

CLINICAL STUDY

Therapeutic effects of low-frequency phonophoresis with a Chinese herbal medicine versus sodium diclofenac for treatment of knee osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial

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Abstract

OBJECTIVE: To evaluate the therapeutic effects of low-frequency phonophoresis with a Chinese herbal medicine (CHM) compared with sodium diclofenac (SD) for knee osteoarthritis (KOA).

METHODS: In this double-blind, randomized, placebo-controlled trial, 100 KOA patients were assigned randomly to a placebo group, a CHM group, or SD group. Low-frequency phonophoresis was used to improve the efficiency of drug delivery. Pain at rest [using a visual analog scale (VAS)], pain on movement (VAS), and range of motion (degrees) in the three groups were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMACAI) scores. Safety assessments comprised emergency adverse events, as

well as laboratory tests of blood biochemistry, creatinine, blood urea nitrogen, alanine aminotransferase and aspartate aminotransferase.

RESULTS: Significant improvements were found after treatment in all outcome measures except stiffness and range of motion in patients in the CHMP group and SDP group ($P < 0.05$). No significant differences in all outcome measures were found between the CHMP group and SDP group.

CONCLUSION: CHMP and SDP can show good therapeutic effects for KOA in terms of relieving pain and improving physical function.

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Key words: Osteoarthritis, knee; Phonophoresis; Drugs, Chinese herbal; Diclofenac; Ultrasonography

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease characterized by: chronic pain and stiffness in joints; joint deformity; articular instability; reduction in the range of motion (ROM); limited physical activity; and muscle weakness. It is seen commonly in weight-bearing joints [e.g., knee osteoarthritis (KOA)].¹

Approximately 250 million people worldwide have KOA.² In the USA, it is estimated that 80% of the population aged > 65 years may have radiographic KOA, but only 60% of these subjects may have symptoms.³ The World Health Organization estimated that the incidence of KOA in China in 2009 was 320-340 per 100 000 inhabitants.⁴ With an aging population, the challenge facing China will soon become severe.

The primary aim of KOA management is pain alleviation. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for KOA, but can give rise to gastrointestinal bleeding, cardiac risks, and stroke. Corticosteroids given *via* the oral route are not recommended for KOA treatment because of the: (a) hepatic first-pass effect and (b) high risk of adverse effects. Increasing the efficacy of drugs is one way to avoid (or reduce) these adverse effects.

Phonophoresis (also called "sonophoresis") involves the use of ultrasound to deliver therapeutic compounds through the skin in a non-traumatic manner. In this way, the hepatic first-pass effect and side effects of NSAIDs can be avoided. The NSAID sodium diclofenac (SD) is used for the treatment of acute or chronic conditions involving pain and inflammation. However, its application for KOA may be limited in view of its side effects. According to the literature,⁵ phonophoresis using SD is effective for knee-joint pain.⁶ However, whether sodium diclofenac phonophoresis (SDP) can relieve knee-joint stiffness and improve physical function is not known.

Chinese herbal medicine (CHM) has been used for thousands of years to treat all types of diseases and disorders, including KOA.⁷⁻⁹ However, the color, appearance, and taste of CHMs are not particularly attractive for patients. Hence, we screened several CHM prescriptions to find an efficacious recipe and created a gel formulation (Chinese patent number: CN102091158A). The main ingredients of this CHM prescription were Guizhi (cassia twig) and cinnamic aldehyde (C₉H₈O).

Previously, we showed that the amount of cinnamic aldehyde that could permeate the skin can be increased by using a low-frequency ultrasound appliance.¹⁰ Whether phonophoresis using this CHM is effective treatment for KOA and how its effects compare with those of SDP are not known.

Based on preliminary studies on SDP and the pure ingredients used for Chinese herbal medicine phonophoresis (CHMP) in KOA treatment in our previous research, we compared the effects of CHMP, SDP, and phonophoresis using 10% sodium chloride (placebo-controlled group (PC) group) for KOA treatment in terms of improvement of pain, ROM, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMACAI).

METHODS

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Beijing University of Chinese Medicine (Beijing, China). All patients provided written informed consent.

Research design

We designed a double-blind, randomized controlled trial. A table of random numbers was generated by a per-

sonal computer. The opaque-envelope method was used to hide this randomization.

All patients were assigned randomly to the CHMP group, SDP group, or PC group. Patients underwent CHMP, SDP, or placebo treatment once a day, five times a week, for 2 weeks. There was a 4-week follow-up observation after treatment cessation.

Subjects

Patients were recruited from January 2010 to November 2013 from the Third Affiliated Hospital of Beijing University of Chinese Medicine. All the patients participated in this research had signed an informed consent. Ultimately, 100 patients (100 affected knees) were recruited.

Inclusion criteria

The first set of criteria that patients had to fulfil was that set by the American College of Rheumatology for KOA:¹¹ (a) age 40-75 years; (b) symptomatic for ≥ 1 month; (c) primary source of pain did not respond adequately to anti-inflammatory drugs, and the number of leukocytes in synovial fluid was < 2000/mL; (d) a minimum score of 2 on a visual analog scale (VAS); (e) duration of stiffness in the morning ≤ 30 min.

The second set of criteria that patients had to fulfil was for the diagnosis of blood-stasis syndrome used in traditional Chinese medicine: (a) "stabbing" pain, and pain at a fixed location; (b) spotted, blue or purple tongue; (c) "choppy" pulse.

Exclusion criteria

Patients were excluded if they: (a) had severe disease of cardio-cerebral blood vessels, liver, kidneys, hematopoietic systems or a psychiatric disease; (b) were allergic to adhesive plasters, liniments, lotions, or external applications; (c) had received other therapies that could influence indices of the effects measured in this study; (d) were pregnant or lactating; (e) were undergoing glucocorticoid treatment < 4 weeks before study enrollment; (f) were receiving NSAID treatment < 2 weeks before study enrollment.

Therapies

Drug phonophoresis was implemented at points (2 cm in diameter) on the skin of medial and lateral patellar tendons. Participants were asked to suspend all other therapies during the trial.

Simultaneous low-frequency phonophoresis (40 kHz, 5000 Pa) was undertaken for 30 min each time.¹² For the CHMP group, the prescription was Guizhi (*Ramulus Cinnamomi*), Xixin (*Herba Asari Mandshurici*), Taoren (*Semen Persicae*), Baishao (*Radix Paeoniae Alba*), Huajiao (*Pericarpium Zanthoxyli Bungeani*), Honghua (*Flos Carthami*), Niuxi (*Radix Achyranthis Bidentatae*), Caowu (*Radix Aconiti Kusnezofii*), Ruxiang (*Olibanum*), and Moyao (*Myrrh*). Each of these drugs (100 g) was extracted and made into an ointment. Then, the

ointment was imported into gel chips, with each gel chip containing 3 mL of the ointment (Chinese patent number: CN102091158A).

For the SDP group, 10 mg of sodium diclofenac was contained in each gel chip. For the PC group, each gel chip contained 3 mL of sodium chloride.

Gel chips used in the three groups were made in China or by the US Medical Research Institute, and were similar in appearance, odor and texture. Personnel involved in the manufacture and packaging of medications were not allowed to communicate with study participants or research personnel.

Measurements

For all subjects, routine blood tests as well as levels of creatinine, blood urea nitrogen, alanine aminotransferase and aspartate aminotransferase were recorded before and after treatment to ensure patient safety. Investigators recorded adverse events and concomitant use of medications.

Outcome measurements were recorded 4 weeks after treatment cessation, and were based on changes in pain at rest (VAS), pain upon movement (VAS), range of motion (degrees) and WOMACAI scores.

Statistical analyses

SPSS v17.0 (IBM, Armonk, NY, USA) was used. All demographic and quantitative data are the mean \pm standard deviation ($\bar{x} \pm s$). The Student's *t*-test was employed to assess differences between two groups. The paired *t*-test was used to assess differences before and after treatment in the same group. A non-parametric test was employed for data with a non-normal distribution. One-way analysis of variance was used to assess intergroup differences (CHMP vs SDP vs PC) in various measurements. $P < 0.05$ was considered significant.

RESULTS

Study cohort

The diagram for assignment of randomization is shown in Figure 1. Four patients dropped out because follow-up information was not available for them, and they were excluded from statistical analyses. Hence, 96 patients were evaluated. No adverse events were observed.

Patient characteristics

Baseline characteristics of patients are shown in Table 1. There were no significant differences in age, sex, BMI, pain duration (months), pain at rest (VAS), pain upon movement (VAS), ROM (degrees) and WOMACAI scores among groups before treatment ($P > 0.05$).

Changes in outcome between groups after treatment

Significant differences were found for all outcome measures after treatment among the three groups ($P < 0.05$) (Table 2). Intergroup comparison revealed significant differences in all outcome measures after treatment except for stiffness and ROM between the CHMP group and PC group, and between the SDP group and PC group. No significant differences in all outcome measures were found after treatment between the CHMP group and SDP group.

DISCUSSION

We found that CHMP and SDP were effective for KOA treatment compared with the placebo group. CHMP and SDP could help relieve pain and improve physical function significantly. There were no significant differences in improvement of stiffness and ROM

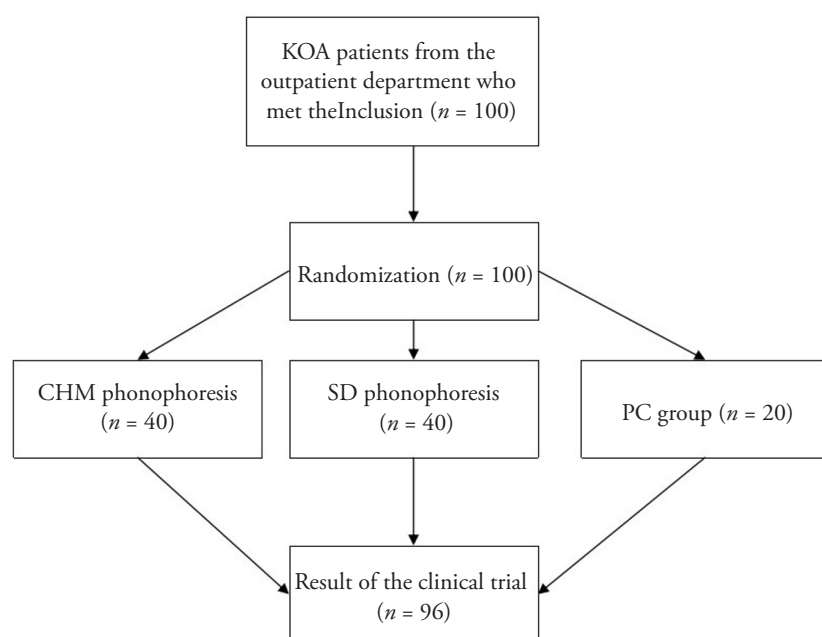


Figure 1 Flow diagram for randomized subject assignment

KOA: knee osteoarthritis; CHM: Chinese herbal medicines; SD: sodium diclofenac; PC: placebo controlled.

Table 1 Demographic and baseline characteristics of the patients ($\bar{x} \pm s$)

Item	CHM group (n = 38)	SD group (n = 39)	PC group (n = 19)	P value	
Age (years)	60.3±9.2 (41-70)	59.4±8.9 (44-72)	60.8±9.0 (43-75)	0.3	
Gender (female/male)	31/7	31/8	15/4	0.4	
BMI (kg/m ²)	30.6±4.5 (22.7-41.8)	31.0±5.2 (22.3-43.7)	30.9±4.8 (23.8-44.2)	0.5	
Pain duration (months)	7.5±6.2 (1-35)	6.9±3.9 (1-37)	7.3±5.9 (1-31)	0.3	
Pain at rest (Vas, 0-10)	5.7±2.4	5.1±2.0	5.6±1.4	0.8	
Pain on movement (Vas, 0-10)	8.2±2.3	8.6±1.5	8.3±1.9	0.5	
Range of motion (degrees)	125.0±15.6	124.4±14.5	123.0±15.3	0.8	
WOMAC scores	Pain	11.8±3.7	11.5±3.4	11.7±3.8	0.9
	Stiffness	2.8±1.6	3.1±1.6	2.9±1.7	0.9
	Physical function	42.3±9.5	42.1±11.6	41.7±10.2	0.5
Total	56.9±12.3	56.1±14.5	56.4±11.2	0.6	

Notes: CHM group: treated with CHM phonophoresis; SD group: treated with SD phonophoresis; PC group: treated with 10% sodium chloride phonophoresis. BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (Likert version); VAS: visual analog scale (0: no pain, 10: most severe pain); CHM: Chinese herbal medicine; SD: sodium diclofenac; PC: placebo-controlled.

Table 2 Changes in clinical outcome measures after treatment ($\bar{x} \pm s$)

Item	CHM Group (n = 38)	SD Group (n = 39)	PC Group (n = 19)	P value	
Pain at rest (Vas, 0-10)	1.42±0.41 ^a	1.06±0.57 ^a	5.62±1.41	0.016	
Pain on movement (Vas, 0-10)	1.22±0.34 ^a	1.62±0.52 ^a	7.31±0.89	0.001	
Range of motion (degrees)	175.00±5.61	172.40±4.54	123.80±10.33	0.062	
WOMAC scores	Pain	2.36±0.79 ^b	2.09±0.90 ^b	9.70±0.50	0.010
	Stiffness	2.10±0.20	2.10±0.60	2.0±0.79	0.752
	Physical function	12.70±2.51 ^b	13.10±1.61 ^b	37.70±8.20	0.013
Total	16.90±3.30 ^b	17.10±4.51 ^b	48.40±11.20	0.002	

Notes: CHM group: treated with CHM phonophoresis; SD group: treated with SD phonophoresis; PC group: treated with 10% sodium chloride phonophoresis. BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (Likert version); VAS: visual analog scale (0: no pain, 10: most severe pain); CHM: Chinese herbal medicine; SD: sodium diclofenac; PC: placebo-controlled. Compared with the baseline before treatment among the three groups, ^a $P < 0.01$, ^b $P < 0.05$.

between the two groups of subjects who received CHMP or SDP. This is the first double-blind, randomized controlled clinical trial designed to evaluate the efficacy of CHMP in KOA management.

The primary purpose of KOA treatment is to relieve pain and improve joint function so as to improve quality of life. Low-frequency phonophoresis can promote transdermal transport of various drugs, including macromolecules.¹³ However, not all drugs have increased permeation if used with ultrasound because of their different physicochemical properties.

The present study suggests that low-frequency phonophoresis using CHM and SD is effective for KOA treatment. The primary mechanism of phonophoresis is to increase skin permeability. Hence, we can infer that low-frequency phonophoresis can increase transdermal permeation of a CHM and SD.

Three major factors govern phonophoresis: (a) the

physicochemical properties of the drug formulation; (b) the ultrasound parameters; (c) skin.¹⁴ The ultrasound parameters used and the skin condition (all of the participants had a normal skin and without any skin disease) in the present study were identical. The only factor that could have influenced the outcome of our study was the physicochemical properties of the drug formulation. There are huge differences in terms of physical and chemical composition between CHMs and SD. The latter was a mixture of bioactive compounds, whereas SD is a drug of certain composition. A possible explanation as to why no differences were found between subjects who underwent CHMP or SDP was that although the physicochemical properties of different drugs may influenced the rate of permeation into skin, there was no difference between the delivery speed of a single drug and mixture of drugs.

However, the results of some studies are not in accor-

dance with those of our study in terms of SD permeation and improvements in stiffness and ROM after treatment with phonophoresis. Jaqueline *et al*¹⁵ found that SD permeation decreased in the presence of ultrasound. Falconer *et al*¹⁶ and colleagues reported a randomized controlled trial in which ultrasound relieved stiffness and pain for KOA patients with chronic contractures. Possible explanations for the different results are (a) Jaqueline *et al.* used pig skin (instead of human subjects) and ultrasound parameters that differed from ours and (b) none of our patients had a long-standing contracture.

This study could provide evidence for clinical treatment of KOA using phonophoresis. A multi-center, randomized controlled clinical trial is needed for a more definitive answer on the use of CHMP and SDP for KOA.

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