Effect and safety of Shengxuening (extract from excrement of bombyxin) for renal anemia: a systematic review

Zhang Lei, Zhang Wenjin, Jin Hua, Wang Dong, Wei Ning, Wang Yiping

OBJECTIVE: To assess the effect and safety of Shengxuening (SXN), extract from excrement of bombyxin, in the treatment of renal anemia, compared to ferrous succinate and ferrous sulfate.

METHODS: According to the participant, intervention, comparison, outcomes, study design (PICOS) principles, we searched the Chinese Biomedical Literature Database, China National Knowledge Infrastructure Database, Chinese Evidence-Based Medicine Database, Wanfang Database (From establishment to December 2014). Two reviewers selected articles independently according to the inclusion and exclusion criteria. The quality of included studies was assessed by using the Cochrane Handbook. All statistical analyses were conducted by using Revman (vision 5.2) software.

RESULTS: A total of 14 randomized controlled trials (RCTs) were enrolled in the review. The results revealed that, when compared with blank group, SXN significantly improved the hemoglobin (P >) levels [MD = 6.29, 95% CI (1.65-10.94), P < 0.0008] and albumin (ALB) [MD = 10.98, 95% CI (6.97-14.99), P < 0.00001]. In addition, SXN could significantly increase the P > levels [MD = 10.98, 95% CI (6.97, 14.99), P < 0.00001]. Compared with other oral medicine SXN could improve the P > levels effectively [MD = 8.49, 95% CI (2.40, 14.58), P = 0.006]. And the subgroup analysis shown that compared with ferrous-sulfate there were significant differences [MD = 17.4, 95% CI (15.06, 19.73), P < 0.0001] and the result of ferrous-succinate had significant differences [MD = 5.34, 95% CI (2.12, 8.56), P = 0.001]. Compared with Intravenous iron groups, there were statistical differences [MD = −5.04, 95% CI (−9.59, −0.50), P = 0.03]. In the safety analysis, the rate of adverse reactions in SXN groups and control groups were 19.3% and 3.7%, respectively (P < 0.0001). Due to our studies were of poor methodological quality, and the sample size were small, the results were influenced by bias.

CONCLUSION: Our findings suggest that the SXN had better effect and was safer in the treatment of RA than ferrous succinate and ferrous sulfate.

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Key words: Kidney failure, chronic; Anemia; Review; Shengxuening
INTRODUCTION

Renal anemia (RA) is caused by kidney diseases that lead to the relative or absolute lack of erythropoietin. In addition, and uremic toxins shortening red cell survival also contributes to RA. Anemia induces the development of left ventricular hypertrophy and cardiovascular disease, which is significantly associated with mortality and morbidity in End Stage Renal Disease (ESRD) patients. The prevalence of anemia in chronic kidney disease (CKD) is 22.0%, 37.0%, 45.4%, 85.1% and 98.2% respectively from CKD stage 1 to 5 in China. Anemia in ESRD patients was mostly treated with erythropoiesis-stimulating agents (ESA) for erythropoietin deficiency. However, the response to ESA is sometimes poor due to iron deficiency. Therefore, iron supplementation was widely used in CKD patients to treat iron deficiency, prevent its development in erythropoiesis-stimulating agents (ESA) treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment. Iron therapy could be provided with oral and intravenous (IV) preparations. IV iron preparations had been recommended by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) for all hemodialysis (HD) patients for whom the demand for iron cannot be met by oral therapy alone, and for those on peritoneal dialysis (PD) therapy or who had nondialysis dependent CKD (NDD-CKD) who remained iron deficient despite attempts at oral supplementation. In contrast, the use of i.v. iron was more costly than oral iron when accounting for drug cost, administration costs, and indirect costs to the patient for time and travel and can cause rare but serious short-term effects including anaphylactic-type reactions, hypotension, and arthralgia. The frequency of these reactions varies among i.v. iron products and was highest with high-molecular-weight products, which had also been associated with long-term effects such as infection, atherosclerosis, endothelial dysfunction, and renal injury.

Oral iron had been associated with adverse gastrointestinal effects. Absorption of oral iron may also be limited by decreased gastrointestinal absorption due to the inflammation associated with CKD. Accordingly Shengxuening (SXN) had been widely used in the treatment of RA, after successfully used in the treatment of various kinds of anemia. The aim of this meta-analysis was therefore to assess the effect and safety of SXN in the treatment of renal anemia.

METHODS

Criteria for considering studies for this review
Types of studies: randomized controlled trials (RCTs), without language restriction; types of participants: Patients met the diagnostic criteria for RA; types of interventions: SXN was used in treatment groups; types of outcome measures: (a) primary outcomes: Hemoglobin (HB), Serum transferrin saturation (TSAT), Hematocrit (Hct), serum iron (SI), adverse events; (b) secondary outcomes: hypersensitive c-reactive protein (Hs-crp), albumin (ALB). Animal research, patients with other chronic disease which influences the iron metabolism were excluded.

Search methods for identification of studies
(a) Electronic searches: Two authors independently searched the databases as follows: Chinese Biomedical Literature Database, China National Knowledge Infrastructure Database, Chinese Evidence-Based Medicine Database, Wanfang Database (From establishment to December 2014). We used the keywords in the search according to the PICOS principles. The MeSH of chronic renal insufficiency, chronic renal failure, end-stage renal disease, toxuria, chronic kidney disease, hemodialysis, peritoneal dialysis, renal anemia, anemia, Shengxuening and randomized was used in search strategy. The search strategy of China National Knowledge Infrastructure Database was as follows: #1 chronic renal insufficiency; #2 chronic renal failure; #3 end-stage renal disease; #4 toxuria; #5 chronic kidney disease; #6 hemodialysis; #7 peritoneal dialysis; #8 #1OR#2OR#3OR#4OR#5OR#6OR#7; #9 renal anemia; #10 anemia; #11 #9OR#10; #12 randomized; #13 #8AND#11AND#12. (b) Searching other resources: hand searching the reference lists of relevant papers and literature reviews. (c) Gray literature: searching the unpublished literature and contacting the author if necessary.

Data collection
Two reviewers (Zhang Lei and Zhang Wenjin) selected articles independently for inclusion, evaluated the methodological quality and extracted data. Disagreement between reviewers was resolved through discussion and additional information was sought from trial authors when necessary.

Risk of bias assessment
The Cochrane Collaboration’s risk of bias list was taken as follows: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective reporting; (g) other biases. According to these six projects two authors who had been trained, evaluated the literatures independently. Three categories of “yes” (low risk of bias), “no” (high risk of bias), or “not clear” (the risk of bias cannot be determined) were used in the assessment.

Statistical analysis
Statistical analysis was performed using Review Manager Version 5.2 software (Copenhagen the Nordic Cochrane center the Cochrane collaboration 2012). The risk ratio (RR) with 95% confidence interval (CI) was
calculated for binary data, and the mean difference with 95% CI for continuous variables. Random and fixed-effects models were used to calculate the combined outcomes of both binary and continuous data. Heterogeneity was assessed based on the χ² test. A random effects model was used for meta-analysis where there was statistical heterogeneity (P < 0.10) and a fixed effects model where there was not statistical heterogeneity (P ≥ 0.10). Subgroup analysis was conducted with the reason of heterogeneity.

RESULTS

Literature search and characteristics of the included trials

Literature search identified 75 studies. Fifty-five studies were excluded by reading the title and abstract. A total of 14 studies were eligible (Figure 1). A total of 747 participants were included in the 14 studies. Totally 373 participants were in treatment group, and 374 in control group (414 males, 333 females) (Table 1).

Methodological quality assessment

We used the risk of bias assessment tool in the Cochrane Handbook to assess the methodological quality of trials were shown in Figures 2 and 3.

Statistical analysis

Table 2 presents a summary of the results of the meta-analysis. Analysis revealed that SXN statistically significantly improved the HB [MD = 6.29, 90% CI (1.65-10.94), P < 0.0008] (Figure 4) and ALB [MD = 1.37, 90% CI (−2.04, −4.78), P < 0.00001] only (Figure 5). No significant effect was found for TSAT, Hct, SI and Hs-crp. According to the studies we did some subgroups analysis on HB. Blank control were used in three articles. There was no statistical heterogeneity (I² = 0%) among those studies, the fixed effect model was used for meta-analysis. The results (Figure 6) showed that there were significant differences [MD = 10.98, 95% CI (6.97, 14.99), P < 0.00001], which indicated that the SXN group could increase the HB levels compared with blank group. Eight studies used oral iron in control groups, which had statistical heterogeneity (I² = 94%), the random effect model was used for Meta-analysis. The results (Figure 7) showed that there were significant differences [MD = 8.49, 95% CI (2.40, 14.58), P = 0.006], which indicated that compared with other oral medicine, SXN could improve the HB levels effectively. What’s more, in oral groups there were three studies using ferrous-sulfate as placebo. Also ferrous-succinate was used in three studies. While, only one study took ferrous-vitamin-complex sustained-release and tablets-polysaccharide-iron in control group, respectively. Naturally, the meta-analysis of SXN vs ferrous-sulfate and SXN vs ferrous-succinate be done. There was no statistical heterogeneity (I² = 0%) in both analyses, compared with ferrous-sulfate differences were significant [MD = 17.4, 95% CI (15.06, 19.73), P < 0.00001] (Figure 8), and the result of ferrous-succinate had significant differences [MD = 5.34, 95% CI (2.12, 8.56), P = 0.001] too (Figure 9). Intravenous iron was used for treatment of iron deficiency in three studies using ferrous-sulfate as placebo. There was no statistical heterogeneity (I² = 17%) among the three studies, the fixed effect model was used for meta-analysis. The results (Figure 10) showed that differences were statistically significant [MD = −5.04, 95% CI (−9.59, −0.50), P = 0.03].

![Figure 1 Flow chart of article screening and selection process](image-url)
### Table 1: Characteristics of the included studies (Mean ± SD)

<table>
<thead>
<tr>
<th>Included study</th>
<th>Case (T/C)</th>
<th>Sex M/F</th>
<th>Age (year)</th>
<th>CKD Stage</th>
<th>Baseline of HB (g/L)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Duration (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma XH et al 2014&lt;sup&gt;10&lt;/sup&gt;</td>
<td>20/20</td>
<td>24/16</td>
<td>43.0 ± 19.5</td>
<td>CKD5 HD</td>
<td>70.1 ± 5.5</td>
<td>SXXN+EPO, Ferrous Sulfate+EPO</td>
<td>a.b.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>TANG JP et al 2013&lt;sup&gt;10&lt;/sup&gt;</td>
<td>58/58</td>
<td>61/55</td>
<td>52.7 ± 11.4</td>
<td>CKD5 ND</td>
<td>82.7 ± 9.58</td>
<td>SXXN+EPO, Ferrous Sulfate+EPO</td>
<td>a.b.c.d.e.f.</td>
<td>12</td>
</tr>
<tr>
<td>Mi CX 2013&lt;sup&gt;10&lt;/sup&gt;</td>
<td>30/30</td>
<td>34/26</td>
<td>52.7 ± 11.3</td>
<td>CKD5 HD</td>
<td>74.5 ± 11.2</td>
<td>SXXN+EPO, Ferrous Succinate+EPO</td>
<td>a.b.c.d.e.</td>
<td>12</td>
</tr>
<tr>
<td>Long L et al 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>34/34</td>
<td>33/35</td>
<td>53.2 ± 12.0</td>
<td>CKD5 ND</td>
<td>83.0 ± 17.98</td>
<td>SXXN+EPO, Ferrous Sulfate+EPO</td>
<td>a.b.c.d.e.f.</td>
<td>12</td>
</tr>
<tr>
<td>Liu F et al 2013&lt;sup&gt;5&lt;/sup&gt;</td>
<td>30/30</td>
<td>31/29</td>
<td>21.0 ± 67.0</td>
<td>CKD5 ND</td>
<td>93.6 ± 18.2</td>
<td>SXXN+EPO, Ferrous Succinate+EPO</td>
<td>a.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>ZhaoXJ et al 2012&lt;sup&gt;4&lt;/sup&gt;</td>
<td>27/28</td>
<td>29/26</td>
<td>53.0 ± 11.0</td>
<td>CKD5 HD</td>
<td>75.0 ± 15.0</td>
<td>SXXN+EPO, Ferrous Succinate+EPO</td>
<td>a.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>Li HB et al 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>35/35</td>
<td>35/35</td>
<td>43.2 ± 15.8</td>
<td>CKD5 PD</td>
<td>72.8 ± 9.6</td>
<td>SXXN+EPO, EPO</td>
<td>a.b.</td>
<td>12</td>
</tr>
<tr>
<td>Tang CY et al 2011&lt;sup&gt;5&lt;/sup&gt;</td>
<td>18/18</td>
<td>25/11</td>
<td>52.6 ± 10.5</td>
<td>CKD5 HD</td>
<td>64.5 ± 10.27</td>
<td>SXXN+EPO, EPO</td>
<td>a.b.</td>
<td>8</td>
</tr>
<tr>
<td>Xu QH et al 2012&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22/22</td>
<td>28/16</td>
<td>55.6 ± 11.1</td>
<td>CKD5 HD</td>
<td>67.6 ± 10.32</td>
<td>SXXN+EPO, EPO</td>
<td>a.b.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>Wang WY et al 2013&lt;sup&gt;8&lt;/sup&gt;</td>
<td>21/21</td>
<td>22/20</td>
<td>45.4 ± 9.2</td>
<td>CKD5 HD</td>
<td>65.0 ± 3.4</td>
<td>SXXN+EPO, Ferrous and Vitamin Complex Sustained-release Tablets+EPO</td>
<td>a.b.c.d.</td>
<td>16</td>
</tr>
<tr>
<td>Liao XY et al 2012&lt;sup&gt;2&lt;/sup&gt;</td>
<td>20/20</td>
<td>22/18</td>
<td>52.4 ± 10.8</td>
<td>CKD5 HD</td>
<td>75.4 ± 10.8</td>
<td>SXXN+EPO, EPO</td>
<td>a.b.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>Yang Y et al 2011&lt;sup&gt;8&lt;/sup&gt;</td>
<td>20/20</td>
<td>26/14</td>
<td>51.6 ± 14.3</td>
<td>CKD5 HD</td>
<td>73.5 ± 7.7</td>
<td>SXXN+EPO, EPO, polysaccharide-iron+EPO</td>
<td>a.b.c.d.</td>
<td>8</td>
</tr>
<tr>
<td>Wang L et al 2012&lt;sup&gt;8&lt;/sup&gt;</td>
<td>23/23</td>
<td>25/11</td>
<td>53.6 ± 10.0</td>
<td>CKD5 HD</td>
<td>80.2 ± 18.3</td>
<td>SXXN+EPO, Iron sucrose+EPO</td>
<td>a.b.c.d.</td>
<td>12</td>
</tr>
<tr>
<td>Lu JB et al 2013&lt;sup&gt;8&lt;/sup&gt;</td>
<td>15/15</td>
<td>19/11</td>
<td>41.5 ± 14.0</td>
<td>CKD5 HD</td>
<td>71.5 ± 12.3</td>
<td>SXXN+EPO, Iron sucrose+EPO</td>
<td>a.b.c.d.</td>
<td>12</td>
</tr>
</tbody>
</table>

Notes: HD: hemodialysis; PD: peritoneal dialysis; ND: nondialysis; T/C: total number of cases; a: HB; b: HCT; c: SI; d: TSAT; e: ALB; f: hs-CRP; HB: hemoglobin; Hct: hematocrit; TSAT: serum transferrin saturation; ALB: albumin; SI: serum iron; Hs-CRP: hypersensitive C-reactive protein; EPO: erythropoietin; CDK: chronic kidney disease; SXN: Shengxuening.

**Discussion**

In this review, the baseline of hemoglobin (HB) for RA patients was significantly lower than other medicine therapy, which indicated a higher risk for RA patients. (d) SXN improves nutritional status, with less adverse events. SXN has less adverse events than other medicine therapy, which was mainly manifested as vomiting, bloating, and diarrhea. SXN has higher security than other medicine therapy, which was mainly manifested as vomiting, bloating, and diarrhea. SXN has lower adverse reaction rate of adverse reactions was 19.3% and 7.7% respectively. Varying degrees of adverse reactions were reported in 13 studies, which was mainly manifested as vomiting, bloating, and diarrhea.
Random sequence generation (selection bias)  
Allocation concealment (selection bias)  
Blinding of participants and personnel (performance bias)  
Blinding of outcome assessment (detection bias)  
Incomplete outcome data (attrition bias)  
Selective reporting (reporting bias)  
Other bias

Figures 2 Bar graph showing risk of bias

Random sequence generation (selection bias)  
Allocation concealment (selection bias)  
Blinding of participants and personnel (performance bias)  
Blinding of outcome assessment (detection bias)  
Incomplete outcome data (attrition bias)  
Selective reporting (reporting bias)  
Other bias

Figures 3 summary of risk of bias

Table 2 Summary of the results of the meta-analysis for all outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Mean difference (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>14</td>
<td>747</td>
<td>6.29 [1.65, 10.94]</td>
<td>0.008</td>
</tr>
<tr>
<td>HCT</td>
<td>12</td>
<td>623</td>
<td>2.71 [-0.94, 6.36]</td>
<td>0.15</td>
</tr>
<tr>
<td>SI</td>
<td>12</td>
<td>641</td>
<td>44.86 [-6.59, 96.31]</td>
<td>0.09</td>
</tr>
<tr>
<td>TSAT</td>
<td>12</td>
<td>641</td>
<td>3.31 [-1.25, 7.87]</td>
<td>0.16</td>
</tr>
<tr>
<td>ALB</td>
<td>3</td>
<td>244</td>
<td>2.74 [1.17, 3.11]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>2</td>
<td>184</td>
<td>0.11 [-0.84, 0.62]</td>
<td>0.77</td>
</tr>
</tbody>
</table>


Figures 4 Comparison of Hemoglobin of Shengxuening groups vs control groups
from the excrement of bombyxin. The study showed that the main ingredient in it was ferrous derivative, which was mainly composed of Fe chlorin p₆, Fe chlorin e₆ and Fe isochlorin e₄. A single-center research found that 73.6% CKD patients had abnormal upper gastrointestinal endoscopic findings. The gastroduodenal lesion observed was hemorrhagic gastritis (31.5%), followed by hemorrhagic gastroduodenitis (26.3%), gastric nodular gastritis (10.5%), and polyps (10.5%). However, oral iron is mainly absorbed in the duodenum.
num and upper jejunm mucosa with an acid environment, which would cause gastrointestinal reaction. While, chlorophyll which is contained in SXN has the same structure with as heme in human body, so it can directly compound hemoglobin, which increases the bioavailability. The organic hematin chloride in SXN and the human’s haematoporphyrin are similar, which can be immediate absorbed by the intestinal mucosal cells of the gastric mucosa with less irritation that increase the absorption of protein.

Several limitations in our analysis merit consideration. First, all included studies were from the same country. A publication bias was inevitable. Second, the power of our analysis is limited by the heterogeneity among the results. We could not analyze the heterogeneity in HCT, SI and TSAT, which may add the risk of bias. Third, due to the sample size was small. The subgroup analysis of the hemodialysis patients and non dialysis patients had not been done, which would increase the limitations of our study.

According to our analysis, SXN had better effect and was safer in the treatment of RA than ferrous succinate and ferrous sulfate. But the findings should be further confirmed with rigorous, large sample size, multicenter studies.

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