

The Efficacy of Topical Basil Essential Oil on Relieving Migraine Headaches: A Randomized Triple-Blind Study

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Keywords

Complementary medicine · Headache · Herbal medicines · Migraine · *Ocimum basilicum*

Abstract

Objective: Complementary therapies have been increasingly used for the prevention and treatment of migraine so that there is a need for studies in this setting. This study sought to determine the effects of basil essential oil on the severity and frequency of migraine attack headaches. **Methods:** A triple-blind clinical trial study was performed on 144 patients diagnosed with migraine. Patients were randomly allocated by a stratified method to four groups of 36 titled basil essential oil 2, 4, 6%, and placebo groups. Medications were used topically every 8 h for 3 successive months. In addition, each individual received 325 mg of acetaminophen every 12 h. The severity and frequency of migraine attacks were measured prior to the study, at weeks 2, 4, 8, and 12. The visual analog scale was used to measure pain intensity. The marginal model and generalized estimation equations were used to compare changes in the intensity and frequency of pain over time. **Results:** The interaction of the dose and time factors was significant on both pain intensity ($p < 0.001$) and frequency of attack ($p < 0.001$). The odds ratio of higher pain intensity and rate ratio of higher frequency of attack in the

intervention groups compared to the placebo group were decreased over the study time. **Conclusion:** Time lapse and higher doses of basil essential oil would reduce both the intensity and frequency of migraine attacks.

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Wirksamkeit von topischem ätherischem Basilikumöl zur Reduktion von Migränekopfschmerzen: eine randomisierte Studie

Schlüsselwörter

Komplementärmedizin · Kopfschmerzen · Pflanzliche Arzneimittel · Migräne · *Ocimum basilicum*

Zusammenfassung

Ziel: Komplementäre Behandlungsansätze finden zunehmend Anwendung in der Prävention und Therapie der Migräne, daher bedarf es auch wissenschaftlicher Studien zu diesem Setting. Das Ziel dieser Studie war es, die Auswirkungen von ätherischem Basilikumöl auf die Schwere und Häufigkeit von Migräneattacken und damit einhergehenden Kopfschmerzen zu untersuchen. **Methoden:** Es handelte sich um eine dreifach verblindete klinische Studie, an der 144 Patienten mit diagnostizierter Migräne

teilnahmen. Nach Randomisierung und Stratifizierung wurden die Patienten in vier Gruppen zu je 36 Patienten aufgeteilt: je eine mit essenziellem Basilikumöl 2, 4 und 6% behandelte Gruppe und eine Placebogruppe. Das Arzneimittel wurde drei aufeinanderfolgende Monate lang alle acht Stunden topisch angewendet. Zusätzlich erhielt jeder Patient alle zwölf Stunden 325 mg Acetaminophen. Die Erhebung der Schwere und Häufigkeit von Migräneattacken erfolgte vor Studienbeginn und nach Woche 2, 4, 8 und 12. Die Schmerzstärke wurde auf einer visuellen Analogskala gemessen. Vergleiche erfolgten anhand der Veränderung der Schwere und Häufigkeit der Schmerzen im Zeitverlauf laut marginalen Modellen und verallgemeinerten Schätzgleichungen. **Ergebnisse:** Die Wechselwirkungen zwischen den Faktoren Dosis und Zeit waren signifikant, sowohl im Hinblick auf die Stärke der Schmerzen ($p < 0,001$) als auch auf die Häufigkeit der Attacken ($p < 0,001$). Die Odds Ratio für eine höhere Schmerzstärke und die Rate Ratio für eine höhere Anfallshäufigkeit in den Interventionsgruppen im Vergleich zur Placebogruppe nahmen im zeitlichen Verlauf der Studie ab. **Schlussfolgerung:** Zeitverlauf und höhere Dosierung des ätherischen Basilikumöls scheinen die Stärke und Häufigkeit von Migräneattacken zu reduzieren.

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Introduction

Migraine is an episodic disorder which affects 12% of the total population. It presents with unilateral headache, nausea, vomiting, and sensitivity to light and sound. Half of the attacks are triggered by physiologic or psychological stressors [1, 2]. When untreated or unsuccessfully treated, these attacks usually last 4–72 h [3]. On average, it happens to occur 1.5 times a month; however, there are people who suffer from migraine even once a week [4]. Medications recommended for treating acute migraine include triptans, ergots, and nonsteroidal anti-inflammatory drugs. The latter group of medication is commonly used to control an attack of migraine, although that is not a specific treatment and has major side effects. Ergots are moderately effective and preferred for frequent attacks of migraine. Triptans are considered as the most effective group of medication; however, they are avoided among patients with underlying cardiovascular diseases [5–7].

None of the above medications works satisfactorily for the management of migraine attacks [1, 8–10]. Insufficient treatment of migraine can increase the risks of developing chronic migraine by 2.5–3.5 times [11–13]. On the other hand, there is an ever-increasing interest in complementary and alternative medicine (CAM), especially by patients who suffer from chronic pain and dis-

eases [14]. CAM is repeatedly used for the prevention or self-treatment of headaches [15] and is very popular among patients, so that the studies have shown a proportion of 49.5% of Americans and 32% of British people with migraine using CAM throughout the year [15, 16]. CAM has lesser-known side effects with fewer dependency on medication [17]. Existing literature shows promising effectiveness for the treatment of migraines [10, 18–24].

Basil (*Ocimum basilicum* L.; Lamiaceae family) is among the most important medicinal plants and has many useful compounds including linalool, cineole, estragole, gamma-terpinene, geraniol, menthol, eugenol, and many others [6, 25–27]. These ingredients provide effects like anti-inflammatory, anxiolytic, tunic, diuretic, digestive enhancer, anti-flatulence, anti-dandruff, anti-coagulant, cough suppressant, antiseptic, anti-diabetes, and immune-modulatory effects [28, 29]. Zarshenas et al. [30] state that in Iranian traditional medicine, basil was used to treat general headaches. The basil plant has broad antioxidant effects [31, 32], and studies have shown that some antioxidants can help relieve migraine pain [33–35]. Gamma-terpinene and linalool have both analgesic and anti-anxiety properties [28, 36, 37]. Due to the anti-inflammatory properties of the basil plant and inflammatory nature of migraine, it seems that basil can be used to treat migraine headaches [38]. Upon a broad search through manuscripts, no study has been found to investigate the effect of basil on the severity and frequency of migraine attacks; therefore, this study was conducted to examine the impact of different doses of basil essential oil on controlling migraine headaches.

Material and Methods

Study Design and Participants

This study was designed as a randomized triple-blind placebo-controlled clinical trial. The study population included all patients who were already diagnosed with migraine and referred to Rahimi Clinic, which is affiliated to the Lorestan University of Medical Sciences, Khorramabad, Iran. The inclusion criteria consisted of age range 18–46 years, having been diagnosed with migraine based on the International Headache Society (IHS) criteria (3rd edition – beta version) [38] for more than 1 year with more than two attacks per month, lack of mental disorders such as depression, anxiety, and psychosis, ability to report pain intensity, not being at risk of upcoming menopause, and willingness to participate in the study. Exclusion criteria comprised pregnancy, unwillingness to continue the study, use of other medications during the study, absence of referrals to the clinic at specified times, and sensitivity to basil essential oil.

Interventions

Migraine was diagnosed by a neurologist based on the IHS criteria. Prior to the intervention, participants were asked to explain their most severe headaches experienced until now based on the visual analogue scale (VAS) and express the number of attacks over the previous month. Participants were assigned randomly to basil

Table 1. Comparison of baseline and demographic characteristics among the study groups

Variables	Placebo	Basil 2%	Basil 4%	Basil 6%	Total	<i>p</i> value
Age, years	34.5±9.7	34.0±9.3	32.7±9.2	33.4±9.2	33.6±9.3	0.859 ^a
Gender						0.923 ^b
Male	26 (74.3)	26 (72.2)	25 (69.4)	26 (76.5)	103 (73)	
Female	9 (25.7)	10 (27.8)	11 (30.6)	8 (23.5)	38 (27)	
BMI						0.985 ^b
<18.50	4 (11.4)	4 (11.1)	6 (16.7)	4 (11.8)	18 (12.8)	
18.50–24.99	16 (45.7)	15 (41.7)	16 (44.4)	16 (47.1)	63 (44.7)	
25–29.99	15 (42.9)	17 (47.2)	14 (38.9)	14 (41.2)	60 (42.6)	
Baseline pain intensity						0.814 ^b
Moderate	5 (14.3)	8 (22.2)	8 (22.2)	7 (20.6)	28 (19.9)	
Severe	30 (85.7)	28 (77.8)	28 (77.8)	27 (79.4)	113 (80.1)	
Baseline frequency of attacks	5.0 [5.0]	5.5 [4.50]	5.0 [2.87]	5.2 [2.62]		0.904 ^b

Values represent mean ± SD, *n* (%), or median [IQR]. ^a One-way ANOVA test. ^b Chi-square test.

essential oil 2%, basil essential oil 4%, basil essential oil 6%, and placebo groups. The subjects were asked to apply the drugs topically to the frontal and temporal areas every 8 h for a length of 3 months. Individuals of all groups received acetaminophen pills 325 mg every 12 h as well.

A three-part questionnaire was prepared. The first part contained tree variables such as age, gender, and body mass index (BMI). The second part of the questionnaire consisted of the VAS, which measures the pain intensity from a scale of zero to 10. The last part of the questionnaire contained inquiries about the frequency of the migraine attacks. The content validity of the questionnaire was evaluated by ten faculty members at Lorestan University of Medical Sciences.

Plant Material

Aerial parts of basil (*Ocimum basilicum* L.; Lamiaceae family) were purchased from a local market in Khorramabad, western Iran. The plant sample was identified by an herbalist and a voucher sample. A voucher specimen was kept at Razi Herbal Medicine Research Center, Khorramabad, Iran.

Drug Preparation and Analysis

The leaves and stem were separated by hand from one another. The samples were dried in the shade then hydro-distilled for 4 h, using a Clevenger-type apparatus. The chemical composition of the basil essential oil was analyzed using gas chromatography method. The main components through gas chromatography included cineole 3%, gamma-terpinene 1.5%, linalool 1.5%, estragole 93%, and eugenol 1%. The extract appeared liquid, clear, and yellowish. The essential oil was then prepared in doses of 2, 4, and 6%. The essential oils and placebo were poured in 30-mL bottles. Basil essential oil was prepared and analyzed at Abatag pharmaceutical commercial company, Tehran, Iran. The placebo consisted of identical liquid containing pharmaceutical paraffin. The appearance and odor of the placebo were designed by Abatag Company to match that of the basil essential oil.

Outcome Measures

The subjects were asked to visit the clinic at 2, 4, 8, and 12 weeks of the intervention. During the visit, they were asked to find the most severe headache attack from the previous visit to the current visit based on the VAS. They were also asked for the number of at-

tacks from the previous visit to the current one. Information was collected and recorded by the research assistant.

Sample Size Estimation

The sample size was estimated to be about 30 in each group based on a similar study [39] and a table from a book entitled Applied Linear Statistical Models [40] ($r = 4$, $\Delta/\sigma = 0.84 \approx 1$, $\sigma = 2.39$, $\Delta = 2$, $\alpha = 0.05$, $\beta = 0.1$). However, considering average attrition of 20%, 36 individuals for each group and a total of 144 people for the purpose of the study were selected ultimately.

Randomizing Method

Sampling was done in a non-probability sampling technique. Participants were allocated randomly to four groups according to stratification method [41, 42]. Stratification was done based on variables such as gender, BMI, baseline pain intensity, and frequency of attacks. In each stratum, a permutation blocks method was used. The blocks were quadruple. Since there are 24 different permutations of the letters A–D, the following method was used to select any permutations (ABCD: 0–3, ABDC: 4–7, and DABC: 93–96). Eligible participants were assigned randomly to basil essential oil 2% ($n = 36$), basil essential oil 4% ($n = 36$), basil essential oil 6% ($n = 36$), and placebo ($n = 36$) groups from March to December 2017. A biostatistician designed the random allocation procedure and enrolled participants. Research assistants assigned participants to groups.

Blinding Method

Different doses of basil essential oil and placebo were placed in dark bottles by a research assistant. Each bottle was coded confidentially (A, B, C, or D) and drug codes remained with the research assistant until the end of the analysis. The researchers, the biostatistician, and participants were all unaware of the content of the bottles.

Data Analysis

In this study, the intention-to-treat approach was used to analyze the data, while we utilized imputation for the missing data (last observation carried forward). To compare the groups in terms of underlying and demographic variables, univariate tests like chi-square, one-way analysis of variance, and Mann-Whitney and Fisher's exact tests were used. A longitudinal data analysis was used to compare changes in the severity and frequency of pain be-

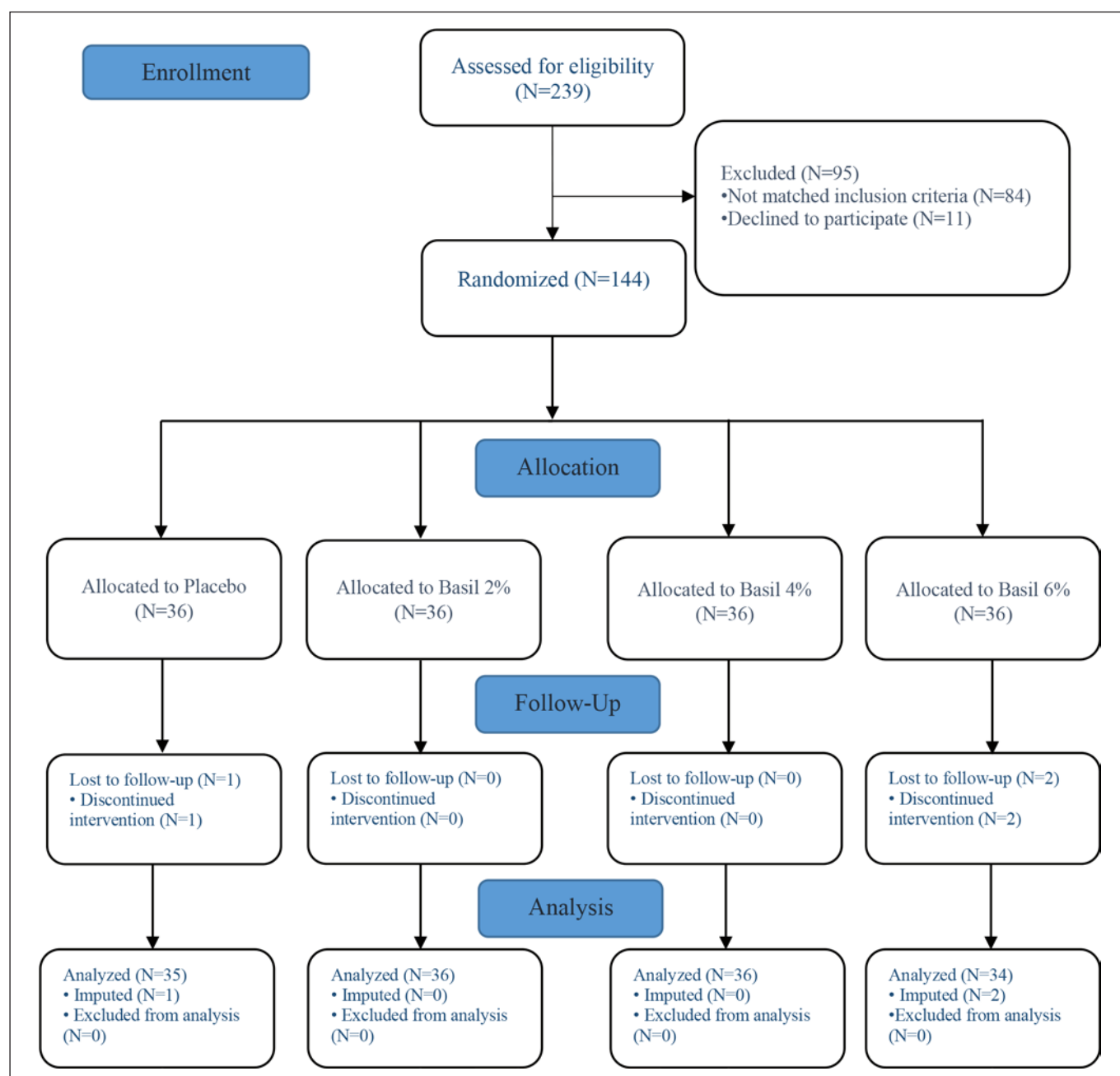


Fig. 1. Study flow diagram.

tween the four groups over time. This analysis method included marginal model for data modeling and generalized estimating equations for parameter estimation procedure.

We applied the main effects of the “dose” and “time” factors, as well as the interaction between dose and time factors in the model. Since, the nature of pain was of an ordinal type, a cumulative logit link function was used in the marginal model. As the number of attacks was a count variable, the negative binomial link was recognized as the best option. Likewise, an exchangeable covariance matrix structure was employed to account for the intra-individual correlation of the observations. SPSS version 22 was deployed for data analysis. p values less than 0.05 were considered as statistically significant.

Results

One hundred forty-four patients were included in this study (Fig. 1). The mean age of participants was 33.6 ± 9.3 years. Male patients constituted 73% (103 persons) of the study population. No statistically significant differences were observed between groups in terms of age ($p = 0.859$), gender ($p = 0.923$), BMI ($p = 0.985$), baseline pain intensity ($p = 0.814$), and baseline frequency of attacks ($p = 0.904$) (Table 1). Figures 2 and 3 show the intensity of pain as well as the frequency of migraine attacks in the

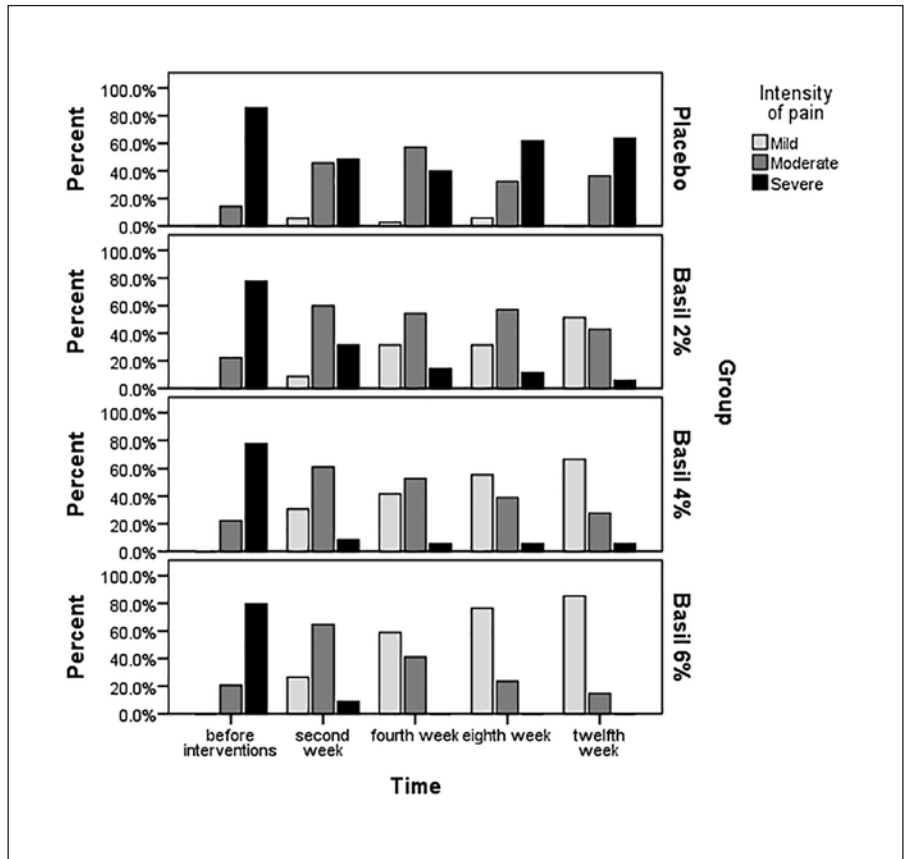


Fig. 2. Comparison of pain intensity in the four groups over time.

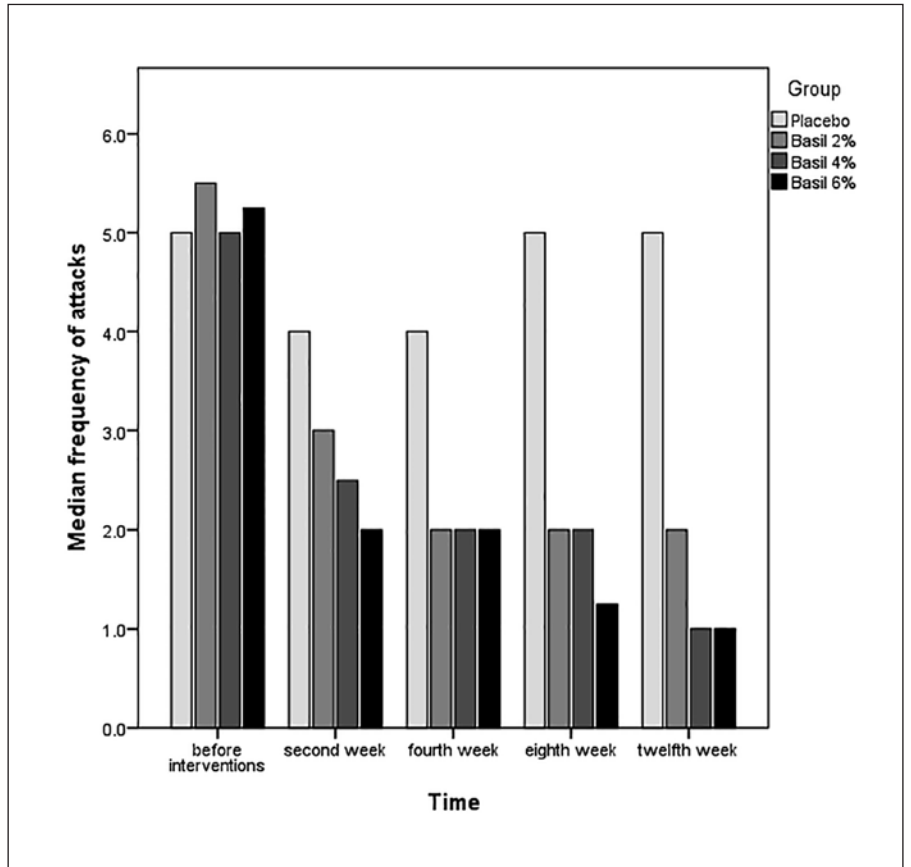


Fig. 3. Comparison of frequency of attacks in the four groups over time.

Table 2. Effects of dose and time factor on pain intensity using marginal model

Pairwise comparisons	Odds ratio formulas in terms of time	$t = 0$	$t = 2$	$t = 4$	$t = 8$	$t = 12$
Basil 2% vs. placebo	$e^{-0.2954-0.2507t}$	0.74	0.45	0.27	0.10	0.03
Basil 4% vs. placebo	$e^{-0.8531-0.2816t}$	0.42	0.24	0.13	0.04	0.01
Basil 6% vs. placebo	$e^{-0.6458-0.4563t}$	0.52	0.21	0.08	0.01	0.00

Table 3. Effects of dose and time factor on frequency of migraine attacks using marginal model

Pairwise comparisons	Rate ratio formulas in terms of time	$t = 0$	$t = 2$	$t = 4$	$t = 8$	$t = 12$
Basil 2% vs. placebo	$e^{-0.0571-0.1163t}$	0.94	0.74	0.59	0.37	0.23
Basil 4% vs. placebo	$e^{-0.1171-0.1244t}$	0.88	0.69	0.54	0.32	0.20
Basil 6% vs. placebo	$e^{-0.0663-0.1736t}$	0.93	0.66	0.46	0.23	0.11

four groups at various times. The results of the marginal model indicate that the interaction between the dose and time factors was significant on both pain intensity ($p < 0.001$) and frequency of attacks ($p < 0.001$).

Based on significance of interaction term in the aforementioned model, the effect of dosage on pain intensity varied over time. In other words, the odds ratio (OR) of higher pain intensity in the intervention groups compared to the placebo group depended on time and followed a subsequent formula where t is the time of measurement of pain intensity per week, which can take values of 0, 2, 4, 8, or 12. For example, in the fourth week ($t = 4$), the OR of pain intensity was lower by 87% in the basil 4% group compared to the placebo group (OR = 0.13) and in the eighth week ($t = 8$), the OR of pain intensity was lower by 90% in the basil 2% group compared to the placebo group (OR = 0.10) (Table 2). Likewise, the rate ratio (RR) of attacks in the intervention groups compared to the placebo group was a function of time. Put differently, the RR of attacks in the intervention groups compared to the placebo group depended on time and followed a subsequent formula. For example, in the second week ($t = 2$), the RR of occurring migraine attacks was lower by 34% in the basil 6% group compared to the placebo group (RR = 0.66) and in the twelfth week ($t = 12$), the RR of occurring migraine attacks was lower by 80% in the basil 4% group compared to the placebo group (RR = 0.2) (Table 3).

Discussion

This clinical trial was conducted to investigate the effect of basil essential oil on reducing the frequency and severity of pain in migraine patients. Since the effect of

basil dose and the effect of time agent on the pain intensity and frequency of attacks was significant, it has been certainly not possible to talk about the superiority of a basil dose compared to other doses. Therefore, according to the results, over time and higher doses of basil essential oil would reduce both the severity and frequency of migraine attacks. In vivo studies have also shown that basil essential oil may inhibit pain due to migraine by reducing the level of amino acids that interfere with pain [28, 43]. It has been observed that basil plant may relieve pain through interaction with the opioid system in the brain [44]. During the course of the trial, when we increased the dosage, the severity and frequency of pain both decreased. Likewise, as time went on, a lower percentage of patients were suffering from pain. As such, none of the participants in the basil essential oil 6% group expressed severe pain by the 12th week.

In traditional Iranian medicine, basil is used as a sedative and analgesic drug [28]. Previous studies on the impact of other herbal medication on controlling migraine headaches have brought up similar results [10, 23]. An in vivo study by Abdolmaleki et al. [45] shows that the analgesic and anti-inflammatory effects of peppermint depend on dosage [41], and since basil has the same family as peppermint, this would apply to basil as well. Likewise, the impact of rose on the intensity of pain was studied among migraine patients, which indicated that the severity of pain decreases as time goes on [9]. Similarly, when lavender extract is taken orally, it can gradually reduce the pain and frequency of migraine attacks by the passage of time and higher doses [10].

The analgesic effect of basil has been attributed to its compounds. Cineole, geraniol, flavonoids, and estragole have anti-inflammatory properties [45–49]. Extract of

chamomile [50], rose [10], lavender [23], and *Lippia alba* [51] also contain anti-inflammatory properties which can help relieve migraine symptoms. The spasmolytic effect of menthol as a part of basil essential oil can reduce the sensitivity of the pre-cranial muscles; therefore, it may lessen migraine pain [52]. There is also evidence that menthol available in the extract of peppermint can effectively reduce the symptoms of migraine and pain intensity [53]. Linalool essentially has an analgesic effect of its own as well [54, 55].

The route of administration is another point which alters the efficacy of the herbal medications. In this study, basil essential oil was used over the forehead and temporal area. This is because it would be absorbed much faster and gets to the targeted organs such as the brain and axonal arborization throughout the scalp [10]. Almost all other studies in which herbal medicine was taken orally [23], topically [10], or through inhalation [39] in order to relieve the pain caused by migraine came up with promising results. Between these routes, the topical form of herbs is most often preferred because it is more accepted by the patients, it is more effortless to use, and has fewer side effects [30, 54]. Studies have also shown that topical use of herbal drugs can have a beneficial effect on neuropsychological diseases. In addition, these extracts may stimulate the olfactory pathway of the central nervous system as an additional mechanism to reduce response to a painful stimulus [10].

Our study has a number of advantages which enhance the validity of the results. The sample size was large enough, and the groups were matched in terms of demographic and basic information in order to minimize the confounding effects of variables. We also examined the effects of different doses of basil essential oil and the study was a triple-blind one. Nonetheless, there was a limitation. Because of the diversity of geographic location, type of soil, weather, altitude, genetic structure, and planting season, a plant species may contain different chemical structures; therefore, a single species may produce different qualities of extract, each with own specific compounds [53]. Thus, the results of this study may not be generalized to other environmental conditions.

Conclusion

The closer we get from the beginning of the study to the 12th week, the greater the dose superiority of basil essential oil compared to the placebo group in controlling the severity of pain and the number of attacks. It is suggested that more in vivo and in vitro studies be conducted to demonstrate the mechanism of action through which basil essential oil controls migraine headaches. In addition,

it is recommended that the impact of basil essential oil on controlling migraine attacks be investigated when the compound is taken orally as well as through inhalation.

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Statement of Ethics

Ethical approval was obtained from the Ethics Committee of the LUMS. Permissions were obtained from the Rahimi Hospital Clinic authorities. The study was recorded in the Iranian Registry of Clinical Trials under the code of IRCT20130825014472N3. Patients were informed about the purpose and the course of the study and that they were free to withdraw at any stage. Patients were assured about the confidentiality of the data and the absence of any constraints to participate. They were also asked to complete a written informed consent form before enrolling in the study.

Disclosure Statement

The authors declare that there is no conflict of interests.

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Author Contributions

Study concept and design: Mahdieh Ahmadifard; acquisition of data, analysis and interpretation of data: Sajad Yarahmadi, Parviz Bahrami, Elham Sheikhi; statistical analysis: Farzad Ebrahimzadeh; administrative, technical, and material support: Mahdieh Ahmadifard, Sajad Yarahmadi; translation and edit: Arash Ardalan, Sajad Yarahmadi.

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