Cutaneous application of menthol 10% solution as an abortive treatment of migraine without aura: a randomised, double-blind, placebo-controlled, crossed-over study

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Introduction

Migraine, a chronic, incapacitating syndrome of headache imposes a significant burden upon the general population. Indeed, over 70% of migraineurs are not completely satisfied with their current treatment (1).

Menthol (C_{10}H_{20}O), the most important ingredient of peppermint has long been used for the treatment of various pain conditions, including headache (2). At least one clinical trial has shown the efficacy of peppermint oil in the alleviation of tension type headaches (3,4).

Here, a randomised, triple-blind, placebo-controlled, crossed-over study for the evaluation of efficacy, safety and tolerability of the cutaneous application of menthol 10% as a treatment for migraine without aura was conducted.

Methods

Study population
This study was conducted in the Neurology Clinic at Nemazee Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, southern Iran, from March 2007 to March 2008. The patients were recruited via local newspaper advertisements. Eligible patients were categorised into two groups and a 10% ethanol solution of menthol (as drug) and 0.5% ethanol solution of menthol (as placebo) were applied to the forehead and temporal area in a crossover design. Pain free, pain relief, sustained pain free and sustained pain relief end-points were measured by questionnaires using a visual analogue scale. Results: The intent-to-treat population consisted of 35 patients (80% women, 20% men, mean age: 29.6 ± 6.2) with 118 migraine attacks. In the intent-to-treat population, the menthol solution was statistically superior to the placebo on 2-h pain free (p = 0.001), 2-h pain relief (p = 0.000), sustained pain free and sustained pain relief end-points (p = 0.008). The menthol solution was also more efficacious in the alleviation of nausea and/or vomiting and phonophobia and/or photophobia (p = 0.02). In the per-protocol population, there was significantly higher number of patients who experienced at least one pain free/pain relief after the application of menthol rather than the placebo (p = 0.002). No significant difference was seen between the adverse effects of the drug and the placebo groups (p = 0.13). Conclusion: Menthol solution can be an efficacious, safe and tolerable therapeutic option for the abortive treatment of migraine.

SUMMARY

Objective: To investigate the efficacy and safety of the cutaneous application of menthol 10% solution for the abortive treatment of migraine. Background: Peppermint and its active ingredient menthol have long been used for the treatment of various pain conditions including headache. Methods: This is a randomised, triple-blind, placebo-controlled, crossed-over study conducted in the neurology Clinic of Nemazee Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, southern Iran, from March 2007 to March 2008. The patients were recruited via local newspaper advertisements. Eligible patients were categorised into two groups and a 10% ethanol solution of menthol (as drug) and 0.5% ethanol solution of menthol (as placebo) were applied to the forehead and temporal area in a crossover design. Pain free, pain relief, sustained pain free and sustained pain relief end-points were measured by questionnaires using a visual analogue scale. Results: The intent-to-treat population consisted of 35 patients (80% women, 20% men, mean age: 29.6 ± 6.2) with 118 migraine attacks. In the intent-to-treat population, the menthol solution was statistically superior to the placebo on 2-h pain free (p = 0.001), 2-h pain relief (p = 0.000), sustained pain free and sustained pain relief end-points (p = 0.008). The menthol solution was also more efficacious in the alleviation of nausea and/or vomiting and phonophobia and/or photophobia (p = 0.02). In the per-protocol population, there was significantly higher number of patients who experienced at least one pain free/pain relief after the application of menthol rather than the placebo (p = 0.002). No significant difference was seen between the adverse effects of the drug and the placebo groups (p = 0.13). Conclusion: Menthol solution can be an efficacious, safe and tolerable therapeutic option for the abortive treatment of migraine.

What’s known
Menthol, consisting of about 33–60% of peppermint oil, is present in a large number of medications for external application and has long been used in empirical and traditional medicine for treatment of various pain conditions, including headache. Various mechanisms of action for menthol are proposed till now.

What’s new
Menthol can be an affordable, safe and efficacious addition to our weaponry against acute attacks of migraine without aura. Cutaneous application is a rapid acting route which probably minimizes systemic complications.
Menthol solution for the treatment of migraine

2007 to March 2008. The patients were recruited from the local community via local newspaper advertisements. They were interviewed and examined by a qualified neurologist, and Brain CT scans (without contrast infusion) were then performed.

Study criteria
All patients between 18 and 65 years, who had a definite diagnosis of migraine headache according to the standards of the International Headache Society (IHS 1.1) (5), with at least a 1 year history of migraine, first attack started under the age of 50 years, and with 1–6 migraine attacks per month were included in the study. Patients who had a history of eczema and any kind of hypersensitivity reaction, any skin lesion in the temporal and forehead areas of the head, severe headache which does not respond to at least three types of abortive behind the counter medications, headache lasting more than 15 days per month for 3 months or more, and a history of any neurological disorder except migraine were excluded. Other exclusion criteria included receiving any medication for prophylaxis of migraine from 1 month before the beginning of the study, pregnancy, breast feeding and an inability to read, comprehend and complete diary forms.

Study ethics
This study was conducted according to the second edition of guidelines for controlled trials of drugs in migraine (6) and approved by the Ethics Committee of Shiraz University of Medical Sciences (no. #85-3000). The study and possible outcomes were explained for all participants and written informed letters of consents were obtained.

Randomisation (crossed-over design)
Eligible patients, who were to be studied for four attacks of migraine headache were randomised into two groups using computer-generated random number tables. In Arm A, the initial two migraine attacks were treated with menthol and the second two attacks with the placebo. Subjects in Arm B were managed in the opposite order receiving the placebo for the first two attacks and menthol for the second two attacks of migraine. Safety population was defined as patients who were randomised and recommended to apply drug or placebo. Intent-to-treat population was defined as randomised patients who applied drug or placebo for 1–4 migraine attacks and had complete data for at least one attack. A per-protocol population was defined as randomised patients who applied drug or placebo for all four attacks and fully adhered to study criteria.

Triple blinding
Patients and all investigators including a qualified neurologist, interviewers, research assistants and a statistician were completely blinded to the drug and placebo. Only the pharmacist preparing study medication who had no contact with study participants was not blinded. The codes were not broken till the study results were entirely analysed.

Study questionnaires
The study included three questionnaires. Questionnaire-1, which was completed by a qualified interviewer, included demographic data, IHS criteria, inclusion and exclusion criteria. Questionnaire-2 included columns of a Visual Analogue Scale (VAS) indicating intensity of headache, questions about nausea, vomiting, photophobia, phonophobia in minutes 0, 15, 30, 45, 60, 90, 120, and hours 6, 12, 24 after application of drug or placebo. Results of hours 6 and 12 were not considered for data processing if a rescue drug had been used. Questionnaire-3 was a complete headache diary including headache quality, assessment of correct consumption of the solution and adverse events. The instructions on how to fill out the forms were explained for each patient at the beginning of the enrolment.

Drug and placebo preparation
Active study medication was prepared as a 10% solution of menthol crystals in ethanol. We prepared a 0.5% ethanol menthol solution as the placebo, based on the results of a pilot study which showed that the odour of 10% peppermint oil solution is not qualitatively different from the odour of 0.1%, 0.5% or 1% peppermint oil solution (7). The active study medication and the placebo had the same colour and odour and were prepared in the same packages labelled A and B solution with respect to the triple-blind design of the study.

Drug and placebo application
The forehead and temporal area of the painful side (or more painful side if the headache was bilateral) was cleansed by tap water and dried to increase drug absorption. One ml of the drug or placebo was applied with a piece of sponge on a surface area 5 × 5 cm on the mentioned areas. The patients rested in a dark and quiet place after application of the drug or placebo and were asked not to press the temporal area to prevent the alleviative effect of vascular compression. The drug or placebo was applied again after 30 min in the same manner as the first application. If the pain was not relieved after 2 h of the first application, the patient was allowed to use
any rescue medication for pain relief and associated symptoms.

End-points
The primary end-point was the comparison of ‘pain free’ attacks after application of the drug or placebo. Secondary end-points included ‘pain relief’, ‘sustained pain free’, pain intensity and alleviation of associated symptoms. Being ‘pain free’ was defined as the absence of headache (0 recorded in VAS) 2 h after the application of drug or placebo. ‘Pain relief’ was defined as more than 50% decrement in the VAS score in comparison to the baseline. ‘Sustained pain relief’ was defined as more than 50% decrement in the VAS score compared with the baseline without accentuation of headache. Recurrence was defined as headache return after initial pain relief within 24 h. Relapse was defined as headache return after initial pain freedom within 48 h. ‘Sustained pain free’ was defined as being pain free 2 h after application of drug or placebo and absence of relapse or recurrence. Alleviation of associated symptoms was defined as absence of nausea, vomiting, photophobia and phonophobia 2 h after the application of the drug or placebo.

Study statistics
Repeate measures ANOVA was used to assess the effect of menthol on pain intensity over time periods. In this way, pain at the baseline was considered as covariate.

Twenty-five patients received a drug and a placebo in two attacks, separately (two with placebo, two with menthol). An MC Nemar test was used to determine whether the drug and placebo had different effects in terms of at least one pain relief and pain free response after 2 h.

Other statistical analyses include χ² and Fisher’s Exact tests.

The data in the tables are reported as mean and SD or as a count and percentage. A probability value of less than 0.05 was considered significant for all statistical tests. Statistical analyses were performed using a statistical program (spss 13.0; SPSS Inc., Chicago, IL, USA).

As it was the first study assessing the use of menthol, a pilot study was carried out prior to this trial. Thirty migraine attacks were managed with menthol and placebo. In menthol treated group, 8 out of 15 attacks were pain free after 2 h, while in placebo group this rate was 4 out of 15. On the basis of the results obtained in this pilot study, the required sample size was estimated to be 104 migraine attacks (α = 0.05, power = 80%).

Results
Study population
Fifty-one patients were recruited via newspaper advertisements. Seven patients were excluded because of concomitant tension type headaches (three patients), the presence of aura (2) and history of skin hypersensitivity (2). Safety population included 44 patients who were randomised and recommended to apply a drug or placebo. Of this group, seven patients had incomplete diary data and two had total incompliance. The intent-to-treat population consisted of 35 patients with 118 migraine attacks. Of this group, six patients had incomplete diary data for all attacks, two patients had partial incompliance and two patients had adverse events. The per-protocol population was made up of 25 patients with 100 attacks.

Baseline characteristics
As shown in Tables 1 and 2, the demographic and migraine characteristics of the intent-to-treat population was quite similar among attacks treated with drug and placebo.

Primary and secondary end-points
It was shown in Figure 1 that time by itself had been a determining factor on pain intensity drop (p = 0.000), however this drop is significantly different between the placebo and menthol groups during the first 2 h (p = 0.010).

In the intent-to-treat population (23/60) 38.3% of attacks treated with the study drug and (7/58) 12.1% of attacks treated with the placebo were ‘pain relief’ 2 h after cutaneous application (p = 0.001).

Also, (35/60) 58.3% of attacks treated with the study drug and (10/58) 17.2% of attacks treated with the placebo had ‘pain relief’ 2 h after the cutaneous application (p = 0.000). A total of (20/60) 33.3% of drug treated attacks and (7/58) 12.1% of placebo treated attacks had sustained pain free response during the first 24 h (p = 0.008). For 48 h sustained pain free results, these rates were (17/60) 28.3% and (5/58) 8.6% respectively (p = 0.008).

In the intent-to-treat population, (81/118) 68.6% of attacks were associated with nausea and/or vomiting. Two hours after the cutaneous application of the drug or placebo, these ratios decreased to (23/40) 57.5% and (17/41) 41.4% respectively (p = 0.02). In this population, (79/118) 66.9% of attacks were associated with photophobia and (81/118) 68.6% attacks with phonophobia. Photophobia associated attacks decreased to (22/39) 56.4% and (18/40) 45% in
drug and placebo treated attacks respectively. Phonophobia associated attacks also decreased to (20/39) 51.2% and (18/42) 42.8% respectively, in drug and placebo groups (p = 0.02).

In the per-protocol population, 12 patients (48%) had pain free attacks with neither the drug nor the placebo. Ten (40%) patients had at least one pain free response after application of the drug; however, they had no response to the placebo. Three (12%) patients had at least one pain free attack after application of either menthol or the placebo (p = 0.002). Similarly, eight (32%) patients had no pain relief response to the drug or placebo. Ten (40%) patients had at least one pain relief response after application of the drug, while they had no response to the placebo. Six (24%) patients had at least one pain relief after application of the drug and placebo (p = 0.002). It should be mentioned that regarding both pain free and pain relief responses, there were no patients in the per-protocol population who did not respond to menthol while responding to the placebo.

### Table 1 Demographic data of intent-to-treat population and cross-over arms

| Gender       | Intent-to-treat population (n = 35) | Menthol-placebo group (n = 17) | Placebo-menthol group (n = 18) | Significance (p) |
|--------------|------------------------------------|--------------------------------|--------------------------------|------------------|
| Women        | 28                                 | 13                             | 15                             | NS (0.69)        |
| Men          | 7                                  | 4                              | 3                              |                  |
| Age          |                                    |                                |                                |                  |
| Mean ± SD    | 29.65 ± 6.23                       | 29.78 ± 6.14                   | 29.52 ± 6.37                   | NS (0.87)        |
| Education, years |                                |                                |                                |                  |
| ≤ 12         | 9                                  | 4                              | 5                              | NS (0.95)        |
| > 12, ≤ 16   | 7                                  | 4                              | 3                              |                  |
| ≥ 16         | 19                                 | 9                              | 10                             |                  |

NS, not significant.

### Table 2 Baseline migraine characteristics of attacks treated by drug or placebo

| Mean ± SD of headache intensity (according VAS score) | Total attacks (n = 118) | Drug group (n = 60) | Placebo group (n = 8) | Significance (p) |
|------------------------------------------------------|-------------------------|---------------------|-----------------------|------------------|
| Associated symptoms                                   |                         |                     |                       |                  |
| Nausea and/or vomiting (%)                           | 81 (68.6)               | 40 (33)             | 41 (34)               | NS (0.55)        |
| Photophobia (%)                                       | 79 (66.9)               | 39 (33)             | 40 (33)               | NS (0.43)        |
| Phonophobia (%)                                       | 81 (68.6)               | 39 (33)             | 42 (35)               |                  |
| Headache quality                                      |                         |                     |                       |                  |
| Unilateral (%)                                       | 88 (74.5)               | 42 (35.5)           | 46 (38.9)             | NS (0.29)        |
| Pulsating (%)                                        | 91 (77.1)               | 42 (35.5)           | 49 (41.5)             | NS (0.08)        |
| Interaction with activity (%)                         | 80 (67)                 | 37 (31)             | 43 (36)               | NS (0.17)        |

NS, not significant; VAS, visual analogue scale.

### Adverse events

No considerable side effects were reported up to 48 h in 85% of drug treated and 93.1% of placebo treated attacks respectively (p = 0.13). Adverse events

![Figure 1](image_url) Pain intensity after cutaneous application of menthol analysed by repeated measurement test. Time (p = 0.000), Time × Menthol or Placebo (p = 0.010)
after menthol application included a burning sensation on the temporal area in 8.3% of attacks, laceration in 5% of attacks and aggravation of headache because of menthol odour in 1.6% of attacks. Two patients (5.7% of intent-to-treat population) discontinued the trial because of severe burning sensation and aggravation of headache.

Discussion

This study showed cutaneous application of a 10% solution of menthol in ethanol was statistically superior to the placebo on pain free, pain relief, sustained pain free and sustained pain relief end-points. Menthol solution was also more efficacious in alleviation of associated symptoms. Although menthol application was associated with more adverse events in comparison to the placebo, this difference was not significant. Also, only 5.7% of the intent-to-treat population discontinued the trial because of drug intolerance.

It has been shown that less than 50% of migraineurs have compliance for preventive treatments over a 1-year period (8). Meanwhile, our present armamentarium for the abortive treatment of migraine has some limitations such as restricted efficacy, extended side effect profile, contraindication in specific groups and high costs (for triptans) (9). Using oral medications in migraine attacks which are associated with nausea and vomiting is another obstacle. Cutaneous application of analgesic, which was proposed by Avecina for the first time (10), should be studied as a route of administration for symptomatic treatment of migraine attacks.

Menthol is a commonly used, affordable herbal medicine. Considering its safety, a patch test study of 4000 patients showed that menthol and peppermint oil provoked neither allergic nor irritant reactions (11). Menthol has pleuripotential characteristics compatible with different speculated pathogeneses of a migraine headache (12).

Menthol might inhibit the transmission of nociceptive impulses from the pain-producing cranial vessels, via branches of the trigeminal nerve, to higher brain centres. The analgesic effect of menthol can be explained by its potency to stimulate the two classes of ‘transient receptor potential cation channel, subfamily M’ (TRPM) receptors. There are two classes for TRPMs receptors. The first class is termed ‘the menthol sensitive/capsaicin insensitive neuron class’ (MS/CIS) and the other is ‘the menthol sensitive/capsaicin sensitive neuron class’ (MS/CS). The response induced by menthol is significantly larger in MS/CIS than in MS/CS receptors, producing an analgesic effect. New evidence shows that the molecular site of action of menthol is an excitatory ion channel expressed by small-diameter neurons in trigeminal and dorsal root ganglia (13,14).

In the Vascular–Supraspinal–Myogenic model of migraine pain perception, the increased tenderness of cranial myofacial tissues during a migraine attack and the effect of trigger point injections are explained (15). Antispasmodic properties of menthol, via interference with transmembrane movement of calcium have been shown (16,17). Therefore, as a spasmyolytic agent, menthol is hypothesised to influence the spasm of cranial musculature and by modulating the myofacial inputs, reduce the intensity of tension like headache perception in migraines.

Considering ‘sterile inflammation’ theory for the pathogenesis of migraine, menthol whose anti-inflammatory action via suppression of prostaglandin E2, leukotriene B4 and Interleukin-1beta has been shown (18,19), can be a putative therapeutic agent.

In previous studies, conducted by Gobel et al. (4), significant analgesic effect with a reduction in sensitivity to headache through measures of pericranial muscle tension was produced by a combination of peppermint oil and ethanol, and 10% peppermint oil in ethanol solution significantly reduced the clinical headache intensity after 15 min (3).

Small sample size is the major shortcoming of our study. In addition, per-protocol and intent-to-treat populations were 57% and 79% of safety population respectively. This relatively high attrition was because of incomplete diary data rather than lack of efficacy or adverse effects. Larger trials with same or more sophisticated design and less complicated paperwork should be conducted for further evaluation of menthol in treatment of migraine.

In conclusion, we showed the efficacy, safety and relative tolerability of menthol solution for the abortive treatment of migraine without aura through a randomised, triple-blind, crossed-over study. Menthol or its odourless derivatives can be considered as a new weapon in the antimigraine arsenal. Its cutaneous application is a rapid acting route which, in all likelihood, probably minimises systemic complications. Menthol can also be used as an adjuvant agent in transdermal patches which carry other abortive treatments of migraine such as triptans and ergots.

Acknowledgement

This work was supported by a grant from Student Research committee, Shiraz university of medical sciences, Shiraz, Iran (No. #3085).
Author contributions

A. Borhani Haghighi: concept and design, drafting article, critical revision of article, approval of article.
S. Motazedian: design, drafting article, critical revision of article, data collection.
R. Rezaii; F. Mohammadi, L. Salarian, M. Pourmokhtari, S. Khodaei; Z. Shiravani: data collection, drafting article.
M. Vossoughi: data analysis, interpretation.
M. Vossoughi: help with the concept, funding.

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Paper received May 2009, accepted June 2009