

# INPLASY PROTOCOL

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**Conflicts of interest:**  
The authors have no conflicts of interest to disclose.

## Retention enema with Traditional Chinese Medicine for hepatic encephalopathy: A protocol for a systematic review and meta-analysis

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**Review question / Objective:** Patients with hepatic encephalopathy. Both groups were given routine comprehensive medical treatment, including the therapy of protein restriction diet, liver protection, maintenance of water, electrolyte, and acid-base balance, anti-infection, supplementation of plasma and branched chain amino acids, etc. On the basis of these treatments, the experiment group used retention enema with traditional Chinese medicine, while the control group applied for placebo, or no treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators. The primary outcomes include the total effective rate. Total effective rate = (markedly effective + effective) / total cases × 100%. According to the standard of marked effect, the patient's consciousness completely returned to normal, and the total bilirubin decreased. Effective standard, the patient's consciousness is restored, but not completely normal, and there is no significant change in total bilirubin. Invalid criteria: the patient's consciousness has not recovered, or the total bilirubin has increased. The secondary outcomes include the awake time (time from start of treatment to wake up), total bilirubin(TBIL), blood ammonia, aspartate transaminase (AST), alanine transaminase(ALT),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GGT), albumin, etc.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2020 and was last updated on 26 August 2020 (registration number INPLASY202080107).

### INTRODUCTION

**Review question / Objective:** Patients with hepatic encephalopathy. Both groups were given routine comprehensive medical

treatment, including the therapy of protein restriction diet, liver protection, maintenance of water, electrolyte, and acid-base balance, anti-infection, supplementation of plasma and branched

chain amino acids, etc. On the basis of these treatments, the experiment group used retention enema with traditional Chinese medicine, while the control group applied for placebo, or no treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators. The primary outcomes include the total effective rate. Total effective rate = (markedly effective + effective) / total cases × 100%. According to the standard of marked effect, the patient's consciousness completely returned to normal, and the total bilirubin decreased. Effective standard, the patient's consciousness is restored, but not completely normal, and there is no significant change in total bilirubin. Invalid criteria: the patient's consciousness has not recovered, or the total bilirubin has increased. The secondary outcomes include the awake time (time from start of treatment to wake up), total bilirubin(TBIL), blood ammonia, aspartate transaminase(AST), alanine transaminase (ALT),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GGT),albumin, etc.

**Condition being studied:** Hepatic encephalopathy is one of the common complications of many serious liver diseases. Western medicine treatment focuses on symptomatic treatments such as neutralization of blood ammonia and liver protection, which treat the symptoms but not the root cause, easy to repeat and high mortality. Clinically, it has been shown that the retention enema of traditional Chinese medicine is effective in treating hepatic encephalopathy and has good safety. But there is absent convincing evidence-based medicine to confirm the efficacy of retention enema with traditional Chinese medicine for hepatic encephalopathy. Thus, we aimed to conduct this meta-analysis to summarize the efficacy of retention enema with traditional Chinese in patients with hepatic encephalopathy.

## METHODS

**Participant or population:** The patients with clinically diagnosed hepatic encephalopathy and treatment with

retention enema with traditional Chinese medicine, regardless of race, gender, and age. Hepatic encephalopathy by other causes and patients with severe heart disease, liver and kidney dysfunction, mental illness, or a relevant drug allergic history will be not included.

**Intervention:** The experiment group used retention enema with traditional Chinese medicine.

**Comparator:** The control group applied for placebo, or no treatment.

**Study designs to be included:** The study only selects clinical randomized controlled trials of retention enema with traditional Chinese medicine for hepatic encephalopathy published in both Chinese and English. However, animal experiments, reviews, case reports, and non-randomized controlled trials are excluded.

**Eligibility criteria:** The patients with clinically diagnosed hepatic encephalopathy and treatment with retention enema with traditional Chinese medicine, regardless of race, gender, and age. Hepatic encephalopathy by other causes and patients with severe heart disease, liver and kidney dysfunction, mental illness, or a relevant drug allergic history will be not included.

**Information sources:** We will retrieve each database from the built-in until December 31, 2020. The English literature mainly searches Cochrane Library, Pubmed, EMBASE, and Web of Science. While the Chinese literature comes from CNKI, CBM, VIP, and Wangfang database. We adopt the combination of heading terms and free words as search strategy which decided by all the reviewers. Search terms: retention enema with traditional Chinese medicine, retention enema with Chinese medicine, retention enema with TCM, Chinese medicine enema, Chinese medicine retention enema, herbal retention enema, herbal enema, herb retention-enema, hepatic encephalopathy, HE, portal-systemic encephalopathy, hepatocerebral

encephalopathy, portosystemic encephalopathy, hepatic coma, hepatic comas, hepatic stupors, fulminant hepatic failure with cerebral edema. We will simply present the search process of the Cochrane library, adjusting different search methods according to different Chinese and English databases. Searching other resources. At the same time, we will retrieve other resources to complete the deficiencies of the electronic databases, mainly searching for the clinical trial registries and gray literature about retention enema with traditional Chinese medicine for hepatic encephalopathy on the corresponding website.

**Main outcome(s):** The primary outcomes include the total effective rate. Total effective rate = (markedly effective + effective) / total cases × 100%. According to the standard of marked effect, the patient's consciousness completely returned to normal, and the total bilirubin decreased. Effective standard, the patient's consciousness is restored, but not completely normal, and there is no significant change in total bilirubin. Invalid criteria: the patient's consciousness has not recovered, or the total bilirubin has increased.

**Additional outcome(s):** The secondary outcomes include the awake time (time from start of treatment to wake up), total bilirubin (TBIL), blood ammonia, aspartate transaminase (AST), alanine transaminase (ALT),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GGT), albumin, etc.

**Quality assessment / Risk of bias analysis:** The quality assessment of RCTs adopts the risk of bias (ROB) assessment tool provided by the Cochrane Handbook. The following 7 items, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias, are evaluated by 3 grades of "low bias," "high bias," and "unclear bias." The discrepancies will get a consistent conclusion by discussing between both

reviewers or seeking the third-party consultation.

**Strategy of data synthesis:** Review Manager software version 5.3 provided by the Cochrane Collaboration will be performed for data synthesis and analysis. The dichotomous data is represented by RR, continuous data is expressed by MD or SMD. If there is no heterogeneity ( $I^2 < .1$ ), the data is synthesized using a FEM. Otherwise ( $I^2 \geq 50\%$ ,  $P < .1$ ), a random effect model is used to analyze. Then subgroup analysis will be conducted basing on the different causes of heterogeneity. If a meta-analysis cannot be performed, it will be replaced by a general descriptive analysis.

**Subgroup analysis:** If the results of the study are heterogeneous, we will conduct a subgroup analysis for different reasons. Heterogeneity is manifested in the following several aspects, such as race, age, gender, different intervention forms, pharmaceutical dosage, treatment course.

**Sensibility analysis:** Sensitivity analysis is mainly used to evaluate the robustness of the primary outcome measures. The method is that removing the low-level quality study one by one and then merging the data to assess the impact of sample size, study quality, statistical method, and missing data on results of meta-analysis.

**Country(ies) involved:** China.

**Keywords:** retention enema with traditional Chinese medicine, hepatic encephalopathy, meta-analysis, protocol.

**Contributions of each author:**

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