Meta-analysis of Clinical Efficacy of Traditional Chinese Medicine in the Treatment of Aplastic Anemia

Le-Min Xia, Le-Le Cui, Yi-Ling Jiang, Zheng Qin, Mei-Hong Luo
Department of Hematology, Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (Baoshan Branch of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine), Shanghai, China

Abstract

Background: The “Diagnosis and Treatment Guidelines for Chinese Medicine Internal Common Diseases” issued by the Chinese Institute of traditional Chinese medicine (TCM) offers many methods for the treatment of aplastic anemia (AA). However, there is a lack of corresponding evidence. Objective: The study aimed to evaluate the clinical efficacy of TCM in the treatment of AA, and provide evidence for the development of guidelines for the diagnosis and treatment of AA using TCM. Methods: Data of randomized or semi-randomized control trials of AA treatments with TCM were retrieved, and the selected literature was scored using the Jadad scale. The data were extracted, and RevMan 5.2.6 software was used for the meta-analysis. Results: Two studies on the treatment of AA using Liuwei Dihuang pills combined with compound Zaofan pill were included. The results of the meta-analysis showed that there were no statistically significant differences in the efficacy between Liuwei Dihuang pills combined with compound Zaofan pill and androgen in the treatment of AA ($P = 0.65$). However, there were less adverse reactions, including liver damage and the hirsutism of women, with the former than the latter ($P < 0.05$). Other studies on the treatment of AA with TCM did not include reports from clinical trials. Conclusion: TCM had a certain curative effect when used to treat AA. However, the quality of the literature is generally low, and the sample size is small, which makes the validation of the results poor. Further high-quality studies are needed to provide high-level evidence.

Keywords: Aplastic anemia, meta-analysis, traditional Chinese medicine

INTRODUCTION

Aplastic anemia (AA) is a failure of hematopoiesis in the bone marrow induced by chemical, physical, biological, or unknown causes. Immune dysfunction plays the main role in the pathogenesis of the disease. Clinical treatment of AA includes androgens and immunosuppression. However, the desired therapeutic effect is often not achieved. Treatment with Chinese medicine using conventional therapies, including Liuwei Dihuang pill, Jinkui Shenqi pill, Zuogui Yin, and Yougui Yin have achieved a certain effect.

There are many methods for the treatment of AA offered by the “diagnosis and treatment guidelines for Chinese medicine internal common diseases” issued by the Chinese Institute of traditional Chinese medicine (TCM). However, there is a lack of corresponding evidence. With the increasing demand for the evaluation of the curative effect of TCM on AA, providing evidence of them has become urgent. This meta-analysis evaluates the clinical curative effect of TCM and refers to approaches dealing with evidence-based diagnosis and treatment guidelines of TCM as proposed by Wang et al.[2] These provide corresponding evidence for the diagnosis of and treatment guidelines for the treatment of AA using TCM.

METHODS

Search strategy

The scope of the search included the following databases: Chinese biomedical literature database, VIP database, etc.

Address for correspondence: Prof. Mei-Hong Luo, Department of Hematology, Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (Baoshan Branch of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine), Shanghai 201999, China. E-mail: lmh021009@163.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2018 World Journal of Traditional Chinese Medicine | Published by Wolters Kluwer - Medknow

Received: 30-10-2016, Accepted: 25-02-2017

Data extraction and analysis

Two reviewers independently selected the trials and extracted the data according to the predefined inclusion criteria. Differences were resolved by a discussion. The consistency of the results was calculated by two reviewers using the Kappa value and checked by the third reviewer.

Statistical analysis

Meta-analysis was performed using RevMan 5.2 (Copenhagen, Denmark) software provided by the Cochrane collaboration network. A heterogeneity test was carried out in the study group and \( P < 0.01 \) was used as the test level. When the study was not statistically different, the fixed effect model was used; otherwise, the random-effects model was used for combination analysis. A forest map was drawn, an evaluation of the funnel plots of publication bias was carried out, and the odds ratios (ORs) and 95% confidence interval (CI) were calculated. A descriptive analysis was used when the study was not sufficiently similar.

Results

Search results

According to the search strategy and data collection methods, 66 studies were searched, among which 21 studies were on the Liuwei Dihuang pill, 3 were about the Jinkui Shenqi pill, 2 about Zuogui Yin, 9 about Yougui Yin, 2 about the Sijunzi decoction, 2 about the Huanglian Ejiao decoction, 1 about the Qingying decoction, 26 about the Xijiao Dihuang decoction, and there were no studies about Dihuang Yinzi, the spot dragon pill, Dabu Yuanjian, and ten ash powder. Based on a further reading of the full text, 2 clinical trials on the Liuwei Dihuang pill combined with compound Zaofan pill in the treatment of AA were ultimately included [Table 1 and Figure 1].

Quality evaluation and analysis of the studies

The scores (Jadad scale) of two studies included\(^5,6\) were 0, which was an indication of low quality. The results of the heterogeneity test showed that there was no significant heterogeneity between them (\( P = 0.32, I^2 = 1\% \)), and the fixed-effect model was used to merge them, as shown in Figure 2. The overall efficacy showed no statistical significance after the merge (\( Z = 0.45; P = 0.65 \)), indicating that there was no statistically significant difference in the total efficacy.
between the Liuwei Dihuang pill combined with compound Zaofan pill and androgen alone for the treatment of AA. Since the two included studies were non-randomized small samples, the studies were recommended as Grade D.

The comparison of liver damage is shown in Figure 3. The results of the heterogeneity test show that there was no significant heterogeneity between them ($P = 0.91, I^2 = 0\%$) and the fixed-effect model was used to merge them. The overall effect test was statistically significant after the merge ($Z = 2.87, P = 0.004$), and the difference was statistically significant. An OR of 0.05 and 95% CI of (0.01, 0.38) suggested that the liver damage from the Liuwei Dihuang pill combined with compound Zaofan pill for the treatment of AA was 0.05 times that of androgen. Diarrhea and other digestive tract side effects were different between the two treatments. As shown in Figure 4, the results of the heterogeneity test showed that there was no significant heterogeneity between the two studies ($P = 0.86, I^2 = 0\%$), so the fixed-effects model was used to merge them. The overall effect test was statistically significant ($Z = 2.46, P = 0.01$), and the difference was statistically significant. An OR of 13.69 with a 95% CI of (1.70, 110.54) suggested that the liver damage caused by the Liuwei Dihuang pill combined with compound Zaofan pill for the treatment of AA was 13.69 times that of androgen.

**Others**

One study on the Jinkui Shenqi pill for the treatment of AA was reviewed.\cite{6} Twenty cases of AA patients were treated with the Jinkui Shenqi pill combined androgen treatment in the experimental group, while 20 cases were treated with androgen in the control group. After the treatment, the efficacy in the experimental group was 85%, while the efficacy in the control group was 55%. Due to this study, being a small sample randomized study, the literature was recommended as grade C. In addition, Luo\cite{7} used Yougui Y to treat thirty patients with AA, while another 30 patients were treated with cyclosporine A, in the control group. The efficacy of

---

**Table 1: Details of the included studies**

<table>
<thead>
<tr>
<th>First publication author time</th>
<th>Group</th>
<th>Medicine</th>
<th>Sample number</th>
<th>Valid cases</th>
<th>Invalid cases</th>
<th>Male and female cases</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver damage</td>
<td>Diarrhea</td>
<td>Hirsutism of women</td>
<td></td>
</tr>
<tr>
<td>Wang W 2001</td>
<td>Experimental group</td>
<td>Liuwei Dihuang pill + compound Zaofan pill</td>
<td>20</td>
<td>16</td>
<td>4</td>
<td>12/8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>Androgen</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>13/7</td>
<td>6</td>
</tr>
<tr>
<td>Wang W 2007</td>
<td>Experimental group</td>
<td>Liuwei Dihuang pill + compound Zaofan pill</td>
<td>30</td>
<td>22</td>
<td>8</td>
<td>18/12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>Androgen</td>
<td>30</td>
<td>23</td>
<td>7</td>
<td>20/10</td>
<td>8</td>
</tr>
</tbody>
</table>

---

**Figure 2:** The comparison of the overall efficacy between the Liuwei Dihuang pill combined with compound Zaofan pill and androgen for the treatment of aplastic anemia

**Figure 3:** The comparison of liver damage between the Liuwei Dihuang pill combined with compound Zaofan pill and androgen in the treatment of aplastic anemia
treatment in the experimental group was 86.67%, while the efficacy of treatment in the control group was 66.7%. Due to this study, being a small sample randomized study, the literature was recommended as Grade C. The Wei Qiumin used Xijiao Dihuang decoction in the treatment of 30 cases of patients with AA and another 23 cases were treated with androgen and cyclosporine A. The efficacy of the treatments were 90% and 60.9%, respectively. The two studies were small samples of nonrandomized studies, and therefore, the literature recommendation level was D. No clinical trials were reported, only reviews, expert experiences, and a case report on the treatment of AA with Zuogui Yin, the Sijun Zi decoction, Huanglian Ejiao decoction, and Qingying decoction was reported; therefore, the literature recommendation level was E.

**DISCUSSION**

AA is a syndrome characterized by the reduction of whole blood cells. The Practical Internal Medicine edited by Chen et al. described the conventional treatment of chronic AA as androgen therapy. The total efficacy was 34.9%–81%. However, the treatment cycle was long, and adverse reactions were severe; hence, the treatments of some patients were interrupted because of the damage to the liver and hirsutism of women. TCM believes that the essence of AA was spleen and kidney damage; and yin, yang, qi, and blood deficiency, which is currently divided into seven card types including kidney yin deficiency and kidney yang deficiency, yin and yang deficiency, yang deficiency of spleen and kidney, yin deficiency of liver and kidney, internal heat toxin, and bleeding. The Liuwei Dihuang pill nourishes the liver and kidney and also treats or improves bone marrow suppression caused by immune disorders. It is clinically used for kidney yin deficiency syndrome. In this study, we found that there were no statistically significant differences in the total efficacy of androgen alone and the Liuwei Dihuang pill combined with compound Zaofan pill and in the treatment of AA; however, the latter reduced the possibility of occurrence of the two side effects, the liver damage and hirsutism of women.

The methodological quality of the studies included in this meta-analysis was generally low. The two articles, in the final analysis, did not mention whether the study was random, blinding, had allocation concealment, or not. They also did not give baseline data, but only said the conditions of two groups were similar. Hence, there was a certain risk of bias, and the literature recommended levels were low.

Evidence-based medicine advocates making medical decisions and deciding the treatment based on scientific research results, as opposed to the previous personal experiences with the medicine. Clinical trials with a large sample, multicenter, and randomized control are the best way to evaluate a treatment, and also form a reliable basis for the evaluation of efficacy and safety. Chinese medicine has the characteristics of individualized treatment. In the evaluation of curative effect, there is a great deal of descriptive data, but a lack of well-designed clinical trials. The randomized control trials are lacking enough samples and calculated evidence. Indicators of outcome and other peoples’ observations are not clear. There is a lack of endpoint indicators for long-term follow-up. Since these not high-quality clinical research studies, there is a return of established diagnostic criteria into clinical practice, as well as, the randomized controlled trial. It is difficult to establish the applicability and reference values of the diagnostic criteria for Chinese medicine clinics. Many serious problems still need to be solved in the development of evidence-based diagnosis and treatment guidelines of TCM. With more clinical randomized control trials in the future, the literature update and the reevaluation of evidence level can be conducted based on the results of this study.
Financial support and sponsorship
The study was supported by Research Project of Shanghai Municipal Health and Family Planning Commission (No. 201640144), Baoshan Health Systems of Young Medical Talent Training Project (No.bswsyq-2016-A11), National Nature Science Foundation Project of Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (No. GZRPYJJ-201601).

Conflicts of interest
There are no conflicts of interest.

REFERENCES