

Review Article

Meta-analysis of Huangqi injection for the adjunctive therapy of aplastic anemia

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Received April 25, 2015; Accepted July 6, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: Aplastic anemia therapy remains difficult, due to lack of effective treatment regimens. In recent years, Huangqi injection for the adjunctive therapy of aplastic anemia has been reported in many clinical trials. Considering that Huangqi injection may be a novel approach to aplastic anemia treatment, we conducted a meta-analysis of clinical controlled trials to assess the clinical value of Huangqi injection in the treatment of aplastic anemia. We searched the Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-text Database (VIP), Wanfang Database, PubMed and EMBASE database to collect the data about the trials of Huangqi injection combined with androgens for treating aplastic anemia. A total of ten studies involving 720 patients with aplastic anemia were included in this study. The meta-analysis showed significant increases in the pool effectiveness rate, white blood cells (WBC), haematoglobin (Hb), platelets (PLT), and reticulocytes (Ret) between the experimental group versus the control group. No severe side effects were found in this study. However, the lower Jadad scores and asymmetric funnel plot degrades the validity of the meta-analysis as the clinical evidence. Therefore, Huangqi injection may significantly enhance the efficacy of androgens for aplastic anemia, suggesting that the novel approach of Chinese traditional medicine combined with Western medicine is promising. The exact outcome required confirmation with rigorously well-designed multi-center trials.

Keywords: Meta-analysis, huangqi injection, therapy, aplastic anemia, Chinese herbs

Introduction

Aplastic anemia refers to inability of the stem cells to generate the mature blood cells. This causes a deficiency of all three blood cell types: red blood cells (RBC), white blood cells (WBC), and platelets (PLT). Congenital aplastic anaemia is very rare and most of the cases of aplastic anaemia belong to acquired aplastic anaemia. The incidence of acquired aplastic anaemia in Europe and North America is around 2 per million population per year [1, 2]. The incidence is 2-3 times higher in East Asia. There is no significant difference in incidence between males and females [3]. Aplastic anaemia can be due to congenital (20%) or acquired causes (80%). Aplastic anemia can be caused by exposure to chemicals, radiation, infection, drugs, immune disease, and heredity; in some cases, the cause is unknown [4].

For a long term, aplastic anemia therapy has perplexed clinicians due to uncertain efficacy with the present regimen. In recent years, it is reported that Huangqi injection for the adjunctive treatment of aplastic anemia has been valuable in some clinical trials in China, suggesting that the traditional Chinese patent drug may be a novel approach to aplastic anemia treatment. Since that aplastic anemia is a rare disease, there need a meta-analysis to assess the clinical value of Huangqi injection in the therapy of aplastic anemia. Therefore, we conducted the following study aiming to the published clinical controlled trials.

Methods

Eligibility criteria

The included literatures were the clinical controlled studies. The experimental group used

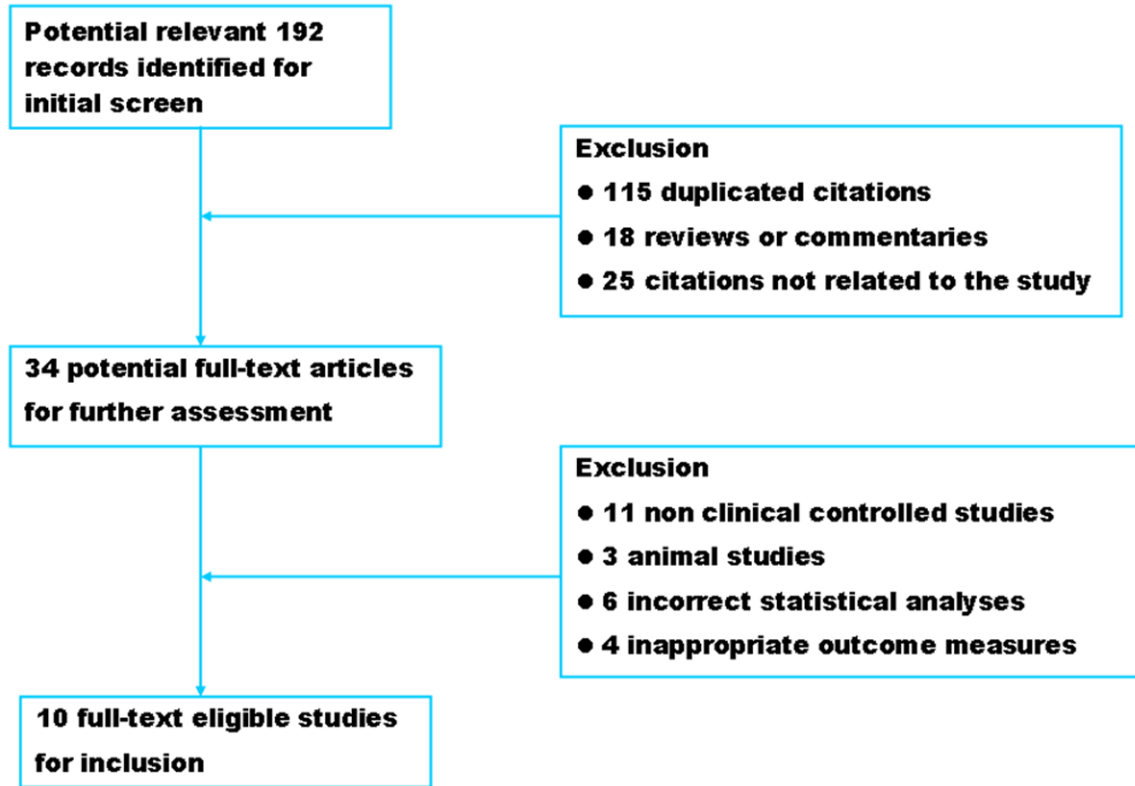


Figure 1. The flow diagram of literature retrieve in this study.

Table 1. Characteristics of the randomized controlled trials included in this study

Author [reference]	Published year	Cases T/C	Age (years) Range, mean	Sex Male/female	Treatment Time
Wang YM [7]	1999	36/30	E: 15-72, 37 C: NR	E: 15/21 C: NR	4 months
Gong GH [8]	2000	15/15	14-45, 22	E: 9/6 C: 9/6	3 months
Tao LJ [9]	2001	22/26	E: 13-63, 32 C: 14-60, 31	E: 14/8 C: 16/10	1-2 months
Wang JR [10]	2002	72/48	11-67, 28	NR	50 days
Yin ZD [11]	2004	36/30	E: 15-72, 37	E: 15/21	2 months
Li ZL [12]	2004	61/53	E: 3-63, 26 C: 7-60, 23	E: 35/26 C: 28/25	NR
Wang MS [13]	2007	30/30	E: 15-63, 36 C: 15-60, 34	E: 17/13 C: 16/14	4 months
Cai GL [14]	2010	40/40	E: 14-69, 34 C: 16-70, 34	E: 21/19 C: 20/20	3 months
Jia XH [15]	2012	31/31	E: 16-76, 38 C: 17-74, 37	E: 15/16 C: 17/14	2 months
Huang J [16]	2012	34/34	E: 16-64, 36 C: 16-63, 34	E: 18/16 C: 17/17	2 months

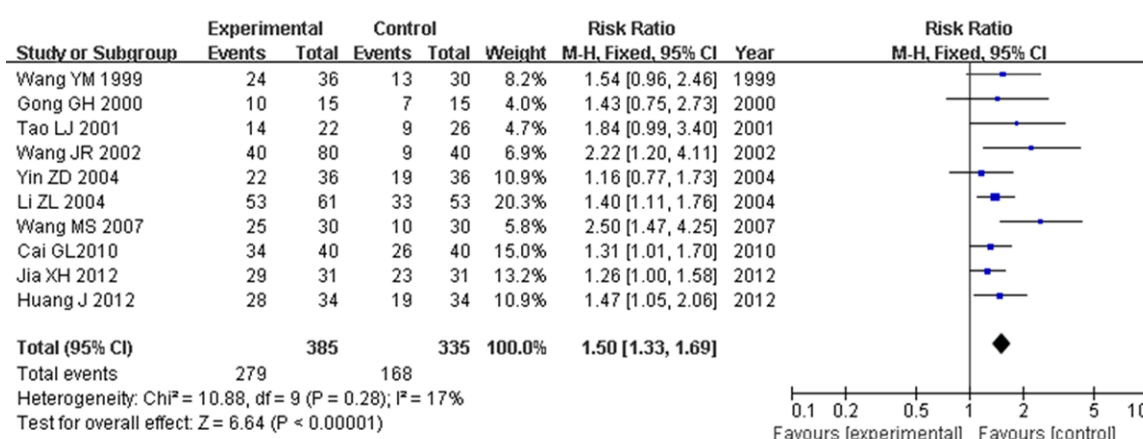
E: experimental group, C: control group. NR: not reported. Intervention measures in the experimental group: Huangqi injection + androgens (stanozolol or testosterone undecanoate); intervention measures in the experimental group: androgens (stanozolol or testosterone undecanoate).

Huangqi injection and the control used androgens treatment. The subjects were diagnosed

as definite aplastic anemia by clinicians. The preferred reporting items for systematic review

Table 2. Quality of reports of the included trials using the Jadad assessment scale

Author [reference]	Random ization	Randomization methodology description	Double- blinding	Withdrawals/ dropouts	Allocation concealment	Scores
Wang YM [7]	Yes	Yes	No	No	No	2
Gong GH [8]	Yes	No	No	No	No	1
Tao LJ [9]	Yes	No	No	No	No	1
Wang JR [10]	Yes	Yes	No	No	No	2
Yin ZD [11]	Yes	Yes	No	No	No	2
Li ZL [12]	Yes	No	No	No	No	2
Wang MS [13]	Yes	No	No	No	No	1
Cai GL [14]	Yes	No	No	No	No	1
Jia XH [15]	Yes	No	No	No	No	1
Huang J [16]	Yes	No	No	No	No	1


Figure 2. The overall effectiveness of Huangqi injection for the adjunctive therapy of aplastic anemia.

and meta-analyses (PRISMA) statements [5, 6] were followed in this present meta-analysis. And the population, intervention, comparison, outcomes and study design (PICOS) format was adopted to perform the analysis. The outcome measure mainly includes effectiveness rate, side effect, WBC, hemoglobin (Hb), PLT, and reticulocytes (Ret). Prior to the treatment, the baseline in peripheral WBC was comparable between the experimental group and the control group ($P > 0.05$). In this study, we hadn't set any restrictions on gender, race, and literature language.

Exclusion criteria

Reviews or commentaries, non-clinical studies, duplicated literatures, case observations, and non-controlled trials literatures were excluded in this study.

Research strategy and information sources

Anaemia, anaemic, aplastic anemia, pancytopenia, anemia, leukopenia, thrombocytopenia, astragalus, Huangqi, huang qi, astragali, astragalus miltiorrhiza, and Chinese traditional medicine herb were selected as the search terms. The Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Full-text Database (VIP), PubMed and EMBASE database were searched by computer. Data extraction and quality assessment was independently performed by two researchers [ZCT and TJ] and any discrepancies were resolved by consensus or in consultation with a third reviewer [HC]. The lack of information was supplemented by contact with the authors in charge of the clinical trials.

Meta-analysis of Huangqi injection for aplastic anemia

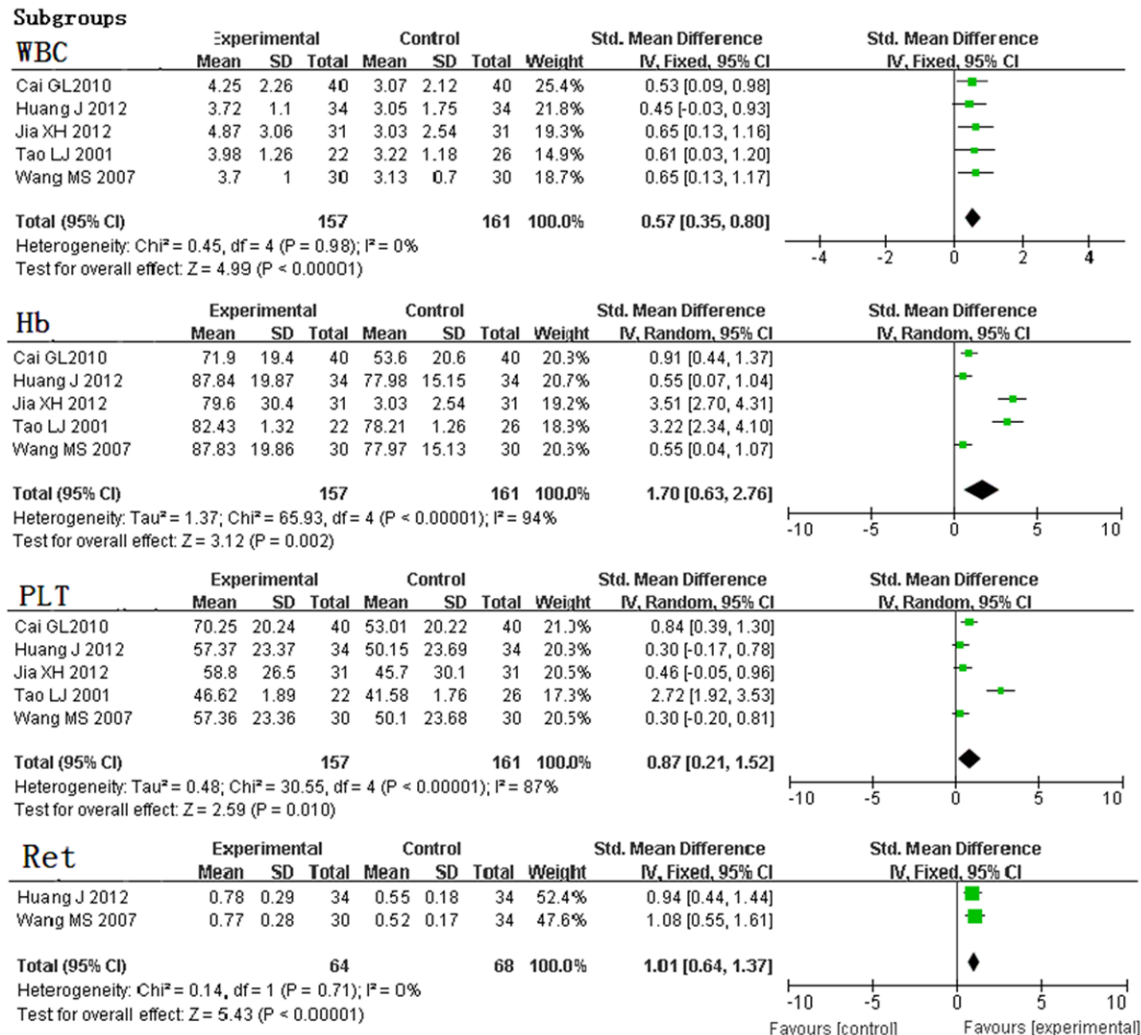


Figure 3. The effect of Huangqi injection on white blood cells, haematoglobin, platelets and reticulocytes.

Statistical analysis

Data synthesis was performed by Cochrane RevMan 5.2. Categorical variables were compared using relative risk (RR), and continuous variables using standard mean difference (SMD). 95% confidence interval (CI) was calculated and Chi-square test was used for the heterogeneity of inclusion trials. Assessments of heterogeneity determined to adopt a random effects model or a fixed effects model. A funnel plot was used for the assessment of reporting biases.

Results

Characteristics of included studies

Ten articles [7-16] involving 720 subjects (the experimental group: 385 cases; the control

group: 335 cases) were included in this study. Database retrieval process is shown in **Figure 1**. The general characteristics, interventions, treatments and outcomes were seen in **Table 1**.

The quality assessment

The Jadad scale was scored by randomization, randomization methodology, double-blinding, withdrawals/dropouts, and allocation concealment [17-19]. The Jadad scores ranged from 1 to 2 (**Table 2**), suggesting that the overall quality of the literatures were lower.

Meta-analyses of the effectiveness of androgens combined with Huangqi injection compared with androgens alone

There was no heterogeneity in ten studies [7-16] that evaluated the effectiveness rate. So

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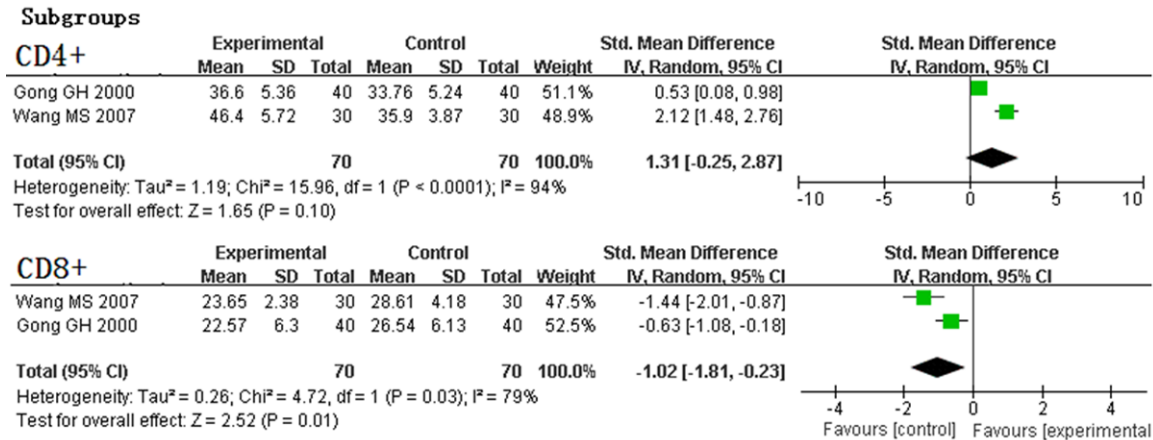


Figure 4. The effect of Huangqi injection on CD4+ and CD8+ lymphocyte cell.

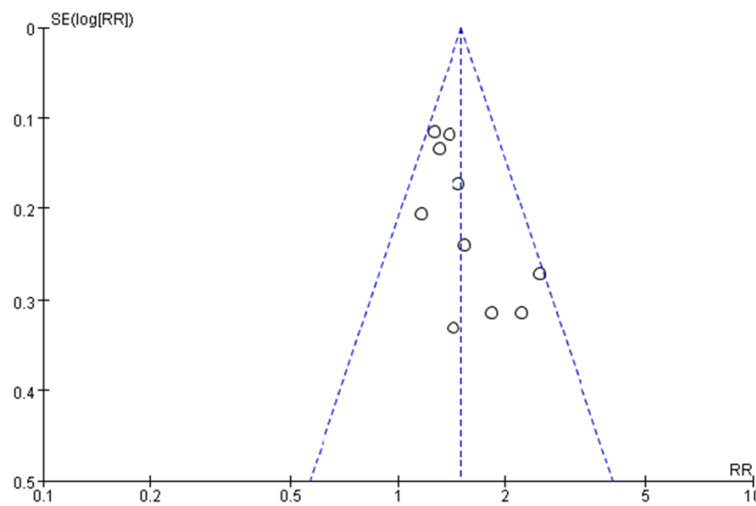


Figure 5. The funnel plots based on the data of the overall effectiveness.

a fixed effects model was adopted. According to meta-analysis result, the pool effectiveness rate in the experimental group was higher than that in the control group [RR = 1.50, 95% CI (1.33, 1.69), $P < 0.05$] (**Figure 2**).

Subgroup analyses of the effect of the adjunctive therapy with Huangqi injection on WBC, Hb, PLT and Ret

Five studies [9, 13-16] including 318 subjects reported the indices of WBC, Hb, and PLT (**Figure 3**). The pool Standard Mean Difference (SMD, fixed, 95% CI) in WBC was 0.57 [0.35-0.80, fixed model] (**Figure 3**), and the (SMD, random, 95% CI) in Hb and PLT were 1.70 [0.63,

2.76] and 0.87 [0.21, 1.52], respectively. Two studies [13, 15] including 132 subjects reported the Ret measure outcomes and the (SMD, fixed, 95% CI) was 1.01 [0.64, 1.37] (**Figure 3**). The indices of WBC, Hb, PLT, and Ret in the treatment group were significantly higher than that in the control group ($P < 0.05$).

Subgroup analyses of CD4+ and CD8+T lymphocyte cell

Two studies [8, 13] including 140 subjects reported the T lymphocyte cell measure outcomes. According to the subgroup analyses, the (SMD, random, 95% CI) in CD4+, CD8+ were 1.31 [-0.25, 2.87; $P > 0.05$] and -1.02 [-1.81, -0.23; $P < 0.05$], respectively (**Figure 4**).

Adverse effects

In this study, six literatures [7, 9, 12, 13, 15, 16] reported side effects, of which only one study observed a case of moderate allergic response during Huangqi injection drip. No severe side effects were reported in this study.

Publication bias

The funnel plot drawn by Cochrane Revman 5.2 was asymmetric (**Figure 5**), suggesting that the publication biases may occur in this study.

Discussion

Aplastic anemia therapy has perplexed clinicians, due to lack of available approaches. Allogeneic bone marrow transplantation (BMT) from a human leucocyte antigen (HLA)-identical sibling donor is the initial treatment of choice for newly diagnosed patients if they have severe or very severe aplastic anaemia, are less than 40 years old and find an HLA-compatible sibling donor [20]. BMT can achieve more long-term survival, but the majority of patients can not find the compatible donor. Some immunosuppressive drugs such as antithymocyte globulin, cyclosporine, and growth factors (G-CSF and GM-CSF) can improve the relief of aplastic anemia. However, these drugs were expensive and had stronger side effect, which limited their clinical application.

In Recent years, Huangqi injection (a Chinese patent drug) combined with androgens for the treatment of aplastic anemia has been reported in many clinical trials in China. Huangqi injection is from the extract of *Radix Astragali Mongolici* root. The preparation procedure is briefly described as following [21]. *Radix Astragali Mongolici* root has been boiled using water for three times, each time for 1 h, and filtrates the mixed decoction liquid, and then the filtration was concentrate at 1:2. It was treated with ethanol for 40 h. After filtrating, the liquid was concentrated at 1:6 and then added alcohol for 40 h again. After another filtration, the filtrate was concentrated at 1:5. Added injection water to the full amount, after discoloring, boiling and filtration, the filtrate was added into benzyl alcohol and then the sterilization was conducted.

In fact, *Radix Astragali Mongolici* pure herb has been used in traditional Chinese medicine for centuries. Its main use has been to enhance the body's immune system. But it has also been used to treat many diseases, including cardiovascular disease, liver disease, kidney disease, autoimmune diseases, etc [22-25]. The animal experiments revealed that Huangqi injection can increase the expression level of anti-apoptosis protein (B-cell lymphoma-extra large molecule protein) and then reduce the apoptosis of nucleated cells in bone marrow and promote hematopoiesis [26]. Modern pharmacological studies have demonstrated that astragalus fla-

vonoids, one of the effective components of Huangqi injection, can regulate the body immunity and upgrade the level of granulocyte colony-stimulating factor so as to promote stem cell proliferation [27-30]. Recent more one decade, Huangqi injection has been also used to treat chronic heart failure [31, 32], hepatitis [33, 34], cirrhosis [35], chronic nephritis [36], and diabetic nephropathy [37] in China.

According to this meta-analysis, the overall effectiveness of Huangqi injection in the experimental group was significantly higher than that in the control group (RR = 1.50, 95% CI: 1.33-1.69). It implied that Huangqi injection can raise the overall effectiveness rate by 50% (95% CI: 30%-69%), which had great significance for the therapy of aplastic anemia. In this meta-analysis, five studies including 318 subjects reported the indices of WBC, Hb, and PLT. The pool SMD with 95% CI in WBC, Hb and PLT was 0.57 [0.35-0.80], 1.70 [0.63, 2.76] and 0.87 [0.21, 1.52], respectively. Two studies including 132 subjects reported the Ret measure outcomes and the pool SMD with 95% CI was 1.01 [0.64, 1.37]. Subgroup analyses revealed that the indices of WBC, Hb, PLT, and Ret in the treatment group were significantly higher than that in the control group, demonstrating that the Western drug combined with Huangqi injection can increase peripheral blood cells and improve haematogenesis compared with androgens alone. Besides, two studies including 140 subjects reported the T lymphocyte cell measure outcomes. According to the subgroup analyses, the pool SMD with 95% CI in CD8+T lymphocyte cell was -1.02 [-1.81, -0.23], suggesting that Huangqi injection may exert some effect on T lymphocyte subgroups and then regulate the body immunity. In this study, six studies reported that no severe side effects were found, suggesting that Huangqi injection is rather safe. However, other studies rarely reported moderate side effects such as dizziness, and facial flushing and mild nausea [38-40]. After treatment or slowing down of the intravenous drip, the patients recovered. There weren't severe side effects reported according to our retrieve. Therefore, we believe that Huangqi injection may have potential clinical value in the adjunctive therapy of aplastic anemia, suggesting that the novel approach has potential clinical value.

However, there were two major limitations in this meta-analysis. One limitation is that, the overall quality of the included studies was low according to Jadad score, indicating that the methodological design in these literatures may be problematic. Another limitation is that, the asymmetric funnel plot implies that publication biases may occur in this study. Presently, the clinical trials in the traditional Chinese medicine field often have some weaknesses in methodological design such as absence of sample size estimation, failure in use (or reporting) randomization as well as unclear study objective and hypothesis are common [41-44]. Undoubtedly, these weaknesses would degrade the validity of evidence-based medicine of this meta-analysis. Therefore, it is significant to perform a rigorously well-designed, large sample study assessing Huangqi injection for aplastic anemia. We proposed that the clinical trials about Chinese traditional medicine should abide CONSORT protocol [45, 46] in the future. It would significantly promote the quality and validity of the study.

Conclusions

Huangqi injection may have potential clinical value in the adjunctive therapy of aplastic anemia, Huangqi injection may significantly enhance the efficacy of androgens for aplastic anemia, suggesting that the novel approach of Chinese traditional medicine combined with Western medicine is promising. The exact outcome required confirmation with rigorously well-designed multi-center trials.

Disclosure of conflict of interest

None.

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