Efficacy and safety of Danggui Buxue Decoction in combination with western medicine treatment of anemia for renal anemia: a systematic review and meta-analysis

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Background: To evaluate the efficacy and safety of Danggui Buxue Decoction for renal anemia when combined with western medicine treatment of anemia.

Methods: Electronic searching Medline, Embase, Web of Science, Cochrane Library, Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), WanFang data, Chinese Sci-tech periodical full-text database (VIP). Randomized controlled trials reported results of efficacy and safety of Danggui Buxue Decoction in combination with western medicine treatment of anemia for renal anemia. The "risk of bias assessment tool (Version 5.1.0)" of Cochrane Handbook was applied to assess the quality of included trials and RevMan 5.3 software was used for data analysis.

Results: A total of 111 studies was retrieved, seven studies including 460 cases were included, the methodological quality of included trials was poor. The result of meta-analysis demonstrated that there was no difference in hemoglobin (Hb) [weighted mean differences (WMD) =–8.75, 95% confidence interval (CI): (–18.64, 1.13), P=0.08], whereas the subgroup analysis showed the difference was significant when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1 [WMD =–16.27, 95% CI: (–28.73, –3.80), P=0.01], increase of Hb was more effective in experimental group than control group and the difference was not significant when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5≠1 [WMD =–0.57, 95% CI: (–4.52, 3.39), P=0.78]. There were significant differences in red blood cell (RBC) [WMD =–0.49, 95% CI: (–0.69, –0.28), P<0.00001], hematocrit (HCT) [WMD =–1.92, 95% CI: (–3.15, –0.69), P=0.002] and clinical efficacy [odd ratio (OR) =0.30, 95% CI: (0.13, 0.69), P=0.004] between Danggui Buxue Decoction combination group and control group, the experimental group was better than control group. There was no adverse event reported in the experimental group.

Conclusions: Danggui Buxue Decoction in combination with conventional western medicine (CWM) for renal anemia might be superior to CWM alone and there was no adverse event in the experimental group, it might be more effective when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1. However, the quality of included studies was not high, and less attention was paid to the safety, high quality randomized controlled trials are needed to further confirm the findings.

Keywords: Danggui Buxue Decoction; combine traditional Chinese and western medicine; renal anemia; systematic review; meta-analysis

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Introduction

Anemia in chronic kidney disease (CKD) is caused by reducing production of the erythropoietin (EPO) in the kidney and shortening the red cell survival (1). Anemia appears with the decline of renal function of CKD caused by multiple causes (2). Anemia could occur in the early CKD, and it's a very common phenomenon in the 5th stage of CKD. At present, iron supplements, EPO and blood transfusion therapy are applied to the treatment of CKD (3). Danggui Buxue Decoction, a widely used traditional Chinese medicine, was created by Dongyuan Li during the Jin dynasty, the ratio of Radix Astragali to Radix Angelicae Sinensis is 5:1 (4). Danggui Buxue Decoction was recommended as reinforcement "Qi" (energy) and blood tonic, used to treat anemia in clinic (5). The serious adverse reactions caused by EPO included pure red cell aplasia, hypertension, hyperglycemia, and so on (6), meanwhile, the cost is expensive; excess iron supplements could cause chronic iron overload.

Thus, we conducted this meta-analysis aiming to assess the efficacy and safety of Danggui Buxue Decoction for renal anemia when combined with western treatment of anemia.

Methods

Inclusion criteria

(I) Type of study: randomized controlled trial (RCT), application of blinding or not is available. (II) Patients: diagnosed with renal anemia, chronic renal failure meets the diagnostic criteria of *Clinical Practice Guidelines for Chronic Kidney Disease and Dialysis* (7) and *Minutes of the Symposium of Classification and Treatment of Primary Glomerular Disease and Diagnostic Criteria* (8). There are no limitations for the age, gender, and primary disease. (III) Intervention: experimental group: on the basis of Danggui Buxue Decoction (DBD), according to syndrome differentiation prescribes medication, meanwhile, in combination with conventional western medicine (CWM), Western medicine treatment of anemia meets the criteria of *Diagnosis and Treatment of Renal Anemia with Chinese Expert Consensus (Revision 2014)* (3) (including iron supplements, EPO and blood transfusion therapy), and can be combined with folic acid and vitamin B_{12} (9); control group: CWM only. Control the blood pressure and glucose, regulate fluid and electrolyte balance and conduct hemodialysis depending on the specific situation in the experimental group and the control group. The course of treatment is not less than 4 weeks. (IV) Outcomes: the primary outcome is hemoglobin (Hb) (g/L); the secondary outcome is red blood cell (RBC) (10^{12}/L), hematocrit (HCT) (%), clinical efficacy, creatinine (SCr, μmol/L), urea nitrogen (BUN, mmol/L), adverse events.

Exclusion criteria

Combined with other therapies, for example, enema, acupuncture, etc.

Search strategy

Two authors electronic searched Medline, Embase, Web of Science, Cochrane Library, Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), WanFang data, Chinese sci-tech periodical full-text database (VIP) by the method of combining subject headings with free-text terms from their inception through February 2016. The search terms used in this search were as follows: "Danggui Buxue", "renal anemia", "chronic renal failure accompanied by anemia". Take CBM for example, #1 Danggui Buxue, #2 anemia, #3 #1 and #2.

Document screening and quality assessment

According to inclusion criteria and exclusion criteria, two authors filtered documents independently, differences further confirmed by a third party. The individual quality of included studies was assessed based on the "risk of bias assessment tool (Version 5.1.0)" of Cochrane Handbook, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. RevMan 5.3 software was applied to perform risk of bias graph and risk of bias summary.

Data extraction

General information of the eligible studies including name of the first author, baseline, sample volume, gender, age, intervention, course of treatment, outcomes, adverse events.

Statistical analysis

RevMan 5.3 provided by the Cochrane Collaboration was

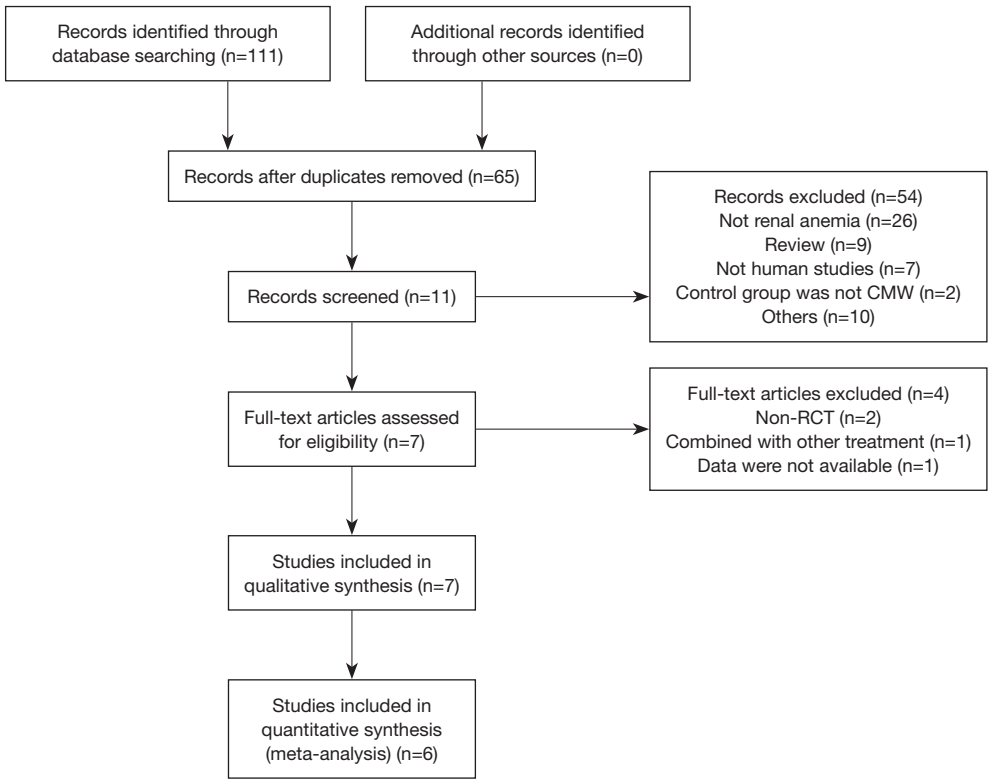

Figure 1 Flow diagram of searching for eligible studies.

used to perform the meta-analysis. Z-test analysis and I^2 test were applied to evaluate the overall heterogeneity of included studies in the meta-analysis. The estimated outcomes of included trials were calculated with the random effect model if $P<0.05$, $I^2>50\%$, otherwise the fixed effect model was used. The pooled odd ratio (OR) was calculated with 95% confidence interval (CI) for dichotomous data. The weighted mean differences (WMD) were calculated with 95% CI for continuous data. Subgroup analysis and sensitivity analysis were conducted to evaluate the robustness of results when heterogeneity was present.

Results

Search results

Medline (n=6), Embase (n=2), Web of Science (n=3), Cochrane Library (n=0), CBM (n=29), CNKI (n=32), WanFang data (n=28), VIP (n=11) were searched, a total of 111 studies were retrieved. According to inclusion criteria and exclusion criteria, seven studies were included in the final analysis. The process of selection of the eligible studies was illustrated in *Figure 1*.

Characteristics of included studies

A summary of the baseline characteristics of included studies was showed in *Table 1*. There were seven RCTs (N=460) in this systematic review. All RCTs were conducted in China and all studies published in Chinese. The duration of treatment ranged from four weeks to twelve weeks. Formula composition of included studies was presented in *Table 2*.

Risk of bias assessment

The overall quality of included studies was poor. The random number table was used for randomization in only one study (10), the remaining six trials simply mentioned "randomization", specific methods hadn't been reported. None of the studies mentioned the allocation concealment and blindness. There was neither any information about incomplete outcome data, selective reporting and other bias. The risk bias assessment of the methodological quality is shown in *Figures 2,3*.

Table 1 Characteristics of included studies

Studies	Baseline	N (T/C)	Gender (M/F)		Age (Y)		Intervention		Duration (weeks)	Outcomes	Adverse events
			T	C	T	C	T	C			
Wang, 2015 (10)	Comparable	30/30	15/15	16/14	61.2±2.4	61.3±2.4	DBD + CWM	CWM	6	a, b, c,	2 cases of cutaneous pruritus and 1 case of palpitation in the control group
Gao, 2014 (11)	Comparable	34/34	19/15	16/18	54	51	DBD + CWM	CWM	12	a, b, c, d	NA
Zhao, 2014 (12)	NA	20/20	NA	NA	NA	NA	DBD + CWM	CWM	8	a, c, d	NA
Xu, 2013 (13)	Comparable	40/40	25/15	23/17	42.15	41.35	DBD + CWM	CWM	4	d	NA
Li, 2013 (14)	Comparable	43/43	22/21	24/19	43.2	41.5	DBD + CWM	CWM	8	d	NA
Yang, 2013 (15)	Comparable	38/38	42/43		47.2±4.9		DBD + CWM	CWM	8	a, b, c	NA
Tong, 2003 (16)	NA	32/18	17/15	10/8	NA	NA	DBD + CWM	CWM	8	a, b, c, e, f	NA

Outcomes: a, Hb; b, RBC; c, HCT; d, clinical efficacy; e, SCr; f, BUN. T, treatment; C, control; M, male; F, female; age, average age; Y, year; CWM, conventional western medicine; DBD, Danggui Buxue Decoction; NA, not available.

Table 2 Formula composition of included studies

Studies	Formula composition
Wang, 2015 (10)	Radix Astragali (Huangqi) 30 g, Radix Angelicae Sinensis (Danggui) 6 g, Glabrous Greenbrier Rhizome (Tufuling) 30 g, Motherwort Herb (Yimucao) 30 g, Suberect Spatholobus Stem (Jixueteng) 30 g, Mulberry Fruit (Sangshen) 15 g, Fleeceflower Root (Heshouwu) 15 g, Rhubarb (Shengdahuang) 9 g
Gao, 2014 (11)	Radix Astragali (Huangqi) 10 g, Radix Angelicae Sinensis (Danggui) 10 g
Zhao, 2014 (12)	Radix Astragali (Huangqi) 30 g, Radix Angelicae Sinensis (Danggui) 6 g, Prepared Rehmannia Root (Shudihuang) 10 g, Tangshen (Dangshen) 10 g, White Atractylodes Rhizome (Baizhu) 10 g, Poria (Fuling) 10 g, Liquorice Root (Gancao) 6 g
Xu, 2013 (13)	Radix Astragali (Huangqi) 50 g, Radix Angelicae Sinensis (Danggui) 10 g, Sichuan Lovage Rhizome (Chuanxiong) 10 g, Ass Hide Glue (Ejiao) 10 g, Dried Tangerine Peel (Chenpi) 10 g, Suberect Spatholobus Stem (Jixueteng) 30 g
Li, 2013 (14)	Radix Astragali (Huangqi), Radix Angelicae Sinensis (Danggui), Epimedium Herb (Xianlingpi), Suberect Spatholobus Stem (Jixueteng), White Atractylodes Rhizome (Baizhu), Poria (Fuling), the ratio of Radix Astragali (Huangqi) to Radix Angelicae Sinensis (Danggui) was 5:1
Yang, 2013 (15)	Radix Astragali (Huangqi) 30 g, Radix Angelicae Sinensis (Danggui) 6 g, Tangshen (Dangsheng) 15 g, Poria (Fuling) 20 g, White Atractylodes Rhizome (Baizhu) 15 g, Common Yam Rhizome (Shanyao) 20 g, Lotus Seed (Lianzirou) 6 g, Hyacinth Bean (Baibiandou) 15 g, Coix Seed (Yiyiren) 20 g, Epimedium Herb (Yinyanghuo) 10 g, Ass Hide Glue (Ejiao) 10 g, Villous Amomum Fruit (Sharen) 6 g, Platycodon Root (Jiegeng) 6 g, Liquorice Root (Gancao) 6 g
Tong, 2003 (16)	Radix Astragali (Huangqi) 30 g, Radix Angelicae Sinensis (Danggui) 15 g, Debark Peony Root (Baishao) 15 g

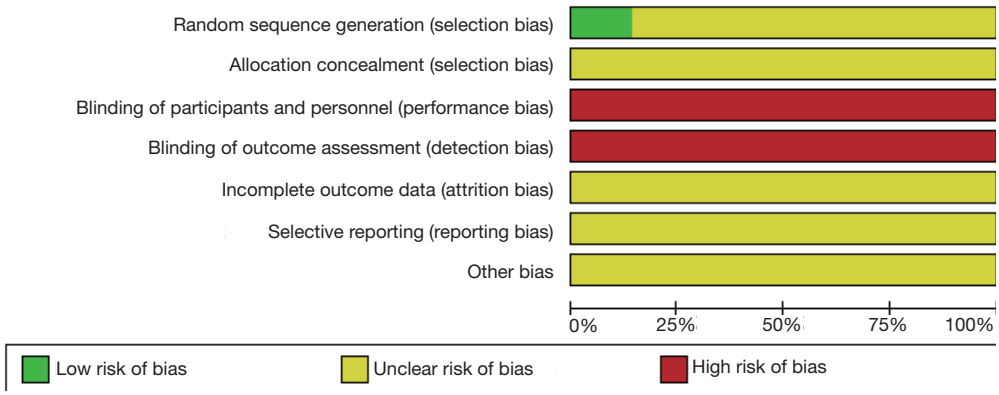

Figure 2 Risk of bias graph.

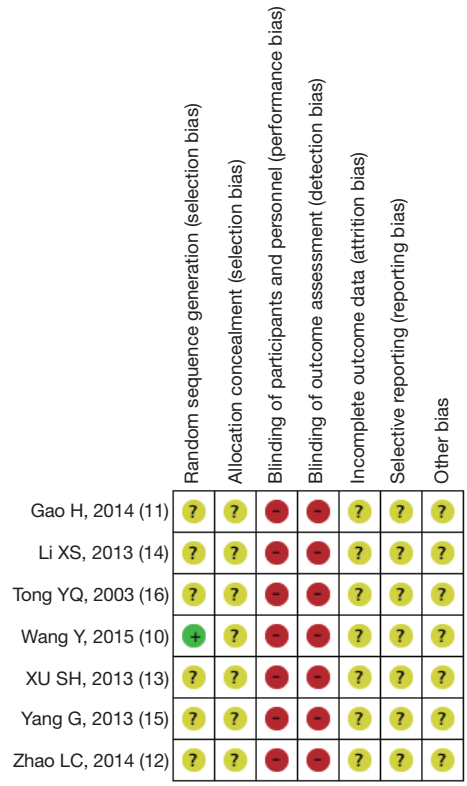

Figure 3 Risk of bias summary (10-16).

Result of meta-analysis

Six studies (10,11,13-16) included for meta-analysis, one study (12) included for descriptive analysis.

Hb

Four studies (10,11,15,16) included in this analysis provided the data of Hb. There was statistical heterogeneity (P<0.00001, I^2=95%), the random effect model was used for meta-analysis. There was no statistically significant difference in Hb between experimental group and control group [WMD =–8.75, 95% CI: (–18.64, 1.13), P=0.08], whereas the subgroup analysis showed the difference was significant when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1 [WMD =–16.27, 95% CI: (–28.73, –3.80), P=0.01], increase of Hb was more effective in the experimental group than the control group. The difference was not significant when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5≠1 [WMD =–0.57, 95% CI: (–4.52, 3.39), P=0.78] (*Figure 4*).

RBC

Four studies (10,11,15,16) reported data on the changes of RBC. These data were not found to be homogeneous (P<0.0001, I^2=87%), the random effect model was applied in this meta-analysis. As shown in *Figure 5*, Danggui Buxue Decoction combined with CWM had an advantage of increasing the RBC compared with control group [WMD =–0.49, 95% CI: (–0.69, –0.28), P<0.00001].

HCT

There were four studies (10,11,15,16) included in the meta-analysis on improvement of HCT. There was significant heterogeneity among data from the included studies (P<0.00001, I^2=93%). Sensitivity analysis were conducted to evaluate the robustness of the result, there was no statistically significant heterogeneity among three (10,11,16) studies (P=0.16, I^2=45%) except Yang (15), the fixed effect model was applied (*Figure 6*). Experimental

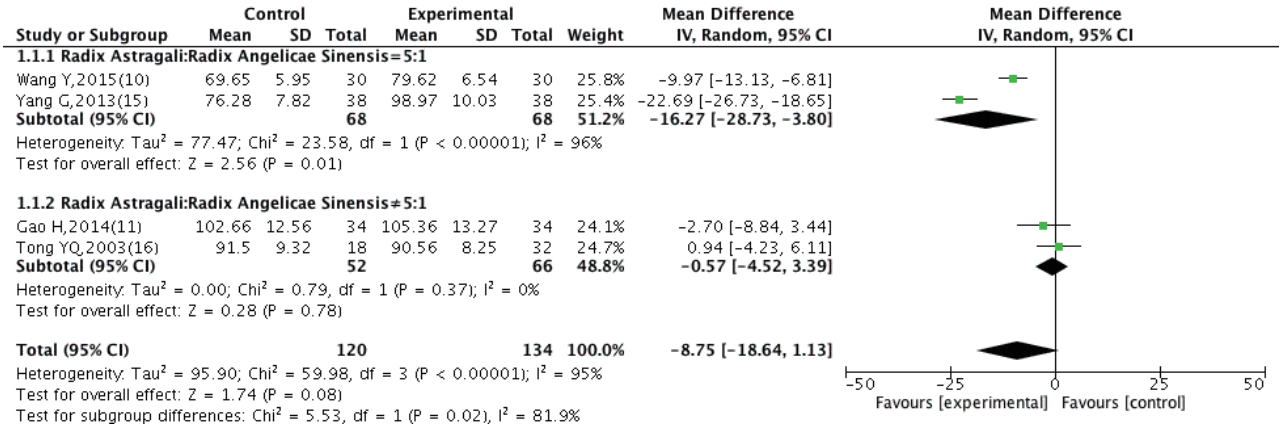

Figure 4 Subgroup analysis of Hb after treatment with DBD and CWM. Hb, hemoglobin; DBD, Danggui Buxue Decoction; CWM, conventional western medicine.

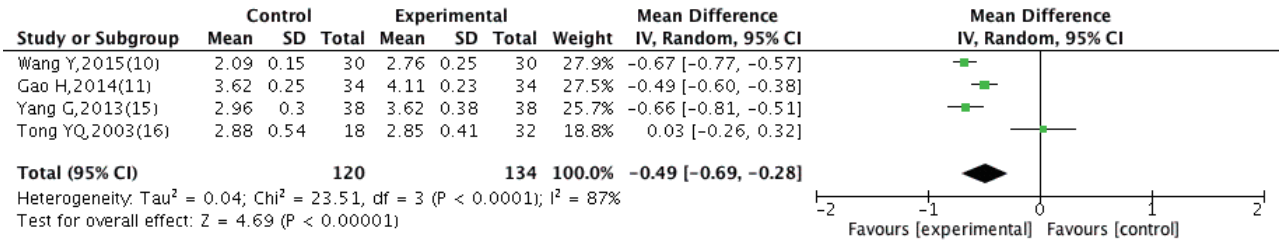

Figure 5 Forest plot comparison of RBC after treatment with DBD and CWM. RBC, red blood cell; DBD, Danggui Buxue Decoction; CWM, conventional western medicine.

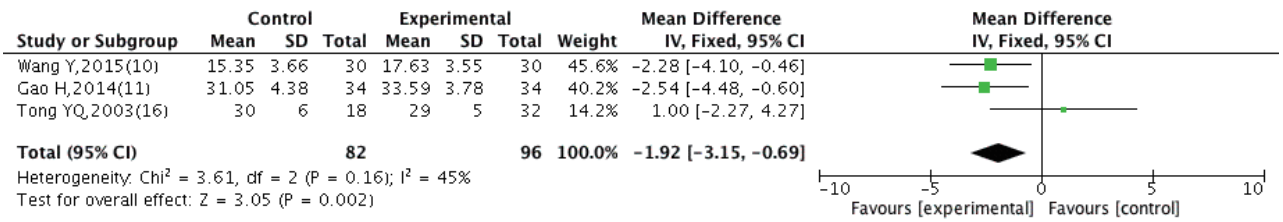

Figure 6 Forest plot sensitivity analysis of HCT after treatment with DBD and CWM. HCT, hematocrit; DBD, Danggui Buxue Decoction; CWM, conventional western medicine.

group exhibited significant improvement of HCT, compared with control group [WMD =–1.92, 95% CI: (–3.15, –0.69), P=0.002].

Clinical efficacy

Three studies (11,13,14) evaluated the clinical efficacy. There was no statistically significant heterogeneity among three studies (P=0.95, I^2=0%), justifying the fixed effect model. As illustrated in *Figure* 7, result of clinical efficacy of the experimental group was significantly better than the control group [OR =0.30, 95% CI: (0.13, 0.69), P=0.004].

Other analysis results

Only one study (16) reported the data of SCr and BUN, the result revealed that SCr and BUN decreased significantly in the experimental group compared with the control group.

Only one (12) of eligible studies reported outcomes with mean ± standard of difference value of the result before and after treatment. There was statistically significant difference between experimental group and control group (P<0.05), experimental group was more effective than control group in terms of increasing RBC, Hb and HCT.

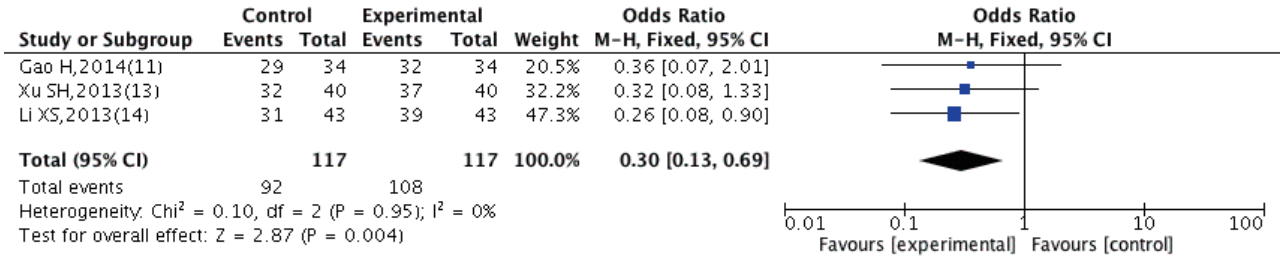

Figure 7 Forest plot comparison of clinical efficacy after treatment with DBD and CWM. DBD, Danggui Buxue Decoction; CWM, conventional western medicine.

Adverse events

There were no adverse events reported in the experimental group. One (10) of included studies mentioned two cases of cutaneous pruritus and one case of palpitation in the control group.

Discussion

Danggui Buxue Decoction could not only withstand significantly decreation of blood cells by immune-mediated, but also stimulate on the growth of bone marrow colony cell and increase the weight of hemopoietic progenitor of bone marrow (17). In animal experiments, the ability of Danggui Buxue Decoction was to promote hematopoiesis and proliferative actions on hematopoietic progenitor cells, researchers have reported constituents related to various Danggui Buxue Decoction activities (18). The improvement of modified Danggui Buxue Decoction on blood deficiency might be related to increase of the expression of EPO and granulocyte-macrophage gene and protein (19). One of positive regulators for Danggui Buxue Decoction is Radix Angelicae Sinensis-derived ferulic acid, which enhanced the solubilities of active ingredients derived from astragali radix, therefore increased the biological efficacies of Danggui Buxue Decoction (20). Radix Angelicae Sinensis significantly enhanced the recovery of platelets, other blood cells and their progenitor cells, as well as the formation of colony forming unit (21). Modern pharmacological experiments showed Danggui Buxue Decoction not only promoted hematopoietic function, also had a role in immune regulation and liver protection (22), and attenuated renal lesion (23). Astragaloside IV could attenuate the apoptosis of renal tubular epithelial cells induced by transforming growth factor-β1 (TGF-β1) (24). Radix Astragali and Radix Angelicae Sinensis alleviated renal fibrosis by inhibiting the expression of TGF-β1/connective tissue growth factor mRNA (25), astragaloside IV and ferulic acid also can alleviate renal tubulointerstitial fibrosis, associated with not only inhibition of tubular epithelial-mesenchymal transdifferentiation and fibroblast activation, but also an increase in NO production in the kidney (26).

Assessment of methodological quality

Selection bias can be prevented by randomization, experimental design should follow the randomization and select the correct method. Six of included studies mentioned "randomization", but did not report the specific methods, random number table was used in only one study (10).

Allocation concealment can also avoid selection bias, however, included studies didn't describe allocation concealment.

Performance bias and measurement bias might occur if the intervention and assignment known by participators. Seven studies didn't refer to blinding. In terms of appearance and taste, there were significant differences between traditional Chinese medicine decoction and western medicine, blinding is sometimes difficult to implement.

There was neither any information about selective reporting nor incomplete outcome reporting. Other bias could not be determined. There were high risks of selection and performance biases, therefore the overall quality of included studies was low.

Efficiency

The result of meta-analysis demonstrated that there was no difference in Hb [WMD =–8.75, 95% CI: (–18.64, 1.13), P=0.08], whereas the subgroup analysis showed the difference was significant when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1 [WMD =–16.27, 95%

CI: (–28.73, –3.80), P=0.01], increase of Hb was more effective in the experimental group than the control group. Compared with other ratios, higher contents of ferulic acid and Astragaloside IV in Danggui Buxue Decoction when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1 (27). One (11) of two studies (11,16) with the ratio of Radix Astragali to Radix Angelicae Sinensis was 5≠1 adjusted the dosage of EPO, the other study reduced the dosage of EPO when combined with Danggui Buxue Decoction. No matter what the ratio of Radix Astragali to Radix Angelicae Sinensis was, Danggui Buxue Decoction combined with CWM could attenuate renal lesion, it might be more effective when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1. Traditional Chinese medicine can instead of EPO partially, reduced the dosage of EPO (28). Combination of Danggui Buxue Decoction and CWM was more effective in improving the symptoms and RBC, HCT. Danggui Buxue Decoction also has a role in kidney protection.

Due to poor methodological quality, the beneficial effect and safety of Danggui Buxue Decoction combined with CWM needed to be confirmed further.

Safety

Only one study (10) of included studies reported adverse events in the control group, the safety of Danggui Buxue Decoction combined with CWM was supposed to be high, whereas, the result was limited by low-quality studies.

Limitations

Several limitations were existed in this meta-analysis. Firstly, only five (10,11,13-15) of the seven studies mentioned the comparable baselines. Secondly, only seven studies were included and the sample sizes were small, the power of test might be influenced. Thirdly, the sample sizes of included studies was inconsistent, increasing the risk of heterogeneity. Fourthly, we included articles published in English or Chinese only, this might have increased the selection bias.

Conclusions

Danggui Buxue Decoction in combination with CWM for renal anemia might be superior to CWM alone. It might be more effective when the ratio of Radix Astragali to Radix Angelicae Sinensis was 5:1 and there was no adverse event in the experimental group. Future clinical trials on evaluating the efficacy and safety of Danggui Buxue Decoction should be designed more rigorously.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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