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European Journal of Integrative Medicine 5 (2013) 553–560

European Journal of INTEGRATIVE MEDICINE

www.elsevier.com/eujim

Original article

Efficacy of a Chinese herbal medicine in the treatment for patients with knee osteoarthritis: A randomised, double blind, placebo controlled pilot trial

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Received 13 March 2013; received in revised form 5 August 2013; accepted 5 August 2013

Abstract

Introduction: Chinese herbal medicine (CHM) is a popular alternative therapy for osteoarthritis (OA), however the majority of CHM efficacy studies have been methodologically inadequate. This study was the first randomised, double-blind, and placebo-controlled clinical trial of a CHM formula in an Australian OA population.

Methods: Eligible participants were randomised to receive either CHM or placebo over 12 weeks, with a one month follow-up. Each subject attended a total of six clinic visits. Study participants and investigators were both blinded to the block randomisation number code until the statistical analyses were completed. The Western Ontario and McMaster Universities Arthritis (WOMAC) Index was used as the primary outcome variable. Safety monitoring was conducted throughout the study.

Results: 47 participants were recruited into the study. The study had a 62% power to detect a significant difference in the primary outcome variable. Within-group analyses indicated significant improvements ($p < 0.05$) in terms of change of the WOMAC indices of pain, physical activity and total score in both groups, but there was no significant difference ($p > 0.05$) between the groups. The effectiveness of the CHM formula was maintained in the follow-up period but not in the placebo group. Safety data indicated the CHM was safe and well tolerated.

Conclusions: There is some limited indication of a therapeutic effect for the CHM. Larger scale studies over a longer time period are required.

This article belongs to the Special Issue: 'IG000020'.

Keywords: Osteoarthritis; Knee; Chinese herbal medicine; Double blind; Placebo controlled; Randomised clinical trial

Introduction

In Australia, osteoarthritis (OA) is the third largest contributor to life-years-lost due to disability, especially among women, and the second leading reason for patient visits to a rheumatologist [1]. Past research has shown that as many as 40% of OA sufferers used complementary and alternative medicine (CAM) [2]. As an alternative therapy, Chinese medicine includes Chinese herbal medicine (CHM), acupuncture and moxibustion and other therapies such as Qi Gong and Tai Chi (exercise therapy), diet therapy and massage. Limited scientific evidence from randomised controlled trials suggests that acupuncture is useful for pain control and that it can improve physical dysfunction associated with knee OA [3]. There are five published studies supporting the contention that acupuncture is significantly more effective in relieving pain and improving knee function in OA sufferers in comparison with either placebo or another active intervention [4–8].

However, although CHM is a popular form of CAM, there are few rigorous studies of the efficacy and safety of CHM in the treatment of OA to date. A recent review of the Chinese

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http://dx.doi.org/10.1016/j.eujim.2013.08.002

medicine treatment of OA reported that although some clinical studies have suggested that CHM may be effective in the treatment of OA symptoms, in the majority of cases the quality of those trials was poor [9]. Only two studies that were published in Chinese were double-blinded and randomised [10,11] and the Jadad scores (used to assess the quality of randomised controlled trials in pain research) [12] for the majority of the studies were low [9]. In Chinese medicine, it is generally thought that OA should be categorised as the clinical entity 'Bi Syndrome', and more specifically 'Bi Syndrome of Bone'. The word 'Bi' means painful obstruction which causes such symptoms as pain, numbness, paralysis, lack of sensation and stiffness. Bi Syndrome can refer to a range of rheumatologic diseases which demonstrate those symptoms mentioned above, such as rheumatoid arthritis, sciatica, osteoporosis, and gouty arthritis. Thus, the term Bi Syndrome is not a direct correlation with OA. Although OA and degenerative arthritis are both classified as 'Bi Syndrome of Bone' by the official clinical guidelines of the People's Republic of China [13,14], there is a lack of empirical data and rigorous research to support this classification. There have been arguments as to the classification of OA over the past few decades. A new theory which considers OA as a combined pattern of Bi Syndrome and 'Wei (Atony) Syndrome' has been applied in clinical practice relatively recently, with the fundamental disorder understood as being Wei Syndrome and the secondary disorder being Bi Syndrome. Wei Syndrome is characterised by weakness of the muscles and sinews. The ramifications of this different classification are that the therapeutic focus or thrust of the CHMs used to treat the disorder changes, and different herbs are utilised in the medicinal formulae.

Clinical anecdotal evidence from a major hospital in China supports this combination theory and the effectiveness of CHMs developed according to this theory in treating OA. Two clinical trials demonstrated that a CHM formula, which was designed based on this combination theory, achieved better clinical effectiveness than Ibuprofen and Viartril-s (a chondro-protective drug) [15,16]. In addition, there have also been some animal studies that found the same formula could improve the cartilage quality of OA mice at the histopathological level [17,18]. However, none of previous studies were conducted using a placebo control, nor were they double blinded. Given the encouraging but limited scientific evidence available in support of this emerging theory, a novel CHM formula of six herbs was developed using a CHM previously investigated in China as its basis [10,15], and its efficacy in the treatment of symptoms of OA of the knee was investigated using strict scientific protocol.

Materials and method

This randomised, double blind and placebo controlled study was conducted in the Alfred Hospital in conjunction with the Centre for Clinical Trials, Nucleus Network, Australia. Ethics approval was granted by the Alfred Hospital Human Research Ethics Committee and Victoria University Human Research Ethics Committee.

Study participants

Patients were recruited through newspaper advertisements and all gave consent to participate. The inclusion criteria were:

1. Unilateral or bilateral OA of the knee fulfilling the criteria provided the American College of Rheumatology (ACR) 1995 [19] were eligible to participate.
2. Radiographic ranking score of the primary tibio-femoral OA either grade II or grade III (Kellgren and Lawrence grading system) was considered as a condition of inclusion [20].

The exclusion criteria of the study included secondary OA or rheumatoid inflammatory or any other type of arthritis, accompanying OA of hip of sufficient severity to interfere with the functional assessment of the knee, having received intra-articular treatment of the involved joint or joint lavage in the previous 6 months or knee surgery during the previous 3 months.

Herbal preparation and dispensing

The herbal medicine and placebo were manufactured as soft gelatin capsules by Australian Good Manufacturing Practice (GMP) standards. Each capsule of the CHM formula contained concentrated herbal granules. The CHM formula was composed of six Chinese herbs commonly used in Australia and China, Bai Shao (*Radix Paeoniae Lactiflorae*), Qin Jiao (*Radix Gentianae Macrophyllae*), Mu Li (*Concha Ostreae*), Zhi Gan Cao (*Radix Glycyrrhizae Preparata*), Dang Gui (*Radix Angelicae Sinensis*) and Huai Niu Xi (*Radix Achyranthes bidentata*). The dosages of each herb were all within the conventional range according to Chinese herbal pharmacology [21].

The placebo capsules were filled with lactose for pharmaceutical use. The capsules were identical in appearance and could not be identified based on smell. Manufacture was based on the capacity of each capsule (500 mg), the ratio between the herbal extract and excipient (1:1.5).

Eligible participants were dispensed six bottles of herbal medicine or placbeo capsules (12 weeks dosage) at the randomisation visit (visit 2). The dose of the study medication was five capsules three times a day.

Randomisation and blinding

A block randomisation number code was generated by computer. Study participants were administered study medications sequentially in order of participation in the study. The randomisation code was only revealed after the statistical analyses were completed.

Study procedure

Each subject attended a total of six clinic visits including the screening visit (visit 1), the baseline/randomisation visit (visit 2/week 0), three visits during the treatment period (visit 3/week 2, visit 4/week 6, and visit 5/week 12), and the follow-up visit after cessation of the medication (visit 6/week 16).