INPLASY PROTOCOL

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Gegen Huangqin Huanglian Decoction for Children Rotavirus Enteritis: A protocol for systematic review and meta-analysis

Wu, Y[1]; Tu, X[2]; Liang, X[3]; Chen, J[4]. Wan, X[5]; Zhang, T[6]; Jiang, J[7]; Zhong, S[8].

Review question / Objective: **The patients of children under the age of 5 with rotavirus enteritis.These patients will not be included: patients with acute complications of rotavirus enteritis, like severe dehydration or serious electrolyte disorder and consciousness disorder; patients with immune deficiency, severe cardiovascular, liver and kidney, hematopoietic system or other primary diseases, mental illness; patients with allergic history and hypersensitivity to relevant drugs. Interventions. Both groups were cured with conventional children rotavirus enteritis treatments recommended by the 2016 Clinical Practice Guidelines for Children with Acute Infectious Diarrhea in China. Including fluid replenishment therapy to maintain balance of water and electrolyte, diet therapy, drug therapies (such as probiotics, montmorillonite, zinc supplementation. The experiment group used GHHD or modified GHHD, while the control group applied for placebo or no TCM treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators. The choice of routine treatment in each RCT does not have to be exactly consistent, but GHHD or modified GHHD should be the only difference between interventions and controls. Outcomes. The primary outcomes include the total effective rate (%), the time of stopping diarrhea (there were two times of defecation or no defecation for 24 hours), the level of IL-6 serum concentration, fecal microflora ratio, the conversion of fecal rotavirus antigen. The secondary outcomes include the quantitative integral grade of TCM symptoms , recovery time of normal stool, treatment period (from the first symptom appear to recovery).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 October 2020 and was last updated on 07 October 2020 (registration number INPLASY2020100023).

INTRODUCTION

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Rationale: This systematic review aims to evaluated the benefits and harms of GHHD for the treatment of children rotavirus enteritis reported in randomized controlled trials, and provide more options for clinicians and patients to treat children rotavirus enteritis.

Condition being studied: Rotavirus infection is the main cause of severe dehydration enteritis in children under 5 years old. It gives rise to malnutrition and even death in children even though there were rotavirus vaccines. However, there is no effective anti-virus drugs for rotavirus, supporting treatments are used in the clinics. Traditional Chinese medicine has been treating diarrhea for many years. Gegen Huangqin Huanglian Decoction is a classic prescription for diarrhea in TCM. With the development of clinical trials and basic studies, GHHD has been proved that a good curative effect on diarrhea. Therefore, a systematic review is necessary to improve available evidence for GHHD in therapy of children under 5 years old with rotavirus enteritis.

METHODS

Search strategy: This review will include grey literature sourced from China Conference Paper Database on the corresponding website, manual searching. Electronic database includes PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, WanFang, VIP, and CBM will also be retrieved. We will simply present the search process of PubMed . The data will be searched in English and Chinese databases from their inception to August 2020, adjusting different search methods according to different Chinese and English databases.

Participant or population: The patients of children under the age of 5 with rotavirus enteritis.

Intervention: Both groups were cured with conventional children rotavirus enteritis treatments recommended by the 2016 Clinical Practice Guidelines for Children with Acute Infectious Diarrhea in China. Including fluid replenishment therapy to maintain balance of water and electrolyte, diet therapy, drug therapies (such as probiotics, montmorillonite, zinc supplementation, etc). The experiment group used GHHD or modified GHHD.

Comparator: The control group applied for placebo or no TCM treatment. In addition, the 2 groups did not take any drugs that interfered with the outcome indicators. The choice of routine treatment in each RCT does not have to be exactly consistent, but GHHD or modified GHHD should be the only difference between interventions and controls.

Study designs to be included: Only clinical randomized controlled trials (RCTs) (expect Quasi-RCTs and cluster RCTs) will be

selected published in both Chinese and English. Animal mechanism studies and non-RCTs will be excluded. Article that substantially overlaps with another published article in print or electronic media will be excluded. Duplicate publications produced by a single experiment and published as separate papers with different criteria for measuring results, p.

Eligibility criteria: The patients of children under the age of 5 with rotavirus enteritis (using criteria from Guidelines for the Treatment of Acute Gastroenteritis in Outpatient Pediatrics, which released by the Washington International Children ' s Medical Center, Zhu Futang's Practical Pediatrics (7th Edition), and the 2016 clinical practice guidelines for children with acute infectious diarrhea in China). These patients will not be included: patients with acute complications of rotavirus enteritis, like severe dehydration or serious electrolyte disorder and consciousness disorder; patients with immune deficiency, severe cardiovascular, liver and kidney, hematopoietic system or other primary diseases, mental illness; patients with allergic history and hypersensitivity to relevant drugs.

Information sources: This review will include grey literature sourced from China Conference Paper Database on the corresponding website, manual searching. Electronic database includes PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, WanFang, VIP, and CBM will also be retrieved. We will simply present the search process of PubMed (Table 1). The data will be searched in English and Chinese databases from their inception to August 2020, adjusting different search methods according to different Chinese and English databases.

Main outcome(s): The primary outcomes include the total effective rate (%), the time of stopping diarrhea (there were two times of defecation or no defecation for 24 hours), the level of IL-6 serum concentration, fecal microflora ratio, the conversion of fecal rotavirus antigen.

Additional outcome(s): The secondary outcomes include the quantitative integral grade of TCM symptoms [], recovery time of normal stool, treatment period (from the first symptom appear to recovery). Besides, incidence of adverse events (such as irritation and toxicity) and costs will be also considered.

Data management: There will be 2 researchers carry out the literatures that meet the requirements independently using endnote X9 software. We will make the preliminary selection by screening titles and abstracts firstly. Secondly, we will download full text of the relevant studies and read carefully for further selection according to the inclusion criteria. If there is any different opinion, 2 researchers will discuss and reach an agreement. If a consensus could not be reached, there will be a third researcher who makes the final decision. Details of the selection process were shown in the flow chart. Finally, the results were cross-checked repeatedly by reviewers.

Quality assessment / Risk of bias analysis: The risk of bias (ROB) assessment tool which provided by the Cochrane Handbook for Systematic Review of Interventions would be used for the quality assessment of RCTs. Interventions . The quality of each trial will be categorized into “low bias”, “unclear bias”, and “high bias” according to the following items: adequacy of generation of the allocation sequence, allocation concealment, blinding of participants and personal, blinding of outcome assessors, incomplete outcome data, selected reporting the results and other sources of bias (such as comparable baseline characteristic, inclusion and exclusion criteria). Assessment of reporting biases. Reporting biases and small-study effects will be detected by funnel plot and Egger test if there are 10 more studies included in this Meta-analysis. For Egger test, p-value of $<.10$ was considered to

indicate the existence of reporting biases and small study effects.

Strategy of data synthesis: We will use Review Manager software version 5.3 provided by the Cochrane Collaboration for the data analyze and synthesis. Binary outcomes will be summarized using risk ratio with 95 % confidence interval (CI) for relative effect. Continuous outcomes will be summarized by using weighted mean difference with 95 % confidence interval. We will use random-effect model for meta-analysis in this review according to research recommendations . Statistical heterogeneity will be assessed by X2 and I2 statistical tests. Where p-value ≥ .1 and I2 ≤ 50 %, there is no obvious statistical heterogeneity among the studies, and then we will choose fixed effect model (FEM) to synthesize the data. On the contrary, if p-value < .1 or I2 > 50 % , it indicates that there is a considerable heterogeneity, we will integrate data by the random effect model (REM). Meta-analysis will be performed when the statistical heterogeneity is acceptable (p-value ≥ .1 and I2 ≤ 50 %), otherwise, subgroup analysis will be applied to explore the influence of potential factors on the outcome measures.

Subgroup analysis: Subgroup analysis will be applied to explore the influence of potential factors on the outcome measures. We will conduct subgroup analyses by different race, age, gender, course of treatment, and different type of GHHD (intervention forms, pharmaceutical dosage form, dosage, etc).

Sensibility analysis: We will conduct sensitivity analyses by omitting studies one by one to probe the impact of an individual study. If a meta-analysis cannot be performed, we will conduct descriptive analysis instead.

Language: No limits.

Country(ies) involved: China and English.

Other relevant information: No.

Keywords: Gegen Huangqin Huanglian Decoction, protocol, systematic review, rotavirus enteritis.

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