INPLASY PROTOCOL

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None declared.

Efficacy and Safety of Huanglian Jiedu Decoction in Type 2 Diabetes: Current State of Evidence

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Review question / Objective: **P: Patients diagnosed with type 2 diabetes using clearly defined or internationally recognized criteria, irrespective of gender, age and ethnicity. I: Huanglian Jiedu Decoction is used orally, including decoction, pills, granules and other forms of traditional Chinese medicine. C: The guide recommends a placebo, lifestyle intervention or routine therapy (including ADA and Chinese Medical College Guideline). Excluded control measures include Chinese medicine as a control. O: The primary outcome measures were: Blood glucose tests (fasting blood glucose, post-prandial blood glucose, hemoglobin a1c); The secondary outcomes were: Blood lipid metabolism indicators (triglyceride, cholesterol); b-cell function indicators: fasting serum insulin (Fins); HOMA-IR(IR); Body Mass Index (BMI); Adverse events (AEs). S: Randomized controlled trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 March 2021 and was last updated on 22 March 2021 (registration number INPLASY202130078).

INTRODUCTION

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Blood glucose tests (fasting blood glucose, post-prandial blood glucose, hemoglobin a1c); The secondary outcomes were: Blood lipid metabolism indicators (triglyceride, cholesterol); b-cell function indicators: fasting serum insulin (Fins); HOMA-IR(IR); Body Mass Index (BMI); Adverse events (AEs). S: Randomized controlled trials.

Condition being studied: The prevalence of T2DM is ever-increasing with years. According to statistics, in 2015, 415 million adults aged 20-79 years around the world had diabetes (more than 90% are T2DM), and China ranked first (109.6 million). One of the most obvious differences between China and the West in the treatment of type 2 diabetes(T2DM) is the use of Chinese herbal medicine(CHM). Cochrane's assessment evaluated the efficacy of CHM on T2DM in 2004, suggesting that some herbs exhibit hypoglycemic effects in T2DM, but, no evaluation has been made on specific CHM. Diabetes belongs to the category of “Xiao Ke” in TCM. It is roughly divided into three types, such as yin deficiency and dryness type, qi and yin deficiency type, and yin and yang deficiency type. Bitter-taste Chinese materia medica (CMM) is mainly used for the treatment of diabetes in yin deficiency and heat type. In ancient times, there was a saying that “bitter can restrict sweetness,” and there are records in ancient books of using CMM to treat diabetes, because “strengthening Yin with bitter-flavor herbs,” which means that some CMMs can protect the yin by reducing heat. Huanglian Jiedu Decoction (HLJDD) comes from the classic book “The Handbook of Prescriptions for Emergencies” of TCM; it is the first clinical emergency manual in China, which consists of four herbs, namely, Coptidis rhi zome, Scutellariae radix, Phellodendri chinensis cortex, and Gardeniae fructus, known as Huanglian (HL), Huangqin (HQ), Huangbo (HB), and Zhizi (ZZ) in Chinese, in the ratio of 3 : 2 : 2 : 3, respectively. HL, HQ, HB, and ZZ in HLJDD formula are all CMM and have the effect of clearing away heat. However, there is no systematic review of the efficacy of HLJDD. In recent years, many new high-quality trials have been published, and it is necessary to make a whole evaluation of HLJDD. The main purpose is to provide the basis for clinicians to make treatment choices.

METHODS

Participant or population: Patients diagnosed with type 2 diabetes using clearly defined or internationally recognized criteria, irrespective of gender, age and ethnicity.

Intervention: Huanglian Jiedu Decoction is used orally, including decoction, pills, granules and other forms of traditional Chinese medicine.

Comparator: The guide recommends a placebo, lifestyle intervention or routine therapy (including ADA and Chinese Medical College Guideline). Excluded control measures include Chinese medicine as a control.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: 1. Participants: Patients diagnosed with type 2 diabetes using clearly defined or internationally recognized criteria, irrespective of gender, age and ethnicity. 2. Type of Interventions: Huanglian Jiedu Decoction is used orally, including decoction, pills, granules and other forms of traditional Chinese medicine. 3. The guide recommends a placebo, lifestyle intervention or routine therapy (including ADA and Chinese Medical College Guideline). Excluded control measures include Chinese medicine as a control. 4. Outcomes: Type of Controls: The primary outcome measures were: Blood glucose tests (fasting blood glucose, post-prandial blood glucose, hemoglobin a1c); The secondary outcomes were: Blood lipid metabolism indicators (triglyceride, cholesterol); b-cell function indicators: fasting serum insulin (Fins); HOMA-IR(IR); Body Mass Index (BMI); Adverse events (AEs). 5. Study design: Randomized controlled trials.

Information sources: We searched English- and Chinese-language databases and

followed the methods outlined in the Cochrane Handbook of Systematic Reviews. English-language databases included PubMed, Excerpta Medica Database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL), including the Cochrane Library, and Allied and Complementary Medicine Database (AMED); Chinese-language databases included China SinoMed, China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), and Wanfang Databases were searched from inception to March 2021. No restrictions were applied. Search terms were grouped into three blocks: 1) intervention (including Huanglian Jiedu Decoction); 2) clinical condition (including type 2 diabetes mellitus); and 3) trial design (including clinical trial, randomized controlled trial). We also searched reference lists of previous systematic reviews and included studies. Clinical trial registries were also searched including Chinese Clinical Trial Registry (ChiCTR), and USA National Institutes of Health register (ClinicalTrials.gov). When required, we contacted trial investigators by email or telephone to obtain data. If we didn't receive a response after four weeks, we marked the unknown information 'not available'.

Main outcome(s): Blood glucose tests (fasting blood glucose, post-prandial blood glucose, hemoglobin a1c).

Quality assessment / Risk of bias analysis: Risk of bias was assessed using the Cochrane Collaboration's procedures. RevMan software (Version 5.2.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used for risk of bias analysis. Items of bias assessed included sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias including baseline imbalance and funding. Risk of bias assessment was conducted by two independent reviewers and disagreement was resolved by discussion or consultation with a third person.

Strategy of data synthesis: We will use Endnote X8 (Thomson Reuters, USA) to manage our citations, and Review Manager Version 5.2.3 and stata 14.0 software will be used to create forest plots and conduct subgroup analysis and sensitivity analysis. For the binary variable, the effect size will be represented with risk ratio (RR) and 95% confidence interval (CI) and a mantel-haenszel (M-H) method will be used to calculate them. For continuous variable, the effect size can be represented as mean difference (MD) and 95% CI. If one study reports its standard error (SEM) other than Standard Deviation (SD), we will convert SEM into SD. The heterogeneity of data will be investigated by Cochrane χ^2 and I^2 tests. The statistical heterogeneity will be considered substantial when $P < 0.05$ and $I^2>50\%$. If $P > 0.05$ and $I^2<50\%$, then the studies included are homogeneous and the differences between them can be ignored. If there is significant heterogeneity, the random effects model will be used to pool data, and if there is no significant heterogeneity, then the fixed effect model will be used.

Subgroup analysis: Subgroup analysis were performed where possible, including studies with low risk for sequence generation, FBG level at baseline, patient age groups, disease duration, treatment duration, comparator drugs class, and Whether it is combined with obesity.

Sensitivity analysis: Sensitivity analysis will be conducted to evaluate the stability of the results by excluding the studies one by one and then reanalyze the remaining studies in stata 14.0 software. If there are more than 10 studies included, then publication bias will be assessed by conducting funnel plot analysis and Egger's test. Finally, we will use the GRADE tool to evaluate the quality of evidence.

Country(ies) involved: China.

Keywords: Huanglian Jiedu Decoction, type 2 diabetes, systematic review, efficacy, safety, mechanism.

Contributions of each author:

Author 1 - Bei Yin - The author designed the study and wrote the original draft.
Email: 17817315916@163.com
Author 2 - Yiming Bi - The author provided statistical expertise.
Author 3 - Jingzhu Huang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Guanjie Fan - The author read, provided feedback and approved the final manuscript.