

Meta-Analysis on Efficacy and Safety of Modified Guizhi Shaoyao Zhimu Tang with the Western Medicines in Treating Rheumatoid Arthritis

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Abstract

Objective: To assess the efficacy and safety of modified Guizhi Shaoyao Zhimu Tang (GSZT) with the Western medicines in treating rheumatoid arthritis. **Methods:** All the relevant studies were collected by searching the Pubmed, Web of science, Embase, Cochrane Library, SpringerLink, China National Knowledge Infrastructure (CNKI), VIP Journals database, and Wanfang database from their inception to October 2017. After the assessment, the eligible ones were subject to Jadad score. The meta-analysis was conducted by RevMan 5.3 software. **Results:** Totally 10 randomized controlled trials (RCTs) involving 962 patients were enrolled. The clinical efficacy of analysis showed that modified GSZT with the Western medicines can significantly improve the clinical total effective rate [OR = 4.64, 95%CI (3.03, 7.12), $P < 0.00001$], the duration of morning stiff [MD = -14.58, 95%CI (-16.49, -12.68), $P < 0.00001$], erythrocyte sedimentation rate (ESR) [MD = -12.62 95%CI (-18.69, -6.54), $P < 0.001$], rheumatoid factor (RF) [MD = -49.88, 95%CI (-77.6, -22.09), $P < 0.001$], C-reactive protein (CRP) [MD = -5.34, 95%CI (-5.86, -4.82), $P < 0.001$]. The adverse events had been seen in both of the two groups, however, the clinical symptoms of the group on modified GSZT with the Western medicines were obviously reduced than the other one [OR = 0.25, 95%CI (0.10, 0.61), $Z = 3.06$, $P < 0.01$]. This system review shows that the modified GSZT with the Western medicines improved the clinical efficacy, symptoms and the blood biochemical indicators were improved significantly than that of Western medicines alone on rheumatoid arthritis. At the same time, it can reduce adverse effects and enhance safety.

Keywords

Rheumatoid Arthritis, Guizhi Shaoyao Zhimu Tang, RA, Meta

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by joint erosion, stiffness, deformity, loss of function, and with high morbidity [1] [2]. However, the cause of RA is unknown. RA belongs to the category of “bi syndrome” in Traditional Chinese Medicine (TCM). It is caused by invading cold and dampness inside body and blood qi stasis in the theory of TCM. At present, the effective treatments of routine western drugs include glucocorticoid, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and biologic agents. While the long term use of these drugs can produce the multiple side effects, and cause much socio-economic costs and safety, and even some patients cannot tolerate the situation [3]. But the TCM has special effects in the treatment of RA [4]. Recently, the TCM is attracting the attention of the public, because of the potential and positive effects in treatment of autoimmune disease. The TCM mainly contains Chinese herbs. In the ancient period of China, there was a formula that was most commonly used in the management of RA. Guizhi Shaoyao Zhimu Tang (GSZT) is the classical Chinese medicine which is extensively used in clinical application. In this article, the potentially therapeutic effect and safety of the GSZT combined with the Western medicine for the treatment of RA were systematically evaluated.

2. Materials and Methods

2.1. Literature Retrieval Strategy

The search strategy was developed by Cochrane collaboration and the relevant studies were collected by searching the Pubmed, Web of science, Embase, Cochrane Library, SpringerLink, CNKI, VIP Journals database, and Wanfang database from their inception to October 2017. A multiple number of medical terms such as “rheumatoid arthritis”, “RA” and “Guizhi Shaoyao Zhimu Tang” were utilized for medical subject heading (MeSH) to find out the articles, which have been published on the base of combine conventional western medicines for the treatment of RA. The retrieval is conducted in the form of free combination with a keyword, manual retrieval had been used to trace the references in the literature. No language or time restrictions were applied in the search.

2.2. Document Inclusion and Exclusion Criteria

Trials were considered to be eligible for research propose if they fully meet the following criteria: 1) all patients fulfilled the 1987 revised American College of

Rheumatology criteria for the disease [5], 2) the experimental group was treated with the combined conventional Western medicine and the GSZT, and the control group was just treated with conventional Western medicine, 3) the research type satisfied the RCT data, 4) the outcomes included at least one of the following therapeutic effects: duration of morning stiffness (DMS), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), there were no restrictions regarding gender, age, severity or duration of RA. The safety evaluation index is the adverse reactions.

2.3. Data Extraction

The two researchers independently screened and extracted the retrieved documents, and the differences were determined and resolved by the third person, including study design, randomization and diagnostic criteria.

2.4. Quality Evaluation

According to the quality criteria of Cochrane Review's Handbook, the literature quality is evaluated and Jadad scale method was independently used for the evaluation of methodological quality of articles [6]. The specific contents include: 1) random grouping sequence method, 2) blind method, include double-blind method and single blind method, 3) allocation concealment, 4) reports about the withdrawal.

2.5. Statistical Analysis

Data analysis was performed by using the RevMan 5.3 software provided by the Cochrane collaboration. The statistical data were analyzed by odds ratio (OR) and 95% confidence intervals (CI) and the metering data was expressed by mean difference (MD) and 95%CI. A fixed-effect model was employed if there was no statistical heterogeneity among studies, otherwise, the random effect model was used [7]. Heterogeneity is assessed by Chi-square test, and the degree of inconsistency Higgins I^2 is measured between studies whether the percentage of total variation across studies is due to heterogeneity rather than chance [8]. If the source of heterogeneity is unable to be determined, the descriptive analysis will be adopted. The distribution of the research data, in the study, was analyzed by funnel plot. The reliability analysis of publication bias was carried out.

3. Results

3.1. Study Selection and Characteristics

According to the above mentioned research strategy we got information from 1313 articles which are potentially relevant. 1078 studies were screened after removal of duplicates. There were ten relevant studies that finally met the inclusion criteria for the meta-analysis. The general situation of the study selection was shown in **Figure 1**.

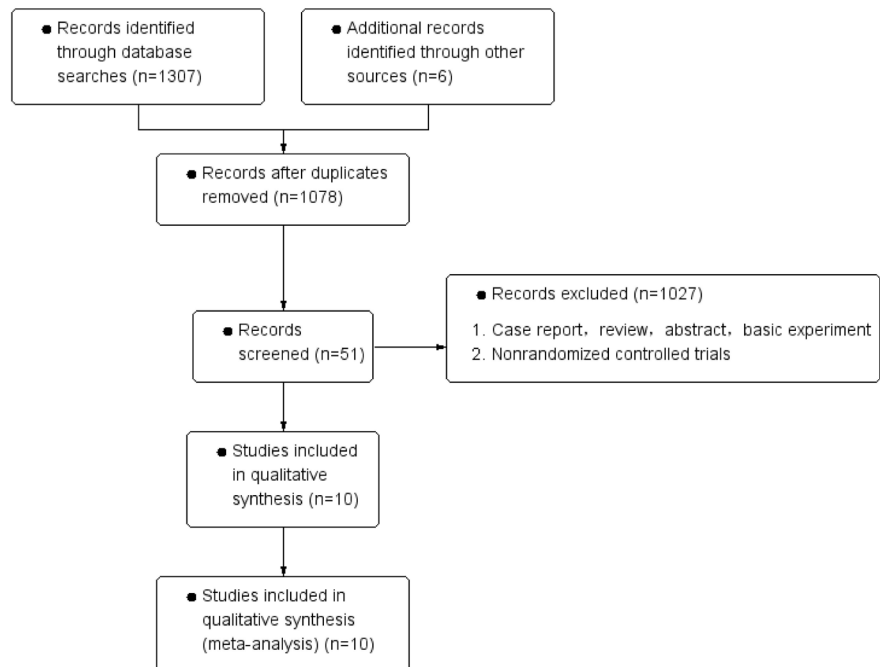


Figure 1. Flow diagram of study selection process.

3.2. General Situation and Quality Evaluation of the Included Literature

A total of 10 RCTs were included [9]-[18], and the conventional Western medicine involves three major categories in these studies. They are non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and glucocorticoids (GCs). NSAIDs included Meloxicam (MLX), voltaren, nimesulide (Nime), celecoxib (CXB), loxoprofen. DMARDs included methotrexate (MTX), sulfasalazine (SSZ) and Leflunomide (LEF). The experimental group was based on the control group with GSZT. The general description about literature and the results of methodological quality evaluation are shown in **Table 1**.

3.3. Meta Analysis Results

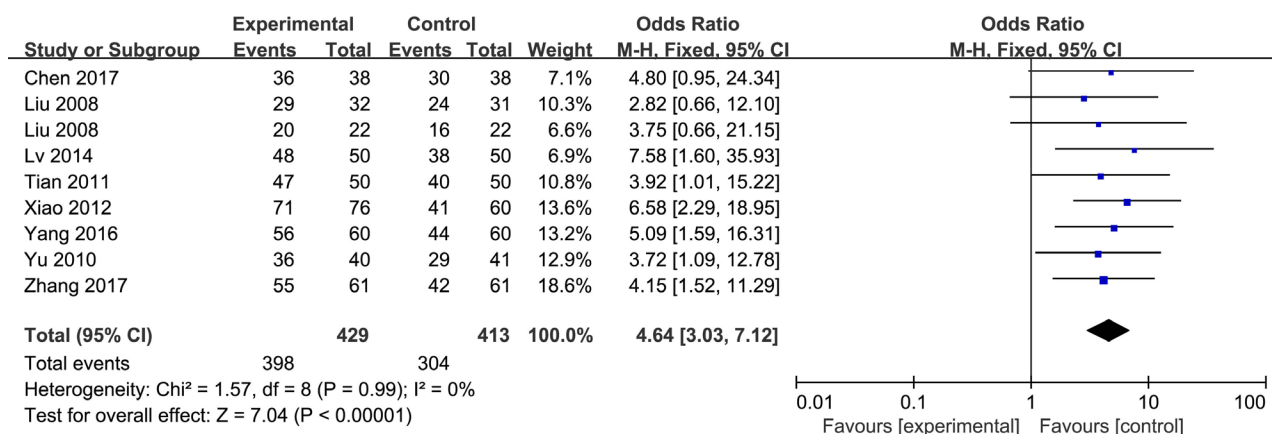
3.3.1. Comparison of Disease Efficacy for RA

In the articles that met the criteria, 9 trials were compared for the efficacy of RA patients and the specific values were given [9]-[17]. According to the data which we had screened in combination, we can see that 9 trials included in the study were homogeneity (no heterogeneity) and showed insignificant difference ($X^2 = 1.57$, $P = 0.99$, $I^2 = 0\%$). The fixed effect model was used and showed [OR = 4.64, 95%CI (3.03, 7.12), $Z = 7.04$, $P < 0.00001$]. Therefore, it is considered that there is a statistically significant difference in the efficacy of the combination therapy between the combination therapy trial group and the Western medicine treatment control group alone. In addition, the lower and lower limit of 95%CI of OR is more than 1. It can be seen that the clinical efficacy of the experimental group is better than the Western medicine alone control group in RA. See **Figure 2**.

Table 1. Characteristics of the ten trials included in the meta-analysis.

Author	random allocation	allocation concealment	blind method	withdraw	Jadad score	Interventions		Duration	Outcomes
						experimental	control		
Yu 2010 [9]	yes	unclear	unclear	unclear	3	GSZT	MTX 7.5 mg qw, SSZ 1 g bid	12 weeks	TE, DMS, ESR, CRP, AE
Liu 2008 [10]	unclear	unclear	unclear	unclear	2	GSZT	MTX 7.5 mg qw, MLX 7.5 mg bid	4 weeks	TE
Liu 2008 [11]	unclear	unclear	unclear	unclear	2	GSZT	LEF 20 mg qd	4 weeks	TE
Lv 2014 [12]	yes	unclear	unclear	unclear	3	GSZT	MTX 7.5 mg qw, voltaren 75 mg qd	12 weeks	TE, ESR, RF, AE
Zhang 2017 [13]	yes	unclear	unclear	yes	4	GSZT	LEF 20 mg qd, Nime 0.1 g bid	12 weeks	TE, DMS, ESR, RF, CRP
Yang 2016 [14]	unclear	unclear	unclear	unclear	2	GSZT	CXB 0.2 g qd	12 weeks	TE
Tian 2011 [15]	unclear	unclear	unclear	unclear	2	GSZT	NSAIDs, GCs	8 weeks	TE, DMS, ESR
Xiao 2012 [16]	unclear	unclear	unclear	unclear	2	GSZT	MTX 5 10 mg qw, voltaren 75 mg qd	12 weeks	TE, ESR
Chen 2017 [17]	yes	unclear	unclear	unclear	3	GSZT	MTX 10 mg qw, voltaren 75 mg qd	12 weeks	TE, DMS, ESR, RF, CRP, AE
Liu 2017 [18]	yes	unclear	unclear	unclear	3	GSZT	LEF 20 mg qd, loxoprofen 60 mg tid	8 weeks	ESR, RF, CRP

Note: *GSZT* Guizhi Shaoyao Zhimu Tang, *MTX* methotrexate, *SSZ* sulfasalazine, *MLX* Meloxicam, *LEF* Leflunomide, *Nime* nimesulide, *CXB* celecoxib, *GCs* glucocorticoids, *TE* therapeutic effect, *DMS* duration of morning stiffness, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *CRP* C-reactive protein, *AE* adverse event.

**Figure 2.** Meta-analysis forest map of the effect comparison.

3.3.2. Effect on Duration of Morning Stiffness

Four trials reported the effects on the DMS between the experimental group and control group was carried out. The meta-analysis showed that 4 trials included in the study were homogeneity (no heterogeneity), and showed a insignificant difference ($X^2 = 1.05$, $P = 0.79$, $I^2 = 0\%$). The fixed effect model was used and showed [MD = -14.58, 95%CI (-16.49, -12.68), $Z = 14.99$, $P < 0.00001$] [9] [13] [15] [17]. According to this analysis, it can be considered that there is a statistically significant difference in the effect of the DMS between the combined trial

group and the Western medicine alone group. The lower and lower limit of 95%CI of the OR was less than 0, indicating that the experimental group could improve the efficacy of the DMS better than the control group. See **Figure 3**.

3.3.3. Effect on Blood Biochemical Indexes

Seven trials reported the effects on the serum level of the ESR [9] [12] [13] [15] [16] [17] [18], four trials reported the effects on the serum level of the RF [12] [13] [17] [18], and four trials reported the effects on the serum level of the CRP [9] [13] [17] [18]. The meta-analysis showed that there was a large heterogeneity between the ESR and RF tests ($P < 0.001$), However, CRP test has homogeneity ($P = 0.91$), we analyzed the outcome in fixed effect model. All three blood biochemical indexes in experimental group were better than those in the control group, and the differences were statistically significant ($P < 0.001$). As shown in **Table 2**.

3.3.4. Safety Evaluation

Only 3 trials were referred to adverse events during the treatment, the cases were clearly mentioned and observed [9] [12] [17]. No heterogeneity was identified among the trials ($X^2 = 1.93$, $P = 0.38$, $I^2 = 0\%$) based on the fixed-effect model. See **Figure 4**, the meta-analysis demonstrated a meaningfully higher rate of AEs induced by the Western medicines alone than by the modified GSZT combined with the Western medicines [OR = 0.25, 95%CI (0.10, 0.61), $Z = 3.06$, $P = 0.002 < 0.01$]. The control group had 6 cases of nausea and vomiting, 7 cases of epigastric discomfort, 3 cases of abnormal liver function, 2cases of leukopenia, 6 cases of oral ulcer and dry mouth. In the experimental group, there are 1 case of nausea and vomiting, 7 cases of epigastric discomfort, 1 case of skin rash, 1 case of

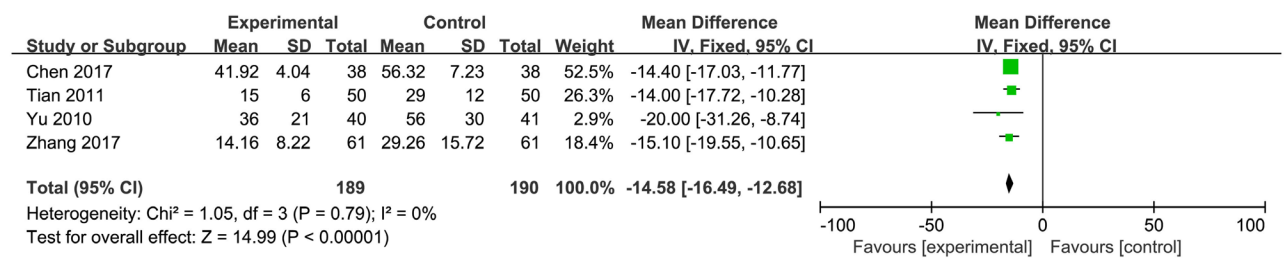


Figure 3. Meta-analysis forest map of the effect on the DMS.

Table 2. Comparison of the improvement of RA on ESR, RF, CRP in the two groups.

Evaluation index	Trials	Interventions		Heterogeneity test			Effect model	Total effect		
		Experimental	Control	X ²	I ²	P		MD [95%CI]	Z	P
ESR	7	317	318	241.67	98%	<0.001	random	-12.62 [-18.69, -6.54]	4.07	<0.001
RF	4	209	209	219.45	99%	<0.001	random	-49.88 [-77.6, -22.09]	3.52	<0.001
CRP	4	199	200	0.55	0%	0.91	fixed	-5.34 [-5.86, -4.82]	20.04	<0.001

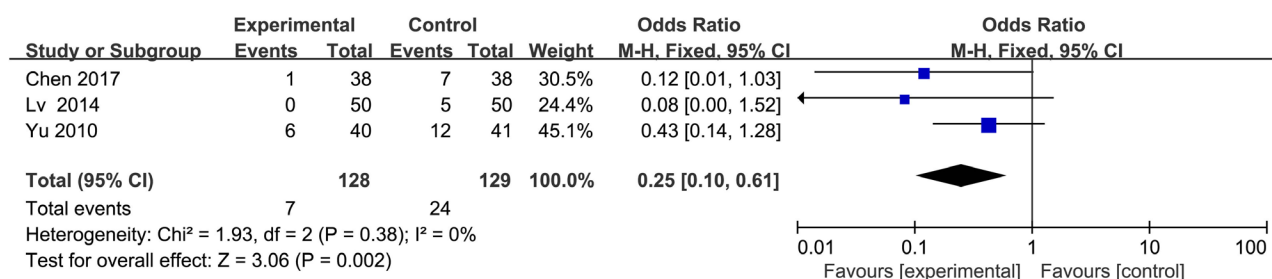


Figure 4. Meta-analysis forest map of the effect on the adverse events.

dizziness, 1 cases of diarrhea and 1 cases of oral ulcer. As shown in **Table 3**, these side effects, however, which could be alleviated or disappeared after symptomatic treatment in experimental group.

3.3.5. Publication Bias

A funnel plot analysis was carried out on the efficacy of the 9 studies in RA, the distribution of each study is symmetrical, and the funnel plot is basically symmetric. It can be concluded that there is no publication bias, and the meta-analysis was credible. See **Figure 5**.

4. Discussions

Guizhi Shaoyao Zhimu Tang, a Chinese medicinal formula, is accepted as the most prevalent and effective treatment for RA in many Asian countries [19]. The essential herbs in this formula, GSZT, are well-known for the book as follow: “Synopsis of Prescriptions of the Golden Chamber”. It is the main prescription for the treatment of “arthralgia syndrome”. The theory of TCM holds that is “Medicinal and Edible”. Modern pharmacological research shows that the formula can significantly reduce the PGE2 content in the inflammatory tissue of adjuvant induced arthritis, inhibit the migration of white blood cells, and reduce the permeability of capillaries [20]. Another study pointed out that the GSZT has similar efficacy to methotrexate in treatment of RA, which could inhibit the secretion of IL-2 and CRP in varying degrees [21]. It also shows the effects in treating RA by adjusting to IL-2, IL-6, IL-17, IL-27, IL-32, TNF- α , HRAS, CD14, CD40, and TLR-MAPKs signaling pathway, TLR-NF- κ B signaling pathway, NLR signaling pathways and TNF signaling pathway [13] [22]. The animal experiments have also been found that the GSZT can have a protective effect on collagen II-induced arthritis (CIA), and can significantly inhibit the histopathological changes of rheumatoid arthritis and restrain the expression of RANKL/OPG [23] [24]. It is indicated that the GSZT has the function of anti-rheumatism, inhibiting the immune response, and also provides the molecular basis for the treatment of RA. Therefore, the treatment of RA is quite effective in clinic.

This system systematically evaluated the inclusion criteria of clinical studies. The results showed that the GSZT combined with the Western medicine was better than the Western medicine alone in the treatment of RA. According to the funnel plot analysis, this meta-analysis is credible. The experimental group was

Table 3. Effect of adverse events in the two groups.

Interventions	Adverse events								Total
	nausea vomiting	epigastric discomfort	skin rash	dizziness	abnormal liver function	leukopenia	diarrhea	oral ulcer dry mouth	
Experimental	1	1	1	1	1	0	1	1	7 [9] [17]
Control	6	7	0	0	3	2	0	6	24 [9] [12] [17]

Note: 1) The conditions of [9] [12] [17] applied the Western medicine shows in **Table 1**. 2) The AEs of [9], 1 case of nausea vomiting, 1 case of epigastric discomfort, 1 case of skin rash, 1 case of dizziness, 1 case of abnormal liver function in the experimental group; 4 case of nausea vomiting and epigastric discomfort, 3 case of oral ulcer, 3 case of abnormal liver function, 1 case of leukopenia in the control group. 3) The AEs of [12], no AEs in the experimental group and 5 case of epigastric discomfort in the control group; 4) The AEs of [17], 1 case of diarrhea in the experimental group; 2 case of nausea vomiting, 2 case of epigastric discomfort, 3 case of dry mouth in the control group.

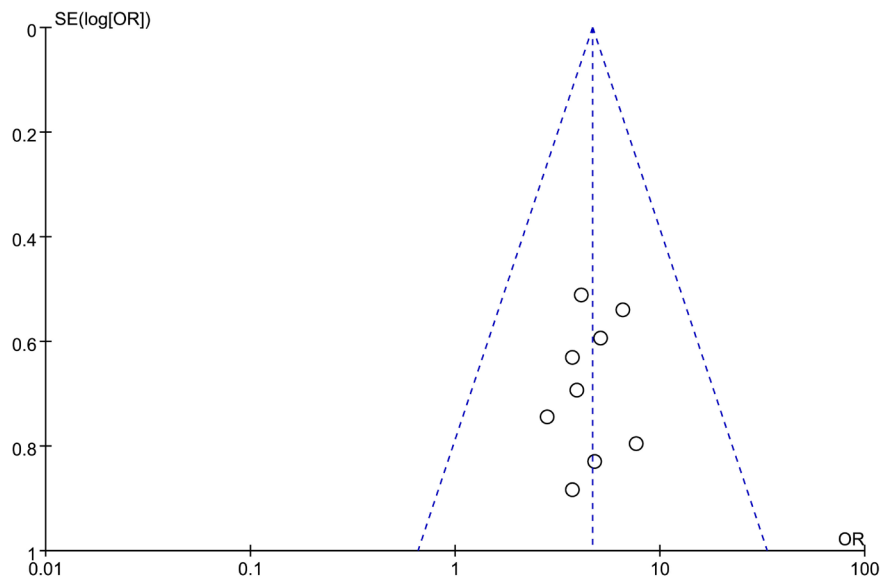


Figure 5. Funnel plot for publication bias in the included trials.

also better than the western medicine treatment group in terms of clinical symptoms, laboratory indicators and adverse reactions. From the large amount of retrieved study, it can be seen that although there are many adverse reactions in the treatment of RA with conventional Western medicine alone, the treatment of western medicine in China is still widely applied due to its exact clinical efficacy and clinical pharmacology. This study confirmed the efficacy and safety that the modified GSZT combined with Western medicine is more effective, regardless of clinical efficacy, or clinical symptoms, laboratory indicators and safety are better, and can better reflect the complementary advantages of Chinese and Western medicine. It would have good clinical promotion and application value.

This study confirmed the efficacy and safety of the GSZT combined with western medicine in the treatment of RA from the perspective of evidence-based medicine. However, through detailed analysis of the articles, the quality of articles was low, and the sample size was also low. Randomization, withdrawal, and loss of follow-up were mostly unknown. They didn't mention the blinded method and allocation concealment, and the specific interventions into the RCT

dose have different size and duration. The factors certainly influenced the reliability of the result of the meta-analysis. In order to guide clinical practice more scientifically, it is necessary to design a randomized double-blind controlled trial with high quality and provide more reliable evidence-based medical evidence for clinical guidance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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