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Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial

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SUMMARY

Objective: To assess the efficacy of thrice daily topical 4Jointz utilizing Acteev technology (a combination of a standardized comfrey extract and a pharmaceutical grade tannic acid, 3.5 g/day) on osteoarthritic knee pain, markers of inflammation and cartilage breakdown over 12 weeks.
Patients and methods: Adults aged 50–80 years ($n = 133$) with clinical knee OA were randomised to receive 4Jointz or placebo in addition to existing medications. Pain and function were measured using a visual analogue scale (VAS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scale at baseline, 4, 8 and 12 weeks. Inflammation was measured analysing IL-6 expression and CTX-2 presence as representative for cartilage breakdown using ELISA, at baseline and 12 weeks.
Results: Pain scores significantly reduced in the group who received 4Jointz compared to the group who received placebo after 12 weeks using both the VAS (−9.9 mm, $P = 0.034$) and the KOOS pain scale (+5.7, $P = 0.047$). Changes in IL-6 and CTX-2 were not significant (−0.04, $P = 0.5$; −0.01, $P = 0.68$). *Post-hoc* analyses suggested that treatment may be most effective in women (VAS −16.8 mm, $P = 0.008$) and those with milder radiographic osteoarthritis (OA) (VAS −16.1 mm, $P = 0.009$). Rates of adverse events were similar in both groups, excepting local rash that was more common amongst participants receiving 4Jointz (21% vs 1.6%, IRR 13.2, $P = 0.013$), but only 26% ($n = 4$) of participants with rashes discontinued treatment. There were no changes in systemic blood results.
Conclusions: Topical treatment using 4Jointz reduced pain but had no effect on inflammation or cartilage breakdown over 12 weeks of treatment.
Trial registration: Australia and New Zealand Clinical Trials registry ACTRN12610000877088.

Introduction

Knee osteoarthritis (OA) is common and is associated with pain and disability. Management of OA involves symptom control, usually non-steroidal anti-inflammatory medications (NSAIDs) or analgesic medication. The controversy surrounding COX-2 inhibitor use and heightened cardiovascular risk[1–4], highlights the importance of finding safer treatment options to minimise adverse side effects[5]. Natural agents such as capsaicin[6], and vitamins[5] have demonstrated improved overall patient outcomes, and may play a role in treatment of OA even if they are only moderately effective.

Comfrey (*Symphytum officinale*) is traditionally used to treat bone fractures, sprains and wounds[7] as it demonstrates anti-inflammatory and analgesic properties. A topical comfrey application (vs placebo) on acute ankle sprains in 142 participants decreased pain and swelling and improved mobility[8].

There were no reported adverse reactions and sole therapy was reported superior to a mixed comfrey and NSAID formulation[9,10]. Comfrey has also been used to specifically treat OA with two-thirds of recipients reducing or discontinuing their NSAID treatment[11]. Moreover, in a study involving 220 patients diagnosed with OA,

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those utilising topical comfrey therapy reported a marked reduction in VAS pain scores[12].

Persons with OA have been reported to have high levels of free radicals and reduced levels of antioxidants within the joint fluid[13]. Antioxidants such as tannic acid protect against the extracellular matrix cartilage degradation that radicals yield[14] and augment glycosaminoglycan binding to collagen. This ultimately contributes to the structural reinforcement of synovial articulating surfaces[15]. Preparations of tannic acid have been found to be superior to placebo in reducing pain and stiffness and improving physical function in primary OA[5].

Therefore, a number of complementary medicinal agents may be effective in reducing pain and inflammation. A pilot study of treatment using two different concentrations of comfrey vs placebo[16] showed that the comfrey mixtures were both superior to placebo in reducing WOMAC pain and stiffness scores, but there was no difference in outcomes between different concentrations. Grube *et al.*[12] also compared a comfrey root extract with placebo for painful knee OA (average duration 6.5 years). They observed a large reduction in pain VAS score, and WOMAC scores between comfrey and placebo after 3 weeks but this trial had methodological shortcomings.

We aimed to compare the effect of thrice daily topical 4Jointz utilizing Acteev technology (a novel and patented combination of a standardized comfrey extract and a pharmaceutical grade tannic acid, 3.5 g/day), or placebo on osteoarthritic knee pain, muscle strength, and markers of inflammation and cartilage breakdown over 12 weeks in participants aged >50 with OA and a pain intensity score >40 mm on a visual analogue scale (VAS).

Methods

Trial design

This study was a two centre double blind parallel-group placebo controlled randomised trial of topical 4Jointz vs placebo with a 1:1 allocation ratio.

Settings and locations

Participants were recruited from September 2010 to May 2011 through advertising in local print media in Hobart, Tasmania and Sydney, New South Wales in Australia. Participants attended clinics at either the Menzies Research Institute Tasmania in Hobart, or the Royal North Shore Hospital in Sydney.

Inclusion and exclusion criteria

Participants were aged >50 years, with clinical knee OA confirmed by a Rheumatologist using American College of Rheumatology (ACR) criteria[17], and had knee pain on most days of >40 mm on a 100 mm VAS on their worst knee. Participants were excluded if they had knee X-rays with Grade 3 joint space narrowing (JSN) using the Osteoarthritis Research Society International (OARSI) atlas[18], read by chief investigators (GJ and LM) on diagnostic radiographs; had other forms of arthritis (including hip OA); had significant knee injury in the last 6 months; or were unable to provide informed consent. Participants who were otherwise eligible and had Grade 3 JSN in their worst knee were able to enter the study if JSN was <3 in the other knee.

Participants

Participants were screened over the telephone. If they met the inclusion criteria and did not meet the exclusion criteria, they were invited to attend a study centre for screening. Screening and examination was undertaken by a rheumatologist (GJ, LM) and a nurse (MC, MG, TF). Participants supplied a blood specimen for serum chemistry, renal function and inflammatory markers; a urine sample for cartilage metabolites; and had a semi-flexed knee X-ray. Use of other medication (including pain medicines) was allowed but kept constant through the trial period where possible. All participants provided written consent. The study was approved by the Human Research Ethics Committee (Tasmania) Network and the Northern Sydney Local Health District Human Research Ethics Committee and was performed in compliance with the Helsinki Declaration.

Interventions

Participants received either 4Jointz cream or identical but inert placebo. This is a combination of a standardized comfrey extract (200 mg/g) and pharmaceutical grade tannic acid (100 mg/g) plus other ingredients including aloe vera gel (300 mg/g), eucalyptus oil (40 mg/g), and frankincense oil (1.0 mg/g).

Participants were instructed to apply enough cream to coat the knee with a thin coating which was then massaged in using gentle circular motions for 3–5 min three times daily. Participants were supplied one 100 g tube of cream at each visit. Therefore the daily dose was approximately 3.5 g/day. Study medication was stored in a locked cupboard prior to dispensing, and dispensed when patients successfully completed the screening visit(s). Treatment continued for 12 weeks, where medication use was discontinued while maintaining the blind in order to observe response to treatment withdrawal. Participants were re-assessed at 16 weeks.

Outcomes

Primary hypotheses were that 4Jointz was superior to placebo at 12 weeks for change in: knee pain [using the pain intensity VAS and the pain scale from the Knee Injury and Osteoarthritis Outcome Score (KOOS) Questionnaire]; markers of inflammation (IL-6), and cartilage breakdown (CTX-2).

Secondary hypotheses were that 4Jointz was superior to placebo for change in: pain between baseline and 4 and 8 weeks; response using the Osteoarthritis Research Society International (OARSI) response criteria[19], lower limb muscle strength and use of paracetamol between baseline and 4, 8 and 12 weeks.

Additionally, we observed the effect of treatment withdrawal on pain, KOOS scales, OARSI response criteria, muscle strength and paracetamol use, by observing change in these outcomes between cessation of treatment at 12 weeks and the last observations at 16 weeks. All hypotheses were *a priori*.

Outcome measures

Pain and function

Knee pain intensity was measured using a 100 mm VAS on four occasions (baseline, 4, 8, 12 and 16 weeks). Participants were asked “on this line, where would you rate your pain today?”.

Knee pain and symptoms were also assessed using the KOOS questionnaire on all five occasions[20]. These two subscales have nine (pain) and seven (symptoms) questions, each with five response levels scored from 0 to 4. Subscales were transformed according to instructions in the original manuscript[20]. The transformed scale had possible values from 0 to 100 with zero representing extreme knee problems and 100 representing no knee problems. Baseline questionnaires were completed in the clinic. Subsequent questionnaires were completed by mail.