatment.

**Eligibility criteria:** Studies meet all the inclusion criteria were included: (1) studies are randomized clinical trials; (2) studies in which patients should be divided into at least two groups and treated with rifaximin, NADs respectively; (3) reported these endpoint related to present meta-analysis: clinical efficacy, clinical resolution or HE grade reduced to 0, ammonia level, therapy related adverse effects.

**Information sources:** A systematic and comprehensive literature retrieval was conducted on PubMed, Cochrane Library and Embase database. The key words used for search strategies are: cirrhosis, hepatic encephalopathy, rifaximin, non absorbable disaccharide, lactulose, or lactitol and their MeSH terms.

**Main outcome(s):** The primary outcomes include mental status of patients, blood ammonia level, and adverse drug effect.

**Additional outcome(s):** The secondary outcome include mortality, hospitalization.

**Data management:** Data were extracted by two reviewers independently, and the extracted data were as follows: the first author's name, year of publication, country, study design, duration, total number of participants, Child-Turcotte-Pugh (CTP) class, the type of hepatic encephalopathy, loss of follow-up, interventions and relevant outcomes.

**Quality assessment / Risk of bias analysis:** Quality assessment will be performed by Review Manager 5.3 according to Cochrane Handbook V.5.2.0. Each item (including Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting and Other bias) will be evaluated as low risk, unclear risk and high risk. Two reviewer will perform the assessment, and another reviewer will decide if there is disagreement.

**Strategy of data synthesis:** Data analysis will be performed on Review Manager 5.3. For dichotomous data, the risk ratio (RR) will be calculate with 95% confidence interval (CI); for continuous data, standardized mean difference (SMD) will be calculate with 95% CI. Heterogeneity will be assessed by the I-square and a fixed model will be conducted if I-square < 50%, otherwise, a random model will be conducted.

**Subgroup analysis:** If the heterogeneity of each study is large and there are sufficient data, the subgroup analysis will be conducted.

**Sensitivity analysis:** No.

**Country(ies) involved:** China.
Keywords: Hepatic Encephalopathy, Rifaximin, non-absorbable disaccharide, lactulose, lactitol.

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