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A Randomized, Double Blind, Placebo Controlled Trial of a Topical Cream Containing Glucosamine Sulfate, Chondroitin Sulfate, and Camphor for Osteoarthritis of the Knee

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ABSTRACT. ***Objective.*** To assess the ability of a topical preparation of glucosamine sulfate and chondroitin sulfate to reduce pain related to osteoarthritis (OA) of the knee.

Methods. Sixty-three patients were randomized to receive either a topical glucosamine and chondroitin preparation or placebo to be used as required over an 8 week period. Efficacy was assessed using a visual analog scale (VAS) for pain as well as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the SF-36 questionnaire.

Results. VAS scores indicated a greater mean reduction in pain for the glucosamine/chondroitin preparation group (mean change –3.4 cm, SD 2.6 cm) compared to the placebo group (mean change –1.6 cm, SD 2.7 cm) after 8 weeks. After 4 weeks the difference between active and placebo groups in their mean reduction from baseline was 1.2 (95% CI 0.1 to 2.4, p = 0.03) and after 8 weeks was 1.8 (95% CI for difference between groups, 0.6 to 2.9 cm; p = 0.002).

Conclusion. Topical application of glucosamine and chondroitin sulfate is effective in relieving the pain from OA of the knee and improvement is evident within 4 weeks. (J Rheumatol 2003;30:523–8)

Key Indexing Terms:
OSTEOARTHRITIS GLUCOSAMINE CHONDROITIN
SHARK CARTILAGE PAIN KNEE

Glucosamine and chondroitin sulfate have been consistently shown to be agents of low toxicity that may relieve the pain and joint stiffness associated with osteoarthritis (OA)[1,2]. Longterm use of glucosamine may reduce radiographic progression of OA of the knee, suggesting it may be a chondroprotective, disease modifying agent in OA of the knee[3]. Although rapidly absorbed from the gastrointestinal tract, pharmacokinetic data show that when administered orally, glucosamine is subject to uptake and degradation by the liver and uptake into non-joint tissues so that the dose reaching the articular cartilage is a fraction of a percentage of the oral dose[4]. While glucosamine has been shown to be active when given intramuscularly[5], direct topical application into the dermis surrounding an affected joint may potentially deliver a more concentrated dose to the affected area. Chondroitin sulfate has also been shown to be effective in reducing OA pain[6] and to enhance the pain relieving action of glucosamine[7,8] despite poor gastrointestinal bioavailability when administered orally[9]. Chondroitin sulfate may further act as a carrier substance to enhance dermal penetration of topical substances[10]. Our study examines the use of a topical glucosamine/chondroitin sulfate preparation containing camphor and peppermint oil in relieving pain from OA of the knee.

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MATERIALS AND METHODS

Study design. We performed a single center, randomized, double blind, placebo controlled trial. Patients were randomly assigned to use either a topical preparation containing glucosamine and chondroitin sulfate or a placebo for a period of 8 weeks. The primary outcome measure was an assessment of subjective pain using a visual analog scale (VAS). Secondary outcome measures included pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[11] and quality of life using the SF-36 questionnaire[12]. The trial was approved by the Monash University Standing Committee on Ethics in Research on Humans and was conducted under the Australian Therapeutics Goods Administration, Clinical Trials Notification Scheme.

Participants. Subjects were recruited from the community by placing advertisements in local newspapers. Having passed a telephone screening interview, subjects were asked to attend a clinic at the Institute of Health Services Research at Monash Medical Centre during which their eligibility was further assessed.

Inclusion criteria. Patients were eligible for study participation if they were diagnosed with OA of the knee based on the American College of Rheumatology definition for OA of the knee[13], which requires meeting criteria 1 and 2 or 1, 3, 5, and 6, or 1, 4, 5, and 6 as follows: (1) knee pain, most days, during the prior month; (2) radiographic osteophytes at joint margins; (3) synovial fluid shows 2 of the following 3 features: clear, viscous, white blood cell count < 2000/mm^3; (4) synovial fluid is not available and patient is at least 40 years old; (5) morning stiffness of knee for ≤ 30 min; (6) crepitus on active joint motion. Patients also had to have knee pain due to OA rated > 4 cm on a 10 cm VAS in one or both knees for > 4 weeks.

Exclusion criteria. Patients who fulfilled any of the following were excluded from the trial: women of child-bearing age not using contraception, pregnancy, a regular requirement for analgesia for conditions unrelated to OA, or use of oral or topical glucosamine in the previous 6 weeks.

Interventions. The active preparation was a water-soluble cream containing glucosamine sulfate (30 mg/g), chondroitin sulfate (50 mg/g), and shark cartilage (140 mg/g), of which 10–30% is chondroitin sulfate, camphor (32 mg/g), and scented with peppermint oil (9 mg/g). Shark cartilage is a minimally processed source of chondroitin sulfate, which is a long chain glycosaminoglycan and an important functional constituent of cartilage. Chondroitin sulfate has been shown to be effective as a transfer agent for dermal drug as well as being orally effective in treating OA[1,8]. The topical cream used in this study is a commercially available preparation that was formulated using a proprietary technique aimed at maximizing skin penetration of the active ingredients, consisting of high efficiency emulsifiers, skin emollients, and micro-encapsulation of the active ingredients. The placebo preparation was a simple cosmetic cream that used conventional skin emollients, petrolatum and mineral oil, conventional emulsifiers, and stearic acid and glycerol stearate rather than the proprietary technology. The placebo also contained a lesser amount of peppermint oil in an amount that provided scent to ensure that the placebo and active preparations had a similar appearance and smell. Subjects were instructed to continue with their usual medications and to apply the study preparation for an 8 week period in accord with the way the commercial preparation is used. As such, subjects were asked to apply the study preparation as required according to the following instructions: Clean, rinse, and dry skin prior to application. Apply generously to painful joints and gently massage until cream disappears. Repeat as necessary.

Randomization and blinding. Subjects who satisfied the inclusion and exclusion criteria were assigned a sequential study ID number upon enrolment. Prior to the study the ID numbers had been randomized using blocked randomization with a fixed block size of 4 and assigned to labels on either active or placebo preparations. The people involved in the randomization and labelling were independent from the investigators and both the investigators and the subjects were blinded as to the treatment allocation. While there may have been some slight differences in the texture of the placebo and active creams, the investigators did not see either cream at any time and were instructed not to ask any questions regarding the actual cream used by a subject. The possibility of contamination was minimized by having the subjects attend their clinic visits separately and being asked not bring their cream to these visits.

Outcome measures. The primary outcome measure was participant pain rating based on a 100 mm VAS that was assessed in the clinic at 0, 4, and 8 weeks. Secondary outcome measures included the WOMAC, a validated, disease-specific questionnaire addressing severity of joint pain, stiffness, and limitation of physical function. A higher WOMAC score indicates a worse symptom severity, with 96 representing the worst possible score. General health related quality of life was also assessed using the SF-36 questionnaire, which provides separate summary scores for subjects' quality of mental and physical health.

Participants also completed a daily diary at home, which included pain rating on a self-administered 100 mm VAS, use of the study medication, use of oral analgesics, and occurrence of adverse events.

Statistical analysis. A statistical power calculation performed prior to the trial determined that to detect a difference of 2 cm in VAS pain reduction between the placebo and active treatment groups with 80% power required 25 patients in each group, and to detect a difference of 1.5 cm required 44 subjects (based on a 2 tailed, 2 sample t test with 5% significance level and assuming the 2 groups had an equal standard deviation of 2.5 cm).

All analyses were based upon intention to treat, in that subjects who completed followup were analyzed according to the group to which they were randomized. Analyses were performed in Stata[14]. Statistics used to describe the 2 treatment groups were proportions for binary variables, means with standard deviations (SD) for continuous variables that followed roughly symmetric distributions, and medians with interquartile (IQ) ranges for continuous variables that followed skewed distributions. Changes over time within a treatment group were described using means with 95% confidence intervals (CI) and SD.

The primary outcome was analyzed by fitting a linear model to the expected VAS scores that consisted of an interaction between the factors visit (baseline, week 4 or 8) and treatment (placebo or glucosamine). The parameters of this model were estimated using generalized estimating equations assuming that an exchangeable correlation structure existed for the repeat VAS scores of an individual subject and that different subjects respond independently[15]. The secondary outcomes, WOMAC, and scales of the SF-36 instrument were analyzed by comparing subjects' baseline-adjusted 8 week responses between treatment groups using 2 sample t tests and corresponding 95% CI.

Daily diary VAS scores were assumed to follow a linear model that included a linear trend over the 56 days of recording, with a different intercept and slope for the 2 treatment groups. This model also included a subject random effect to allow for different levels of pain across individual patients in the study and an autoregressive correlation structure to account for the strong pattern of correlation seen in day-to-day recording of a VAS pain score by each individual patient. Finally, subjects were assumed to respond independently of each other[16].

RESULTS

Of 144 people screened, 63 fulfilled the eligibility criteria. Four subjects withdrew (2 after Day 4, one after Day 14, and one after Day 26). Data from 59 subjects were analyzed (Figure 1). The 2 treatment groups were similar with respect to demographic composition and illness history (Table 1). At baseline visit (Week 0), the 2 groups had very similar mean scores for VAS pain, WOMAC, and SF-36 Physical and Mental Health. Figure 2 shows the raw data for the individual VAS pain scores and Table 2 provides a summary of the data with the changes over the 3 clinic visits. Between 5 and 9 tubes containing 114 g of cream were given to participants (mean 6.5 tubes). In the active group, participants used a mean of 5.5 tubes, with a mean usage of 2.4 times per day (range 1.4 to 3.9) and in the placebo group the participants used a mean of 5.7 tubes, with a mean usage of 2.7 times per day (range 1.4 to 4.8).

Between baseline and Weeks 4 and 8, the subjects in the placebo group improved on average in VAS pain, WOMAC, and SF-36 Physical Health. Similar improvements, although of greater magnitude, were seen in the active treatment

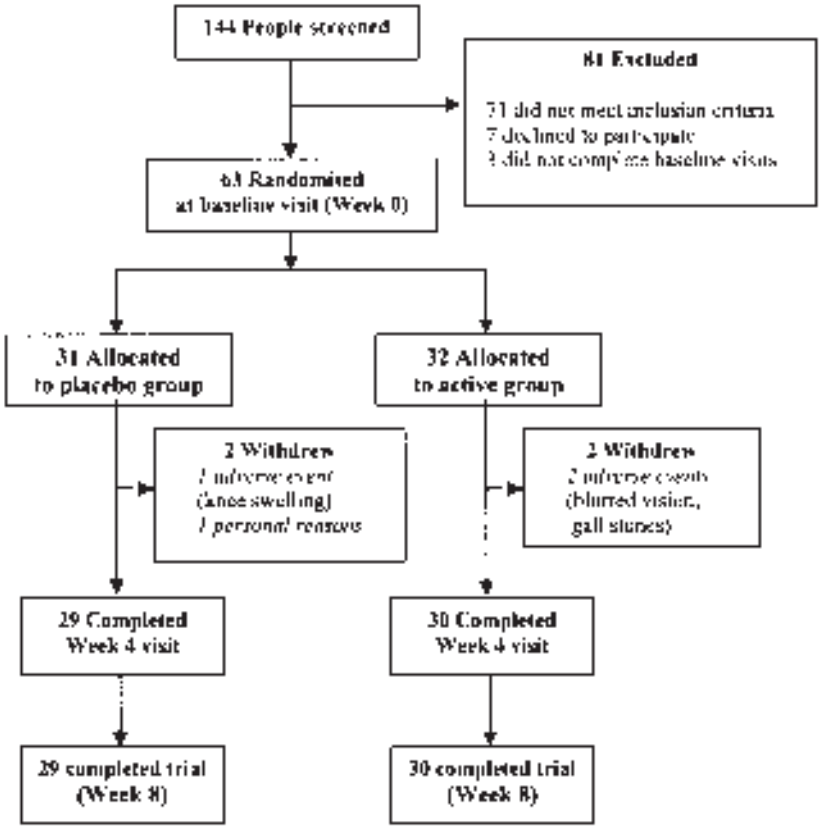

Figure 1. Flow chart of subjects' participation.

Table 1. Baseline data.

Baseline Variable	Placebo, n = 29	Active, n = 30
Women, n (%)	17 (58.6)	15 (50)
Mean age, yrs, mean (SD)	63.2 (7.8)	62.3 (8.4)
BMI men, mean (SD)	28.6 (2.3)	29.0 (4.9)
BMI women, mean (SD)	31.8 (7.6)	33.2 (7.1)
VAS, cm, mean; SD (min, max)	6.2; 1.5 (4.2, 9.3)	6.1; 1.4 (4.0, 9.0)
Length of illness, yrs, median (IQ range)	12 (6, 16)	10 (5, 18)
WOMAC (SD)	45.4 (12.4)	45.0 (10.1)
SF-36 physical health (SD)	35.9 (10.2)	35.1 (9.8)
SF-36 mental health (SD)	55.0 (6.4)	55.7 (7.2)

BMI: Body mass index.

group. The differences in these improvements between placebo and active treatment groups are given in Table 3.

VAS scores indicated a greater mean reduction in pain for the glucosamine/chondroitin preparation group compared to the placebo group at both 4 weeks [mean change –2.6 cm (SD 2.4) vs –1.4 cm (SD 2.4)] and 8 weeks [mean change –3.4 cm (SD 2.6) vs –1.6 cm (SD 2.7)] (Table 2). After 4 weeks the difference between active and placebo groups in their mean reduction from baseline was 1.2 (95% CI 0.1 to 2.4, p = 0.03) and this difference increased to 1.8 after 8 weeks (95% CI for difference between groups, 0.6 to 2.9 cm, p = 0.002) (Table 3). No statistically significant difference between treatment groups was found for the secondary outcomes, although we note that the observed changes in WOMAC score followed the same pattern as for VAS scores with the active group improving by more than the placebo group (Table 3). Adverse events appeared to be of a minor nature and were equally distributed between the 2 groups (Table 4).

Further exploration of the improvement in VAS pain scores was possible from the daily diaries. The model fitted to the daily record of VAS scores indicates that a difference between the 2 treatment groups existed on the first day of use of the cream. On Day 1 the placebo group had a mean VAS of 5.7 (SD 1.4) and the glucosamine/chondroitin group had 4.8 (SD 1.8); therefore the glucosamine/chondroitin cream group had VAS pain scores on average 1.0 cm (95% CI 2.1 to –0.1 cm, p = 0.075) lower than the placebo group. Further improvements in VAS pain scores over the 56 days of recording were gradual: at a rate of –0.10 cm/wk (95% CI –0.15 to –0.05 cm) in the placebo group and –0.20 cm/wk (95% CI –0.25 to –0.15 cm) in the active group. This suggests that use of the glucosamine/chondroitin cream

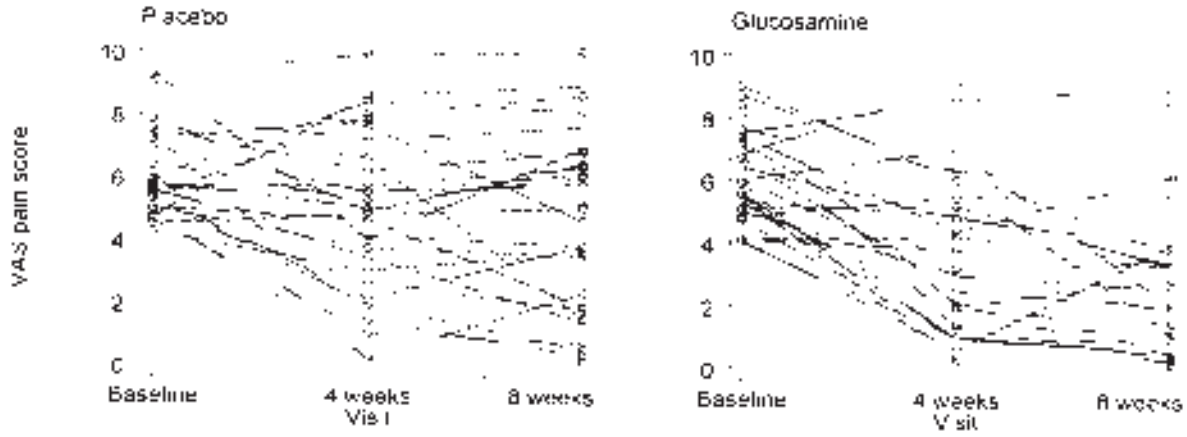

Figure 2. Raw data for VAS pain measures over the 3 visits.

Table 2. Means and standard deviations (SD) of VAS pain at 3 clinic visits and changes from first to third visit.

	VAS Pain Score, cm			Changes in VAS Pain Score From Week 0 to Week 8	
	Week 0, mean (SD)	Week 4, mean (SD)	Week 8, mean (SD)	Mean (95% CI)	SD
Placebo, n = 29	6.2 (1.5)	4.8 (2.6)	4.6 (2.8)	–1.6 (–2.6 to –0.6)	2.7
Active, n = 30	6.1 (1.4)	3.5 (2.5)	2.8 (2.4)	–3.3 (–4.3 to –2.4)	2.6

Table 3. Summary of difference between placebo cream and glucosamine cream groups at followup clinic visits adjusted for baseline.

Outcome; Time of Assessment	Difference Between Groups*	95% CI	p
VAS cm; week 4	1.2	0.1 to 2.4	0.03
VAS cm; week 8	1.8	0.6 to 2.9	0.002
WOMAC; week 8	5.1	2.2 to 12.4	0.17
SF-36 physical health; week 8	–3.1	–8.2 to 1.9	0.2
SF-36 mental health; week 8**	3.9	0.2 to 7.6	0.04

*Adjusted for baseline (i.e., magnitude of increased benefit due to glucosamine).**There were 4 outliers with respect to the SF36 mental health score. Three subjects in the active group improved by 19 points or more and one subject in the placebo group deteriorated by 13 points. When these outliers were excluded from the analysis the difference between the groups was reduced to 1.1 (95% CI–1.4 to 3.5, p = 0.4).

doubled the rate of improvement in comparison with use of the placebo cream over the 56 days, given the Day 1 difference between the treatment groups (p = 0.005). These findings agreed with the results from the analysis of VAS pain as assessed at the regular clinic visits (Tables 2 and 3).

DISCUSSION

The results of the VAS for pain scores suggest that the topical test preparation is more effective than placebo in reducing the pain from OA of the knee. These results support the growing volume of evidence that glucosamine and chondroitin sulfate are active agents against the pain from OA of the knee, and further suggest that these agents are effective when applied topically.

When administered orally, the amounts generally administered are glucosamine 1500 mg, and chondroitin sulfate 1200 mg daily[8], of which only a small percentage is available to the joint[4]. Based on a total usage of 5.5 tubes and an average usage of around 2.5 applications per day, it is estimated that the topical dosages applied in this study were roughly 300 mg glucosamine sulfate and 780 mg chondroitin sulfate per day. If transdermal absorption is between 20 and 40%, then between 60 and 120 mg glucosamine sulfate and 156 to 300 mg chondroitin sulfate was delivered through topical application. The finding that these dosages were able to elicit a clinically significant response suggest that the topical formulation used in this study was able to effectively deliver active agents to the joints. Further, the

Table 4. Reported adverse events.

Adverse Event	Placebo, Baseline VAS	Active, Baseline VAS
Upper respiratory tract infection	3	3
Rash/skin numbness, swelling	3	3
Muscle stiffness/soreness	1	1
Fatigue		1
Nausea		1
Headache	1	
Chest tightness	1	
Leg injury	1	
Ulceration on knee	1	
Increased thirst	1	
Asthma	1	
Withdrawals		
Blurred vision		1 (7.4)
Gall stones		1 (4.5)
Rash/skin numbness, swelling	1 (6.9)	
Personal reasons	1 (8.3)	

finding that adverse events were relatively equally distributed among both groups confirms the results of previous trials that suggest that this application is without toxicity or serious side effects.

The finding that improvement in pain rating in the active group was evident after Day 1, with clinically significant improvement evident at both 4 and 8 weeks, suggests that the topical preparation has a rapid onset of action. The speed of onset of pain relief observed in this study was an unexpected finding. While one can only speculate about the mechanisms underlying the clinical observations, it is possible that the peppermint oil and camphor provided immediate analgesic activity and that repeated application of these agents contributed to the observed results over the 8 weeks. Published studies of peppermint oil do support temporary analgesia, probably due to the menthol content[17]. In contrast, the only study of the sensory effects of camphor in humans suggests that the analgesic effects of up to 20% camphor are mainly illusory and are due to slight enhancement of the perception of temperature changes on the skin[18]. It is also possible that the apparent rapid onset of action may be due to absorption of the glucosamine and chondroitin sulfate into the bloodstream and/or direct uptake into local joint tissue in amounts comparable to those available from oral administration.

Rather than the result of short acting neurological agents, the observed gradual and continual improvement in pain scores is likely to be due to the glucosamine and chondroitin content, and this is consistent with previous studies. For example, in a study comparing glucosamine to ibuprofen, pain scores decreased faster during the first 2 weeks in the ibuprofen group. However, although the rate of decrease was slower in the glucosamine group, the reduction in pain scores continued throughout the trial period, and the difference between the 2 groups was significant after 8 weeks, with glucosamine treatment resulting in an increased reduction in pain scores compared to ibruprofen[19].

It is interesting that the glucosamine/chondroitin group had double the rate of improvement compared to the placebo group, yet the placebo group still reported a considerable reduction in pain (16 mm on the VAS). An initial placebo response is common in trials of OA of the knee[20]. The observed improvement in the placebo group in this trial may be due to multiple factors. These include the presence of potentially active constituents in the placebo cream such as peppermint oil, as well as possible psychological and physiological benefits from rubbing the site of pain during the application process. In addition, the direct application of preparations to the site of pain may have heightened the placebo effect. Other factors that may have contributed to the improvement seen in the placebo group may be due to external confounders such as variations in activity levels, although there is nothing to suggest this may be the case.

Findings on other secondary outcomes were equivocal. There was an observed improvement in the WOMAC score in the active group compared with the placebo group but this could have been a chance finding. (Note that the study was not powered to detect significant differences in WOMAC scores.) This is in agreement with a study of oral glucosamine that failed to observe a statistically significant improvement in WOMAC pain score after 8 weeks, despite finding a significant difference in the response to a daily diary pain question and knee examination after 8 weeks[21]. A statistically significant improvement in SF-36 mental health in the active group compared to the placebo group could be explained by large changes seen in a small number of participants. There was no evidence of any difference on the SF-36 physical health dimension.

Our study supports previous reports that suggest glucosamine and chondroitin sulfate are both safe and effective in treating the pain of OA of the knee, and suggests that topical application of these agents along with camphor and peppermint oil is an effective route of administration. Further research is required to determine the effects of longterm treatment, the possibility of subgroups of responders, and the determination of which components are most critical for the observed effects.

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