

The Clinical Efficacy of Traditional Chinese Medicine Topical Therapy Combined with Sodium Hyaluronate Intra-articular Injection in the Treatment of Patellar Chondromalacia: a systematic review and meta-analysis

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Background: Chondromalacia patellae (CMP) is a cartilaginous degeneration of patellofemoral joint caused by a variety of reasons. Recent studies have shown that the incidence of patellomalacia is getting higher and higher. Our meta-analysis is used to illustrate the clinical effect of external treatment of traditional Chinese medicine combined with joint cavity injection of sodium hyaluronate in the treatment of patellomalacia.

Methods: Literature searches were carried out in various databases, such as PubMed, Cochrane Library, China Biomedical Literature Database, China National Knowledge Infrastructure, Wanfang, and Weipu, with the search timeline extending from the inception of each database until April 2024. Two investigators independently conducted literature screening, data extraction, and quality assessment of the included studies. Review Manager 5.4 software was used to perform a meta-analysis, which evaluated changes in the clinical efficacy rate, visual analogue scale (VAS) scores, and time of symptom onset before and after treatment.

Results: The study included a total of 11 randomized controlled trials (RCTs) involving 1,279 patients. The meta-analysis results indicated that compared to the standalone injection of sodium hyaluronate, the combination of TCM topical therapy significantly enhanced the clinical efficacy rate in treating CMP [RR=1.17, 95% CI=[1.12,1.22], P<0.00001]. Furthermore, the addition of TCM topical therapy lowered the VAS score in patients with CMP five weeks post-treatment compared to the control group. In comparison to the standalone injection of sodium hyaluronate, the combination of TCM topical therapy showed a quicker onset, thus reducing patients' pain [RR=-7.44, 95% CI=(-9.86, -5.01), P<0.00001].

Conclusion: The combination of TCM topical therapy and sodium hyaluronate intra-articular injection demonstrated superior clinical efficacy over the sole intra-articular injection of sodium hyaluronate. This combination effectively mitigated pain in patients and had a faster onset.

Keywords: Traditional Chinese Medicine Topical Therapy, Sodium Hyaluronate, chondromalacia patellae, Meta-analysis.

INTRODUCTION

Chondromalacia patellae (CMP) is a degenerative condition characterized by the breakdown of cartilage in the patellofemoral joint due to various etiological factors. It is primarily typified by anterior knee pain, which becomes more noticeable when performing activities such as climbing stairs, ascending slopes, kneeling, or prolonged sitting and is often exacerbated after rigorous exercise. Frequently, CMP is accompanied by a clicking sound in the knee joint, weakness, and signs of cord entanglement¹. The

precise etiology of CMP is not fully understood, but it is currently thought to be associated with factors such as trauma, increased intrapatellar pressure, cartilage dissolution, cartilage obstruction, and autoimmunity². The primary pathophysiological mechanism involves biomechanical disturbances in the patellofemoral joint, leading to patellar tilt or subluxation and excessive lateral patellofemoral joint pressure. This results in edema, softening, fragmentation, and even detachment of the cartilage on the surface of the patellofemoral joint³. Recent studies have indicated an escalating incidence of CMP, with a

trend toward younger age groups at the time of onset⁴. Consequently, early intervention is crucial to prevent further progression to patellofemoral arthritis.

For the treatment of early- and mid-stage CMP, Western medicine typically advocates conservative approaches, such as oral administration of non-steroidal anti-inflammatory drugs and intra-articular injections of sodium hyaluronate. Traditional Chinese medicine (TCM), on the other hand, employs treatments such as oral and topical herbal remedies, which can include oral herbal decoctions, herbal poultices, herbal fumigations, physiotherapy, acupuncture, and massage⁵. In a clinical setting, the integration of TCM and Western medicine has demonstrated considerable efficacy in the treatment of CMP. The primary focus of this paper is to examine the clinical effectiveness of combining TCM topical therapy and intra-articular injection of sodium hyaluronate compared to the standalone intra-articular injection of sodium hyaluronate in treating CMP. This examination is carried out through the collection of clinical data and the implementation of a meta-analysis.

METHODS

Search Strategy

A computer-aided search was conducted in databases such as PubMed, Cochrane Library, China Biomedical Literature Database, China National Knowledge Infrastructure, Wanfang, and Weipu, with the search period from the inception of each database until April 2024. Search terms included the Chinese terms for “patellar chondromalacia,” “chondromalacia patellae,” “sodium hyaluronate,” “hyaluronic acid,” “TCM,” and the English terms “Chondromalacia Patellae,” “Patella, Chondromalacia Of,” “Acid, Hyaluronic,” “Amo Vitrax,” “Vitrax, Amo,” “Biolon,” “Etamucine,” “Hyaluronan,” “Hyvisc,” “Luronit,” “Sodium Hyaluronate,” “Hyaluronate, Sodium,” “Hyaluronate Sodium,” “Amvisc,” “Healon,” and “TCM”. The reference entries of related literature were also reviewed to prevent the omission of significant research articles.

Selection Criteria

- (1) Type of literature: Only randomized controlled trials (RCTs) were included, without restrictions on the use of allocation concealment, blinding, or the geographical location of the study.
- (2) Study subjects: Subjects had to meet the diagnostic criteria for CMP as acknowledged in the “Diagnostic Criteria and Efficacy Standards

of Traditional Chinese Medicine Diseases and Symptoms”⁶, “Clinical Diagnosis and Treatment Guidelines: Orthopedics Volume”⁷, “Modern Sports Medicine Treatment Manual”⁸, etc. These standards include anterior knee pain, pain exacerbated by prolonged knee flexion or actions such as kneeling or squatting, tenderness on the medial joint surface of the patella, a positive patellar grinding test, and potentially positive imaging test results.

- (3) Intervention measures: The treatment group received traditional Chinese medicine topical therapy combined with intra-articular injections of sodium hyaluronate, while the control group received only intra-articular injections of sodium hyaluronate.
- (4) Outcome measures: The main indicators included the total effective rate (the proportion of cured and significantly effective cases to the total number of cases), the visual analogue scale (VAS) score, and the onset time of effectiveness.

Exclusion Criteria

- (1) Quasi-randomized controlled trials.
- (2) Studies where the treatment group did not receive traditional Chinese medicine topical therapy combined with sodium hyaluronate or where the control group did not receive only intra-articular injections of sodium hyaluronate.
- (3) Non-clinical studies, such as animal experiments, reviews, case reports, and theoretical explorations.
- (4) Studies in which the intervention measures for the treatment group included oral administration of traditional Chinese medicine.
- (5) Multiple reports of the same study.
- (6) Duplicate publications.
- (7) Studies with incomplete data or disorganized data.

Data Extraction and Literature Evaluation

Data Extraction

In accordance with the requirements of the PRISMA flow diagram⁹, two researchers conducted screening, literature quality evaluation, and data extraction according to the inclusion and exclusion criteria. The results were cross-checked, and any disagreements were resolved by a third party. The literature screening involved removing duplicates, browsing titles to exclude irrelevant studies, and reading abstracts and full texts when the information in the title was insufficient for exclusion. A pre-designed data extraction form was used to record specific information, such as (1) publication time and first

author of the included studies; (2) sample size and intervention methods of the treatment and control groups; and (3) total cure rate, overall effectiveness rate, and VAS scores of the treatment and control groups.

Literature Evaluation

The risk of bias in RCT studies was evaluated using the Cochrane Risk of Bias Assessment Tool in Review Manager 5.4.

Statistical analysis

Review Manager 5.4 software was used for the meta-analysis of the data from the included studies. If the data were count data, the relative risk (RR) or odds ratio (OR) was used as the combined statistical measure; if the data were continuous variables, the weighted mean difference (WMD) was used for the meta-analysis, and a 95% CI was provided. In addition, the χ^2 test was used for heterogeneity analysis. If $P > 0.10$ and $I^2 \leq 50$, a fixed-effects model was used to analyse heterogeneity, and the cause of heterogeneity was analysed to determine the source of the heterogeneity for subgroup analysis. If heterogeneity could not be eliminated or if $I^2 > 50$, a random-effects model was

used for analysis. If the heterogeneity was too large to be meaningful for analysis, only descriptive analysis was performed. In addition, subgroup analysis was conducted based on different intervention measures of the studies. A funnel plot was drawn to examine publication bias based on the main outcome indicator of “clinical effectiveness rate”.

RESULTS

Literature Screening Results

Initially, 351 articles were identified. After removing duplicates, reading titles, abstracts, and full texts, and referring to the inclusion and exclusion criteria, 11 articles were finally included. Among them, 11 were in Chinese, and none were in English. Study selection flow chart and Characteristics of studies as shown in Figure 1 and Table I.

Literature quality evaluation criteria

In the 11 RCTs, 2 mentioned that the groups were divided according to a random number table, 5 only mentioned that the groups were randomly divided but did not specify the method of random grouping, 2 were grouped according to the order of visit, and

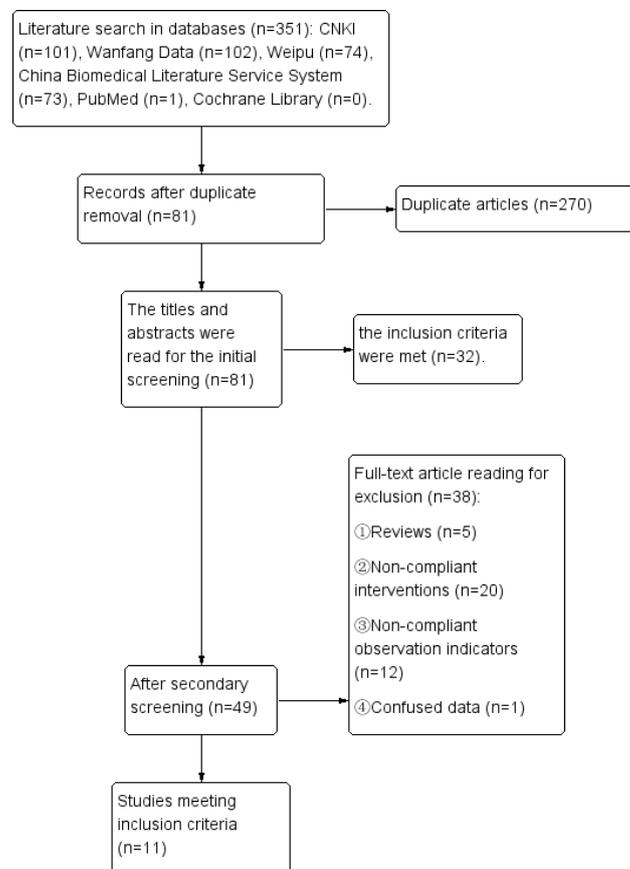


Fig. 1 — Study selection flow chart.

Author	Number of Cases		Intervention Measures		Outcome Indicators
	Experimental Group	Control Group	Experimental Group	Control Group	
Cao Xuewei 2006 [10]	132	103	Chinese Medicine Fumigation + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective Rate, Onset Time
Huang Jingliang 2007 [11]	56	42	Chinese Medicine External Application + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective
Huang Yongsong 2013 [12]	45	45	TCM Directional Drug Permeation + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective
Cao Liping 2013 [13]	46	40	Chinese Medicine External Application + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective, Onset Time
He Jiuyan 2015 [14]	60	60	Electroacupuncture + Chinese Medicine Fumigation + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective
Pu Yunqing 2015[15]	43	39	Chinese Medicine Ion Introduction + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective
Su Yi 2016 [16]	42	38	Chinese Medicine External Application + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective, VAS
He Qiansong 2019 [17]	80	80	Chinese Medicine External Application + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective
Liu Xiaohui 2021[18]	34	34	Warm Acupuncture + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective, VAS, WOMAC, MRI, NF- κ B, TNF- α , IL-1 β
Wang Xu 2021 [19]	30	30	Chinese Medicine External Application + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective, VAS
Pan Zhihua 2021 [20]	100	100	Chinese Medicine Fumigation + Sodium Hyaluronate	Sodium Hyaluronate	Total Effective, VAS, CRP, IL-6

2 did not explain random grouping. The results of the quality evaluation are shown in Figure 2.

Meta-Analysis Results

Comparison of Clinical Efficacy Rates

Eleven studies compared the clinical efficacy rates of the two treatments for CMP, with a total sample size of 1,279 cases (668 in the treatment group, 611 in the control group). There was no statistical heterogeneity between the studies ($P = 0.5$, $I^2 = 0\%$); therefore, a fixed-effects model was selected. The meta-analysis results showed that compared with the use of sodium hyaluronate injection alone, the addition of traditional Chinese medicine external treatment improved the clinical efficacy rate for the treatment of CMP [RR = 1.17, 95% CI = [1.12, 1.22], $P < 0.00001$] (Fig. 3).

Comparison of VAS Scores

Four studies compared the VAS scores of the two treatments for CMP. Among them, two studies observed the scores before treatment and two weeks after treatment, while four studies observed the scores before treatment and five weeks after treatment. Before treatment, the total sample size of both groups was 408 cases (206 in the treatment group, 202 in the control group). There was statistical heterogeneity between the studies ($P = 0.005$, $I^2 = 77\%$); thus, a random-effects

model was chosen. The P-value was 0.69, indicating no significant difference in the VAS scores before treatment.

Two weeks after treatment, the total sample size of both groups was 280 cases (142 in the treatment group, 138 in the control group). There was statistical heterogeneity between the studies ($P < 0.00001$, $I^2 = 97\%$); thus, a random-effects model was chosen. The P-value was 0.10, indicating no significant difference in the VAS scores two weeks after treatment.

Five weeks after treatment, the total sample size of both groups was 408 cases (206 in the treatment group, 202 in the control group). There was statistical heterogeneity between the studies ($P = 0.00006$, $I^2 = 83\%$); thus, a random-effects model was chosen. The P-value was less than 0.00001, indicating a significant difference in the VAS scores five weeks after treatment. The meta-analysis results showed that compared to the control group, the addition of traditional Chinese medicine external treatment reduced the VAS scores of patients with CMP five weeks after treatment (Fig. 4).

Comparison of Efficacy between Traditional Chinese Medicine Fumigation and Topical Application

In the studies of overall effectiveness rate, subgroup analysis was conducted based on the differences between traditional Chinese medicine fumigation and

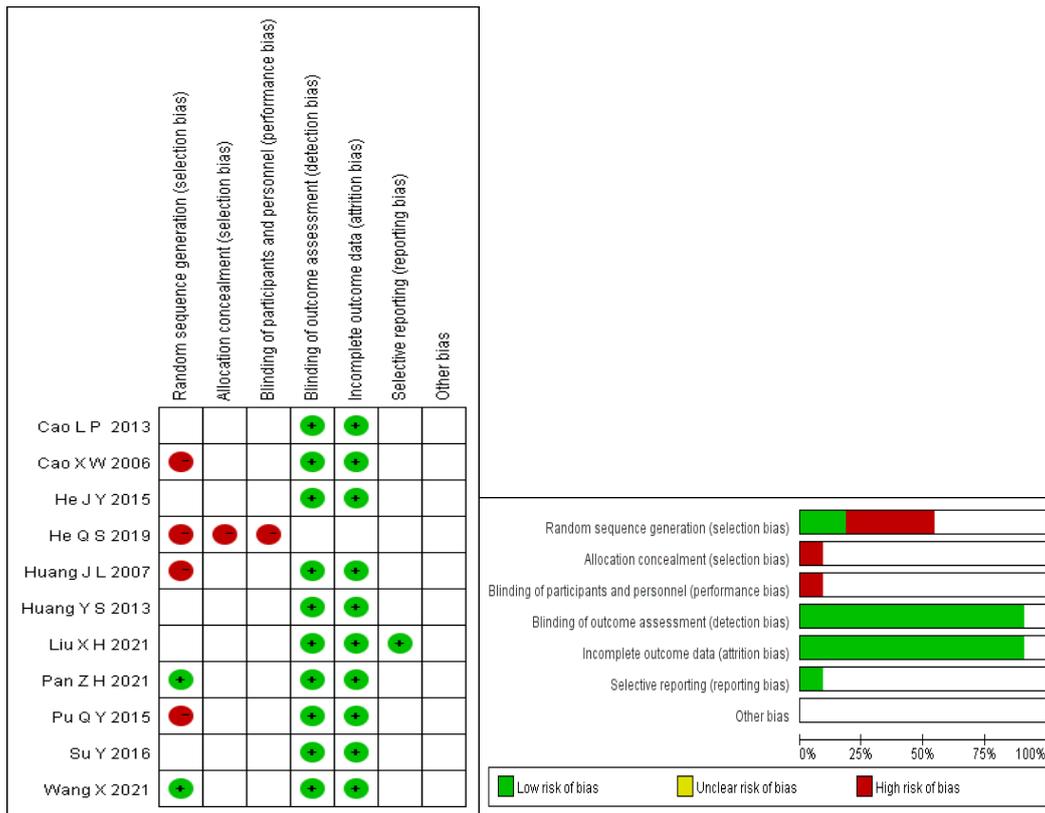


Fig. 2 — Methodological quality of the included studies.

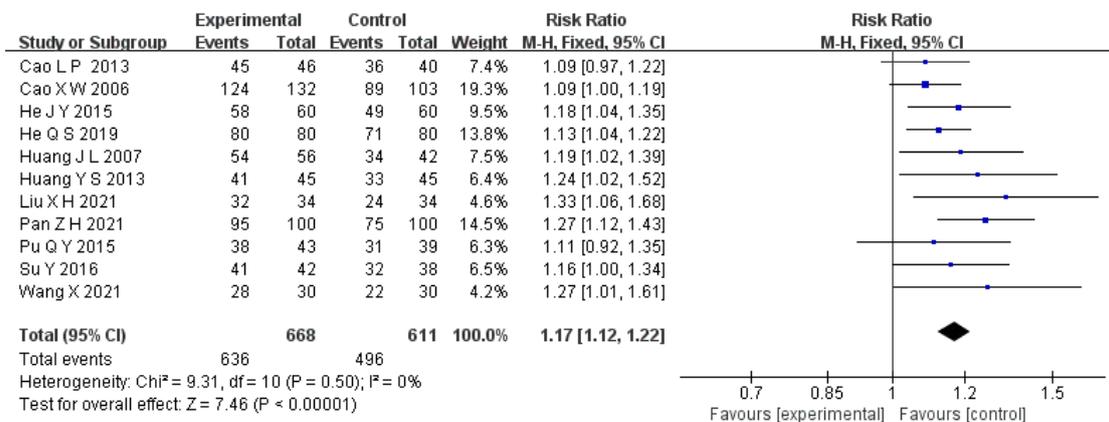


Fig. 3 — Comparison of Clinical Efficacy Rates.

topical application. When the treatment group used traditional Chinese medicine fumigation, the results showed that the treatment effect of the experimental group was significant [RR=1.17, 95% CI (1.06,1.28), P=0.001]; when the treatment group used traditional Chinese medicine topical application, the results showed that the treatment effect of the experimental group was significant [RR=1.14, 95% CI (1.08,1.20), P<0.00001]. In addition, we found that in the subgroup of traditional Chinese medicine fumigation, the heterogeneity was significantly higher than before (I²=54%, P=0.12). Therefore, the different methods

of traditional Chinese medicine external treatment might be one of the sources of heterogeneity in this study (Fig. 5).

Comparison of Time to Onset of Effect

Among the 11 studies, two mentioned the time to onset of effect. The total sample size was 321 cases (178 in the treatment group, 143 in the control group). There was statistical heterogeneity between the studies (P = 0.08, I²= 66%); thus, a random-effects model was chosen. Meta-analysis results showed that compared to the injection of sodium hyaluronate

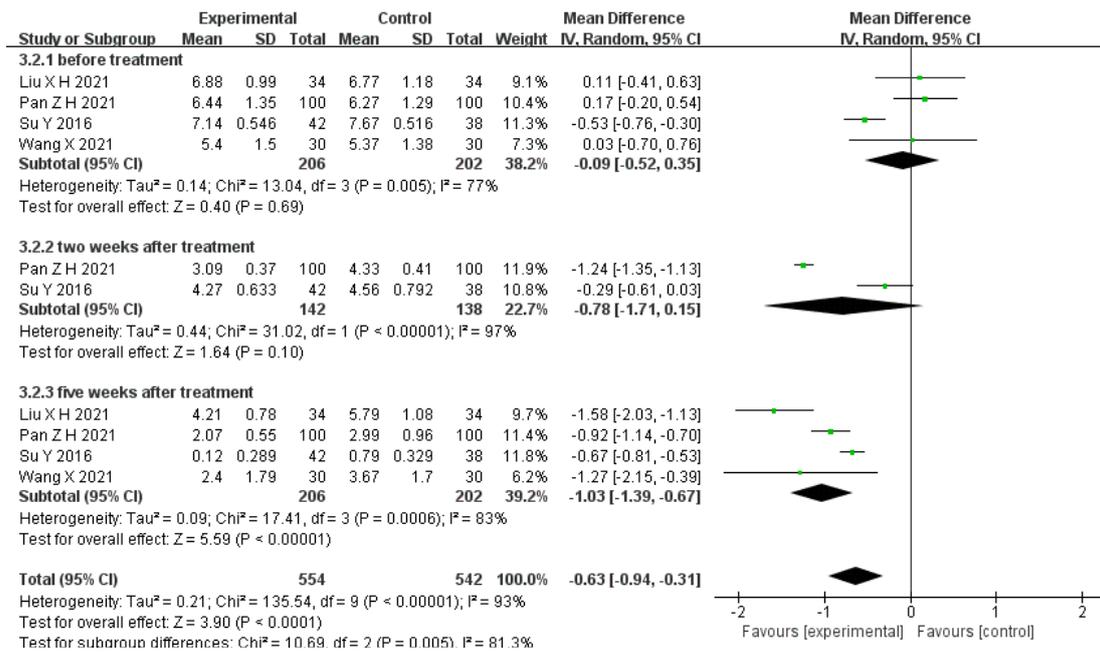


Fig. 4 — Comparison of VAS Scores.

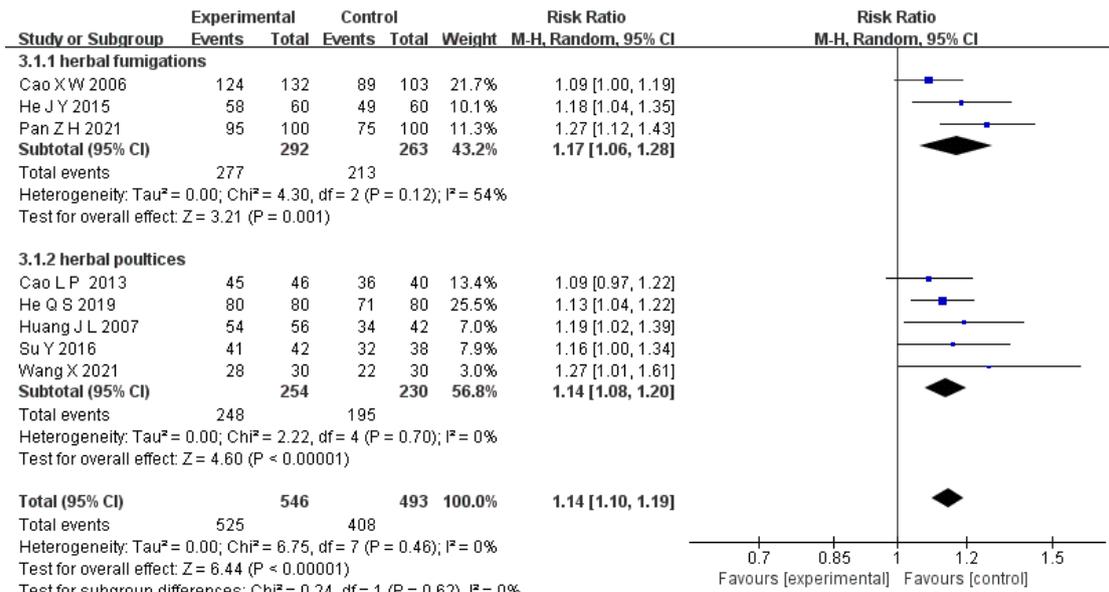


Fig. 5 — Comparison of Efficacy between Traditional Chinese Medicine Fumigation and Topical Application.

alone, the addition of traditional Chinese medicine external treatment could take effect more quickly and alleviate the pain of patients [RR = -7.44, 95% CI = (-9.86, -5.01), P < 0.00001] (Fig. 6).

DISCUSSION

In Western medicine, CMP is often treated with intra-articular injections of sodium hyaluronate, complemented with oral nonsteroidal anti-inflammatory drugs, but the outcomes are frequently

suboptimal. In traditional Chinese medicine, CMP is classified under “bi syndrome” and “tendon injury”, usually triggered by Qi stagnation and blood stasis after trauma or labor-induced Qi and blood deficiency. This can be exacerbated by external weakness and pathogenic invasion. The treatment chiefly involves activating blood and dissolving stasis, nourishing Qi and blood, and warming and activating tendons and vessels. External treatment methods from traditional Chinese medicine have been clinically applied to these types of diseases for thousands of years. They

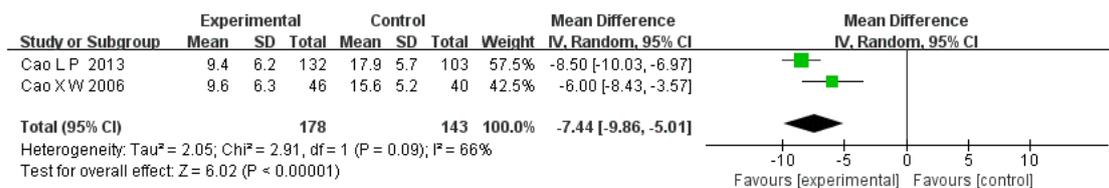


Fig. 6 — Comparison of Time to Onset of Effect.

are widely accepted by patients due to their simplicity, cost-effectiveness, rapid action, and minimal side effects²¹.

Upon conducting a meta-analysis, this study concluded that the clinical efficacy of the combination of traditional Chinese medicine external treatment and intra-articular injection of sodium hyaluronate surpasses that of standalone intra-articular injection of sodium hyaluronate. The combination of traditional Chinese medicine external treatment and intra-articular injection of sodium hyaluronate is more effective than the control group in improving VAS scores and reducing the time to the onset of therapeutic effect. No significant difference was found in clinical efficacy between the topical application and fumigation groups under the traditional Chinese medicine external treatment category.

However, this study has several limitations: The quality of the included studies is relatively low, with all literature being in Chinese and lacking foreign language studies. The studies lacked detailed descriptions of randomization methods, allocation concealment, blinding, dropout, and follow-up, thus presenting a certain risk of bias. The external treatments used in different studies varied. Even with the same method, such as traditional Chinese medicine topical application, there are no standardized guidelines for the medications used, their dosages, or usage time. None of the studies involved the evaluation of imaging data and thus lacked robust objective evaluation indicators. Finally, None of the studies involved long-term follow-up, meaning they can only illustrate short-term clinical effects. Hence, more comprehensive verification requires large-scale randomized controlled double-blind studies in combination with multicenter trials. When necessary, clinical trials should incorporate imaging, pathology, and biomechanics to obtain more comprehensive data support.

In conclusion, existing clinical trials suggest that the combination of traditional Chinese medicine external treatment and intra-articular injection of sodium hyaluronate is more effective than a standalone intra-articular injection of sodium hyaluronate. Although

the existing evidence has certain limitations, it still reflects the efficacy and advantages of the combination of traditional Chinese medicine external treatment and sodium hyaluronate injection in treating CMP. We look forward to more well-designed, high-quality, large-scale, multicenter, randomized double-blind controlled clinical experiments to verify this viewpoint in the future.

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: We declare that we have no conflict of interest.

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Authors' contributions: BHW designed this study, GCH ran the search strategy, BHW and QC extracted data, BHW wrote the manuscript. All authors read and approved the final manuscript. All authors have read and approved the current manuscript.

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