Shenkang injection improves coagulation in patients with chronic kidney disease: a systematic review and Meta-analysis

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OBJECTIVE: To investigate the effect of Shenkang injection (SKI) on chronic kidney disease (CKD).

METHODS: Seven databases including Cochrane Central Register of Controlled Trials, PubMed, EBASE, MEDLINE, China National Knowledge Infrastructure, Wanfang Database, and CQVIP from their inception to March 2018 were searched. Only randomized controlled trials that evaluated conventional treatment and conventional treatment with SKI in CKD patients were investigated. Outcomes such as fibrinogen (FIB), D-dimer, prothrombin time (PT), activated partial thromboplastin time (APTT), and the side effects of SKI were analyzed using Revman 5.3 software. The quality of the studies was assessed using the Cochrane Collaboration’s Risk of Bias tool and the quality of evidence was assessed using GRADEpro.

RESULTS: Four randomized controlled trials were investigated in our analysis, and these studies were of moderate quality. For FIB and D-dimer, SKI had a superior effect compared with the control group [mean difference (MD) = −1.23, 95% confidence interval (CI): −1.46, −0.99, P < 0.01; MD = −0.36, 95% CI: −0.51, −0.21, P < 0.01, respectively]. SKI increased APTT and PT compared with the control (MD = 7.34, 95% CI: 3.05, 11.62, P < 0.01; MD = 3.40, 95% CI: 2.2, 4.61, P < 0.01, respectively). In the four studies, there were no side effects that were related to SKI.

CONCLUSION: SKI may be effective in improving coagulation in patients with CKD without obvious adverse reactions. However, more well-designed studies are required to confirm the findings.

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Shenkang injection (SKI) is a second-class national drug that is prepared as a traditional Chinese medicine (TCM) using Dahuang (Radix Et Rhizoma Rhei Palmata), Shuweicao (Herba Salviae Japonicae), Honghua (Flav Carthami), Huangqi (Radix Astragali Mongolici), and other ingredients; it has been used for decades. Many clinical observations and systematic reviews on SKI have investigated improvement of renal function. In contrast, although many studies have focused on SKI and coagulation, there is yet no systematic review summarizing the effect of SKI on coagulation. From the perspective of traditional Chinese theory, CKD is characterized by Qi deficiency, blood stasis, and turbidity accumulation. SKI functions to increase Qi, activate and eliminate blood stasis, and remove turbidity. Thus, the effect of SKI on coagulation in CKD patients should be investigated. This study aimed to evaluate the effectiveness and safety of SKI in CKD patients in the hypercoagulable state. It was based on a Meta-analysis of important indicators to provide SKI with evidence-based medical support in the treatment of CKD patients.

MATERIALS AND METHODS
This systematic review followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Inclusion criteria
We included all randomized controlled trial (RCTs) (including cross-over trials, cluster-randomized trials, and trials with multiple intervention groups). The patients included were diagnosed based on the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, as follows: reduced glomerular filtration rate (GFR) < 90 mL/min/1.73 m² and/or by the persistence of urinary abnormalities such as albuminuria, proteinuria, or hematuria for at least 3 months or similar criteria such as in Nephrology (3rd Edition).

Exclusion criteria
Patients who took renal replacement therapy or those with uncontrolled severe other systemic diseases were not included in the analysis.

Intervention types
We included all RCTs (including cross-over trials, cluster-randomized trials, and trials with multiple intervention groups) that compared SKI regardless of the dosage and duration of conventional treatment. Conventional treatment included the following: dietary control and symptomatic treatment such as correcting the water, electrolyte, and acid-base imbalance, controlling infection, and removing reversible causes of worsening renal function failure, such as diabetes mellitus, hypertension, and anemia, and abnormal blood lipid and uric acid. Our research did not consider retrospective studies, case reports, non-randomized trials, and animal studies.

The outcomes
We included standard coagulation test results, as follows: D-dimeractivated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB), and D-dimer as side effects.

Search strategy
Two authors searched the following databases: Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE. Three classical Chinese databases were also included: China National Knowledge Infrastructure, Wanfang Database, and the CQVIP Database, which were all searched from their inception to March 2018. There were no language restrictions. The sample search strategy was as follows: ((Shenkang injection [All Fields]) OR SKI [All Fields]) AND (hypercoagulability [All Fields]) OR hemorheology [All Fields]) OR Coagulation [All Fields]) OR Blood Coagulation Disorders [All Fields]).

Data extraction
Two authors screened the titles and abstracts of all citations that were found independently. The two authors then identified the remaining studies based on the inclusion and exclusion criteria. Where discrepancies were observed, a third author was consulted. Data were extracted using a pre-defined form. The extracted information included citation information, study population, treatments, and main findings.

Data collection
The data that was collected were as follows: authors, study year, participant number, age, sex, process details, treatment details, treatment duration, APTT, PT, FIB, D-dimer, and side effects.

Quality assessment
We used the Cochrane Risk of Bias to assess the risk of bias in the included studies based on random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, and selective reporting. Each of the above parts had been considered based on a high, low, or unclear risk of bias. Disagreements were discussed with a third reviewer. The quality of the evidence based on the outcomes was assessed using GRADEpro software (McMaster University, Canada) for the risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding that would change the effect, and the dose-dependent response. There were four levels of the quality: very low, low, moderate, and high.

Statistical analysis
RevMan 5.3 (Copenhagen, Denmark) was used for data analysis. A Meta-analysis was used if the intervention, control, and outcomes were the same or similar.
Dichotomous results were expressed as the risk ratio (RR), continuous outcomes were presented as the mean difference (MD), and 95% confidence intervals (95% CI) were calculated for both types of data. We assessed heterogeneity using the I² test statistic. Heterogeneity was considered to be mild, moderate, or severe, based on the following I² ranges: < 25%, 25%-50%, and > 50%. If the I² value was less than 50%, we pooled the data using a fixed-effect model, otherwise we used a random effects model.

We conducted subgroup analysis or sensitivity analysis based on the quality of the studies. Funnel plot analysis and the Egger test were used to analyze the risk of publication bias when there were at least ten studies included in the meta-analysis.

**RESULTS**

**Description of studies**

We identified 40 articles, among which 4 were from China National Knowledge Infrastructure Database, 35 were from Wanfang, and 1 was from China Science and Technology Journal Database. We did not find any papers in PubMed, Cochrane Central Library, EMBASE, or Clinical Trials. After removing duplicate articles, there were 36 articles that remained. By reading the titles and abstracts, we removed 30 studies for the following reasons: (a) no CKD participants; (b) not an RCT; (c) no outcome of interest; (d) animal experiments; and (e) the article was a review. We considered 6 references as being potentially relevant and assessed them further based on our selection criteria. Then 2 articles were excluded. Overall, we included 4 studies and 231 patients, and all the patients involved in this study were Chinese. The included studies varied as follows: sample size (n = 45 to 72), dose of SKI used (60-100 mL), and duration of treatment (14 d to 3 months). All four of the included studies were RCTs. The details of the four selected studies are presented in Table 1.

**Risk of bias in the included studies**

The risk of bias for each of the included RCTs is shown in Figures 1 and 2. All of the four included trials were RCTs. The Cochrane Risk of Bias was used in this part. Block randomization was used in Bian’s study, while the other studies only mentioned “randomization”. None of the four articles reported the method of allocation concealment. Only Bian, et al. mentioned the lack of blinding of participants and personnel. Because the outcomes in the studies were objective tests, such as PT, APTT, FIB, and D-D, we considered that the quality of blinding for the outcome assessments were high. Because none of the four papers were registered as clinical trials, it was difficult to evaluate the quality of the reporting bias, but by comparing the methods and results, a low risk was determined for this part. All of the articles reported a comparable baseline,

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Table 1: Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample size</th>
<th>Age (T/C)</th>
<th>Sex</th>
<th>Process (T/C)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bian BJ</td>
<td>2011</td>
<td>45</td>
<td>18-54/20-55</td>
<td>M/F</td>
<td>/</td>
<td>Control treatment and SKI 100 mL ivgtt once a day for 3 months</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>2016</td>
<td>39</td>
<td>39/55</td>
<td>M/F</td>
<td>/</td>
<td>Control treatment and SKI 100 mL ivgtt once a day for 3 months</td>
</tr>
<tr>
<td>Xu et al.</td>
<td>2012</td>
<td>68</td>
<td>65/35</td>
<td>M/F</td>
<td>/</td>
<td>Control treatment and SKI 60 mL ivgtt once a day for 4 months</td>
</tr>
<tr>
<td>Xu et al.</td>
<td>2016</td>
<td>30</td>
<td>30/60</td>
<td>M/F</td>
<td>/</td>
<td>Control treatment and SKI 100 mL ivgtt once a day for 4 months</td>
</tr>
</tbody>
</table>

Notes: Y: year; T: treatment; C: control; M: male; F: female; SKI: Shenkang injection; MMF: mycophenolate mofetil; LMWH: low molecular weight heparin; FIB: fibrinogen; D-D: D-dimer; PT: prothrombin time; APTT: activated partial thromboplastin time.
clear diagnostic criteria, the intervention, and the outcomes, so we considered the risk of other biases were low. Overall, the methodology of the included studies was moderate.

**Fibrinogen**

Four studies investigated FIB at the end of treatment. SKI significantly decreased the FIB level \( (MD = -1.23, 95\% CI: -1.46, -0.99, P < 0.001) \) compared with control group (Figure 3).

**Activated partial thromboplastin time**

APTT was reported in two studies. Pooled data from the two studies indicated that SKI treatment seemed to cause a longer APTT compared with control treatment \( (MD = 7.34, 95\% CI: 3.05, 11.62, P < 0.01) \) (Figure 4).

**Prothrombin time**

Two studies evaluated the PT after treatment. Pooled analysis of the data revealed that there was a significant difference between the two groups with no heterogeneity among the two studies. SKI prolonged the PT more than the control \( (MD = 3.40, 95\% CI: 2.20, 4.61, P < 0.01); \) Figure 5).

**D-dimer**

Bian et al. reported that SKI lowered the D-D levels compared with basic treatment \( (MD = -0.36, 95\% CI: -0.51, -0.21, P < 0.001) \).

**Side effects**

None of the four studies reported side effects that were related to SKI.

**Quality assessment of evidence**

The evidence was assessed for quality using GRADE pro, and it was found to be moderate. The details are summarized in Table 2.

**Additional analyses**

From the available data, it was not possible to conduct
DISCUSSION

This study included four RCTs with 231 patients to evaluate the effectiveness and safety of SKI on coagulation in patients with CKD. From this analysis, we found that SKI improved the APTT and PT levels and lowered the FIB and D-D without SKI-related side effects. Patients with CKD commonly experienced increased coagulation. The thrombotic-related complications became increasingly serious as well. The coagulation process involves the coagulation, anticoagulant, and fibrinolytic systems. Factor Xa plays an essential role in the coagulation cascade reaction, and it can promote the change from prothrombin to thrombin, thereby increasing the fibrin production to form clots. In the pathological state, the cells release particles that have a large amount of phosphatidylserine (PS), which provides a catalytic surface for the formation of prothrombinase complex that promotes the occurrence of a coagulation reaction and leads to a hypercoagulable state of the blood, thereby contributing to thrombosis. Activated platelets secrete pro-inflammatory proteins and growth factors that increase the likelihood of inflammatory reactions and thromboembolism in CKD patients. On the platelet surface, activated P-selectin can cause neutrophil nuclear mononuclear cell aggregation and stimulate coagulation and inflammation. Additionally, tissue factor is the main activator of the coagulation cascade and it is transduced by the transcription factor NF-κB signaling pathway, which can be inhibited by nitric oxide and activated by free fatty acids. For the anticoagulant system, protein C can inactivate Va and VIIIa, thereby reducing thrombin generation. Recent studies have shown that Activated protein C (APC) also has anti-inflammatory, anti-apoptotic, and profibrinolytic effects. APC binds to the thrombin-thrombomodulin (TM) complex on glomerular endothelial cells to protect the glomerular endothelial cells from apoptosis. In patients with CKD, glomerular endothelial cells are damaged and large amounts of TM on the cell membrane are released into the plasma, which ultimately results in reduced APC production. Another anticoagulant factor is the vascular endothelium: under physiological conditions, the vascular endothelium functions to prevent thrombosis. In patients with CKD, endothelial cell dysfunction causes a reduction in endothelial nitric oxide synthase and an increase in reactive oxygen species, which up-regulates both inflammatory mediator and inflammatory molecule expression that damages endothelial cells. Endothelial cell damage results in an increase in von Willebrand factor, a decrease in Prostaglandin I2 and heparan sulfate, thereby increasing the blood procoagulant activity and impairing antithrombotic function. The fibrinolytic system includes plasmin activator inhibitor-1 (PAI-1) and plasminogen activator (PA). PAI-1 is an antagonist of PA that can inhibit protease hydrolysis, and it plays a pivotal role in cell adhesion and proliferation. Activation of the immune and inflammation system in CKD patients can increase PAI-1. Activated PAI-1 inhibits fibrin dissolution in the glomerulus, thereby increasing the hypercoagulable state, and it also increases transforming growth factor-β levels, which causes the glomerular extracellular matrix to accumulate resulting in fibrosis, and eventually leading to glomerulosclerosis.

SKI consists of Dahuang (Radix et Rhizoma Rhei Palmati), Huangqi (Radix Astragali Mongolici), Danshen (Radix Salviae Miltiorrhizae) and Honghua (Flos Carthami). Many studies suggested that the composition of SKI can improve coagulation. Protocatechuic aldehyde, salvianolic acid C, dihydrotanshinone I, cryptotanshinone, and tanshinone II A, which were found in
Table 2 Quality assessment of the evidence (GRADE)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Participants (studies)</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB</td>
<td>231 (4 studies)</td>
<td>high</td>
<td>1.23 lower (1.46 to 0.93)</td>
<td>⊕⊕⊕⊕ high</td>
<td>/</td>
</tr>
<tr>
<td>PT</td>
<td>78 (2 studies)</td>
<td>moderate</td>
<td>3.4 higher (2.2 to 4.61)</td>
<td>⊕⊕ high</td>
<td>/</td>
</tr>
<tr>
<td>APTT</td>
<td>91 (2 studies)</td>
<td>moderate</td>
<td>3.05 to 1.62 higher</td>
<td>⊕⊕ moderate</td>
<td>/</td>
</tr>
<tr>
<td>D-D</td>
<td>71 (1 study)</td>
<td>moderate</td>
<td>0.36 lower (0.51 to 0.21)</td>
<td>⊕⊕ weak</td>
<td>/</td>
</tr>
</tbody>
</table>

Notes: ⊕, confidence interval; SKI: Shenkang injection; FIB: fibrinogen; D-D: D-dimer; PT: prothrombin time; APTT: activated partial thromboplastin time; GRADE: the Grading of Recommendations Assessment, Development and Evaluation. The basis for the assumed risk (e.g. the median control group risk across studies) is provided in the footnotes. The corresponding risk [and its CI 95%] is based on the assumed risk in the comparison group and the relative effect of the intervention (and its CI 95%). High quality: further research is very unlikely to change our confidence in the estimate of effect; very low quality: we are very uncertain about the estimate.

The finding that safflower extract and its pure isolated compounds have anticoagulation, antioxidation, anti-platelet aggregation, and ovarian granulosa cell proliferation effects revealed its possible mechanism. Dahuang (Radix et Rhizoma Rhei Palmati) is a frequently used traditional medicine that has also been reported to have antiplatelet effects. Chrysophanol-8-O-glucoside, one constituent of Dahuang (Radix et Rhizoma Rhei Palmati), had the most potent effect on antiplatelets and anticoagulant function.

There are advantages and disadvantages of this study. First, there are many Meta-analyses about the effect of SKI on improving renal function, but this is the first study to explore the effect of SKI on coagulation. Additionally, we investigated indicators that have been widely used as clinical outcomes, to determine if the results would also benefit clinical practice. During the investigation, we also contacted the authors to obtain more information about the data to ensure its quality. However, there are several limitations in this study. For example, we did not conduct a subgroup analysis because of the small number of research studies, which indicates that there has not been enough attention paid to this area. Thus, it is important to highlight the function of SKI on improving coagulation in CKD patients. Additionally, most of the indicators in the included studies were intermediate indicators, which lacked end point indicators such as mortality, and this may have affected our conclusions about overall efficacy.

In conclusion, SKI may be considered to be an effective and safe treatment option for CKD because it may improve coagulation. However, the long-term effects of SKI treatment were not fully assessed. Additional well-designed studies are required to assess SKI’s potential for use in CKD patients.

REFERENCES
2. Watanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for
36 Xu S, Zhong A, Bu X, et al. Salvianolic acid B inhibits platelets-mediated inflammatory response in vascular en-