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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.

Inflammation and cartilage breakdown

Urine and blood samples were collected at baseline and 12 weeks stored at −80°C. Samples were assayed in duplicate for the cartilage breakdown marker CTX-II (urine) using a Human CTX-2 Enzyme-linked immunosorbant assay (ELISA) kit (Cusabio Biotech Co, Hubei Province, China), and for the inflammatory marker IL-6 (blood) using a Human IL-6 ELISA MAX Deluxe SET kit (Biolegend, California, USA) following the manufacturers' instructions. Urine was diluted 1:2, and blood was used undiluted for the assay. Absorbance was read at 450 nm with reference wavelength at 570 nm. Samples with <1 ng/mL (CTX) or <1 pg/mL (IL-6) were deemed out of range and analysed with a value of zero.

A standard curve was run on each plate, in duplicate ($R^2 > 0.997$). Absorbance was read using SoftMax Pro software, which calculated the standard curves and concentrations for each unknown on a plate by plate basis.

OMERACT–OARSI response criteria

Response to 4Jointz was assessed using a modified version of the OMERACT–OARSI set of response criteria[19]. Participants were classed as responding if they had high improvement in pain (using the VAS) or function (using KOOS function scale) of ≥50% and absolute change ≥20; or if they had improvement in both pain and function of ≥20% or ≥10. Criteria for change in participants' global assessment were not included as we did not ask questions about global assessment.

Paracetamol use

Paracetamol usage was recorded at baseline (along with other medication) and at each subsequent visit. Daily dose was averaged over a 28-day month in participants who did not use paracetamol every day.

Muscle strength

Leg strength was measured to the nearest kilogramme in both legs simultaneously, using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as previously described[21]. This tests isometric strength, predominantly of the quadriceps and hip extensors.

Safety

Adverse events were defined as any untoward event occurring during the trial regardless of whether it was considered medication-related. Serious adverse events were defined as unplanned hospital admissions, new cancer diagnoses (excluding skin cancer) or death during the 16 weeks of the study. Blood tests were performed at baseline and 12 weeks to assess safety, and included general biochemistry, red and white cell parameters and platelet counts.

Sample size

Sample size for pain intensity using VAS was based on demonstrating a 10 mm greater reduction compared to placebo with a standard deviation (SD) of 20 mm[22,23]. Therefore a change of 10 mm reduction on the VAS (compared to placebo) required 62 participants per group with $\alpha = 0.05$ and $\beta = 0.20$. We aimed to enrol 70 participants in each group to allow for dropouts.

Randomisation and sequence generation

Participants were randomly allocated to one of two treatment arms (4Jointz or placebo) using computer generated block randomisation in blocks of four. The random allocation sequence was automatically generated, and a security protected central automated allocation procedure was used to allocate participants to treatment arm 1 or 2. This was then used by one author (LL, who had no contact with participants) to dispense tubes of allocated medication for the Hobart participants. Research nurses enrolled participants in the trial, and then gave tubes to each individual patient. The procedure for Sydney patients was the same except that the pharmacy at the Royal North Shore Hospital dispensed allocated medication to Sydney participants. The active treatment and placebo product were visually and aromatically identical. Participants and staff involved in patient care remained blinded to treatment allocation throughout the trial.

Statistical methods

We used Stata 12.0 (StataCorp LP) for statistical analyses. Statistical significance was set as a P value ≤0.05 (two-tailed). Adjustments for multiple comparisons were not used. We used a modified intent to treat (ITT) approach for data analysis[24], where all patients who were randomised to receive treatment were included in the analysis. Secondly, missing data was imputed using Stata's multiple imputation (MI) functions, using 50 imputations per observation, from non-missing baseline data, using multivariate normal regression to generate outcome data. Change in outcomes was assessed using the difference between the factor at baseline and follow-up, and using linear regression. Data was checked for normality using Stata's pnorm and qnorm functions, and for homogeneity of variance. Since change in CTX-2 and change in IL-6 both had one highly influential outlier (>99th percentile), non-parametric testing was used for the non-imputed analysis (Somers' D). Poisson regression was used to compare numbers of adverse events. There was no evidence of overdispersion. Change in binary outcomes was assessed using logistic regression for panel data (xtmelogit), clustering on ID to account for correlated outcomes within an individual.

Post-hoc analyses on the change in outcomes by sex, OARSI grade and body mass index (BMI) were also performed. Sensitivity analyses were performed on estimates of the effect of treatment between baseline and 12 weeks, adjusting for covariates where there was a statistically or clinically significant difference at baseline (OARSI grade, use of paracetamol, use of glucosamine).

Results

Participants

A total of 167 participants attended screening for the study. Most participants who were subsequently excluded ($n = 34$) had knee OA which was too severe (Grade 3 JSN; $n = 30$). The remaining 133 participants were randomised to receive either 4Jointz or placebo. By 12 weeks 81% of the cohort had been retained, 88% in the placebo group and fewer patients (75%) in the intervention group ($P = 0.03$) (Fig. 1).

Table I shows the characteristics of study participants at baseline by treatment received. At baseline, participants ($n = 133$) had a mean age of 64.8 years, mean BMI of 29.8 and mean VAS score of 53.2. All participants had clinical knee OA, and the majority also had radiographic OA, defined as any score ≥1 for JSN or osteophytes[17]. Participants receiving 4Jointz and placebo were well matched, but the groups differed in their use of glucosamine ($P = 0.04$) and number of pain medicines ($P = 0.049$), which were predominantly differences in use of paracetamol and glucosamine.

Outcomes

For the primary hypotheses of change between baseline and 12 weeks and using the ITT analysis, Table II and Fig. 2 show that the

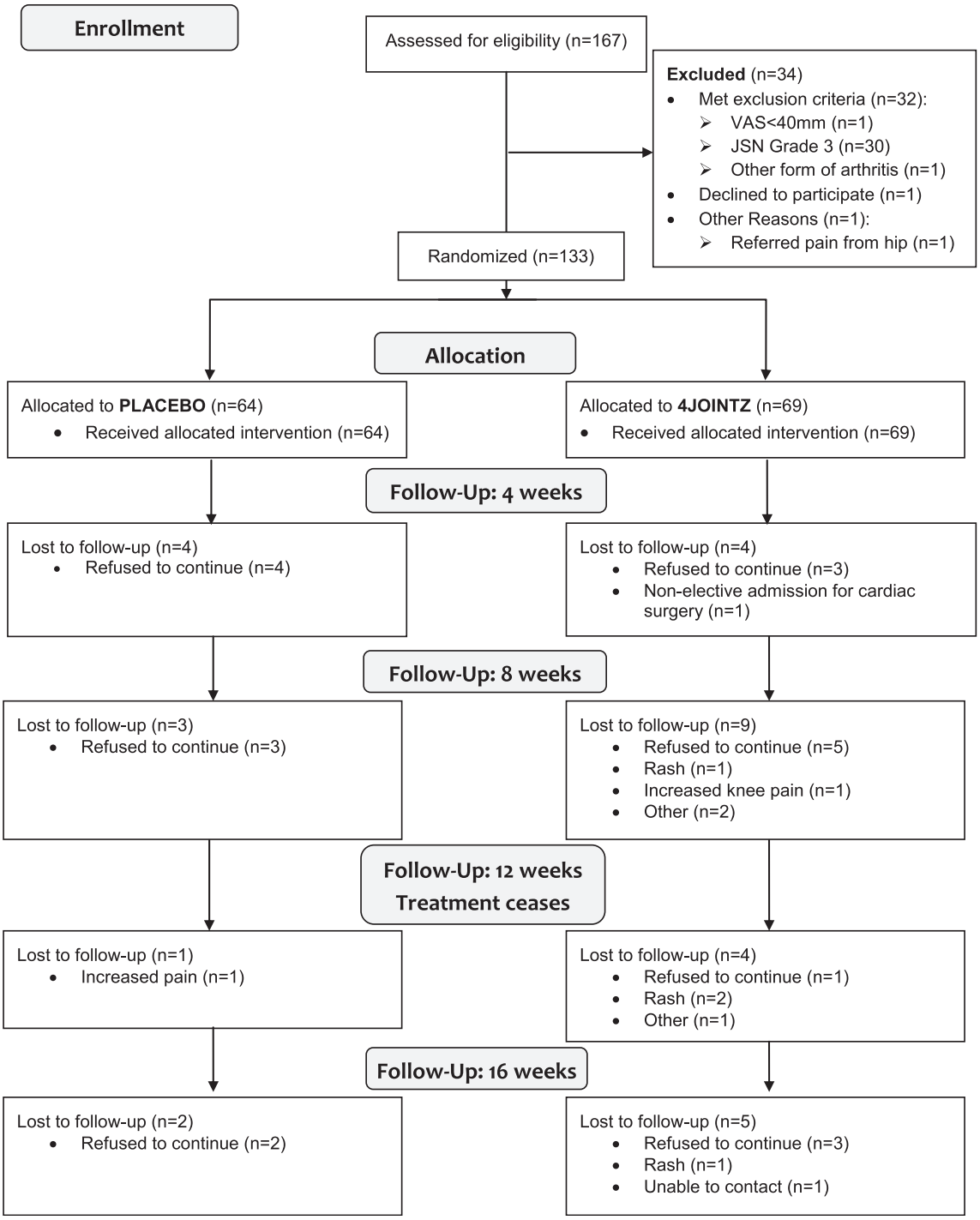

Fig. 1. Study flow chart.

treated group had an average 9.9 mm ($P = 0.034$) greater reduction in knee pain on the VAS scale and a 5.7 ($P = 0.047$) point improvement on the KOOS pain scale, with the effect size of the estimates remaining similar after adjustment for baseline differences. Neither change in IL-6 [−0.04, 95% CI (−0.2–0.07; $P = 0.48$)] nor change in cartilage breakdown (−0.01, 95% CI −0.1 to +0.1; $P = 0.68$) changed significantly between baseline and 12 weeks.

For the secondary outcomes, change in pain using the KOOS pain scale was significantly different by 8 weeks, with patients receiving 4Jointz experiencing less pain (6.1, $P = 0.025$). Participants receiving 4Jointz also had greater leg strength (2.9 kg, $P = 0.02$) after 12 weeks of treatment, this result remained statistically significant after adjustment for baseline differences. Treatment with 4Jointz did not change clinical response (using the OMERACT–OARSI response criteria), and reductions in paracetamol dose did not reach statistical significance [−404.2 mg (95% CI −1268.8–460.4; $P = 0.35$)].

Using imputation, the effect size reduced slightly for the pain outcomes, with significance becoming borderline at 12 weeks

Table I
Baseline characteristics of study patients

	4Jointz	Placebo
	$n = 64$	$n = 69$
	Mean (SD)	Mean (SD)
Age	64.3 (9.8)	65.5 (8.3)
Sex (% male)	45	36
Weight	83.3 (15.9)	81.6 (16.6)
BMI	29.7 (4.9)	29.9 (5.1)
Medication use		
Paracetamol (%)	30	41
Average paracetamol dose (mg)	1710 (1374.9)	1475 (1165.7)
Fish oil (%)	30	34
Glucosamine (%)	22	38
COX-2 inhibitors (%)	14	16
Radiographic OA (*n*, %)*		
Grade 0	12 (17)	18 (28)
Grade 1	24 (35)	13 (20)
Grade 2	22	21 (16)
Grade 3	0	0
Number of pain medicines (*n*, %)		
0	31 (45)	16 (25)
1	18 (26)	17 (27)
2	7 (10)	16 (25)
3	13 (19)	15 (23)
Previous knee surgery, self-reported (%)	10	14
Pain intensity (VAS score)	52.7 (15.7)	53.8 (14.5)
Pain intensity (KOOS)	57.0 (12.7)	56.2 (15.5)
Symptoms score (KOOS)	59.6 (14.9)	58.6 (16)
IL-6 (pg/mL)	5.7 (7.2)	6.4 (13.9)
CTX-2 (ng/mL)	20.8 (48.4)	21.5 (38.5)

* Radiographic OA is using OARSI criteria.

($P = 0.06$ for VAS and 0.08 for KOOS) but was significant at 8 weeks for KOOS and remained significant for muscle strength.

Treatment ceased at 12 weeks. By 16 weeks, pain, symptoms and leg strength had returned to baseline (Table II).

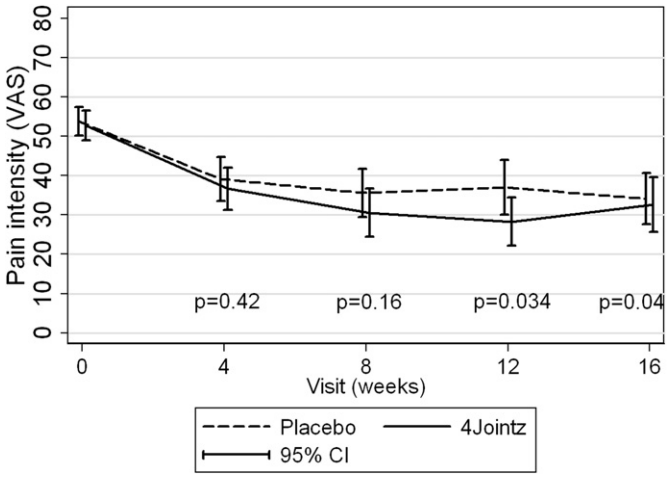

Fig. 2. Pain intensity (using visual analogue score) over the study time frame, using unadjusted data and 95% CI of the point estimates. *P* values are for the effect of treatment using change in VAS scores from baseline, excepting 16 weeks where *P* is for the effect of treatment cessation.

Post-hoc analyses

We conducted some additional *post-hoc* analyses on the pain measures. Interactions between treatment and sex were significant or almost significant using a *P* value of 0.1. Women responded better to treatment than men, using both the VAS pain intensity score and the KOOS pain scale; and persons with early OA (OARSI grade 0 or 1) responded better than persons with late OA (OARSI grade 2) (Table IV).

Adverse events

Adverse events were common, but the prevalence and number of adverse events were not different between patients receiving

Table II
Effect of treatment with 4Jointz: change in study outcomes between baseline and 4, 8 and 12 weeks of treatment, and change in outcomes after treatment cessation (between 12 and 16 weeks)

	4 weeks		8 weeks		12 weeks		Offset effect 12–16 weeks	
	Effect size (β coefficient) (95% CI)	*P*	Effect size (β coefficient) (95% CI)	*P*	Effect size (β coefficient) (95% CI)	*P*	Effect size (β coefficient) (95% CI)	*P*
No imputation	$n = 124$		$n = 112$		$n = 106$		$n = 99$	
Pain (VAS)	−3.0 (−10.4–4.4)	0.42	−5.7 (−13.8–2.3)	0.16	**−9.9 (−19.1 to −0.8)**	**0.034**	**9.2 (0.4–17.9)**	**0.04**
Pain (KOOS)	1.3 (−3.3–5.9)	0.58	**6.1 (0.8–11.4)**	**0.025**	**5.7 (0.1–11.3)**	**0.047**	**−6.8 (−13.0 to −0.5)**	**0.03**
Symptoms	1.7 (−2.6–6)	0.45	−0.2 (−5.3–4.9)	0.94	4.7 (−1.3–10.7)	0.12	**−8.5 (−14.1 to −2.8)**	**<0.001**
Leg strength (kg)	−0.02 (−2.4–2.4)	0.99	1.9 (−0.6–4.5)	0.13	**2.9 (0.5–5.3)**	**0.02**	**−2.5 (−4.9 to −0.1)**	**0.04**
IL-6	–		–		−0.04 (−0.2–0.07)	0.48		
CTX-2	–		–		−0.01 (−0.1–0.1)	0.68		
OMERACT–OARSI response criteria†	1.2 (0.7–2.1)	0.56	1.4 (0.82–2.4)	0.22	1.3 (0.8–2.2)	0.34	1.1 (0.7–2.0)	0.63
Paracetamol use (yes/no)*	1.0 (0.6–1.7)	0.85	1.0 (0.8–1.4)	0.82	1.0 (0.8–1.2)	0.80	0.2 (0.02–1.5)	0.11
Paracetamol dose (in those using at baseline)	−70.7 (−759.9–618.6)	0.84	−247.6 (−925.6–430.5)	0.46	−404.2 (−1268.8–460.4)	0.35	−308.9 (−802.8–185)	0.21
Using imputation	$n = 133$		$n = 133$		$n = 133$		$n = 133$	
Pain (VAS)	−2.5 (−10–5.0)	0.52	−4.2 (−12.4–4)	0.31	−8.7 (−17.9–0.5)	0.06	8.1 (−1.4–17.7)	0.09
Pain (KOOS)	1.1 (−3.6–5.8)	0.64	**5.4 (0.02–10.9)**	**0.049**	5.3 (−0.7–11.3)	0.08	−4.6 (−11.8–2.6)	0.20
Symptoms (KOOS)	1.2 (−3.3–5.7)	0.59	−0.4 (−5.5–4.7)	0.87	3.6 (−2.4–9.5)	0.24	**−6.3 (−12.5 to −0.03)**	**0.049**
Leg strength (kg)	0.2 (−2.2–2.7)	0.85	1.8 (−0.9–4.4)	0.19	**3.0 (0.2–5.8)**	**0.035**	−2.1 (−4.6–0.5)	0.11
IL-6	–		–		0.04 (−4.4–4.5)	0.99	–	
CTX-2	–		–		−23.3 (−90.7–44.2)	0.49	–	
OARSI–OMERACT	1.2 (0.6–2.1)	0.63	1.4 (0.8–2.5)	0.24	1.3 (1.3–2.2)	0.43	−0.8 (−1.2 to −0.4)	0.67
Paracetamol use (yes/no)*	0.4 (0.1–1.5)	0.20	0.4 (0.1–1.6)	0.18	0.4 (0.1–1.6)	0.21	0.81 (0.31–2.1)	0.66
Paracetamol dose (in those using at baseline)	−77.5 (−685.3–530.2)	0.80	−251.7 (−834.7–331.3)	0.39	−356.2 (−1053.7–341.3)	0.31	−222.0 (−570.5–126.5)	0.21

The statistics presented are the change in the outcome between baseline and the time point of interest except the response criteria.
The number presented is the beta coefficient (and 95% CI) for the additional effect of treatment over that of placebo except for *odds ratios or †incidence rate ratios, as indicated.
Treatment ceased after 12 weeks.
Bold typeface indicates statistically significant result ($\alpha \leq 0.05$).

Table III
Prevalence and number of adverse events, by treatment received

	Placebo	4Jointz	*P*
	n = 62	*n* = 67	
Adverse events			
Prevalence of at least one adverse event (*n*, %)	38 (61)	48 (72)	0.47
Number of adverse events	67	78	0.85
Prevalence of (*n*, %) rash	1 (1.6)	14 (21)	**0.013**
Upper respiratory tract infection	11 (18)	10 (15)	0.69
GI upset	4 (6.5)	2 (3)	0.37
Headache	3 (4.8)	6 (9.1)	0.38
Increased knee pain	3 (4.8)	2 (3)	0.60
Knee swelling	1 (1.6)	1 (1.5)	0.96
Abnormal blood results	24 (41)	29 (44)	0.82
Elective hospital admissions	3 (4.8)	1 (1.5)	0.31
Serious adverse events			
Number of non-elective hospital admissions	0	1	
Cancer	0	0	
Death	0	0	

Bold typeface indicates statistically significant result ($\alpha \leq 0.05$).

4Jointz or placebo (Table III). Prevalence of rash (localised skin irritation at the site of application) was significantly higher in patients receiving 4Jointz (risk ratio 13.2, $P = 0.013$). Participants experiencing localised irritations were advised to cease using the treatment, then rechallenge with ointment after a few weeks. Treatment ceased if the rash recurred. This was severe enough to discontinue the study drug in four participants (26% of those with rash) (Fig. 1). One participant had a serious adverse event, which was a non-elective hospital admission where they received a cardiac stent, which we considered not causally related to the study drug.

Discussion

This study demonstrates that 4Jointz is a safe and effective topical treatment for mild to moderate knee OA in participants aged 50–80 years. 4Jointz was effective in reducing pain at 12 weeks using both pain measures, and by 8 weeks using the KOOS scale. 4Jointz also increased quadriceps strength by an average of 3 kg after 12 weeks, but had no effect on systemic inflammation or cartilage breakdown over 12 weeks of treatment. When treatment was discontinued after 12 weeks, we observed rapid worsening of pain, symptoms and leg strength. This implies that 4Jointz is symptom modifying.

This is the longest reported duration of use of comfrey for osteoarthritic knee pain, with previous trials being of 3 [12] or 6 weeks duration[16]. Patients had the largest responses to treatment at the last occasion during treatment in this study (12 weeks). All three trials support a role for comfrey as a topical treatment for knee pain and OA. However, it is not possible to directly compare results between our study and these others because the patient populations are different. The study described in Grube *et al.*[12] included participants with knee pain but not necessarily knee OA, and with pain scores (on VAS) as low as 23 mm suggesting that participants in the Grube trial may not have knee OA, or are earlier in the disease course. The larger effect observed in this study is consistent with our results in early OA. They also requested participants discontinue other medication. Omitting participants taking analgesics or anti-inflammatory medications would rule out nearly 60% of our participants and thus our results should be seen as an additional benefit with 4Jointz rather than the sole benefit. Grube *et al.*[12] also observed a much greater reduction in pain with the use of comfrey than we did at a comparable time point, but this may be due to the use of an aggregate of two WOMAC subscales, artefactually doubling the apparent magnitude of benefit.

While our results show that 4Jointz is superior to placebo, we observed clinically important changes in self rated outcomes in both treatment groups. These were most evident with pain but we also observed them in the KOOS symptom score.

The skin irritation appears causally related to the use of 4Jointz. Otherwise, the side effect profile we observed is similar to reported in a pilot study of 4Jointz[12,16]. Only the study by Smith *et al.* [16] reported the rash. Overall 4Jointz appears safe and well tolerated. Most importantly, the renal toxicity associated with pyrrolizidine-type alkaloids, associated with oral use of comfrey[25] appears absent in topical use, as expected, with no change in systemic blood tests. The skin irritation reversed on cessation of treatment, and only reappeared in around one-quarter of those with rash.

We supplied participants with one tube of cream per month. We have observed clinically significant changes with one tube of cream per month or about 3.5 g/day. Since only one dose of 4Jointz was used in this study we cannot compare with other concentrations. However, Smith *et al.* compared formulations of, 10% and 20% comfrey extract and pseudoplacebo, and whilst both were superior to placebo, the treatment arms were not significantly different from each other[16].

Since *post-hoc* analyses suggested that treatment may be most effective in women and those with milder radiographic OA, future studies should consider studies specifically in these populations.

Strengths of this study include the comparatively long duration of treatment, the defined study population and standardised meaningful outcome measures. The major limitation of this study is the difference in dropout rates between the groups receiving placebo and 4Jointz, with more patients ceasing treatment in the 4Jointz group. This included but was not limited to patients who experienced rash and were advised to cease treatment. However, we have imputed missing data and the results are similar but of slightly lower magnitude to those obtained in the main analysis, giving us confidence that our results have not been substantially influenced by unequal dropouts between groups.

Conclusions

Topical treatment using 4Jointz is a safe and effective treatment for the symptoms of knee OA in participants with moderate knee

Table IV
Change in pain scores between baseline and 12 weeks by sex, OARSI grade and BMI, by treatment group

Change in:		*n*	Placebo	*n*	4Jointz	Diff.	*P*
VAS score	Females	36	−12.9 (−21.7 to −4.1)	24	−29.7 (−37.1 to −22.2)	−16.8	**0.008**
	Males	20	−20.4 (−31.8 to −8.9)	26	−21.6 (−31.4 to −11.7)	−1.2	0.87
KOOS pain score	Females	35	1.9 (−2.8–6.6)	23	10.6 (5.2–16.0)	8.7	**0.018**
	Males	19	11.0 (6.0–16)	26	10.9 (3.8–18.1)	−0.1	0.99
VAS score	Early OA*	29	−9.9 (−20.3–0.5)	26	−26 0 (−31.6 to −20.4)	−16.1	**0.009**
	Late OA	17	−22.3 (−33.7 to −10.9)	16	−29.6 (−42 to −17.3)	−7.3	0.36

Bold typeface indicates statistically significant result ($\alpha \leq 0.05$).
* Early OA is OARSI grade 0 or 1, late OA is OARSI grade 2.

pain on most days, and clinical OA. In particular, it reduces pain and increases muscle strength, but has no effect on systemic inflammation or cartilage breakdown over 12 weeks of treatment.

Authors roles

LM and GJ were involved in the conception and design of the study and obtained study funding. TF was involved in acquisition of data. LL, ED-S and MK were involved in analysis of data; SQ provided statistical advice. HK provided technical expertise and advice on the laboratory tests. LL, SQ, LM, ES and GJ were involved in data interpretation. All authors have been involved in drafting the article or revising it critically for intellectual content, and all authors approved the final version to be submitted.

Role of the funding source

Arthritis Relief Plus Ltd (Queensland, Australia) provided tubes of 4Jointz and placebo, and finance for the study. They had no role in data analysis or interpretation.

Conflict of interests

GJ received funding from Arthritis Relief Plus to run this investigator-initiated trial.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.joca.2012.07.019.

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