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Assessment of Marhame-Mafasel Pomade Effect on Knee Osteoarthritis with Non-Compliance

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Abstract

Background: Osteoarthritis is the most prevalent chronic non-infective joint arthritis. In the present study, the effect of new herbal pomade (Marhame-Mafasel) on knee osteoarthritis was investigated in a randomized trial. The objective of this study was to assess efficacy of Marhame- Mafasel pomade, which was consisted of several medic herbs like Arnebia euchroma and Martricaria chamomilla in primary osteoarthritis of the knee with non-compliance.

Methods: The 2×2 crossover trial enrolled 42 osteoarthritis patients (Marhame-Mafasel versus placebo) in 2006. The instrument of data collection was Western Ontario and McMaster Universities (WOMAC) LK3.1 standard questionnaires. We used conditional estimation to adjust non-compliance effect.

Results: The participants in each group were 21 patients. About 30 (71.4%) were female. The participants were between 40-76 years old. Positive analgesic effect of herbal pomade "Marhame-Mafasel" on knee osteoarthritis severity was considerable ($P< 0.01$). After adjusting results to compliance level, the estimators were sharper than crude results.

Conclusion: Herbal joint pomade "Marhame-Mafasel" has significant positive analgesic effect on primary knee osteoarthritis.

Keywords: *Osteoarthritis, Herbal medicine, Compliance, Randomized trials*

Introduction

Osteoarthritis was known as 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 knee joint (the area where two bones come together) (1). Osteoarthritis of the knee often leads to pain, swelling, limitation in range of motion, stiffness, or the formation of bone spurs (tiny growths of new bone) (1). Osteoarthritis is the most prevalent chronic non-infective joint arthritis. Approximately 25% of people at age 55 yr or above have daily knee pain in (2). There is a significant positive correlation between age and osteoarthritis of the knee (3). The prevalence of this disease in women is greater than men (4). Prevalence of osteoarthritis of the knee in America is approximately 0.9% (1.2% in women and 0.4% in men) (5). Osteoarthritis of the knee is one of the main leading causes of impaired mobility in the elderly people (6). Many patients with knee pain have limitations in their physical functions, which prevented them from engaging in their usual daily activities.

Drugs more frequently used in osteoarthritis are analgesics, supporter of cartilage, steroid, and non-steroidal anti-inflammation drugs (NSAD). In addition, there are many pharmacological,

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supportive, and surgical interventions, which depend on the disease severity. The disease is chronic; hence, drugs used locally are preferred due to less complication. As steroid and non-steroidal anti-inflammation drugs have systemic side effects like digestive and renal impairment, they should be used carefully (7, 8). Local drugs like 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, a few studies were carried out to investigate the effect of herbal medication on osteoarthritis. In order to reduce pain in patients suffering from osteoarthritis, the effect of new herbal pomade on osteoarthritis of the knee was investigated in a double-blinded crossover trial.

Materials and Methods

Double-blinded crossover randomized trial on efficacy of herbal joint pomade (EHJP)

The EHJP study(9) conducted a double blinded placebo controlled randomized crossover trial involving 42 osteoarthritis patients aged 40 to 80 yr who had explicit symptoms of arthritis disease to investigate the effect of herbal joint pomade "Marhame-Mafasel" (EHJP) on knee osteoarthritis, which participants drown from patients attending the Clinic of Mostafa- Khomeini Hospital in 2006. Pomade "Marhame-Mafasel" (MM) consisted of several medic herbs (like Arnebia euchroma and Martricaria chamomilla) and was made by Pharmacology Division of Shahed University, Iran. MM pomade and placebo were inserted in the similar tubs. Patients with acute knee arthritis or secondary osteoarthritis were excluded from the study. The protocol was approved by the Research Ethics Committee at Shahed University, Tehran. Before starting of the study, participants signed the informed consent forms according to Helsinki Declaration rule. Then a computer random number generator was used to allocate participant to either placebo or treatment groups. Patients used locally either MM pomade or placebo 3 times a day for 3 wk. After 3 wk, subjects were assessed using checklist. Subjects were evaluated based on three characteristics including: a) pain score ranged from 0 (no pain) to 100 (extreme pain); b) physical function score ranged from 0 (no difficulty) to 100 (extreme difficulty); and c) stiffness score ranged 0 (no stiffness) to 100 (extreme stiffness) at the end of both periods. These characteristics were measured using Western Ontario and McMaster universities (WOMAC) checklist. After 1 wk wash out period, participants received alternative intervention in period II. In this study, we had two sequences: AB (MM pomade followed by placebo) and BA (placebo followed by MM). The participants were known as compliance if they had consumed 50% or more of the assigned pomade, otherwise they were known as non-compliance. In this study, the non-compliance and compliance distribution was showed in Table 1.

Table 1: The Distribution of Compliance status (two levels) in two periods of two sequences

Sequences	Compliance Level	Period I		Period II		Total	
		Frequency	Proportion of Compliance	Frequency	Proportion of Compliance	Frequency	Proportion of Compliance
AB*	Noncompliance	5	0.76	5	0.76	10	0.76
	Compliance	16		16		32	
BA	Noncompliance	9	0.57	6	0.71	15	0.64
	Compliance	12		15		27	

* In AB sequence MM pomade, A, followed by placebo, B; and in BA sequence placebo followed by MM pomade.

Statistical model and analysis

We used principle component analysis and considered a new outcome that was a linear compound of three characteristics including pain, physical function, and stiffness scores. The new outcome was named osteoarthritis intensity score ranged 0(no intension) to 100(extreme intensity). In the EHJP study, the observed compliance status of each subject was classified to a binary variable (1 or 0) based on the amount of pomade in tubes taken by the subject. One subject was considered to comply with the assigned treatment (compliance= 1) if more than 50% of the pomade in the tubes was taken. Otherwise, the subject's observed compliance to the assigned treatment was classified as 0. Under complete data assumption (9), potential outcome (Y_{ijk}) for individual *k* in period *j (j= 1, 2)* of sequence *i (i=1, 2)* may be modeled as a function of treatment effect ($\tau_{d[i,j]}$, is treatment effect in period *j* of sequence *i*), period effect (Π_j, is j^{th} period effect), effect of subject *k* in sequence *i* (S_{ik}), carryover effect (λ) and error term (ε_{ijk}). When there is no carry-over effect and all subjects comply with their assigned treatment, the widely used model is (10):

$$Y_{ijk} = \mu + \tau_{d[i,j]} + \Pi_j + S_{ik} + \varepsilon_{ijk}$$
$$(i=1,2\ ;\ \ j=1,2\ ;\ \ k=1,2,\ldots,n), \qquad [1]$$

The equation (1), standard model is appropriate to estimate of treatment effects without non-compliance. Since there is non-compliance we suggest equation 2 (adjusted model) that outcome was modeled by treatment effect ($\tau_{d[i,j]}$), period effect (Π_j), effect of subject *k* in sequence *i* (S_{ik}) and error term (ε_{ijk}).

$$Y_{ijk}^{(R,D(R))} = \mu + \tau_A \cdot W_{ij} \cdot C_{ij} + \tau_B \cdot (1 - W_{ij}) \cdot C_{ij} + \Pi_j + S_{ik} + \varepsilon_{ijk} \qquad [2]$$

where, R=r (r=A, B) to denote the assigned treatment and $W_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases}$, $(i, j = 1,2)$ is indicator of patient at period *j* of sequence *i*. We use D(R) to denote the observed treatment received of the subject in j^{th} period of i^{th} sequence with assigned treatment *r*. D(r)= r (r= A, B) if the subject k took more than 50% of the assigned dose of R=r and D(r)=0 otherwise. We let $Y_{ijk}^{(R,D(R))}$ to denote the potential outcome of the k^{th} subject in the j^{th} period of the i^{th} sequence with assigned treatment R and treatment received D(R), which has a normal distribution. $C_{ijk} = \begin{cases} 1 & ,D(r) = r \\ 0 & ,D(r) = 0 \end{cases}$ is an indicator for observed treatment received for subject *k* in the period *j* of the sequence *i*; S_{ik} is the random effect of the k^{th} subject in the i^{th} sequence, which has a normal distribution with mean 0 and variance σ_s^2; ε_{ijk} is the random error term, which has a normal distribution with mean 0 variance σ_e^2. In this study, Chi-square or Student's t-Test tests were used to analysis of baseline demographic and scores. Statistical analysis was performed by SAS Institute Inc. Version 9.1 (2002). All statistical tests were two-sided and were performed at the 0.05 significance level.

Results

Forty two patients participated in the present study. Thirty (71.4%) were female (Table 2). One third of participants had family history of joint arthritis. Based on clinical symptoms and results of radiography, 6 patients (14%) had low arthritis, 15 patients (36%) had moderate arthritis and 21 patients (50%) had severe arthritis. However, the difference was not statistically significant in both treatment groups (*P*> 0.05).

We did not evaluate the side effect of the new treatment (MM pomade). There was not a statistical significant difference at baseline scores between herbal joint pomade and placebo (Table 2) for pain, physical function, stiffness, and osteoarthritis intensity. There was not carry over effect.

Compliance to assigned drug dosage between participants was divided into two categories (compliance= 1, noncompliance= 0; Table 1). Table 3 shows mean of outcomes (osteoarthritis intension scores) in two periods having two sequences corresponding to complete compliance (standard model) and non-compliance (adjusted model) assumption. The results indicated that MM pomade in comparison with placebo had more positive effects on decreasing the knee pain and symptoms of arthritis disease where the patients did not have a complete compliance to the treatment (Table 3). In addition, Table 3 showed that *t*-test statistics corresponding to equation [1] and [2] was 1.96 and 2.01, respectively. Effect size based on standard model (equation 1) and adjusted model (equation 2) was 0.62 and 0.64, respectively (see Table 3).

Table 2: Baseline demographic and characteristics of patient in both treatment groups

	Placebo (n=21)	**MM pomade (n=21)**	***P*-value**
Age (yr)[a]	58.48±10.25	58.56±10.67	0.979
Weight (kg)[a]	75.81±17.58	69.56±10.97	0.138
Height (cm)[a]	158.1±8.9	164.44±9.53	0.023
Children (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)[b]	75.81	69.55	0.074
Sex (Female) [b]	81	55.6	0.04
Pain score [a]	50±21.6	41.63±25.4	0.236
Physical function score [a]	40±26.48	53.9±40.1	0.61
Stiffness score [a]	71.77±26.48	63.95±40.1	0.085
Osteoarthritis intension score*[a]	48.8±13.94	41.3±21.16	0.16

[a] Data are presented as $mean \pm SD$; [b] Data are presented as percent.

* Osteoarthritis intension score was a compound of pain, physical function and stiffness scores by principle component analysis, ranged 0 (no osteoarthritis) to 100 (extreme osteoarthritis)

Table 3: Summary statistics of parameters, without pretreatment variables, under the model (1), based on completely compliance assumption; and model (2), based on non-compliance assumption (Standard deviation in parentheses)

	Period I			**Period II**			**Based on model (1)**		**Based on model (2)**	
	Mean (SD)			**Mean (SD)**						
	Standard Model	**Adjusted Model**		**Standard Model**	**Adjusted Model**					
	$(\overline{Y}_{i1.})$	$\overline{Y}_{i1.}^{(R,R)}$	$\overline{Y}_{i1.}^{(R,0)}$	$(\overline{Y}_{i2.})$	$\overline{Y}_{i2.}^{(R,R)}$	$\overline{Y}_{i2.}^{(R,0)}$	τ_D	**Effect size**	τ_D	**Effect size**
Sequence BA	38.45 (16.27)	37.92 (12.05)	39.17 (21.47)	31.61 (16.17)	26.94 (11.31)	43.26 (21.45)	3.94* (2.01)	0.62	- 1.97* (0.98)	0.64
Sequence AB	33.73 (22.41)	27.67 (23.29)	35.62 (20.39)	37.93 (19.94)	35.82 (17.40)	44.67 (27.88)				

* $P< 0.01$;

SD= Standard deviation; Standard model is a model based on complete compliance assumption or equation (1); Adjusted model is a model based on non-compliance assumption or equation (2); B to denote placebo and A to denote Marhame-Mafasel pomade

Discussion

Osteoarthritis is the most prevalent chronic non-infective joint arthritis and it does not have an absolute remedy (1). The oral and injection forms of existing treatments have systemic side effects and are not recommended for a long time. MM pomade does not have systemic side effects. MM pomade like Piroxicam gel, Diclofenac ointment, and comfrey root extract ointment (11-20) has suitable anti-inflammation effect. Capsaeicine ointment (chili extract) has cutaneous and mucoid side effects, while MM pomade is a suitable pomade with no side effects (like itch, bleb) (21, 22). The palliative effects of MM pomade on painful osteoarthritis of the knee was more than Copper-Salicylate gel ointment, because previous studies indicated that efficacy of Copper-Salicylate gel ointment was similar to placebo effects; and, occasionally it had severe side effect (19). This study like other randomized trials may be marred by deviations from protocol, notably some patients failing to comply with the prescribed treatment. Therefore, we adjusted the treatment effects (τ_D) corresponding to compliance levels.

In this study, we estimated conditional averages and variances in two periods including two sequences (based on equation 2 or adjusted model) rather than unconditional summary statistics (based on equation 1 or standard model).

In conclusion, herbal joint pomade "Marhame-Mafasel" in comparison with placebo has more positive analgesic effects on primary knee osteoarthritis. In addition, according to these findings, treatment effect should be adjusted for non-compliance in randomized trials.

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