Mixture of *Arnebia euchroma* and *Matricaria chamomilla* (Marhame-Mafasel) for pain relief of osteoarthritis of the knee – a two-treatment, two-period crossover trial

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Abstract

Introduction: Osteoarthritis is the most prevalent chronic non-infective joint arthritis. Because of its chronic disease nature, local drugs are preferred due to lower complications. In the present study, the new herbal pomade Marhame-Mafasel for knee osteoarthritis was used in a double-blind crossover trial.
The aim of the study was to assess the efficacy and safety of Marhame-Mafasel pomade, which consists of several medical herbs including *Arnebia euchroma* and *Matricaria chamomilla*, in osteoarthritis of the knee.
Material and methods: This study was a placebo-controlled double-blind crossover trial. Forty-two patients with pain associated with osteoarthritis of the knee (diagnosed by criteria of the European League against Rheumatism and physical examination) were drawn from patients attending the Clinic of Mostafa-Khomeini Hospital. In this study we assessed efficacy (analgesic effect and improved function) of herbal pomade Marhame-Mafasel, which was used locally in patients with primary osteoarthritis of the knee over three weeks. The instrument of the study was the Western Ontario and McMaster Universities (WOMAC) LK3.1 standard questionnaires.
Results: The participants in each group were 21 patients; 30 (71.4%) were women and 12 (28.6%) of them were men. The participants were between 40 and 76 years old. Six patients had mild arthritis, 15 had moderate arthritis and 21 had severe arthritis. The positive analgesic effect of the herbal pomade Marhame-Mafasel in primary knee osteoarthritis was proven. The herbal joint pomade Marhame-Mafasel had a significantly greater mean change in score compared to the placebo group for osteoarthritis severity ($p < 0.05$).
Conclusions: Herbal pomade Marhame-Mafasel in comparison to placebo has more effect on reduction of pain of primary knee osteoarthritis.

Key words: osteoarthritis, herbal medicine, non-compliance, principal component analysis

Introduction

Osteoarthritis, or degenerative joint disease, occurs when the cushiony cartilage between two bones becomes worn down, and the bones begin to rub against each other in the joint (the area where two bones come together) [1].

This often leads to pain, swelling, a decrease in motion at the joint, stiffness, or the formation of bone spurs (tiny growths of new bone) [1]. Osteoarthritis is the most prevalent chronic non-infective joint arthritis and approximately 25% of people aged 55 or above have knee pain almost every day [2]. The prevalence of this disease in women is greater than in men [3, 4] and there is a significant positive correlation between age and osteoarthritis of the knee [3]. The prevalence of osteoarthritis of the knee in the U.S. is approximately 0.9% (1.2% in women and 0.4% in men) [5]. Osteoarthritis in the knee is one of the main causes which lead to impaired mobility in the elderly [6]. Many patients with knee pain have limitations in their physical functions which prevent them from engaging in their usual daily activities. Drugs frequently used in osteoarthritis are analgesics, cartilage protective drugs and steroidal and non-steroidal anti-inflammatory drugs (NSAID). In addition, there are many pharmacological, supportive and surgical treatment options which depend on the disease severity. Because it is a chronic disease, local drugs are preferred due to lower complications. As steroidal and non-steroidal anti-inflammatory drugs have systemic side effects such as digestive and renal impairment, they should be used carefully [7]. Local drugs such as pomade, cream, gel, etc., are simply used. Thus, preparing pomade to reduce pain and disability of patients is very important. Despite the long history of herbal medicine in Iran, only a few studies have been carried out to investigate the effect of herbal medication on osteoarthritis. Therefore, due to the necessity of appropriate treatments to decrease pain of patients suffering from osteoarthritis, a new herbal pomade for osteoarthritis of the knee in a double-blind clinical trial was used.

Material and methods

Participants and inclusion/exclusion criteria

The study was a double-blind randomized crossover trial with two treatments and two periods in 42 osteoarthritis patients. In this study, participants were referred to the orthopaedic clinic of Mostafa-Khomeini Hospital in Tehran. The protocol was approved by the Research Ethics Committee at Shahed University, Tehran. In addition, before starting the study, patients signed an informed consent form according to the Helsinki Declaration. Inclusion criteria specified non-pregnant women and age 40-80 years, with primary osteoarthritis of at least one knee. Patients were eligible for the study if they had pain associated with osteoarthritis of the knee (diagnosed by criteria of the European League against Rheumatism and physical examination) [8, 9]. Patients with acute arthritis of the knee or secondary arthritis related to systemic inflammatory arthritis (including rheumatoid arthritis, post-infectious arthritis and metabolic arthritis, psoriatic arthritis, traumatic arthritis or surgical joint replacement) were excluded from the study.

Intervention and randomization

Marhame-Mafasel pomade (MM) consisted of several medical herbs (including *Arnebia euchroma* and *Matricaria chamomilla*) and was made by the pharmacology division of Shahed University, Iran; its formula is at the pharmacology division of Shahed University. Marhame-Mafasel pomade and placebo were inserted into similar tubs by a pharmaceutical firm.

At the start of the study, participants underwent a comprehensive physical examination, and a medication history was taken by a physician. Patients were randomized according to a random number table to receive either Marhame-Mafasel pomade or placebo. In the first sequence, 21 participants in the treatment arm received Marhame-Mafasel pomade (herbal medication) followed by placebo; and in the second sequence, 21 patients received placebo followed by Marhame-Mafasel pomade. Subjects were instructed to apply 1.5 g of pomade every 8 hours over six weeks, massaging it firmly into the skin until it disappeared completely. After three weeks subjects were assessed and researchers completed questionnaires at periods.

Outcome measures

Subjects were evaluated in terms of three components (pain score ranged from 0 (no pain) to 100 (extreme pain); physical function score ranged from 0 (no difficulty) to 100 (extreme difficulty); stiffness score ranged 0 (no stiffness) to 100 (extreme stiffness)) at the end of both periods I and II. These components were measured by the Western Ontario and McMaster Universities osteoarthritis index (WOMAC), which is a validated questionnaire [10] consisting of 24 questions (5 on pain, 17 on physical function and 2 on stiffness), each scored on a 5-point Likert scale. After a one-week wash-out period, participants received the opposite treatment in period II and researchers completed the WOMAC questionnaire again for each patient. The secondary measure was severity

of osteoarthritis, a linear compound from three components (pain, physical function and stiffness scores) that ranged from 0 (no pain) to 100 (extreme pain). In the study, a subject's observed compliance level was classified to an ordinal variable based on the amount of pomade in tubes taken by the patient. A patient was considered to comply (Compliance) with the assigned treatment if more than 75% of the pomade in the tubes was taken and moderate compliance if 25-75% of the pomade in the tubes was taken. Otherwise the subject's observed compliance to the assigned treatment was classified as poor compliance (if less than 25% of pomade in the tubes was taken).

Safety analysis

Safety was assessed during all weekly clinic visits and telephone visits by physicians. Safety variables included: adverse events, which were identified using a checklist covering common oral NSAID (non-steroidal anti-inflammatory drugs) side effects; application site dermatological reactions and vital signs, which was based on standard predictive testing [11], and any abnormality was recorded as an adverse event.

Statistical analysis

We used principle component analysis and made a linear compound from three components (pain, physical function and stiffness scores), namely severity of osteoarthritis, which ranged from 0 (no disease) to 100 (extreme disease). Data for the Marhame-Mafasel pomade and placebo were analysed corresponding to the new response variable, severity of osteoarthritis. Since in our study there were moderate and poor compliance, we estimated treatment effects given compliance levels that we considered moderate and poor compliance as non-compliance in the final analysis. Chi-square test and Fisher's exact test (for small numbers) were used to compare categorical baseline demographic differences and t-test was used to compare average differences. The continuous variable (severity of pain, which was a linear compound from pain, physical function and stiffness scores) was analysed by ANCOVA with baseline scores and compliance level as the covariate. All statistical tests were two-sided and were performed at the 0.05 level of significance. Statistical analysis was performed with SAS Institute Inc. Version 9.1 (2002).

Results

The 42 patients enrolled in the present study were randomized to treatment with either Marhame-Mafasel pomade (n = 21) or placebo (n = 21). All patients were followed to the end of the study. Participants in active treatment and placebo did not have access to the opposite treatment. There were no missing data, loss to follow-up or withdrawal. Thirty (71.4%) subjects were women and 12 (28.6%) were men (Table I). Age of patients was 40-76 years (Table 1). During the trial, some patients had moderate or poor compliance (Table II). More patients in the Marhame-Mafasel group (83.3%) completed the entire 6-week treatment period compared to the placebo group (78.6%, $p < 0.05$), while dropout and discontinuation did not occur in the entire study. There was no significant difference between treatment groups in baseline characteristics (Table I; $p > 0.05$). One third of participants had a family history of arthritic joints. In our study, based on clinical symptoms and results of radiography,

Table I. Baseline demographics and characteristics of patients in placebo and Marhame-Mafasel groups

	Placebo	Marhame-Mafasel	*p*
Age [years][a]	58.48 ±10.25	58.56 ±10.6	0.979
Weight [kg][a]	75.81 ±17.58	69.56 ±10.97	0.138
Height [m][a]	1.58 ±0.08	1.64 ±0.09	0.023
Parity [number][a]	4.57 ±1.91	3.85 ±2.1	0.229
BMI [kg/m^2][a]	30.26 ±6.18	25.77 ±3.89	0.004
Education (illiterate) [%]	75.81	69.55	0.074
Sex (female) [%]	81	75.6	0.064
Pain score[a]	50 ±21.6	41.63 ±25.4	0.236
Physical function score[a]	40 ±26.48	63.9 ±40.1	0.61
Stiffness score[a]	81.77 ±26.48	63.95 ±40.1	0.085
Severity of disease score*[a]	48.8 ±13.94	38.3 ±21.16	0.08

[a]Data are presented as mean ± SD

**Severity of disease score was a component of pain, physical function and stiffness scores by principle component analysis, ranging from 0 (no osteoarthritis) to 100 (extreme osteoarthritis)*

Table II. Distribution of patient compliance in two periods and two sequences of the study

Assigned treatment (groups)	Compliance levels	Period		Total
		I	II	
Placebo followed by Marhame-Mafasel	Poor compliance (< 25%)	2 (0.09)	1 (0.05)	3 (0.07)
	Moderate compliance (25-75%)	3 (0.14)	3 (0.14)	6 (0.14)
	Compliance (≥ 75%)	16 (0.76)	17 (0.81)	33 (0.79)
	Total	21	21	42
Marhame-Mafasel followed by placebo	Poor compliance (< 25%)	1 (0.05)	1 (0.05)	2 (0.05)
	Moderate compliance (25-75%)	2 (0.09)	3 (0.14)	5 (0.12)
	Compliance (≥ 75%)	18 (0.86)	17 (0.81)	35 (0.83)
	Total	21	21	42

** I – the first period (or first three weeks) of the study, II – the second period (or second three weeks) of the study after a one-week washout period*

6 (14%) patients had mild arthritis, 15 (36%) patients had moderate arthritis, and 21 (50%) patients had severe arthritis, which were not significantly different between treatment groups ($p > 0.05$). Mean body mass index was 28.2 (BMI for men and women was 26 and 29, respectively). Approximately 60% of participants skipped from stairs and 13% of them had heavy work each day. More than half of patients (56%) did not have efficient mobility and daily routine sport programming. After treatment, there was a significant difference between Marhame-Mafasel and placebo effects ($p < 0.05$) for pain, physical function, stiffness and disease severity in both periods I and II. In our study we showed an effect size of 0.40 for pain reduction, 0.32 and 0.38 for improving physical function and stiffness, respectively. In this study, compliance to assigned drug dosage among participants was divided into three categories (Table II). In this study, we did not observe a carry-over effect ($p = 0.063$). The results indicated that Marhame-Mafasel pomade in comparison with placebo had more positive effects on decreasing the knee pain of arthritic disease when the patient did not show complete compliance with the treatment. However, adjusted results based on compliance levels showed that Marhame-Mafasel pomade had a significantly greater effect on reduction of disease-associated pain severity in comparison with placebo (Tables III, IV).

Discussion

Osteoarthritis is the most prevalent chronic non-infective joint arthritis and it does not have an absolute remedy. The existing oral and injected treatments have systemic side effects such as digestive and renal impairment entailing that they must not be consumed over a long period. Marhame-Mafasel pomade has no internal side effects such as digestive and renal impairment. This

Table III. Efficacy evaluation of continuous variables

Efficacy variable	Treatment group	*N*	Change in score, mean (SD)	
			Period I – baseline (A)	Period II – baseline (B)
Pain score	Placebo	21	–8.38 (21.83)	–7.48 (18.88)
	MM	21	–14 (18.44)[a]	–14.48 (21.46)[a]
Physical function score	Placebo	21	–9.28 (14.17)[a]	–8.33 (27.91)[a]
	MM	21	–10.37 (13.29)[a]	–15 (20)[a]
Stiffness score	Placebo	21	–6.82 (15.28)	–10.72 (24.38)
	MM	21	–21.12 (28.73)[a]	–24.04 (31.69)
Severity of disease score	Placebo	21	–4.82 (15.28)	–4.72 (15.69)
	MM	21	–10.83 (16.63)[a]	–11.39 (18.34)[a]

MM – Marhame-Mafasel pomade; (A) and (B) show mean difference of change in score before intervention (baseline score) and after intervention in first and second periods, respectively;

$$\text{where } A, B = \frac{\sum_{k=1}^{21} (\text{intervention score}_k - \text{baseline score}_k)}{21}$$

Table IV. Outcomes in different periods and groups

Sequence or group	Period I, mean (SD)	Period II, mean (SD)	Treatment effect, mean (SD)
Placebo followed by MM	38.45 (16.27)	31.61 (16.17)	3.94* (2.01)
MM followed by placebo	33.73 (22.41)	37.93 (19.94)	

** P < 0.05; SD – standard deviation; MM – Marhame-Mafasel pomade*

pomade has a similar anti-inflammatory effect as piroxicam gel, diclofenac ointment and comfrey root extract ointment [12-22]; on the other hand, we found a significant difference between Marhame-Mafasel and placebo in pain relief for patients with knee osteoarthritis ($p < 0.05$). Since capsaicin ointment (chili extract) had skin and mucoid side effects, it appears that Marhame-Mafasel pomade was more tolerable, because it had no major local side effects (Table V) such as intolerable itch and blebs [23, 24]. In the study, efficacy of Marhame-Mafasel pomade in comparison to placebo in decreasing painful osteoarthritis of the knee was shown, while the efficacy of copper-salicylate gel was similar to placebo effects ($p > 0.05$) in a previous study [21]; also, copper-salicylate gel occasionally had severe side effects [19, 21]. In line with the findings of other studies [8], in our study the majority of participants were women. The result was confirmed by other studies [25]. We calculated an effect size of 0.40 for pain reduction, 0.32 for improving physical function, and 0.38 for stiffness. Baer *et al*. in a study of diclofenac effect on treatment of knee osteoarthritis calculated a pooled effect size of 0.41 for pain relief, 0.44 for improved physical function, and 0.43 for stiffness [26]. Lin *et al.* calculated a pooled effect size of 0.04 for pain reduction [25]. Lee *et al*., in a meta-analysis of 14 osteoarthritis trials, found a pooled effect size of 0.37 for pain reduction with oral NSAIDs [27]. Zhang *et al*., using data from 2 oral NSAID studies, calculated a pooled effect size for osteoarthritis pain reduction of 0.34 [28]. The results showed that herbal joint pomade (Marhame-Mafasel) had no harmful side effects. The data in this report provide substantial evidence for the efficacy and safety of herbal joint pomade Marhame-Mafasel solution in chronic osteoarthritis of the knee.

A criticism of the study may be that some patients had non-compliance with the assigned treatment. The main reason for non-compliance was participants' forgetfulness.

The Marhame-Mafasel pomade has benefit in treatment of knee osteoarthritis without any major local reactions.

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DM was involved in evaluation of patients and was a major investigator in the trial. SF was an investigator in analysis and writing of the manuscript. MN was involved in trial design and the production process of herbal joint pomade Marhame-Mafasel. ARS was another investigator in analysis and interpretation of the data and writing of the manuscript. AG was involved in trial analysis and data reviewed.

Table V. Comparison of treatment and placebo groups in a trial of mixture of *Arnebia euchroma* and *Matricaria chamomilla* pomade for pain relief of osteoarthritis of the knee

	Marhame-Mafasel pomade ($n = 42$)	Placebo ($n = 42$)
Withdrew before treatment, *n* (%)	0 (0)	0 (0)
Withdrew during trial, *n* (%)	0 (0)	0 (0)
Number of adverse reactions, *n* (%)		
Skin	2 (4.76)*	0 (0)
Miscellaneous	0 (0)	0 (0)
Number of actions taken, *n* (%)		
Treatment lacked efficacy	0 (0)	0 (0)
Treatment discontinued	0 (0)	0 (0)
Treatment interrupted	0 (0)	0 (0)
Concomitant illness, *n* (%)	0 (0)	0 (0)
Lost to follow-up, *n* (%)	0 (0)	0 (0)
Partial compliance, *n* (%)	7 (16.7)	9 (21.4)

**Skin reaction was not major and was treated by drug*

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