

Shengxuening versus oral iron supplementation for the treatment of renal anemia: A systematic review

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ABSTRACT

Shengxuening (SXN), as an effective supplement to heme-like iron, has been widely used in China to treat renal anemia. However, proof of its use for improving inflammation is scarce in the past decades. This work aimed to evaluate the effectiveness of SXN with inflammatory factors as primary endpoints. By searching PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), VIP Information/China Science and Technology Journal Database, and WANFANG Database, we identified previous studies that met the inclusion criteria and included them in the systematic review. Analyses were performed using STATA. Nine randomized controlled trials were included in this systematic review. The results revealed that, when compared with oral iron supplementation, SXN can reduce the level of inflammatory factors, including hs-CRP (WMD -1.93 mg/L; 95% CI -2.14 to -1.72), IL-6 ($P < 0.05$), and TNF- α ($P < 0.05$), and significantly enhance the level of Hb (WMD 13.40 g/L; 95% CI 12.95 to 13.84), TSAT (WMD 6.88%; 95% CI 6.50 to 7.26), and SF (WMD 38.46 μ g/L; 95% CI 23.26 to 53.67). Moreover, SXN exhibits a superior security than oral iron supplementation with less gastrointestinal adverse reactions (RR 0.14; 95% CI 0.06 to 0.32). In patients with renal anemia, SXN is more effective and safer than oral iron supplementation, especially in reducing the level of inflammation.

Key words: Shengxuening, inflammation, renal anemia, oral iron supplementation, systematic review

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INTRODUCTION

Anemia as a frequent complication of chronic kidney disease (CKD) is a risk factor of increasing mortality.^[1] As a matter of fact, common causes of renal anemia include relative erythropoietin (EPO) deficiency, disordered iron homeostasis, circulating uremic-induced inhibitors of erythropoiesis, shortened red blood cell survival, and various metabolic and mechanical factors.^[2,3] KDIGO (Kidney Disease: Improving Global Outcomes) recommended erythropoiesis-stimulating agents (ESAs) and iron supplementation as first-line treatments for patients with

renal anemia in 2012.^[4] However, there still have been a lot of clinical cases in which sufficient supplementation of EPO and iron cannot correct anemia. The study has shown that, aside from EPO and iron deficiency, inflammation and hepcidin are also involved in the mechanisms of renal anemia, which have renewed interest in understanding the molecular mechanisms of anemia in CKD.^[2] A new therapy for effectively targeting the underlying pathophysiology of renal anemia is highly desirable but remains challenging.

Shengxuening (SXN), as an effective supplement to heme-like iron, has been widely used in China to treat renal anemia.

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A number of clinical studies have indicated that SXN tablets were highly effective for iron deficiency anemia, blood loss anemia, and perinatal anemia.^[5] Zhang L *et al.*^[6] have done a systematic review, which showed that SXN is more effective and safer than ferrous succinate and ferrous sulfate in the treatment of renal anemia in 2016. On the one hand, iron supplementation is administered either orally or intravenously, while it is generally accepted that intravenous iron supplementation has a higher risk of increasing inflammatory reaction than oral iron supplementation. On the other hand, recently, new studies have shown that SXN could exhibit good improvement on inflammatory reaction in patients with renal anemia, while without systematic assessment on the effect as yet. Therefore, we decided to make a systematic review that evaluated the attribute of SXN versus oral iron supplementation, with inflammatory factors as primary endpoints, for the treatment of renal anemia.

METHODS

Data sources and search strategy

We searched PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), VIP Information/China Science and Technology Journal Database, and WANFANG Database for eligible articles from database inception to February 2020. We used the following combined title/abstract and Medical Subject Headings (MeSH terms: “Shengxuening” OR “Faeces bombycis extract” OR “Sodium iron chlorophyllin” AND “Renal Insufficiency, Chronic” OR “Renal dialysis” AND “Anemia” AND “Randomized controlled trials.” The complete search used for PubMed was: (Shengxuening [Title/Abstract] OR Faeces bombycis extract [Title/Abstract] OR Sodium iron chlorophyllin [Title/Abstract]) AND (Renal Insufficiency, Chronic [Mesh] OR Kidney Insufficiency, Chronic [Title/Abstract] OR Chronic Kidney Diseases [Title/Abstract] OR Chronic Renal Diseases [Title/Abstract] OR Nephropathy [Title/Abstract] OR Hemodialysis [Title/Abstract] OR Peritoneal dialysis [Title/Abstract] OR End-stage renal disease [Title/Abstract]) AND (Renal anemia [Title/Abstract] OR Anemia [Title/Abstract]) AND (Randomized controlled trials [Title/Abstract] OR Random [Title/Abstract]). References of relevant articles were manually searched for additional potentially relevant trials.

Study selection

Trials satisfying the following inclusion criteria were included: (1) randomized controlled trial (RCT) design in both English and Chinese languages, (2) adult (age ≥ 18 years) patients with renal anemia defined by KDIGO in 2012, (3) comparison of SXN and oral iron supplementation, and (4) primary endpoint was

hypersensitive C-reactive protein (hs-CRP). Interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), hemoglobin (Hb), serum transferrin saturation (TSAT), serum ferritin (SF), and adverse reactions were secondary endpoints. Trials were excluded if: (1) different regimens applied between two treatment groups apart from SXN and oral iron supplementation; (2) kidney transplant patients; (3) patients with other chronic disease, which influences the inflammatory state; and (4) retrospective studies or duplicated publication. Two reviewers (Qin Zeng and Xin-Hui Wang) independently inspected the retrieved literatures, based on the inclusion criteria. For possibly relevant articles or in cases of disagreement between the two reviewers, we independently inspected the full article.

Data extraction and quality assessment

Two reviewers (Qin Zeng and Xin-Hui Wang) independently extracted data from included trials and assessed methods quality. In case of disagreement between the two reviewers, a third reviewer (Li-Ping Yang) extracted the data and guaranteed the results attained to reach a consensus. Data extracted included the first author's name, publication year, trial design, sample sizes, age, sex, baseline hs-CRP, Hb, TSAT, SF, doses of SXN and oral iron supplementation, duration of treatment, outcome measures, and adverse reactions.

We evaluated all potentially relevant sources of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, binding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We graded each domain as low risk of bias, unclear risk (lack of information or uncertainty over the potential for bias), or high risk of bias according to criteria specified in the Cochrane Handbook, version 5.1.0.^[7]

Statistical analysis

In this systematic review, pooled effect sizes were summarized as weighted mean difference (WMD) or standard mean difference (SMD) with its 95% confidence intervals (CI) for continuous data. Dichotomous data were pooled as the risk ratio (RR) with 95% CI. The chi-square test and Cochrane Q statistic were used for assessment of heterogeneity. Significant heterogeneity was defined as the I^2 value $\geq 50\%$ and the Cochrane's Q statistic $P < 0.10$. A random effect model was selected when significant heterogeneity was identified. Otherwise, a fixed-effect model was used.

In order to find the reason of significant heterogeneity, subgroup analysis was conducted for the primary endpoint and several secondary endpoints (Hb, TSAT, SF, adverse reactions) by patient type (non-dialysis versus dialysis). All

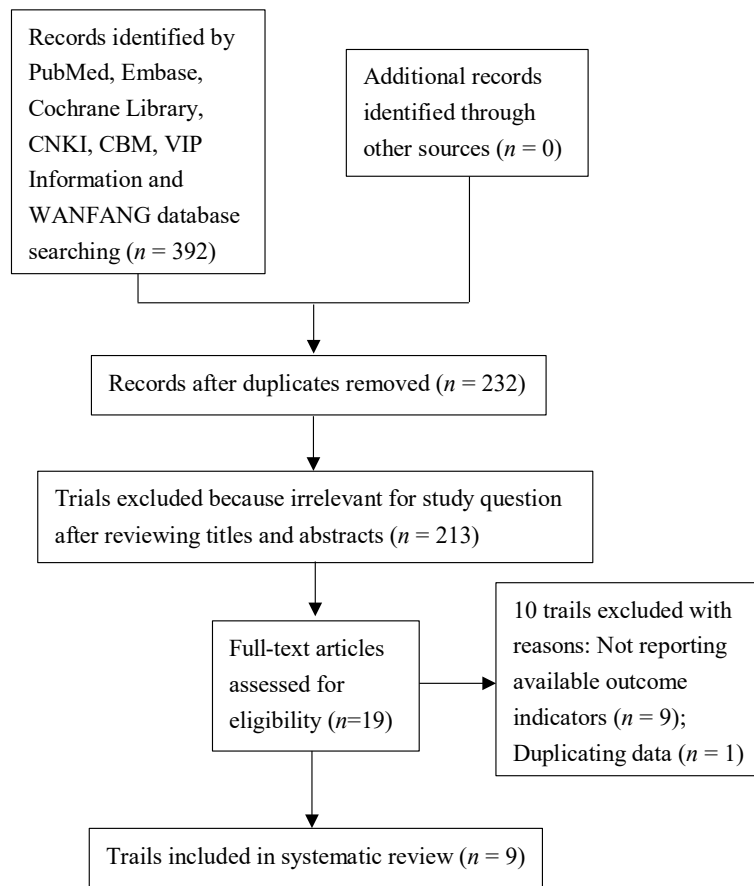


Figure 1: Flow chart of trial selection process.

the analyses were carried out using STATA 12.0 software (Stata Corp, College Station, TX, USA). A P -value < 0.05 was considered significant for all outcomes.

RESULTS

Search results and trial characteristics

The literature search identified 392 publications; nine trials^[8-16] were included in this systematic review after screening based on the inclusion criteria. The selection process is shown in Figure 1, and the main characteristics of the included trials are provided in Table 1. All the included trials were carried out in China and reported in Chinese journals between 2012 and 2020. A total of 688 (280 males, 408 females) patients with renal anemia were identified, 344 of whom were treated with oral iron, and the others treated with SXN, the dosage of SXN was ranged from 0.5 to 1.0 g, tid. There were three trials^[8-10] including 242 patients with renal anemia who were not dialyzed, and six trials^[11-16] including 446 patients with renal anemia who were dialyzed, with sample sizes of the individual trial varying from 40 to 134. The mean baseline hs-CRP levels in the trials ranged from 4.33 ± 1.03 (standard deviation) to 7.22 ± 2.47 mg/L, and the baseline Hb levels ranged from 67.48

± 10.01 to 88.56 ± 11.09 g/L. All the treatment duration was three months.

Risk-of-bias assessment of the included trials is detailed in Figure 2. Regarding sequence generation, three trials^[11,12,14] were of low risk of bias, whereas six^[8-10,13,15,16] were of unclear risk. Regarding allocation generation, six trials^[8-10,13,15,16] were of unclear risk of bias, whereas three^[11,12,14] were of high risk. All included studies^[8-16] were unblinded, which were all of high risk of bias. Six trials^[8-10,12,13,16] were considered as low risk for incomplete outcome data (attrition bias), and three trials^[11,13,16] were considered as high risk for selective outcome reporting (reporting bias).

Hypersensitive C-reactive protein

Nine trials^[8-16] reported on the outcome of hs-CRP. As shown in Figure 3, there was significant heterogeneity across trials ($I^2 = 98.4\%$, $P < 0.001$). A random-effect model meta-analysis showed a significant beneficial effect of SXN compared with oral iron supplementation in the reduction of hs-CRP (WMD -1.93 mg/L; 95% CI -2.14 to -1.72). Subgroup analyses (Table 2) indicated a strong effect in dialysis patients (WMD -2.15 mg/L; 95% CI -2.37 to -1.92).

Table 1: Characteristics of included studies

Author/ year	Sample sizes (exp; con)	Age(year)	Sex (M/F)	baseline hs- CRP (mg/L)		Baseline Hb (g/L)		Intervention		Dura- tion (m)	Outcome measures	Patient type
				Exp	Con	Exp	Con	Exp	Con			
Long Li 2012 ^[8]	34; 34	exp: 53.2 ± 12.0; con: 51.6 ± 13.8	35/33	4.67 ± 2.53	4.82 ± 3.15	82.75 ± 10.34	83.01 ± 7.98	SXN, 0.5 g, tid + EPO	Oral iron sulfate, 0.3 g, tid + EPO	3	hs-CRP, Hb, Hct, SF, TSAT, SCR, ALB	Non- dialysis
Tan Jinping 2013 ^[9]	58; 58	mean:52.7 ± 11.4	55/61	4.67 ± 2.54	4.83 ± 3.14	82.74 ± 9.58	83.14 ± 8.07	SXN, 0.5 g, tid + EPO	Oral iron sulfate, 0.3 g, tid + EPO	3	hs-CRP, Hb, Hct, SF, TSAT, ALB	Non- dialysis
Guo Aili 2015 ^[10]	29; 29	mean:45.3 ± 19.5	24/34	4.54 ± 2.57	4.43 ± 3.47	67.48 ± 10.01	69.67 ± 10.56	SXN, 0.75 g, tid + EPO	Oral iron fumarate, 0.2 g, tid + EPO	3	hs-CRP, Hb, Hct, SF, TSAT, SCR, ALB, SI, TIBC, dosage of EPO	Non- dialysis
Jin Hua 2016 ^[11]	20; 20	exp:56.24 ± 9.6; con:59.5 ± 10.6	13/27	7.04 ± 2.24	7.22 ± 2.47	87.11 ± 10.39	88.56 ± 11.09	SXN, 0.5 g, tid + EPO	Oral polysac- charide iron complex capsule, 150 mg, qd + EPO	3	hs-CRP, IL-6, Hb, Hct, hepcidin, SF, TSAT, dosage of EPO, ERI	Dialysis
Liu Yongbing 2016 ^[12]	30; 30	mean:50.2 ± 14.6	25/35	4.63 ± 1.46	4.52 ± 1.32	75.30 ± 5.03	74.81 ± 4.83	SXN, 1.0 g, tid + EPO	Oral iron succinate, 0.2 g, tid + EPO	3	hs-CRP, IL-6, TNF- α , Hb, Hct	Dialysis
Zhang Juan 2016 ^[13]	28; 28	mean:51.3 ± 11.4	25/31	4.68 ± 2.38	4.87 ± 2.18	82.36 ± 9.42	83.12 ± 8.78	SXN, 0.5 g, tid + EPO	Oral polysac- charide iron complex capsule, 300 mg, qd + EPO	3	hs-CRP, Hb, Hct, SF, TSAT, SCr, ALB	Dialysis
Zhou Jin 2016 ^[14]	67; 67	exp :54.8 ± 3.6; con :55.3 ± 4.3	55/79	4.85 ± 2.94	4.85 ± 3.09	73.89 ± 5.35	73.92 ± 5.08	SXN, 0.5 g, tid + EPO	Oral iron dextran, 50 mg, tid + EPO	3	hs-CRP, Hb, SF, TSAT, SCR, ALB	Dialysis
Liu Gang 2018 ^[15]	40; 40	exp :49.52 ± 1.45; con :50.32 ± 1.08	23/57	4.33 ± 1.03	4.63 ± 1.03	82.23 ± 1.23	83.23 ± 1.22	SXN, 0.5 g, tid	Oral polysac- charide iron complex capsule, 300 mg, qd	3	hs-CRP, Hb, Hct, SF, TSAT, ALB	Dialysis
Zhong Huiling 2020 ^[16]	38; 38	exp :50.68 ± 13.28; con :50.33 ± 13.25	25/51	4.62 ± 1.45	4.53 ± 1.32	75.31 ± 5.03	74.82 ± 4.84	SXN, 0.5–1.0 g, tid + EPO	Oral iron dextran, 0.2 g, tid + EPO	3	hs-CRP, IL-6, TNF- α , Hb, Hct, Hcy	Dialysis

Exp: experimental group (SXN); Con: control group (oral iron); hs-CRP: hypersensitive C-reactive protein; Hb: hemoglobin; Hct: hematocrit value; SF: serum ferritin; TSAT: serum transferrin saturation; ALB: albumin; SCr: serum creatinine; SI: serum iron; TIBC: total iron-binding capacity; ERI: erythropoietin resistance index; IL-6: interleukin-6; TNF- α : tumor necrosis factor- α ; Hcy: homocysteine.

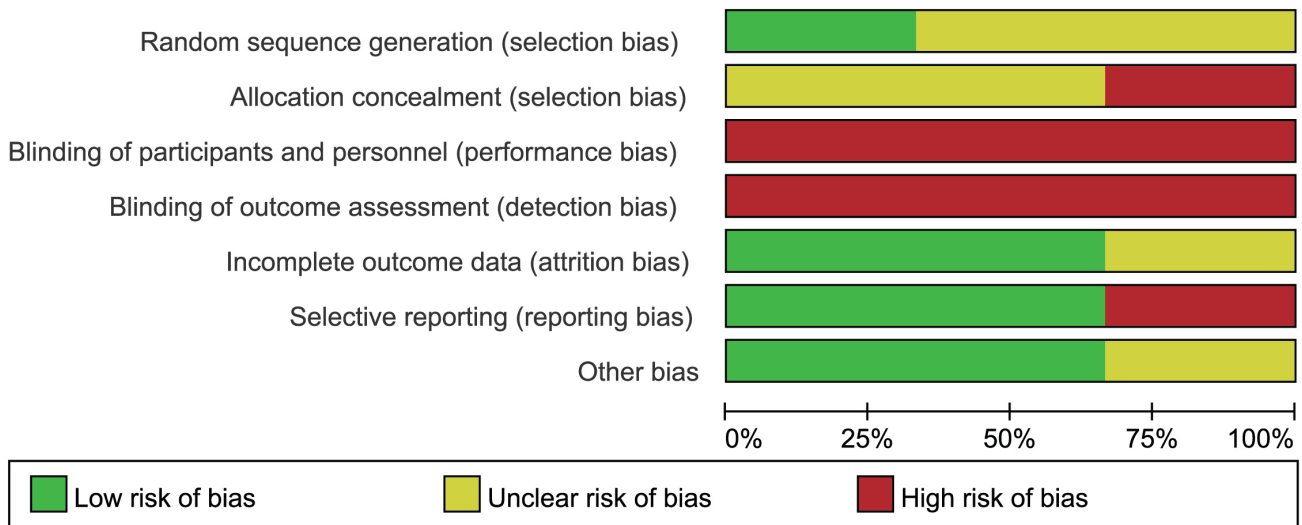


Figure 2: Risk of bias graph.

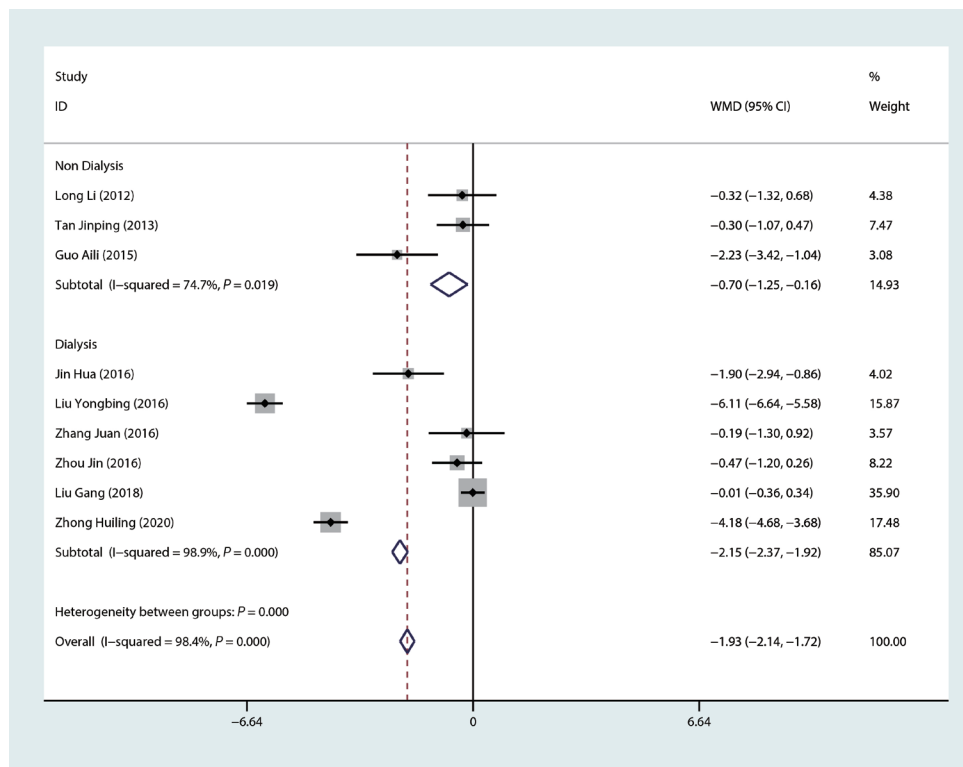


Figure 3: Forest plots of hypersensitive C-reactive protein level for SXN group vs. oral iron group.

Interleukin-6 and tumor necrosis factor- α

Two trials^[11,12] reported on the outcome of IL-6, while we did not merge the two trials' data due to the difference of data units. One trial^[12] reported on the outcome of TNF- α . We observed that there was a significant beneficial effect of SXN compared with oral iron supplementation in the reduction of IL-6 ($P < 0.05$) and TNF- α ($P < 0.05$) (date not shown).

Hemoglobin

Nine trials^[8-16] reported on the outcome of Hb. As shown in Figure 4, there was a significant heterogeneity across trials ($I^2 = 97.3%$, $P < 0.001$). A random-effect model meta-analysis showed a significant beneficial effect of SXN compared with oral iron supplementation in increasing Hb (WMD 13.40 g/L; 95% CI 12.95 to 13.84). Subgroup analyses (Table 2) indicated a strong effect in

Table 2: Subgroup analysis by patient type on hs-CRP, Hb, TSAT, SF, and adverse reactions

Subgroups	Number of studies	WMD	95% CI	Heterogeneity between studies
1.hs-CRP				
Non-dialysis	3	-0.70 mg/L	-1.25 to -0.16	$P = 0.019$; $I^2 = 74.7\%$
Dialysis	6	-2.15 mg/L	-2.37 to -1.92	$P < 0.001$; $I^2 = 98.9\%$
2.Hb				
Non-dialysis	3	15.90 g/L	13.86 to 17.93	$P = 0.020$; $I^2 = 74.3\%$
Dialysis	6	13.27 g/L	12.81 to 13.73	$P < 0.001$; $I^2 = 98.2\%$
3.TSAT				
Non-dialysis	3	7.42%	6.36 to 8.49	$P = 0.072$; $I^2 = 61.9\%$
Dialysis	4	6.80%	6.39 to 7.20	$P < 0.001$; $I^2 = 89.4\%$
4.SF				
Non-dialysis	3	48.87 μ g/L	30.66 to 67.09	$P < 0.001$; $I^2 = 97.7\%$
Dialysis	4	28.60 μ g/L	4.54 to 52.66	$P < 0.001$; $I^2 = 100\%$
5.Adverse reactions				
Non-dialysis	3	0.05	0.01 to 0.23	$P = 0.950$; $I^2 = 0.0\%$
Dialysis	5	0.14	0.08 to 0.52	$P = 0.480$; $I^2 = 0.0\%$

non-dialysis patients (WMD 15.90 g/L; 95% CI 13.86 to 17.93).

Serum transferrin saturation

Seven trials^[8-11,13-15] reported on the outcome of TSAT. As shown in Figure 5, there was significant heterogeneity across trials ($I^2 = 82.7\%$, $P < 0.001$). A random-effect model meta-analysis showed a significant beneficial effect of SXN compared with oral iron supplementation in increasing TSAT (WMD 6.88%; 95% CI 6.50 to 7.26). Subgroup analyses (Table 2) indicated a strong effect in non-dialysis patients (WMD 7.42%; 95% CI 6.36 to 8.49).

Serum ferritin

Seven trials^[8-11,13-15] reported on the outcome of SF. As shown in Figure 6, there was significant heterogeneity across trials ($I^2 = 100\%$, $P < 0.001$). A random-effect model meta-analysis showed a significant beneficial effect of SXN compared with oral iron supplementation in increasing SF (WMD 38.46 μ g/L; 95% CI 23.26 to 53.67). Subgroup analyses (Table 2) indicated a strong effect in non-dialysis patients (WMD 48.87 μ g/L; 95% CI 30.66 to 67.09).

Adverse reactions

Eight trials^[8-10,12-16] reported adverse reactions. The main adverse reactions are gastrointestinal adverse reactions, including loss of appetite, bloating, nausea, constipation, and so on. As shown in Figure 7, there was no significant heterogeneity across trials ($I^2 = 0.0\%$, $P = 0.491$). A fixed-effect model meta-analysis showed that oral iron supplementation was associated with an increased risk of gastrointestinal adverse reactions (RR 0.14; 95% CI 0.06 to 0.32) when compared with SXN. Subgroup analyses (Table 2) indicated a higher risk of gastrointestinal reactions in dialysis patients (RR 0.21; 95% CI 0.08 to 0.52).

DISCUSSION

As nine relevant RCTs involving 688 patients with renal anemia were systematically reviewed above, we found that SXN could provide better effects on patients with renal anemia than oral iron supplementation, including: (a) reduction in the level of hs-CRP, IL-6 and TNF- α ; (b) significant rise in the level of Hb, TSAT and SF; (c) higher security with less adverse reactions.

Under normal conditions, inflammation is a protective and physiological response to various harmful stimuli. However, in several chronic debilitating disorders, such as CKD, inflammation becomes maladaptive, uncontrolled, and persistent. Systemic persistent inflammation has, for almost 20 years, been recognized as a major contributor to the uremic phenotype and a predictor of cardiovascular and total mortality.^[17] Kinetics of iron metabolism illustrate that inflammation and hepcidin can affect iron utilization. Meanwhile, inflammation and impaired renal clearance in CKD increase plasma hepcidin, which will inhibit duodenal iron absorption and sequestering iron in macrophages. These effects of hepcidin can cause systemic iron deficiency, decreased availability of iron for erythropoiesis, and resistance to endogenous and exogenous EPO.^[18] Importantly, inflammation may cause hyporesponsiveness to ESA, which is associated with poor prognosis in patients with renal anemia.^[19] Generally speaking, inflammation is more severe in dialysis patients than non-dialysis patients. Therefore, it is a crucial challenge to be settled urgently that how to reduce the level of inflammation and hepcidin for patients with renal anemia.

Patients with renal anemia who have an absolute or functional iron deficiency were all recommended to treat with

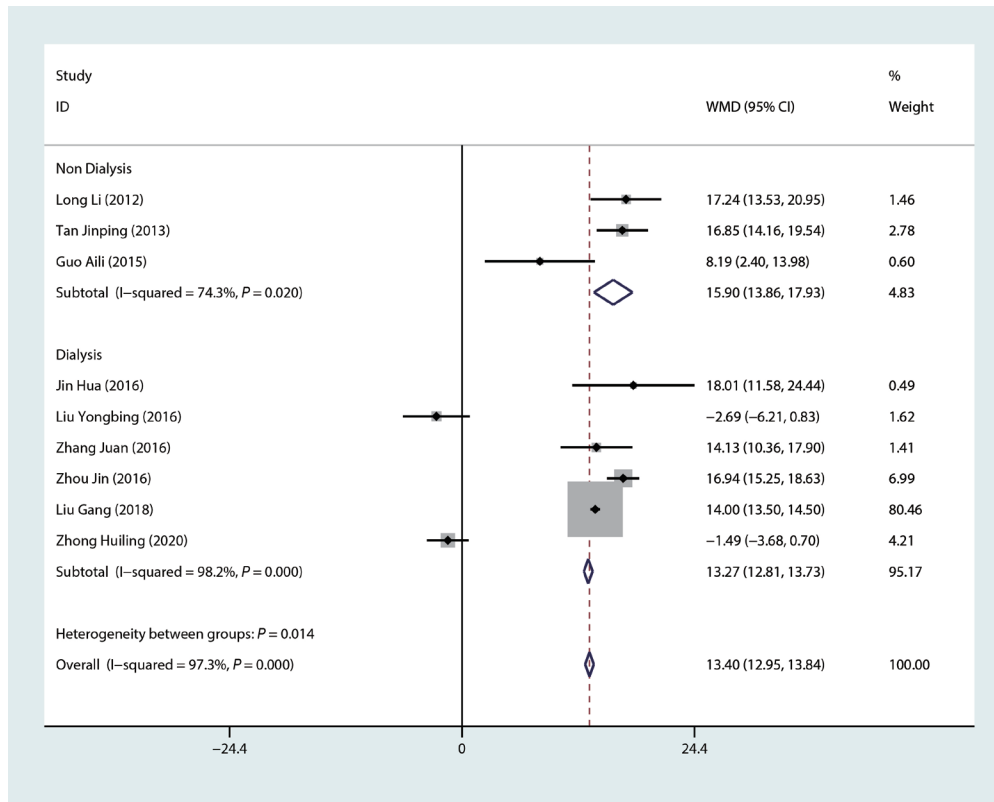


Figure 4: Forest plots of hemoglobin level for SXN group vs. oral iron group.

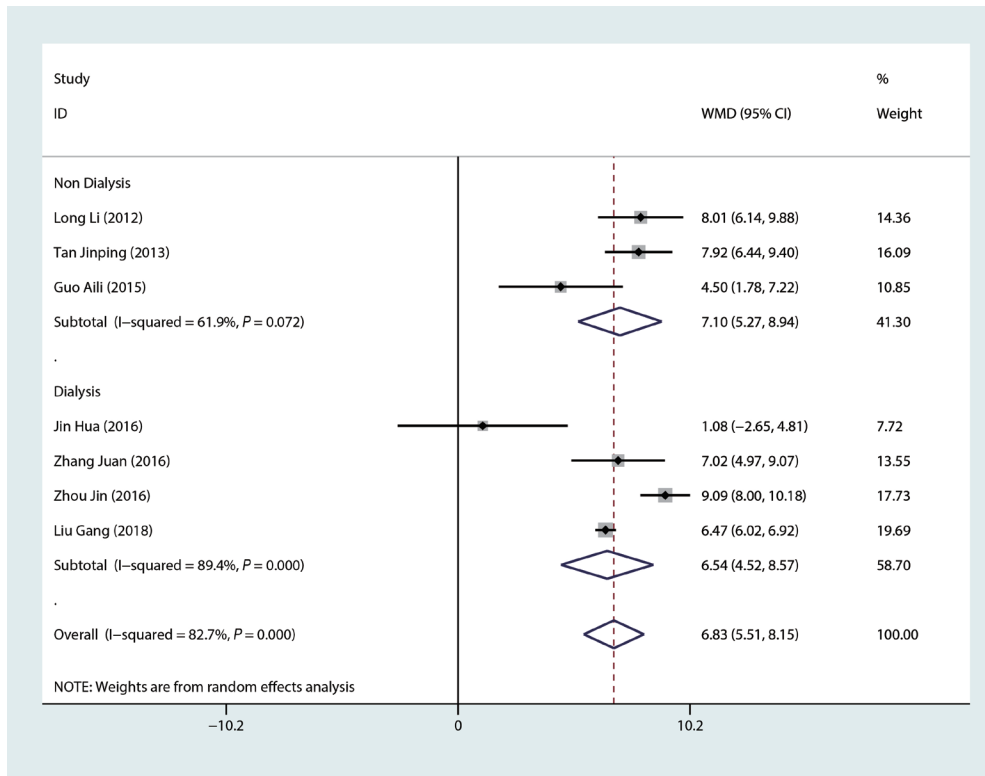


Figure 5: Forest plots of serum transferrin saturation level for SXN group vs. oral iron group.

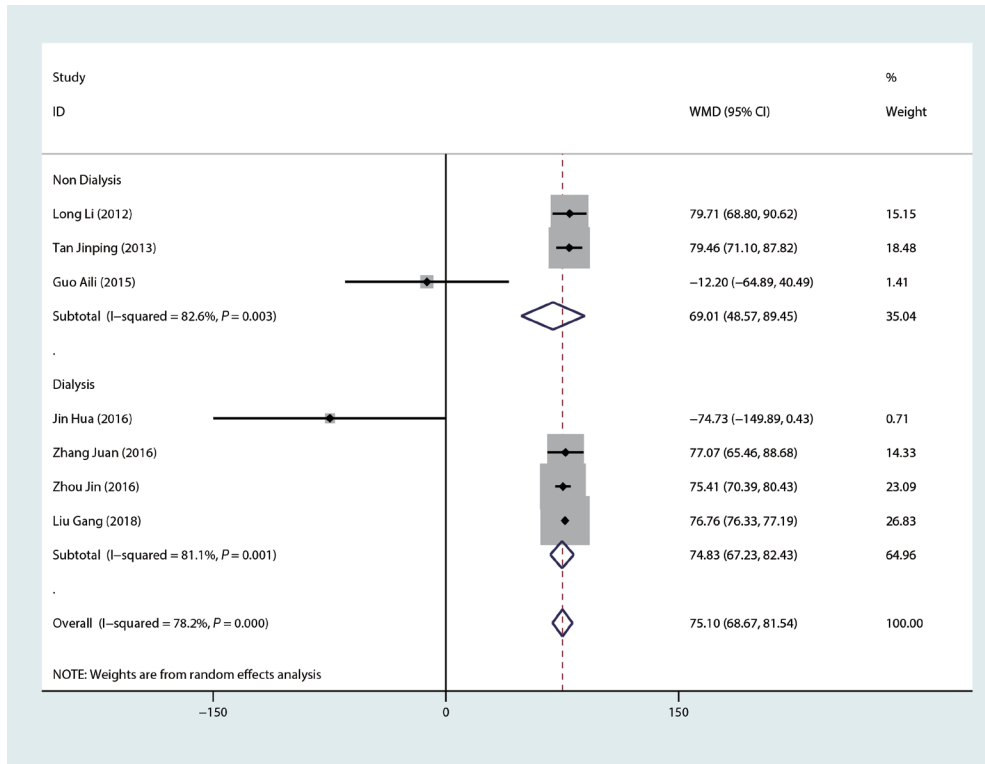


Figure 6: Forest plots of serum ferritin level for SXN group vs. oral iron group.

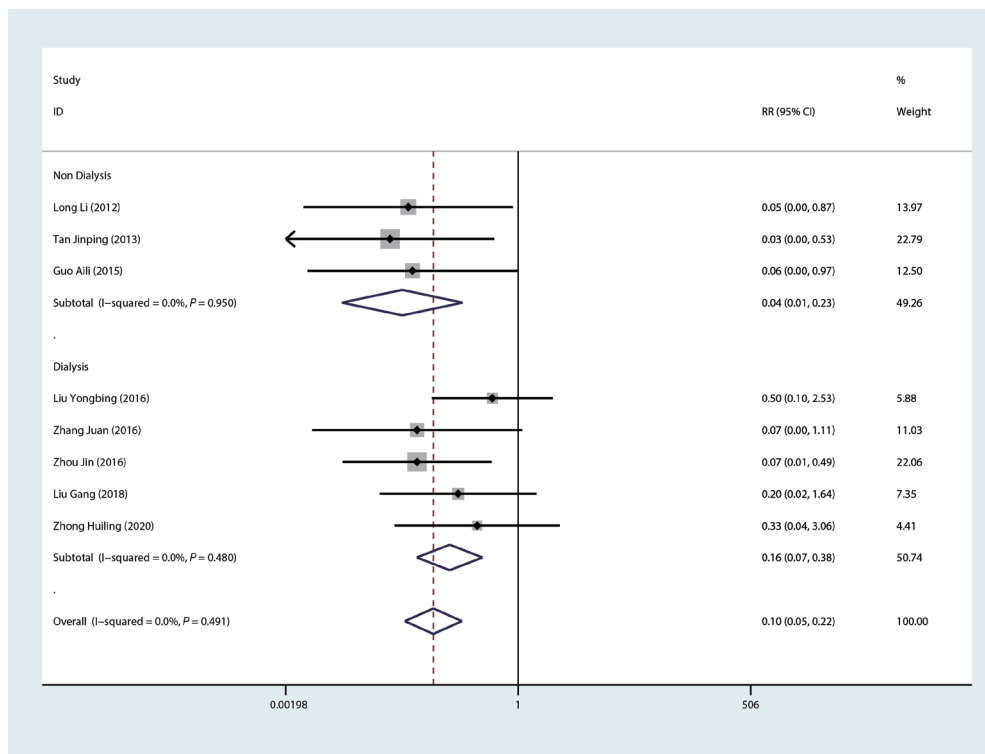


Figure 7: Forest plots of adverse reaction for SXN group vs. oral iron group.

iron supplementation.^[4] However, it may cause iron overload (serum ferritin ≥ 500 $\mu\text{g/L}$) for patients with functional iron deficiency. Serum ferritin is the main form of iron storage in the body, which can reflect the iron reserve. Furthermore, many studies have found elevated levels of hs-CRP in patients taking oral iron,^[8-10,12-16] which may indicate that oral iron supplementation has a risk of increasing inflammation. And oral iron is mainly absorbed in the duodenum and upper jejunum mucosa with an acid environment,^[20,21] which probably causes gastrointestinal reaction.

A study demonstrated that silkworm feces extract (SFE) treatment improved hematological parameters, decreased total iron-binding capacity, increased serum iron, transferrin saturation, liver iron and spleen iron of iron deficiency anemia rats. Western blot analysis showed that SFE can upregulate iron-regulatory protein (IRP) expression and downregulate ferritin expression in livers. Furthermore, SFE can inhibit hepcidin expression and increase ferroportin1 expression by blocking JAK2/STAT3, BMP6/SMAD, and HFE/TfR2 pathways. And, SFE also can attenuate hepcidin expression induced by IL-6 and BMP6 in HepG2 cells.^[22] The main component of SXN is SFE, which means SXN may improve anemia and iron metabolism disorder via reducing the level of inflammation and hepcidin. Furthermore, the animal experiment also showed that SXN had similar effects with EPO,^[23] which could obviously promote the proliferation of erythroid and granulocyte cells of bone marrow in normal mice and increase the proportion of peripheral blood reticulocyte. It has suggested that SXN can increase the synergistic effect with EPO and decrease the dosage of EPO, which were consistent with clinical findings from Guo AL^[10] and Jin H.^[11] We observed that the level of serum ferritin, which was closed to or already in the state of iron overload, had reduced after treated with SXN in the trail of Jin H,^[11] while other included trails^[8-10,12-16] had opposite results, so we consider that SXN can reduce the level of serum ferritin when iron overload and promote it when absolute iron deficiency.

Chemical analysis and structural verification showed that SXN belongs to a ferrous derivative, which was mainly composed of Fe chlorin p6, Fe chlorin e6, and Fe isochlorin e4.^[24] Chlorophyll contained in SXN has the same structure with human heme, so it can directly compound hemoglobin, which increases the bioavailability.^[25] The organic hematin chloride in SXN is similar to human hemaporphyrin, which can be immediately absorbed by the intestinal mucosal cells with less irritation.^[26] And a series of studies showed that SXN has the lowest incidence of adverse reactions compared with ferrous sulfate, ferrous fumarate, polysaccharide iron complex capsule, ferrous succinate, and ferrous gluconate.^[27-29]

Several limitations in our systematic review should be noted. First, a publication bias was inevitable because all included studies were from the same country. Second, the sample size was small, especially the number of non-dialysis patients was small. Third, the quality of included studies was poor, only three trails reported the specific randomized method and the others only mentioned “random”. All included trails were unblinded. Some secondary endpoints were not reported in several studies, this could potentially cause reporting bias. Forth, significant statistical heterogeneity existed, even though we have done subgroups analysis. The possible explanation for it may be correlated with small sample size and poor quality of included studies. Finally, EPO can effectively raise the level of hemoglobin, while only two trails recorded the dosage of EPO, so we were not able to verdict accurately whether the difference of increasing hemoglobin between the two groups was associated with different doses of EPO, which would increase the limitations of our results.

CONCLUSION

According to this systematic review, SXN is more effective and safer than oral iron supplementation in the treatment of renal anemia, especially in reducing the level of inflammation. In the future, high-quality, large sample size, and multicenter trials are necessary to confirm these findings, which must record the dosage of EPO and then evaluate the effect of SXN on EPO dosage systematically.

Author contributions and declarations

Zeng Q wrote the article as the first author and worked with Wang XH on the topic selection, literature selection, data extraction, and system analysis of the article. Yang LP was responsible for handling the different opinions between Zeng Q and Wang XH. Lang R and Liang Y polished the article and Yu RH has been coaching in this process as the correspondence author. This manuscript has been read and approved by all of the authors for publication.

Conflict of Interest

There is no conflict of interest existed in the submission of this manuscript.

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