Shenkang Injection in improving coagulation with chronic kidney disease: a systematic review and meta-analysis

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Abstract

Objective: Shenkang Injection (SKI) is considered to be a promising drug for improving renal function. However, the efficacy and safety of SKI on the coagulation with chronic kidney disease remains inconclusive. This system review aimed to investigate the effect of SKI on people with chronic kidney disease (CKD).

Methods: Seven databases including: Cochrane Central Register of Controlled Trials, Pubmed, EMBASE, MEDLINE and China National Knowledge Infrastructure, Wanfang Database, CQVIP from their inception to March 2018 were searched. Only randomized controlled trials, evaluating conventional treatment and conventional treatment with SKI in CKD patients were investigated. The outcomes such as FIB, D-dimer, PT, APTT and the side of SKI were analysed by the Revman 5.3 software. The quality of the studies was assessed by the Cochrane Collaboration’s Risk of Bias tool and the quality of evidence was assessed by GRADEpro.

Results: Four randomized controlled trials were investigated in our analysis. The included studies were of moderate quality. With regard to FIB and D-dimer, SKI played superior effects than control group (MD = -1.23, 95% CI = -1.46 to -0.99, p < 0.01; MD = -0.36, 95% CI = -0.51 to -0.21, p < 0.01 respectively). Compared with control, SKI increased APTT, PT (mean difference [MD] = 7.34, 95% confidence interval [CI] = 3.05 to 11.62, p < 0.01; MD = 3.40, 95% CI = 2.2 to 4.61, p < 0.01 respectively). As for the side effects, none of the four studies reported the side effects related to SKI.

Conclusion: It can be concluded that SKI may be effective in improving coagulation with CKD without obvious adverse reactions. However, more high-quality studies are required for further analysis and demonstration.

INTRODUCTION

CKD usually followed by the blood coagulation disorders, which leading to the thrombotic complications that ranks the most likely reason of death. Fibrosis is the common pathological of CKD and the main cause of end-stage renal disease. Recently, more and more evidences reveal the close relationship between coagulation and fibrosis as well as CKD. Shen Kang Injection (SKI) which is a second-class national drug prepared of...
traditional Chinese medicine (TCM), i.e. rhubarb, Salvia, Safflower and Astragalus and other ingredients, has been put into practice for decades. Plenty of clinical observations and system reviews about SKI on improving the renal function have been investigated. However, at the same time, there are still a lot of studies focusing on the coagulation but there is no system review to make a summary about the effect of SKI on it. Furthermore, from the perspective of traditional Chinese theory, CKD is characterized by deficiency of qi, blood stasis, and turbidity accumulation. SKI perform the function of increasing the qi, activating and eliminating the blood stasis, and removing the turbidity. So, there must have something which can be done of SKI on coagulation for CKD patients.

Here we aimed to objectively evaluate the effectiveness and safety of SKI on hypercoagulable state of CKD. The study was based on meta-analysis of some important indicators in order to provide SKI an evidence-based medical backing in the treatment of CKD.

Materials and methods

This systematic review followed the principle of Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement.

Inclusion criteria

We included all RCTs (including cross-over trials, cluster-randomized trials and trials with multiple intervention groups). The patients should be diagnosed according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines: by a 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 some similar criterions such as Nephrology(3rd Edition).

Exclusion criteria

People who use renal replacement therapy or with uncontrolled severe other systemic diseases won’t take into account.

Types of intervention

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

The outcomes

We investigated the standard coagulation tests: Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), fibrinogen (FIB), and D-dimer (D-D) as well as side effects.

Search strategy

Two authors searched the following databases: Cochrane Central Register of Controlled Trials, EPIDEMICBASE, MEDLINE. Threeclassical Chinese databases were also included: China National Knowledge Infrastructure, Wanfang Database, CQVIP Database from their inception to March 2018. There would be no language restrictions. Sample searchstrategy was: (((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]). There was no language restrictions.

Data extraction

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

Data items

The data items were as followed: authors, year of study, number of participants, age, sex, the process of the details, details of the treatment, treatment duration, APTT, PT, FIB, D-D and side effects.

Quality assessment

We used the Cochrane Risk of Bias to assess the risk of bias of the included studies from the aspect of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of the above parts had been regarded for three levels: high, low or unclear risk of bias. Disagreements were discussed by a third reviewer. The quality of the evidence of the outcomes was assessed by GRADepro software from the aspect of risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding would change the effect and the dose response gradient. There were four levels of the quality: very low, low, moderate and high.

Statistical analysis

RevMan 5.3 was applied for the data analysis. A meta-analysis was used if the intervention, control, outcomes are the same or similar. Dichotomous was expressed as the risk ratio (RR), and 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 I² test statistic. Heterogeneity was considered as mild, moderate, or severe, based on the following I² ranges: <25%, 25-50%, >50%. If I² value is less than 50%, we pooled data using a fixed-effect model; otherwise we used random effects model.

We conducted subgroup analysis or sensitivity analysis based on study quality. Funnel plot analysis and Egger test were used to analyze the risk of publication bias when there were at least 10 studies included in the meta-analysis.

**Results**

**Description of Studies**

We finally identified 40 articles, of which 4 were from CNKI, 35 from Wanfang, and 1 from VIP. We failed to find any paper on PubMed, Cochrane Central Library, EMBASE, and Clinical Trials. In addition to duplicate literature, there were 36 articles. By reading the titles and abstracts, we considered 6 references as being potentially relevant and assessed them further according to our selection criteria. We removed 30 studies with the following reasons: 1. Not CKD Participants; 2. Not RCTs; 3. No outcome of interest; 4. Animal experiments; 5. Reviews. By reading the full article, 1 article was excluded. Finally, we included 4 documents as all the patients involved in this study were Chinese (S1. PRISMA Flow Diagram). The included studies varied in following aspects: sample size (45 to 72), dose of SKI used (60-100ml), and duration of treatment (14 days to 3 months). All of the 4 included studies were RCT’s. The detail characteristics of the 4 selected studies included in this review are presented in Table 1.

**Risk of bias in included studies**

The risk of bias for each of the included RCTs is shown in Figure 1 and 2. All of the 4 included trials were RCTs. Cochrane Risk of Bias was Wash used in this part. A block random was used in Bian’s study, while others only mentioned “random”. None of the 4 articles reported the allocation concealment. Only Bian mentioned the lack of blinding of participants and personnel. Thinking about the outcomes of the studies were objective projects such as PT, APTT, FIB, D-D, only the side effects was judged subjectively, so we considered the quality of blinding of outcome assessment as high when there was no outcomes about the side effects, otherwise unclear. Bian clearly reported 1 case of exfoliation and was rated as a low risk in incomplete data reporting while others didn’t report. Since none of the 4 papers was registered prior to clinical trials, it was a little hard to value the quality of reporting bias, however by comparing the methods and results slow risk was evaluated at this part. All of the articles reported the comparable baseline, clear diagnostic criteria, intervention and the outcomes, so we regarded the other bias as low risk. Overall, the methodology of the included studies was moderate.

**Fibrinogen (FIB)**

Four studies investigated FIB at the end of treatment. SKI could significantly decrease the FIB (MD=-1.23, 95% CI: -1.46, -0.99, p<0.001) as 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 achieve a longer APTT than control treatment (MD=7.34, 95% CI: 3.05, 11.62, p<0.01), as shown in 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 had more effect on prolonging the PT than control (MD=3.40, 95% CI: 2.2, 4.61, p<0.01). Figure 5.

**D-dimer (D-D)**

Baojuan B reported that SKI could lower the D-dimer as compared to basic treatment (MD=-0.36, 95% CI: -0.51, -0.21, p<0.001).

**Side effects**

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

**Quality assessment of evidence**

The quality assessment of evidence with the standard of GRADEpro was moderate. The details were summarized in the table 2.

**Additional analyses**

From the available data, it was not possible to conduct funnel plot analysis or Egger test because of insufficient number of studies.

**DISCUSSION**

APTT along with PT were two measures of the integrity of the intrinsic, extrinsic and final common pathways of the coagulation cascade. D-dimer which was a degradation product of thrombus could reflect the state of coagulation and the fibrinolytic in the body. It also was a predictor for the incidence of thrombosis in CKD. Fibrin as the primary product of the coagulation cascade as well as the ultimate substrate for fibrinolysis, played important role in the control of blood coagulation. This meta-analysis included 4 RCTs with 231 patients.
to evaluate the effectiveness and safety of SKI on coagulation with CKD. From this analysis, we found that SKI not only could improve the APTT, PT level but also lowered the fibrinogen and D-dimer without obvious SKI related side effects. Patients with CKD commonly experience increased coagulation and the thrombotic related complications is becoming more and more serious. The coagulation process involves the participation of the coagulation, anticoagulant and fibrinolytic system. Factor Xa plays an irreplaceable role in the coagulation cascade reaction, which can promote the prothrombin change to thrombin, thereby increasing the production of fibrin and reaching the state of blood coagulation. In the pathological state, the cells release particles on which there are a lot of Phosphatidylserine (PS) that provides a catalytic surface for the formation of prothrombinase complex, which promotes the occurrence of a coagulation reaction and leads to a hypercoagulable state of the blood contributing to thrombosis. Activated platelets secrete pro-inflammatory proteins and growth factors that increase the propensity for inflammatory reactions and thromboembolism in the disease. On the surface of platelets, activated P-selectin can attract the aggregation of neutrophil nuclear mononuclear cells and aggravate coagulation and inflammation, besides that, tissue factor (TF) is the main activator of the coagulation cascade and is transduced by the transcription factor NF-κB signaling pathway, which can be inhibited by NO and activated by free fatty acids. As for anticoagulant system: Protein C can inactivate Va and VIIIa, thereby reducing thrombin generation. Recent studies have shown that APC also has anti-inflammatory, anti-apoptotic and profibrinolytic effects. APC binds to the thrombin-thrombomodulin (TM) complex on glomerular endothelial cells to protect 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, ultimately resulting in reduced APC production; another anticoagulant factor is vascular endothelium: under physiological conditions, the vascular endothelium has the function of preventing thrombosis. In patients with CKD, endothelial cell dysfunction leading to reduction in eNOS and increase in ROS which upregulates the expression of inflammatory mediators and inflammatory molecules that damages endothelial cells. Endothelial cell damage result in an increase in vWF, a decrease in PG12 and heparan sulfate, thereby increasing the blood procoagulant activity and impairing antithrombotic function. At last the fibrinolytic system include Plasmin inhibitor (PAI-1) and plasminogen activator (PA). PAI-1 is an antagonist ofPA and can inhibit the hydrolysis of proteases and plays apivotal role in cell adhesion and proliferation. Activation of the immune and inflammation system in CKD patients can increase PAI-1. Activated PAI-1 not only inhibits the dissolution of fibrin in the glomerulus, increases the hypercoagulable state, but also induces an increase in TGF-β, which causes the glomerular extracellular matrix to accumulate and fibrosis, eventually leading to glomerulosclerosis.

Shen Kang injection (SKI) consisting of Rhubarb, Astragalus, Radix Salviae miltiorrhizae and Carthami Flos, is a Chinese Material Medica-standardized product. It is formulated based on TCM theory. According to the clinical observation of traditional Chinese medicine, deficiency of qi, blood stasis, and turbidity accumulation are the basic pathological changes of CKD. During the progression of disease, the qi which can gasify the water and transport the blood becomes weaker and weaker, to the most degree, yang qi of the spleen and kidney is impaired, which lead to the water becomes turbidity and the blood becomes blood stasis. The most the important traditional Chinese medicine in SKI is Astragalus, which can increase the content of qi and the transportation of water and blood followed by the decrease of turbidity and blood stasis accumulation. At the same time, rhubarb, Salvia, Safflower all can help Astragalus with its function. So, in total, SKI has the effect of increasing the qi, activating and eliminating the blood stasis, and removing the turbidity which is exactly the medicine for CKD. Further more, many studies suggested that the compositions of SKI could improve the coagulation. Protocatechuic aldehyde, salvianolic acid C, dihydroxyshinoine L, cryptotanshinone and tanshinone IIA which were found in Danshen proved to have the suppression function of thrombin, Astragalus polysaccharide can blocking NF-κB signaling in rat bone marrow EPCs, thus suppressing thrombin-induced ICAM-1 expression and up-regulating expression of VEGF and its receptors. Salvianolic acid, the water-soluble phenolic acids in Salvia miltiorrhiza, possessed antithrombotic activities, and this effect may be related to antiplatelet activity. Hemorheology modulation, suppression of intracellular calcium mobilization, and inhibition of phosphoinositide 3-kinase Carthami Flos also has antithrombotic activity, it significantly enhance the effect of clopidogrel on bleeding time, TT and PT. The finding that safflower extract and its pure isolated compounds have the effects of anticoagulation, antioxidation, anti-platelet aggregation, and ovarian granulosa cell proliferation revealed the possible mechanism of safflower. Rhubarb is a most used traditional medicine that has also been reported it’s antiplatelet effects. Chrysophanol-8-O-glucosidewhich derivatives isolated from rhubarb was found to have the most potent effect on antiplatelet and anticoagulant function. Advantages and Disadvantages of this Study: First of all, there are plenty of meta-analysis about SKI on renal function improvement, but this study is the first one to explore the effect of SKI on coagulation; Beside this, we tried to figure out the indicators which have
been widely used in clinical as the outcomes, hoping the results will benefit the clinical practice as well. Last but not least, the quality of the studies in our paper is moderate, for the authors used random method and the outcomes were objective indicators, and meticulous baseline comparison and so on. During the investigation, we also tried to communicate with the authors to get more information about the data to ensure our quality. However, there are still many shortcomings in this study. For example, we failed to conduct the subgroup analysis because of the insufficient numbers of research studies which indicating that there are not enough attention paid on this area, so it is very emergency to highlight the function of SKI on improving the coagulation in CKD patience. During the investigation, we get more information about the data to ensure our quality. However, there are still many shortcomings in this area, so it is very emergency to highlight the function of SKI on improving the coagulation in CKD patience. Then, most of the indicators of enrolled studies were intermediate indicators, lacking of end point indicators such as mortality, affected our judgment of overall efficacy.

Conclusion: In conclusion, SKI maybe considered as effective and safe treatment option for CKD since it might improve the coagulation. However, the long-term effect of SKI treatment were not fully assessed. Additional studies with well-designed and longer follow-up periods are still needed to address these challenges around the potential on SKI.

Competing interests: The authors declared no financial and non-financial competing interests.

References