INPLASY PROTOCOL

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Conflicts of interest:
We have no competing interests.

Efficacy and safety of Shenkang Injection as adjuvant therapy in patients with diabetic nephropathy: a protocol for systematic review and meta-analysis

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Review question / Objective: **Is Shenkang Injection effective and safe in adjuvant treatment of diabetic nephropathy?**
Condition being studied: **Diabetic nephropathy (DN).**
Information sources: **Literature databases: PubMed, EMBASE, CENTRAL, China Biomedical Literature Database, Chinese National Knowledge Infrastructure, Wanfang Data, and VIP Trial registry: Clinicaltrials.gov, and Chinese Clinical Trial Registry. Source of grey literature: reference lists of relevant reviews.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 November 2020 and was last updated on 04 November 2020 (registration number INPLASY2020110014).

INTRODUCTION

Review question / Objective: **Is Shenkang Injection effective and safe in adjuvant treatment of diabetic nephropathy?**

Rationale: **Diabetic nephropathy (DN), as a common chronic complication of diabetes and a main cause of end-stage renal disease, brings heavy medical and economic burdens to society. Currently there is lack of targeted treatment that can delay the kidney damage for diabetic nephropathy in Western medicine. Shenkang injection is a Chinese patent medicine made of rhubarb, danshen,**

safflower, and astragalus through chemical extraction and refinement. It is widely using as a adjuvant therapy for treating DN in China. Animal studies have found that Shenkang injection can inhibit renal interstitial fibrosis by reducing the expression of NF-KB and TGF in the renal interstitium, thereby delaying chronic renal failure. There were also many randomized controlled trials that assessed the effects of Shenkang injection for DN, while they were small in sample size and thus did not establish a convincing conclusion. Therefore, the purpose of this study is to explore the efficacy and safety of Shenkang injection as adjuvant treatment for DN by pooling the current randomized controlled trials, in order to provide high-quality clinical evidence.

Condition being studied: Diabetic nephropathy (DN).

METHODS

Search strategy: We will systematically search PubMed, EMBASE, CENTRAL, China Biomedical Literature Database, Chinese National Knowledge Infrastructure, Wanfang Data, and VIP. Clinicaltrials.gov, Chinese Clinical Trial Registry, and reference lists of relevant reviews will also search for adding relevant studies. Search strategy in PubMed is: (diabetic nephropathy[mh] OR diabetic nephropathy[tw] OR diabetic kidney disease[tw] OR diabetic renal disease[tw]) AND (shenkang injection[tw] OR shen kang injection[tw]) NOT (animals[mh] NOT humans[mh]).

Participant or population: Patients with DN.

Intervention: Inclusion criteria: Shenkang injection+ basic treatment (e.g., correction of electrolyte disorders, control of urine protein, control of blood glucose, control of blood pressure) Exclusion criteria: We will exclude other preparations with the same herbal components as Shenkang injection, such as granules and capsules.

Comparator: The comparator should be the same basic treatment as the intervention group.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Inclusion criteria - patients should be diagnosed as DN according to the currently recognized diagnostic criteria, such as American Diabetes Association criteria. Exclusion criteria - We will exclude studies enrolling non-diabetic patients with nephropathy, such as hypertensive nephropathy, gouty nephropathy, lupus nephritis, IgA nephropathy, and primary glomerulonephritis.

Information sources: Literature databases: PubMed, EMBASE, CENTRAL, China Biomedical Literature Database, Chinese National Knowledge Infrastructure, Wanfang Data, and VIP Trial registry: Clinicaltrials.gov, and Chinese Clinical Trial Registry. Source of grey literature: reference lists of relevant reviews.

Main outcome(s): Estimated glomerular filtration rate (eGFR) mL/min/1.73 m2; Serum creatinine (μmol/L).

Additional outcome(s): 24-hour urine albumin excretion rate (g/24h); blood urea nitrogen (mmol/L); fasting blood glucose (mmol/L); postprandial blood glucose (mmol/L); hemoglobin A1c (mmol/L); total cholesterol (mmol/L); triglyceride (mmol/L); response to treatment according to recognized classification criteria, such as the Guidance Principles for Clinical Research of New Chinese Medicines; incidence of adverse events related to Shenkang injection.

Data management: Two reviewers will independently and repeatedly screen the literatures and extract relevant information, and will cross-check the results. Disagreements will be determined by a third reviewer. The reviewers will first exclude irrelevant literatures by reading the titles and abstracts, then read the full texts to determine the final included RCTs. The

data extraction will cover the following data: 1) basic characteristics: title, author, publication time, journal; 2) patients' characteristics: gender, age, stage of DN, complications; 3) intervention and control measurements: dose of Shenkang injection, type of control, frequency and course of treatments; 4) outcomes data.

Quality assessment / Risk of bias analysis: Two reviewers will independently and repeatedly assess the risk of bias in the included studies and cross-check the results. The disagreement will be determined by a third reviewer. The risk of bias will be assessed using the risk assessment tool for randomized controlled trial recommended in the Cochrane handbook 5.1.0. It includes 7 items: 1) random list generation method; 2) allocation concealment; 3) blinding of patients and clinicians; 4) blinding of outcome evaluator; 5) data completeness; 6) selective reporting; 7) other bias sources. Each item will be rated as low, high, or uncertain risk of bias.

Strategy of data synthesis: 1) Meta-analysis for continuous outcomes: weighted mean difference or standardized mean difference and 95% confidence intervals (CIs) will be used as the effect measures and the inverse variance method will be used to combine the data; 2) Meta-analysis for dichotomous outcomes: relative risks and 95% CIs will use as the effect measures and the data will be combined using the Mantel-Haenszel method. Cochran's Q test and I2 statistics will be used to evaluate the heterogeneity among studies in the meta-analysis.

Subgroup analysis: 1) DN stage: early stage of DN (stages I and II) versus advanced stage of DN (stage III or severer); we predict that the patients with early stage of DN will have better efficacy. 2) Dose of shengkang injection: ≤ 60ml/d versus >60 ml/d; we predict that the patients patients who received >60 ml/d of shengkang injection will have better efficacy. 3) Course of shengkang injection: ≤14 days versus >14 days; we predict that patients who received >14 days of shengkang injection will have better efficacy.

Sensibility analysis: We will perform the following two sensitivity analyses: 1) excluding studies with high risk of bias; 2) using fixed effects model in meta-analyses.

Language: No restrictions.

Country(ies) involved: China.

Keywords: Shenkang Injection; diabetic nephropathy; protocol; systematic review

Dissemination plans: We aim to publish the results of this systematic review in a peer-reviewed journal.

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