INPLASY PROTOCOL

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Danhong injection for the treatment of early diabetic nephropathy: a protocol of systematic review and meta-analysis

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Review question / Objective: **Whether Danhong injection alone can effectively treat early diabetic nephropathy compared to conventional intervention regimes or western medicine alone?**
Condition being studied: **Several treatment options such as renin-angiotensin system blockers and omega-3 fatty acids have been developed to reduce the progression of kidney damage and then reduce the occurrence of complications resulted from DN.However, these regimes have not potential of preventing or reversing DN, and some regimes have been reported to be associated with increased incidence of adverse events and serious complications. Meanwhile, some of treatment regimes have also been suggested to be contraindicated for patients with severe renal impairment and have a set of serious side effects. As a result, researchers and practitioners have changed their attention from western medicine alone to Chinese medicine alone or integrated regime of western and Traditional medicines. As one of the common use of Chinese medicine, danhong injection (DHI) has been prescribed to treat a variety of conditions in mainland China for many years. It is important that DHI has also been used to treat early diabetic nephropathy, however no consensus about effectiveness and safety of Danhong injection for early DN has been reported.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 September 2020 and was last updated on 01 September 2020 (registration number INPLASY202090005).

INTRODUCTION

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METHODS

Participant or population: Diabetic patients with early DN.

Intervention: Danhong injection alone.

Comparator: Conventional intervention regimes such as diet restriction or western medicine alone.

Study designs to be included: Only randomized controlled trials will be considered.

Eligibility criteria: According to our aims, we designed the following inclusion criteria: (a) all randomized controlled trials (RCTs) which were performed to investigate the comparative efficacy and safety of DHI alone versus conventional regime such as diet restriction or western medicine in diabetic patients with early DN will be considered for eligibility; (b) adult diabetic patients regardless sex are diagnosed as early DN in accordance with definitive diagnosis standards which must be introduced in details; (c) the information of at least one of effectiveness and safety can be accessed; (d) only studies published in English and Chinese language will be eligible for our inclusion criteria.

Information sources: We will assign two independent reviewers to perform a systematic search in several electronic databases including PubMed, Cochrane library, Embase, China National Knowledgement Infrastructure (CNKI), Wanfang database, and Chinese sci-tech periodical full-text database (VIP). We will also check reference lists of all included studies and reviews which were performed to summarize the evidences of danhong injection for the treatment of early diabetic nephropathy in order to capture any potentially eligible studies.

Main outcome(s): In our systematic review and meta-analysis, we will design effective rate as the primary outcome, which will be calculated according to the definitive traditional Chinese medicine effectiveness evaluation criteria. According to evaluation criteria, the effective rate is the ratio of the number of patients who are identified to have healing, significant effect, and effect divided by the number of all patients who are assigned to a certain intervention group.14 We will define 24-hour urine protein quantitation, urinary albumin excretion rate, fasting blood glucose, and glycosylated hemoglobin as the secondary outcomes, which are all quantitatively identified by laboratory test. Moreover, we will calculate the adverse events (AEs) which are related to interventions as the secondary outcomes, which are all recorded by individual study.

Quality assessment / Risk of bias analysis: The overall quality of all included studies is associated with the reliability and robustness of pooled results. Therefore, we will critically evaluate the quality of included study with Cochrane risk of bias assessment tool. Each included study will be assessed from the following six

domains including randomization sequence generation, allocation concealment, blinding of participants, blinding of study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. According to the actual information of each study in terms of risk of bias, individual study will be labeled with 'low risk of bias', 'unclear risk of bias', and 'high risk of bias'. The overall level of all included studies will be determined according to the results of assessing the risk of bias of individual study.

Strategy of data synthesis: In our systematic review and meta-analysis, we will calculate the relative risk (RR) with 95% confidence intervals (CIs) to express dichotomous data, and the mean difference (MD) with 95% CIs to express continuous data. Before performing statistical analysis, we will firstly use the Cochrane Q test to qualitatively assess the heterogeneity across included studies, and then we will use I2 statistic to quantitatively estimate heterogeneity. We will consider included studies for individual outcome as heterogeneity if I2 >50% and P < 0.10. In contrast, studies will be considered as homogeneous when a I2 ≤ 50% and a P ≥ 0.10 was estimated. We will perform all statistical analyses based on a random-effect model because no homogeneous studies will be found in the real world.

Subgroup analysis: In order to exclude the impact of important confounding factors on all statistical analyses, we will perform several subgroup analyses according to the duration of DM and intervention regimes in control group.

Sensibility analysis: We will also check the robustness of pooled results through excluding eligible studies with high risk of bias.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: Chinese medicine, danhong injection, early diabetic nephropathy, systematic review, meta-analysis.

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