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ORIGINAL ARTICLE

Evaluation of the effect of topical chamomile (*Matricaria chamomilla* L.) oleogel as pain relief in migraine without aura: a randomized, double-blind, placebo-controlled, crossover study

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Abstract

Phytotherapy is a source of finding new remedies for migraine. Traditional chamomile oil (chamomile extraction in sesame oil) is a formulation in Persian medicine (PM) for pain relief in migraine. An oleogel preparation of reformulated traditional chamomile oil was prepared and then standardized based on chamazulene (as a marker in essential oil) and apigenin via gas chromatography (GC) and high-performance liquid chromatography (HPLC) methods, respectively. A crossover double-blind clinical trial was performed with 100 patients. Each patient took two tubes of drug and two tubes of placebo during the study. Visual analog scale (VAS) questionnaires were filled in by the patients and scores were given, ranging from 0 to 10 (based on the severity of pain) during 24 h. Other complications like nausea, vomiting, photophobia, and phonophobia were also monitored. There was 4.48 ± 0.01 μl/ml of chamazulene and 0.233 mg/g of apigenin in the preparation (by correcting the amount with extraction ratio). Thirty-eight patients in the drug-placebo and 34 patients in the placebo-drug groups (a total number of 72 patients as per protocol) completed the process in the randomized controlled trial (RCT). Adapted results from the questionnaires showed that pain, nausea, vomiting, photophobia, and phonophobia significantly ($p < 0.001$) decreased by using chamomile oleogel on the patients after 30 min. Results supported the efficacy of chamomile oleogel as a pain relief in migraine without aura.

Keywords Persian medicine · Chamomile · Neurological sciences · Migraine

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Introduction

Migraine is one of the most common types of headache identified as a pulsating, chronic, and mostly one-sided (unilateral) attack [1]. It prevails in about 10–20% of the population [2]. Women are more affected by migraine. It has been reported that migraine is the third most prevalent disorder and the seventh highest specific cause of disability. There is even evidence showing temperamental dysregulation and suicidal behavior in migraine patients, particularly women [3]. Migraine imposes an annual cost of about 27 million Euros to European societies due to patients' decreasing efficacy at work and losing working days [4, 5]. There are two main types of migraine—with aura and without aura. Migraine without aura is the most common kind.

There are three main groups of classical drugs used for pain relief in migraine—triptans or agonists of serotonin 5-HT1B/1D receptor; ergot alkaloids (ergotamine and dihydroergotamine); and non-steroidal anti-inflammatory drugs (NSAIDs) [6–8]. Although triptans are the most effective, they have some limitations like cardiovascular comorbidities [6]. Ergot

alkaloids are used in moderate and frequent migraine attacks, and NSAIDs are applied as analgesics during attacks to relieve pain [6]. None of them can provide complete treatment, and hence, satisfaction of patients is less [9]. Therefore, finding new treatment approaches and remedies for migraine is recommended.

Natural products and also traditional systems of medicine are mentioned as potential sources of finding new drugs. Persian medicine (PM) is one of the oldest and most prominent systems among traditional and complementary systems of medicine, dating back to 10,000 years [10–13]. Amid a range of formulations applied in PM, herbal medicinal oils, currently used in Iran, are one of the most popular [14]. They are prepared by various methods. One of these methods involves infusing water-soluble ingredients of a target non-oily plant part and its essential oil in an oily vehicle [15]. Traditional chamomile is one such oil that is frequently cited in topical formulations of traditional medicine manuscripts for migraine. In PM, migraine is known as *Shaghighe* [16]. Although no direct investigations were found on the effect of chamomile on migraine, there is some current hypothetical support for its probable effect. For example, investigations show that the essential oil (as well as flavonoids like apigenin) in chamomile possesses anti-inflammatory and analgesic (as strong as NSAIDs) effects and decreases nitric oxide (NO) as a stimulating agent of central sensitization [17, 18]. This oil is popular in PM and some of its therapeutic effects (such as its effect on knee osteoarthritis and carpal tunnel syndrome) have previously been tested [19, 20].

In our previous investigations, we standardized the method of preparation of this oil and formulated it as oleogel [20]. This oleogel form of the preparation was chosen because it is better appreciated by patients. In this crossover study, we aimed to evaluate the efficacy of this standardized semi-solid formulation (oleogel) on migraine attacks in a clinical trial.

Material and methods

Preparing traditional chamomile oleogel and placebo

The required amount of chamomile flowers was purchased from a traditional herbal shop (*attari*). It was identified and approved by Miss Sedigheh Khademian, botanist at the Herbarium Center of the School of Pharmacy, Shiraz University of Medical Sciences (voucher number: PM 407). Sesame oil was obtained from Golkaran Co.

Traditional chamomile oil was prepared in advance in accordance with our previous work on optimization and standardization of the method [18, 20]. In this method, essential oil of 200 g of the plant powder (amounts of 5 g packaged in filter paper) in 2.5 L of distillated water is obtained via the Clevenger apparatus method over 3 h. Then, the obtained essential oil is kept aside for the last stage. In the next step, the powder is removed from the water and the remaining aqueous extract is boiled with sesame oil until the entire water content is vaporized (for 3 h). After cooling the oil, the obtained essential oil from the first step is added to it and the final product is prepared. In this method, a maximum amount of essential oil is saved; this method is reproducible [18, 20].

The mixture of 10% traditional chamomile oil (final product of drug) in liquid paraffin (Merck) was used as the oil of placebo.

To achieve better compliance and satisfaction of patients, the chamomile oil and placebo were formulated as oleogel. Based on our previous work, we made oleogels for drug and placebo by using 5.5 and 5.0% *w/w* colloidal silicon dioxide, respectively [21].

The essential oil of chamomile flower, which was obtained and added to the oil during its preparation, was analyzed with the help of a GC instrument (Agilent 7890) with a mass detector (Agilent 5975C) [18, 22]. Then, GC with flame ionization detector (FID) analysis of the essential oil was performed for the qualification of chamazulene as chamomile's main pharmacological volatile active compound in essential oil. The GC/FID analysis was carried out on a gas chromatograph Bruker technologies model with 450-GC apparatus attached to BR-1 ms column (15 m × 0.25 mm ID and 0.25-μm film thickness) and connected to an FID [21]. In the next step, total phenolic and total polyphenol contents of the chamomile oleogel were analyzed via a spectrophotometer (with PG spectrophotometer T90) based on gallic acid content determined by Folin-Ciocalteu reagent and quercetin equivalent, respectively [23, 24]. Then, HPLC analysis was carried out on a Knauer technologies model apparatus attached to an Eurospher 100-5 C18 column (250 × 4.6 mm with pre-column) and connected to a photodiode array (PDA) detector for the qualification of apigenin as the main and active flavonoid compound [23, 24].

Clinical evaluation of chamomile oleogel vs. placebo in a crossover study

Study design

This study was performed in the Imam Reza Clinic of Shiraz University of Medical Sciences from December 2014 to May 2015. Patients diagnosed with migraine without aura, according to the Headache Classification Committee of the International Headache Society or IHS [4], were enrolled in the study.

Ethical issues

Protocol was approved by the Research Ethic Committee of Shiraz University of Medical Sciences (CT-9377-7037). It

was also registered at the Iranian Registry of Clinical Trials website (IRCT2014110819860N1).

Inclusion and exclusion criteria

As per inclusion criteria, all patients with a definite diagnosis of migraine according to the standards of the IHS (1.1) were between 18 and 65 years of age. They had, at least, a year's history of migraine and their first attack started when they were under 50 years.

Exclusion criteria included history of any neurological disorders (except migraine), applying any prophylaxis remedies for migraine at least 1 month before starting the investigation, severe headache (not responding to at least three types of abortive medication), and more than 15 days of lasting headaches per month for a period of 3 or more months; they also included history of skin lesion and eczema, and any kind of hypersensitive reaction in the temporal and forehead areas. Furthermore, breast feeding, pregnancy, and the inability to read (for completing diary forms) were considered to be exclusion criteria. Patients at the risk of committing suicide or those having psychiatric comorbidities were also excluded.

Intervention

This was a crossover, double-blind, controlled, randomized clinical trial. After explaining the procedure to patients and obtaining their informed consent, the participants (100 patients, 18–65 years old) were enrolled in either drug-placebo or placebo-drug groups according to a table of random numbers. Physicians, statisticians, and patients were not informed of the drug type. In each group, when a migraine attack started, patients used 2 ml of drug (or placebo) by rubbing topically in the temporal and forehead areas, and beyond the ears. Patients fully completed the standard VAS forms during 24 h after applying the drug. They used this drug twice. Then, after 14 days of washing time, groups changed from drug to placebo and vice versa, and applied them in the same way as before.

Outcomes

As the primary target was pain relief, patients were asked to fill in VAS questionnaires for each migraine attack (including status of pain and other complications like nausea, vomiting, photophobia, and phonophobia) over 24 h from the beginning of the attack (from the beginning of pain before using drug or placebo in time spots of 15 min, 30 min, 45 min, 1 h, 2 h, 6 h, and 24 h after applying drug or placebo). As per our ethical standards, patients who could not tolerate the pain after 2 h could use their general pain relief; they did not fill in their VAS scores after the 2 h.

Statistics

Considering the design of our study (crossover 2 × 2 with repeated measurements), a linear mixed-effect model was used to compare the effect of drug vs. placebo. As a powerful statistical model, it enabled researchers to study changes of responses during time with regard to correlation duo to measuring data from same subject. Also, the mixed model helped to manage incomplete responses and missing data, and increased statistical power. Fixed effects in the mixed model consisted of sequences of treatment, periods of treatment, types of drug, and time. Effect of subjects was considered to be random. Quantitative and qualitative variables were described by mean ± SD and frequency (percent), respectively. All statistical analyses were performed using SPSS® version 17.0 (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered statistically significant. Also, as primary and secondary endpoints, the percentage of "pain free" and "pain relief" 2 h after coetaneous application, recurrence, relapse, sustained pain relief, and sustained pain-free responses during the first 24 h, as well as alleviation of associated symptoms for both drug and placebo groups were calculated.

Results

Standardization of chamomile oleogel

Matricaria chamomilla used in this study yielded 1% of essential oil. Subsequently, identified components are shown in Table 1. According to the manner in which chamomile oil is

Table 1 Chemical composition of essential oils obtained from *M. chamomilla* by GC/MS

No.	Component	Concentration%	KI
1	Santolina triene	0.26	903
2	Pentanoic acid	0.07	933
3	α-Terpinene	0.07	1018
4	o-Cymene	0.11	1027
5	Artemesia ketone	0.68	1062
6	trans-Chrysanthemol	0.09	1163
7	Borneol	0.16	1169
8	cis-Geraniol	0.19	1228
9	4,8-Dimethyl-3,7-nonadien-2-one	0.15	1241
10	(2S,4R)-p-Mentha-[1(7),8]-diene 2-hydroperoxide	0.25	1381
11	γ-Caryophyllene	0.22	1407
12	β-Caryophyllene	6.86	1417
13	Tetrahydroionol	0.02	1424
14	Germacrene D	0.14	1480
15	Bisabolol oxide B	1.88	1656
16	Bisabolone oxide A	57.37	1684
17	Chamazulene	9.75	1730
18	Bisabolol oxide A	14.29	1748
19	Methyl ester 5,8,11-heptadecatriynoic acid	5.08	1810
	Total identified	97.64	

prepared, the final oil contained 2% of essential oil. The GC/FID analysis showed that this essential oil contained 4.48 ± 0.01 μl/ml of chamazulene.

Measurements of the total amount of polyphenol and flavonoid in the oleogel were 75.43 ± 0.51 and 28.63 ± 0.79 mg L^{-1}, respectively. Peaks of apigenin in sample and standard were checked in advance via a PDA detector for peak purity control [21]. The amount of apigenin in the oleogel was quantified as 0.165 ± 0.006 mg/g by using a calibration curve. Also, the extraction ratio was reported to be 71% in this method [21]. Therefore, the content of apigenin was calculated as 0.233 mg/g of the preparation by correcting with the extraction ratio.

Clinical evaluation of chamomile oleogel vs. placebo in migraine without aura attacks

Enrollment of patients is shown in the CONSORT flowchart (Fig. 1). Among a total number of 100 patients, 72 (38 patients in drug-placebo and 34 patients in placebo-drug groups) completed the therapeutic protocol. The mean ± SD of age was 37 ± 9.3 years, and groups had no significant differences in the age of included patients ($p = 0.31$). The mean duration time of migraine was 10.97 ± 7.65 years and the mean of the number of pain attacks was 12.33 ± 9.21 per month. These variables were not significantly different between therapeutic groups. Demographic information is described with more details in Table 2.

Compared to placebo, a significant decrease in pain (based on VAS scores) was seen when drug was used during the time of this study (beta = − 0.38, $p = 0.001$) (Fig. 2). Table 3 shows a point-to-point comparison of significance of differences between drug and placebo. However, there is no significant difference of mean of decreasing pain between men and women overall and between placebo and drug groups ($p = 0.16$ and 0.65, respectively; Fig. 3). With regard to changes of pain, crossover groups and therapeutic period had no significant differences (for crossover groups: beta = 0.02, $p = 0.94$; for therapeutic period: beta = − 0.09, $p = 0.42$).

In the per-protocol population, 29.2% (42/144) of attacks treated with the study drug and 2.1% (3/144) of attacks treated with the placebo were "pain free," 2 h after coetaneous application ($p = 0.001$). Also, 85.4% (123/144) of attacks treated with the study drug and 19.4% (28/144) of attacks treated with the placebo had "pain relief," 2 h after coetaneous application ($p = 0.001$). Recurrence was 13% (16/123) for the drug group and 46.4% (13/28) for the placebo group ($p = 0.008$). Also,

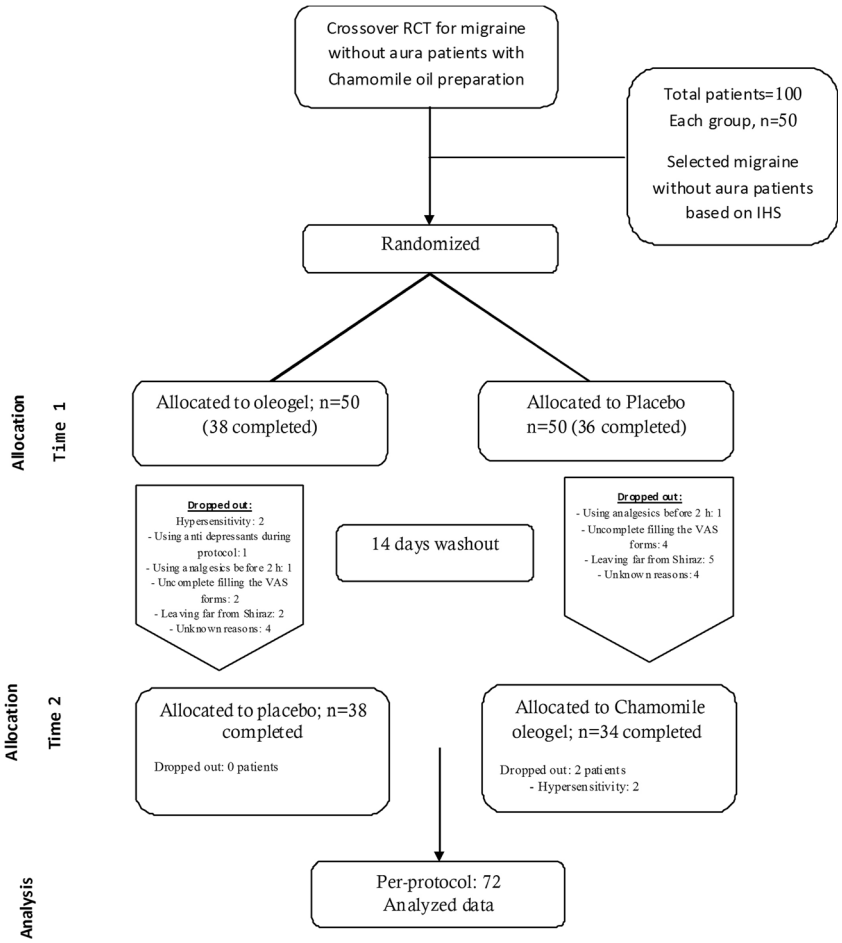

Fig. 1 CONSORT flowchart of crossover RCT for migraine without aura patients treated with chamomile oil preparation

Table 2 Demographic information of the crossed over arms of chamomile oleogel and placebo

Criteria		Completed process ($N = 72$)	Drug-placebo group (38 patients)	Placebo-drug group (34 patients)	p value
Gender	Female	57	33	24	0.11
	Male	15	5	10	
Marriage	Single	17	9	8	0.88
	Married	55	29	26	
Age (mean ± SD, year)		37.01 ± 9.30	37.94 ± 9.77	36.03 ± 8.79	0.31
Duration of illness (mean ± SD, year)		10.97 ± 7.65	11.86 ± 8.55	10.03 ± 6.56	0.07
The number of migraine attacks (mean ± SD, per month)		12.33 ± 9.21	10.41 ± 8.02	14.37 ± 10.05	0.39

relapse was 16.7% (7/42) for the drug group and 33.3% (1/3) for the placebo group ($p = 0.04$). A total of 74.3% (107/144) of drug-treated attacks and 10.4% (15/144) of placebo-treated attacks experienced sustained pain relief during the first 24 h ($p = 0.001$). For 24 h of sustained pain-free results, these rates were 24.3% (35/144) and 1.4% (2/144) for drug and placebo groups, respectively ($p = 0.005$).

In the intent-to-treat population, 68.1% (199/292) of attacks were associated with nausea and/or vomiting. Two hours after cutaneous application of drug or placebo, these ratios decreased to 86.7% (85/98) and 17.8% (18/101), respectively ($p = 0.001$). In this population, 68.6% (151/292) of attacks were associated with photophobia and 31.8% (93/292) with phonophobia. Photophobia-associated attacks decreased to 79.4% (58/73) and 20.5% (16/78) in drug-treated and placebo-treated attacks, respectively ($p = 0.001$). Phonophobia-associated attacks also decreased to 79.0% (34/43) and 34.0% (17/50) in drug and placebo groups, respectively ($p = 0.002$).

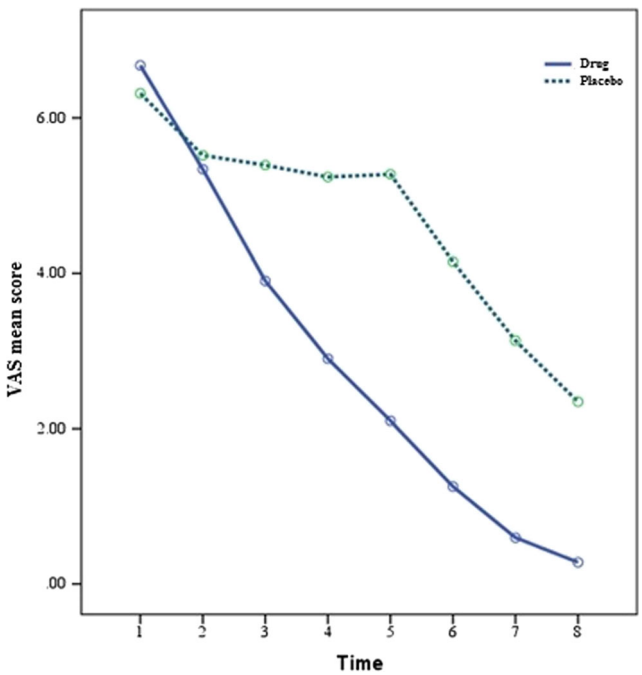

Fig. 2 Changes of VAS score for chamomile oleogel and placebo groups during the time (1 = 0; 2 = 15 min; 3 = 30 min; 4 = 45 min; 5 = 1 h; 6 = 2 h; 7 = 6 h; and 8 = 24 h after coetaneous application of chamomile oleogel [drug] or placebo). There were significant differences between drug and placebo after 30 min; p value < 0.05)

Compared to placebo, use of drug showed a significant decrease of probability of nausea (OR = 0.74, $p = 0.001$). With regard to changes of probability of nausea, crossover groups and therapeutic period had no significant differences (crossover groups: OR = 0.76, $p = 0.46$; therapeutic period: OR = 0.79, $p = 0.06$). Also, the same conditions were seen for vomiting; significant decrease was seen in the probability of vomiting for the drug group as compared to the placebo group (OR = 0.66, $p = 0.001$); no significant differences were seen for crossover groups (OR = 0.76, $p = 0.46$) and for therapeutic period (OR = 0.79, $p = 0.06$). A significant decrease of the probability of photophobia was seen for the drug group as compared to the placebo group (OR = 0.82, $p = 0.001$); no significant differences were seen for crossover groups (OR = 1.18, $p = 0.66$) and for therapeutic period (OR = 0.82, $p = 0.12$). A significant decrease of the probability of phonophobia was seen for the drug group as compared to the placebo group (OR = 0.78, $p = 0.001$); no significant differences were seen for crossover groups (OR = 1.10, $p = 0.84$) and for therapeutic period (OR = 0.95, $p = 0.79$). These comparisons are shown in Fig. 4.

Discussion

This was a crossover study and all patients used both drug and placebo. Therefore, each patient was compared to others as well as to himself or herself. Results (based on standard VAS) showed significant decrease of pain after using drug as compared to using placebo. Furthermore, there was no recurrent pain in our study. Also, we observed a significant effect of drug in decreasing chances of nausea, vomiting, photophobia, and phonophobia, as compared to placebo. Results showed the efficacy of drug as pain relief in migraine without aura as well as its role as a controller of accompanied side effects of nausea, vomiting, photophobia, and phonophobia. These

Table 3 Point to point comparison of significance of difference of pain between chamomile oleogel and placebo during the time

Time	0	15 min	30 min	45 min	1 h	2 h	6 h	24 h	Total *p* value
Chamomile oleogel	6.67 ± 1.46	5.34 ± 1.65	3.90 ± 1.94	2.90 ± 2.03	2.10 ± 2.01	1.26 ± 1.89	0.60 ± 1.57	0.27 ± 1.02	
Placebo	6.31 ± 1.50	5.51 ± 1.42	5.39 ± 1.57	5.24 ± 1.63	5.27 ± 1.97	4.15 ± 1.86	3.13 ± 2.06	2.34 ± 2.31	
p value for chamomile oleogel and placebo difference	0.87	0.35	0.001	0.001	0.001	0.001	0.001	0.001	0.001

results supported our hypothesis regarding the effect of this traditional preparation on migraine attacks. These effects can be due to chamomile ingredients appearing in the oleogel such as chamazulene (in essential oil), and apigenin (as the main flavonoid in chamomile) and its derivatives. Both of these can reduce NO release and synthesis by inhibiting nitric oxide synthase (iNOS) expression in activated macrophages [25, 26]. NO stimulates central sensitization and induces migraine headaches [27, 28]. Also, it can trigger inflammation at the site of action; blocking its synthesis can reduce migraine pain. On the other hand, flavonoids in chamomile (especially apigenin 7-O-glucoside) have selective COX-2 inhibitory effects due to their inhibition on endogenous prostaglandin E2 (PGE2) levels in RAW 264.7 macrophages [29]. COX-2 inhibitors can block sensitization of peripheral meningeal nociceptors, and act as anti-inflammatory and pain relief agents [30]. Therefore, their effects are similar to NSAIDs without the latter's general adverse effect. Another related action mechanism is the inhibition of pro-inflammatory biomarkers in THP1 macrophages by polyphenolic compounds (mostly apigenin) in the preparation [31]. They can affect neuroinflammation of meningeal and dural trigeminal nociceptors (as trigger factors for peripheral sensitization) [30] as well as inflammation on neurovascular units (NVU) at the site of pain [32]. Also, sesame oil (as the oily vehicle of the preparation) includes unsaturated fatty acids, and sesamin has anti-inflammatory and analgesic effects [33–35]. Traditionally, sesame oil has been used solely as pain relief in headaches [33, 36]. Therefore, it is not only an oily vehicle but also an active ingredient in the preparation.

As compared to a similar previous investigation using 10% solution of menthol in ethanol for migraine [37], chamomile oil in our study showed better results including a significant decrease of pain before and after 2 h (menthol led to no significant decrease of pain as compared to placebo after 2 h) as well as associated symptoms. Also, results can be compared to the use of conventional analgesics such as propacetamol hydrochloride [38], intravenous paracetamol, dexketoprofen [39], acetylsalicylic acid, and ibuprofen [40].

Another advantage of chamomile oleogel is its route of administration. One of the most important parameters in developing a drug is its onset of action. It seems that one potential route of administration for migraine can be the dermal and transdermal delivery of drugs in the forehead and temporal areas. Since ends of neurons are in the derma, it can be expected that drug delivery is faster and the target organ is very close to the applied drug. Also, anti-inflammatory agents can be effective faster at the site of action [41, 42]. On the other hand, oral administration in migraine can cause some difficulties because of nausea and vomiting [41].

Four patients (4%) dropped out of this study because of hypersensitivity to the drug. This is caused by both chamomile content as well as sesame oil functioning as the oily vehicle. It has been reported that chamomile can commonly lead to allergic reactions because of anthecotulide content, sesquiterpene lactone, and matricarin, a pro-azulene that produces positive patch tests in patients with sesquiterpene lactone hypersensitivity [43]. Usually, patients with existing hypersensitivity to German chamomile demonstrate cross-sensitivities to other family members of Asteraceae [44]. On the other hand,

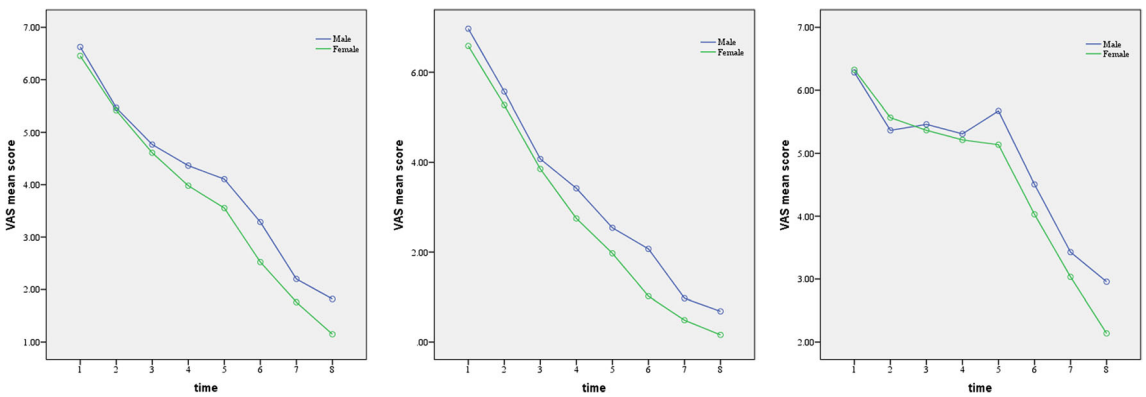

Fig. 3 Differences in decreasing pain (according to VAS score) between men and women in overall (left), in chamomile oleogel group (center), and in placebo group (right)

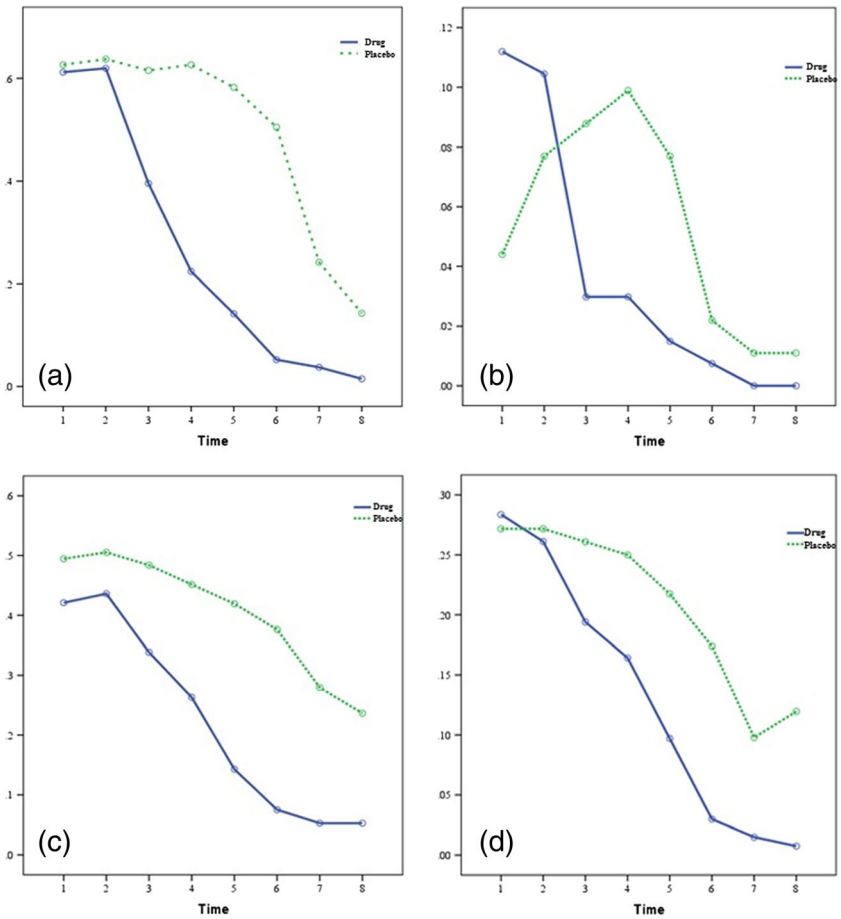

Fig. 4 The probability of changes in happening nausea (**a**), vomiting (**b**), photophobia (**c**), and phonophobia (**d**) for chamomile oleogel and placebo groups during the time (1 = 0; 2 = 15 min; 3 = 30 min; 4 = 45 min; 5 = 1 h; 6 = 2 h; 7 = 6 h; and 8 = 24 h after coetaneous application of chamomile oleogel [drug] or placebo). There were significant differences between drug and placebo after 30 min; p value < 0.05)

sesame oil can trigger immediate hypersensitivity via IgE antibody and delayed hypersensitivity via cell-mediated immune responses [44]; this is due to oleosin, oil, and protein content of sesame oil [44, 45]. Usually, these reactions were reported in oral use of sesame oil, but these skin reactions were also reported in topical uses of Chinese medicines due to their sesame oil content [46]. Despite a drop-out rate of 4% because of hypersensitivity, it was in a good range as compared to herbal drugs [47]. Also, there are no reports of major complications after using sesame oil and chamomile topically [43]. Both sesame oil and chamomile are safe and there is very good tolerability, while using the drug, in patients without hypersensitivity.

Based on pharmaceutical and pharmacological views, there are two main types of pharmacological ingredients of chamomile infused in the oily vehicle (sesame oil) of this preparation—essential oil and flavonoid content. In fact, chamomile essential oil is dissolved in the prepared oil due to its lipophilic nature [48]. But, how is apigenin (as the main pharmacological flavonoid in chamomile) dissolved in the oily vehicle? Apigenin is transferred from the aqueous chamomile extract to the oily vehicle during boiling, and then, the water content is vaporized in sesame oil. Apigenin is defined as a phenolic compound like other flavonoids [49]. On the other hand, sesame oil is rich in sesamin, a polyphenol lignan [50]. Both compounds (apigenin and sesamin) include phenolic rings in their structures. Since they have a planar aromatic structure, they may be linked via a hydrophobic-hydrophobic interaction such as forming stacking complexes. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of the water. This causes some molecules to minimize their contact with water through an aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule [51]. Also, sesame oil is a heat-stable oil; this is due to its sesamin content as well as endogenous antioxidant activity [52]. However, this is only one of the probable mechanisms of trapping apigenin in sesame oil. Sesame oil acts as an oily matrix [53] and too many complexes can be created between ingredients such as oleic acid (as the main fatty acid in sesame oil), ions, apigenin, chamazulene, and bisabolol oxide.

The oily character of the preparation can help in better absorption of active components that cross lipophilic layers of the skin at the site of action [54]. Also, the essential oil plays a critical role as an enhancer to increase penetration and absorption of the drug [55]. Rubbing the oleogel on the forehead has the same effect [56]. In contrast, forming oleogel and using silicon dioxide can lead to a decrease in releasing active components, and creating a sustained and controlled release [57, 58]. In the recent decade, forming oleogel from

sesame oil has been a subject of proving patents for preparing controlled release delivery systems [59]. Also, it acts as a viscose agent and helps to stabilize the preparation.

Limitations

The main limitation of this study was the small sample size. This was the first study on this preparation and more patients should be enrolled in future studies to better evaluate the efficacy of the preparation.

Conclusion

Overall, there is no complete treatment for migraine patients and current medicaments like NSAIDs have many side effects. Also, patients' responses to similar treatments are variable. Therefore, any new efficient and safe remedy can help physicians find more suitable drugs for pain relief. This investigation showed the clinical effect of a standardized preparation of traditional chamomile oil in the renewed form of oleogel. Efficacy was approved in evaluated patients. On the other hand, there were no reported major complications and side effects of using natural ingredients in this formula. Hence, this preparation can be considered a potential natural remedy for patients with migraine without aura.

References

1. Ayatollahi SMT, Sahebi L, Borhani-Haghighi A (2009) Epidemiologic and clinical characteristics of migraine and tension-type headaches among hospitals staffs of Shiraz (Iran). Acta Med Iran 47(2):115–120
2. Láinez MJ, García-Casado A, Gascón F (2013) Optimal management of severe nausea and vomiting in migraine: improving patient outcomes. Patient Relat Outcome Meas 4:61–73
3. Serafini G, Pompili M, Innamorati M, Gentile G, Borro M, Lamis DA, Lala N, Negro A, Simmaco M, Girardi P, Martelletti P (2012) Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. Eur Rev Med Pharmacol Sci 16(10):1389–1398
4. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808
5. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J (2005) Cost of disorders of the brain in Europe. Eur J Neurol 12(Suppl 1):1–27
6. Hoffmann J, Goadsby PJ (2014) Emerging targets in migraine. CNS Drugs 28(1):11–17
7. Tfelt-Hansen PC (2013) Triptans and ergot alkaloids in the acute treatment of migraine: similarities and differences. Expert Rev Neurother 13(9):961–963
8. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML (2013) Impact of NSAID and triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 53(10):1548–1563
9. Lipton RB, Stewart WF (1999) Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache 39:20–26
10. Mohagheghzadeh A, Zargaran A, Daneshamuz S (2011) Cosmetic sciences from ancient Persia. Pharmaceutical Historian 41:18–23
11. Zargaran A (2014) Ancient Persian medical views on the heart and blood in the Sassanid era (224-637 AD). Int J Cardiol 172(2):307–312
12. Zargaran A, Zarshenas MM, Mehdizadeh A, Mohagheghzadeh A (2013) Management of tremor in medieval Persia. J Hist Neurosci 22(1):53–61
13. Zargaran A, Mehdizadeh A, Zarshenas MM, Mohagheghzadeh A (2012) Avicenna (980-1037 AD). J Neurol 259:389–390
14. Abolhassanzadeh Z, Aflaki E, Yousefi G, Mohagheghzadeh A (2015 Apr) Randomized clinical trial of peganum oil for knee osteoarthritis. J Evid Based Complement Altern Med 20(2):126–131
15. Hamedi A, Zarshenas MM, Sohrabpour M, Zargaran A (2013) Herbal medicinal oils in traditional Persian medicine. Pharm Biol 51(9):1208–1218
16. Zargaran A, Borhani-Haghighi A, Faridi P, Daneshamouz S, Mohagheghzadeh A (2016) A review on the management of migraine in the Avicenna's Canon of Medicine. Neurol Sci 37(3):471–478
17. Zargaran A, Borhani-Haghighi A, Faridi F, Daneshamouz S, Kordafshari G, Mohagheghzadeh A (2014) Potential effect and mechanism of action of topical Chamomile (*Matricaria chamomila* L.) oil on migraine headache: a medical hypothesis. Medical Hypothesis 83:566–569
18. Zargaran A, Faridi P, Daneshamouz S, Borhani-Haghighi A, Azadi A, Hashempur MH, Mohagheghzadeh A (2016) Renovation and standardization of a historical pharmaceutical formulation from Persian medicine: chamomile oil. Trad Integ Med 1(3):108–114
19. Shoara R, Hashempur MH, Ashraf A, Salehi A, Dehshahri S, Habibagahi Z (2015) Efficacy and safety of topical *Matricaria chamomilla* L. (Chamomile) oil for knee osteoarthritis: a randomized; controlled clinical trial. Complement Ther Clin Pract 21(3):181–187
20. Zargaran A, Sakhteman A, Faridi P, Daneshamouz S, Akbarizadeh AR, Borhani-Haghighi A, Mohagheghzadeh A (2017) Reformulation of traditional chamomile oil, quality controls and fingerprint presentation based on cluster analysis of ATR-IR spectral data. J Evid Based Complementary Altern Med 22:707–714. https://doi.org/10.1177/2156587217710982.
21. Zargaran A (2015) Semisolid preparation of chamomile oil and study of its effects in migraine without aura via double blind randomized clinical trial with placebo control. PhD thesis. Shiraz: Shiraz University of Medical Sciences.
22. Adams RP (1995) Identification of essential oil components by gas chromatography/mass spectroscopy: Allured Publishing Co.
23. McDonald S, Prenzler PD, Autolovich M, Robards K (2001) Phenolic content and antioxidant activity of olive extracts. Food Chem 73:73–84
24. Pourmorad F, Hosseinimehr SJ, Shahabimajd N (2006) Antioxidant activity, phenol and flavonoid contents of some selected Iranian medicinal plants. Afr J Biotech 5(11):1142–1145
25. Bhaskaran N, Shukla S, Srivastava JK, Gupta S (2010) Chamomile: Aan anti-inflammatory agent inhibits inducible nitric oxide synthase expression by blocking RelA/p65 activity. Int J Mol Med 26(6):935–940
26. Ansari M, Rafiee K, Emamgholipour S, Fallah MS (2012) Migraine: molecular basis and herbal medicine. In: *Advanced Topics in Neurological Disorders*. Chen KS (Ed.), ISBN: 978-953-51-0303-5, INTECH, DOI: https://doi.org/10.5772/32018. Available from: http://www.intechopen.com/books/advanced-topics-in-neurological-disorders/migraine-molecular-basis-and-herbal-medicine.

27. Olesen J (2008) The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. Pharmacol Ther 120(2):157–171
28. Barbanti P, Egeo G, Aurilia C, Fofi L, Della-Morte D (2014) Drugs targeting nitric oxide synthase for migraine treatment. Expert Opin Investig Drugs 23(8):1141–1148
29. Srivastava JK, Pandey M, Gupta S (2009) Chamomile, a novel and selective COX-2 inhibitor with anti-inflammatory activity. Life Sci 85(19–20):663–669
30. Dodick D, Silberstein S (2006) Central sensitization theory of migraine: clinical implications. Headache 46(Suppl. 4):S182–S191
31. Drummond EM, Harbourne N, Marete E, Martyn D, Jacquier J, O'Riordan D, Gibney ER (2013) Inhibition of proinflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. Phytother Res 27(4): 588–594
32. Stanimirovic DB, Friedman A (2012) Pathophysiology of the neurovascular unit: disease cause or consequence? J Cereb Blood Flow Metab 32(7):1207–1221
33. Phitak T, Pothacharoen P, Settakorn J, Poompimol W, Caterson B, Kongtawelert P (2012) Chondroprotective and anti-inflammatory effects of sesamin. Phytochemistry 80:77–88
34. Nekuzad N, Ashke Torab T, Mojab F, Alavi-Majd H, Azadeh P, Ehtejab G (2012) Effect of external use of sesame oil in the prevention of chemotherapy-induced phlebitis. Iran J Pharm Res 11(4): 1065–1071
35. Zahmatkash M, Vafaeenasab MR (2011) Comparing analgesic effects of a topical herbal mixed medicine with salicylate in patients with knee osteoarthritis. Pak J Biol Sci 14(13):715–719
36. Bradley MJ (2002) Food, industrial, nutraceutical, and pharmaceutical uses of sesame genetic resources. In: Janick J, Whipkey A (eds) Trends in new crops and new uses. ASHS Press, Alexandria
37. Borhani Haghighi A, Motazedian S, Rezaii R, Mohammadi F, Salarian L, Pourmokhtari M, Khodaei S, Vossoughi M, Miri R (2010) Cutaneous application of menthol 10% solution as an abortive treatment of migraine without aura: a randomized, double-blind, placebo-controlled, crossed-over study. Int J Clin Pract 64(4):451–456
38. Zhang A, Jiang T, Luo Y, Zheng Z, Shi X, Xiao Z, Fang Y (2014) Efficacy of intravenous propacetamol hydrochloride in the treatment of an acute attack of migraine. Eur J Intern Med 25(7):629–632
39. Turkcuer I, Serinken M, Eken C, Yilmaz A, Akdag Ö, Uyan E, Kiray C, Elicabuk H (2014) Intravenous paracetamol versus dexketoprofen in acute migraine attack in the emergency department: a randomised clinical trial. Emerg Med J 31(3):182–185
40. Goldstein J, Hagen M, Gold M (2014) Results of a multicenter, double-blind, randomized, parallel-group, placebo-controlled, single-dose study comparing the fixed combination of acetaminophen, acetylsalicylic acid, and caffeine with ibuprofen for acute treatment of patients with severe migraine. Cephalalgia 34(13): 1070–1078
41. Pierce MW (2010) Transdermal delivery of sumatriptan for the treatment of acute migraine. Neurotherapeutics 7(2):159–163
42. Schulman EA (2012) Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea. Headache 52(2):204–212
43. Herbal Medicines (2013) London: Pharmaceutical Press; . P. 179
44. Gangur V, Kelly C, Navuluri L (2005) Sesame allergy: a growing food allergy of global proportions? Ann Allergy Asthma Immunol 95(1):4–11
45. Leduc V, Moneret-Vautrin DA, Tzen JT, Morisset M, Guerin L, Kanny G (2006) Identification of oleosins as major allergens in sesame seed allergic patients. Allergy 61(3):349–356
46. Oiso N, Yamadori Y, Higashimori N, Kawara S, Kawada A (2008) Allergic contact dermatitis caused by sesame oil in a topical Chinese medicine, shi-un-ko. Contact Dermatitis 58(2):109
47. Aberer W (2008) Contact allergy and medicinal herbs. J Dtsch Dermatol Ges 6(1):15–24
48. Waleczek KJ, Marques HM, Hempel B, Schmidt PC (2003) Phase solubility studies of pure (−)-alpha-bisabolol and camomile essential oil with beta-cyclodextrin. Eur J Pharm Biopharm 55(2):247–251
49. Bors W, Saran M (1987) Radical scavenging by flavonoid antioxidants. Free Radic Res Commun 2(4–6):289–294
50. Mahendra Kumar C, Singh SA (2015) Bioactive lignans from sesame (Sesamum indicum L.): evaluation of their antioxidant and antibacterial effects for food applications. J Food Sci Technol 52(5):2934–2941
51. Swarbrick J (2007) Encyclopedia of pharmaceutical technology. Marcel Dekker, New York, pp 3327–3329
52. Wu WH (2007) The contents of lignans in commercial sesame oils of Taiwan and their changes during heating. Food Chem 104(1): 341–344
53. Chen GL, Hsu WY (2001) Oral pharmaceutical preparation embedded in an oily matrix and methods of making the same. US Patent 6: 306–435
54. Cal K (2006) How does the type of vehicle influence the in vitro skin absorption and elimination kinetics of terpenes? Arch Dermatol Res 297(7):311–315
55. Herman A, Herman AP (2015) Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. J Pharm Pharmacol 67(4):473–485
56. Slayton TM, Valberg PA, Wait AD (1998) Estimating dermal transfer from PCB-contaminated porous surfaces. Chemosphere 36(14): 3003–3014
57. Vintiloiu A, Lafleur M, Bastiat G, Leroux JC (2008) In situ-forming oleogel implant for rivastigmine delivery. Pharm Res 25(4):845–852
58. Wang C, Hou H, Nan K, Sailor MJ, Freeman WR, Cheng L (2014) Intravitreal controlled release of dexamethasone from engineered microparticles of porous silicon dioxide. Exp Eye Res 129:74–82
59. Mattern C (2014) Controlled release delivery system for nasal applications and method of treatment. US Patent App 14(/322):319