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# Chinese Herbal Medicine Combined with Prednisone for Polymyalgia Rheumatica: A Meta-Analysis of Randomized Controlled Trials

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 September 2023 and was last updated on 05 September 2023.

## INTRODUCTION

**Review question / Objective** To evaluate the effectiveness and safety of Chinese herbal medicines (CHMs) combined with prednisone (PDN) for treating polymyalgia rheumatica (PMR) by performing a meta-analysis.

**Rationale** Polymyalgia rheumatica (PMR) is an inflammatory disease of unknown etiology affecting elderly individuals over 50. It is the second most common inflammatory rheumatic disease, after rheumatoid arthritis (RA). The prevalence of PMR rises with age and reaches a peak between the ages of 70 and 80 years. PMR occurs more often in women than in men. It is characterized by severe pain and stiffness of the shoulders and pelvic girdle, and elevation of inflammatory markers dominated by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Low-dose glucocorticoid (GC) therapy is highly effective and remains the mainstay in treatment. However, 33% of patients experience relapse during the first year of GC tapering, and GC therapy is rarely stopped within 2 years, which unfortunately causes well-recognized adverse effects, including osteoporosis, femoral head necrosis, fragility fractures, and so on. Patients with relapsing disease or with poor response to GCs require other treatments aimed mainly to spare GCs. Among them, methotrexate is the most commonly used, and Janus-kinase inhibitors and new anti-interleukin-6 antagonists are also used for treatment. Nevertheless, different studies show that these drugs yield only a modest effect. Therefore, faced with the limitations of current treatment, a safer and more effective therapeutic strategy need to be explored.

**Condition being studied** Traditional Chinese medicine (TCM) has a history of thousands of years and now still used actively in China and around the world, which have drawn more and more attention from scholars because of its high efficacy and low incidence of adverse events (AEs). Nowadays, Chinese herbal medicine (CHM), one of

main TCM treatment modalities, is widely used in the treatment of PMR. In China, PMR belongs to the category of "blockage syndrome", which we called "Bi Zheng". According to TCM theory, the pathogenesis of Bi Zheng is that pathogenic factors block the main and collateral channels, resulting in poor blood circulation and inability to nourish the limbs. The classic treatment methods are dispelling evil and tonifying deficiency. Dispelling evil mainly refers to removing evil spirits such as wind, cold and dampness, and promoting blood circulation to remove blood stasis (known as Qufeng Sanhan Chushi, Huoxue huayu). Tonifying deficiency mainly refers to supplementing Qi and nourishing Blood, warming Yang and nourishing Yin (known as Buqi Yangxue, Wenyang Ziyin). For example, Wen et al. found that Bee-stinging combined with Shentong Zhuyu decoction (Huoxue huayu method) possessed significant effect on PMR. It could decrease ESR and CRP in patients. Zhu et al. also found that Deanxit combined with Shentong Zhuyu decoction (Huoxue huayu method) had an active therapeutic effect on PMR. Some clinical studies have evaluated the therapeutic effect of CHM combined with prednisone (PDN) on PMR and its positive effect on declining the side-effect of PDN in recent decades. However, there are no reliable evidence-based medical studies to confirm its efficacy for PMR, leading to its clinical benefits are still controversial. Therefore, to further confirm the clinical value of CHM therapy for PMR, we conducted this meta-analysis to evaluate the efficacy and safety of CHM plus PDN for PMR. Thus, it will provide a basis for clinical medication.

## METHODS

**Search strategy** [("Polymyalgia rheumatica") OR ("Polymyalgia rheumatic*") OR ("Rheumatic polymyalg*") OR ("polymyalg*") OR ("PMR")] AND [("Chinese herbal drugs") OR ("Chinese traditional medicine") OR ("Chinese plant extracts") OR ("Integrated Chinese-Western therapy")].

**Participant or population** Patients diagnosed with PMR, without limitations related to gender, age, ethnicity, and the reference standard was classification criteria proposed in 2012 by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR).

**Intervention** The experimental group received combination treatment of CHM and PDN.

**Comparator** The control group received treatment of PDN alone.

**Study designs to be included** All RCTs investigating the use of CHM therapy for PMR were considered, and results published in either English or Chinese.

**Eligibility criteria** Studies were included if they fulfilled the following criteria: (1) Type of studies: all RCTs investigating the use of CHM therapy for PMR were considered, and results published in either English or Chinese; (2) Type of participants: patients diagnosed with PMR, without limitations related to gender, age, ethnicity, and the reference standard was classification criteria proposed in 2012 by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR); (3) Type of intervention: the experimental group received combination treatment of CHM and PDN; (4) Type of control: the control group received treatment of PDN alone; (5) Types of outcome measures: primary outcomes included clinical effective rate, PMR activity score (PMR-AS), final dose of GC at 8 and 12 weeks, secondary endpoints included ESR, CRP, platelet (PLT) and hemoglobin (Hb) level, number of adverse events (AEs). Articles were excluded if they fulfilled the exclusive criteria: (1) study subjects did not meet PMR diagnostic criteria, or study subjects combined other immune system diseases including giant cell arteritis (GCA), RA, polymyositis and so on. (2) both experimental and control groups were treated with CHM only, or both groups were treated with non-steroidal anti-inflammatory drugs (NASIDs), or inappropriate interventions; (3) duplicated articles or animal experiments or case reports or review articles or comments; (4) those reporting unrelated topics or conference abstracts or unavailable data studies or irrelevance to outcome indicators; (5) non-RCT.

**Information sources** Two trained investigators independently searched randomized controlled trials (RCTs) of CHM for PMR from the following databases: PubMed, EMBASE, Cochrane Library, Web of science, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, China BioMedical Literature (CBM), and VIP Journals Database from inception to July 28, 2023. On the other hand, additional relevant records were identified from published reviews and the reference lists of selected RCTs to avoid missing qualified studies.

**Main outcome(s)** A total of 21 RCTs with 1750 participants (891 in the CHM + PDN group and 859 in the PDN group) were included in this meta-analysis. The aggregated results showed that CHM combined with PDN was beneficial to PMR, which could improve the clinical efficacy rate [risk ratio

(RR) = 1.24, 95% confidence interval (CI): (1.16, 1.32), p < 0.00001] and reduce PMR activity score (PMR-AS) [weighted mean difference (WMD) = -6.25, 95% CI: (-7.36, -5.14), p < 0.00001]. Glucocorticoid (GC) dose was significantly reduced in CHM combined with PDN group compared with the PDN group after 8 [WMD = -4.00, 95% CI: (-6.08, -1.92), p = 0.0002] and 12 weeks [WMD = -3.92, 95% CI: (-5.33, -2.51), p < 0.00001]. Furthermore, CHM combined with PDN improved erythrocyte sedimentation rate (ESR) [WMD = -9.74, 95% CI: (-12.08, -7.41), p < 0.00001], C-reactive protein (CRP) [standardized mean difference (SMD) = -1.66, 95% CI: (-2.32, -1.01), p < 0.00001], platelet (PLT) [WMD = -28.91, 95% CI: (-54.08, -3.74), p = 0.02] and hemoglobin (Hb) [WMD = 7.16, 95% CI: (3.54, 10.78), p = 0.0001] compared with used of PDN alone. For the safety analysis, the combination treatment may reduce the incidence of adverse events (AEs) [RR = 0.51, 95% CI: (0.38, 0.68), p < 0.00001].

**Additional outcome(s)** In this study, 28 kinds of Chinese herbal formulas were evaluated, including 20 herbal decoctions, 4 granules, 2 capsules and 2 pills. 2 kinds of Chinese herbal formulas were used simultaneously in 2 articles and 2 Chinese herbal formulas were used successively in 2 literatures. 4 kinds of Chinese herbal formulas were selected for dialectical treatment in 1 article. The herbal components number in the formulae varied from 4 to 16. To determine the characteristics of the CHMs botanical drugs included in the study, the specific drug ingredients and dosage in each included study was listed in detail in Table 2. Meanwhile, we ranked the use frequency of botanical drugs in the original studies (frequency ≥ 3).

**Data management** Statistical analysis was performed by RevMan v5.3 and Stata v14.0.

**Quality assessment / Risk of bias analysis** The methodological quality of the 21 RCTs was relatively low. 19 trials claimed randomized, only 3 trials reported the randomization method, whereas the other 2 trials did not mention randomized. In terms of allocation concealment and blinding method, none of the included articles reported. All studies had the complete outcome data, none of them had selective reporting. Other biases were not determined.

**Strategy of data synthesis** Continuous outcomes were calculated by weighted mean difference (WMD), standardized mean difference (SMD), and a 95% confidence internal (CI). For dichotomous data, risk ratio (RR) and a 95% CI were calculated. I2 and ?2 tests were used to evaluate the statistical heterogeneity between trial and control results. A random-effects model (I2 ≥ 50%) or a fixed-effects model (I2 < 50%) was applied depending on the value of I2. When the value of p < 0.05, statistically significant were considered. The source of the heterogeneity was identified by subgroup analysis and sensitivity analysis if heterogeneity exists. Funnel plot and Egger's tests would be implemented to check the publication bias, when more than 10 studies were included in the meta-analysis.

**Subgroup analysis** Since there was large heterogeneity among the included studies of clinical efficacy rates, PMR-AS, GC dose after 12 weeks and PLT level, we performed a subgroup analysis to report the heterogeneity sources. We divided them into several groups according to different CHM prescription. Heterogeneity was eliminated after subgroup analyses with different prescription information, which may account for the partial heterogeneity.

**Sensitivity analysis** Since the reliability of the GC dose after 8 weeks, ESR, CRP, and Hb results were affected by the huge heterogeneity, we took sensitivity analyses to investigate the heterogeneity sources. After eliminated the included trials one by one, it did not alter the overall results, which indicated that the conclusions were stable and constant.

**Language restriction** All studies were conducted in China, which may present selection bias and limit the generalizability of the findings presented here.

**Country(ies) involved** China.

**Other relevant information** We ranked the frequency of herbal use in the included studies, and those used at a high frequency were described in detail (frequency ≥ 3).

**Keywords** polymyalgia rheumatica, Chinese herbal medicine, prednisone, meta-analysis, randomized controlled trials.

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