Antiemetic activity of volatile oil from *Mentha spicata* and *Mentha × piperita* in chemotherapy-induced nausea and vomiting

Z Tayarani-Najaran¹, E Talasaz-Firoozi², R Nasiri³, N Jalali⁴ and MK Hassanzadeh⁴

¹ Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad 91775-1365, Iran
² El Camino Hospital, 2500 Hospital Drive, Mountain View, CA 94040, USA
³ Research Center of Natural Products Safety and Medicinal Plants, North Khorasan University of Medical Sciences, Bojnurd, 01830-49504, Iran
⁴ Pharmaceutical Sciences Research Center, Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad 91775-1365, Iran

Correspondence to: MK Hassanzadeh. E-mail: hasanzadehm@mums.ac.ir

Abstract

**Background:** This study is aimed at determining the efficacy of *Mentha spicata* (*M. spicata*) and *Mentha × piperita* (*M. × piperita*) in preventing chemotherapy-induced nausea and vomiting (CINV).

**Methods:** This was a randomised, double-blind clinical trial study. Prior to the study, patients were randomly assigned into four groups to receive *M. spicata* or *M. × piperita*. Statistical analysis included the χ² test, relative risk, and Student’s t-test. Fifty courses were analysed for each group that met our eligibility criteria. The treatment and placebo groups applied essential oils of *M. spicata*, *M. × piperita*, or a placebo, while the control group continued with their previous antiemetic regimen. Patients or guardians recorded the number of emetic events, the intensity of nausea over 20 h of chemotherapy, as well as any possible adverse effects that occurred during this time.

**Results:** There was a significant reduction in the intensity and number of emetic events in the first 24 h with *M. spicata* and *M. × piperita* in both treatment groups (p < 0.05) when compared with the control and no adverse effects were reported. The cost of treatment was also reduced when essential oils were used.

**Conclusion:** *M. spicata* or *M. × piperita* essential oils are safe and effective for antiemetic treatment in patients, as well as being cost effective.

**Keywords:** chemotherapy-induced nausea and vomiting (CINV), essential oils, Mentha spicata, Mentha × piperita, Lamiaceae

Published: 31/01/13

Received: 09/07/12

*ecancer* 2013, 7:290 DOI: 10.3332/ecancer.2013.290

**Copyright:** © the authors; licensee *ecancermedicalscience*. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

CINV is a major problem for cancer patients [1]. Approximately 70–80% of all cancer patients receiving chemotherapy, experience nausea and vomiting [2]. Despite advances in antiemetic drugs, side effects continue to be clinically significant. The management of vomiting seems to be improved at the expense of nausea, as has been indicated in reports over the years. Nausea continues to be ranked first on the list of troublesome and distressing symptoms experienced by patients despite the use of 5-HT3 receptor antagonists, and it has profound effects on the quality of life of patients [3].

Aromatic plants were used in ancient times for their preservative and medicinal properties, as well as to impart aroma and flavour to food. Hippocrates, who is sometimes referred to as the ‘father of medicine’ prescribed perfumed fumigations [4], and aromatherapy, which is the inhaled use of essential oils used for therapeutic or medical purposes. Nowadays, herbs are commonly used for cancer symptoms management treatment in adults. Spearmint (Mentha spicata), and peppermint (Mentha × piperita) are recommended for their antiemetic and antispasmodic effects on the gastric lining and colon. Several studies show the efficacy of peppermint in reducing postoperative nausea and vomiting [5, 6].

This study evaluates the efficacy and side effects of the volatile oils from the M. spicata and M. × piperita via the oral route for the prevention of CINV in cancer patients.

Patients and Methods

Identification of Oil Components

Analytical gas chromatography (GC) was carried out using a 3400 varian-star cx GC chromatograph with capillary column DB-5 (30 m × 0.32 mm i.d., 0.32-μm film thickness), a He carrier gas, split ratio of 1:10, and a flame ionisation detector.

The column temperature was programmed at 60°C for one minute and then heated to 240°C at a rate of 3°C/min, then kept constant at 265°C for 20 min. GC–mass spectrometry (MS) was performed on a Thermoquest 2000 with a quadrupole detector on a capillary column DB-5 (see GC), with a He carrier gas, a flow rate of 1.5 ml/min, and an oven temperature of 265°C. The mass spectrometer was operated at 70 eV ionisation energy. Retention indices were calculated by using retention times of n-alkanes, which were injected after the oil, at similar chromatographic conditions. The compounds were identified by comparing retention indices (RRI and DB-5) with those reported in the literature and by comparing their mass spectra with the Wiley library or with published mass spectra (Tables 1 and 2).

| Compounds              | Retention time (min) | Kovat's retention index (%) |
|------------------------|----------------------|-----------------------------|
| Limonene               | 481                  | 1040                        | 5.96 |
| Menthone               | 761                  | 1146                        | 1.12 |
| Borneol                | 789                  | 1156                        | 0.68 |
| Terpinen-4-ol          | 820                  | 1166                        | 0.99 |
| cis-Dihydrocarvone     | 866                  | 1186                        | 19.19|
| trans-Dihydrocarvone   | 885                  | 1191                        | 1.06 |
| Pulegone               | 973                  | 1229                        | 13.30|
| Carvone                | 984                  | 1238                        | 42.53|
| Piperitone             | 1011                 | 1245                        | 1.52 |
| α-Terpinenyl acetate   | 1264                 | 1323                        | 3.45 |
| β-Carvyl acetate       | 1296                 | 1353                        | 1.06 |
| β-Bourbonene           | 1355                 | 1370                        | 1.46 |
| β-Caryophyllene        | 1442                 | 1397                        | 6.78 |
| α-Humulene             | 1527                 | 1435                        | 0.88 |
Table 2. GC–MS data of the components of the essential oils of *M. spicata*

| Compounds     | Retention time (min) | Kovat's Retention index | Composition (%) |
|---------------|----------------------|--------------------------|-----------------|
| α-Pinene      | 319                  | 934                      | 0.82            |
| Sabinene      | 397                  | 989                      | 2.39            |
| Limonene      | 481                  | 1038                     | 6.35            |
| 1,8-Cineole   | 485                  | 1039                     | 2.29            |
| Menthone      | 761                  | 1144                     | 1.75            |
| Isomenthone   | 785                  | 1155                     | 5.75            |
| α-Terpineol   | 852                  | 1185                     | 8.91            |
| Carveol       | 923                  | 1212                     | 0.54            |
| Pulegone      | 973                  | 1240                     | 56.28           |
| Piperitone    | 1011                 | 1252                     | 2.29            |
| Thymol        | 1113                 | 1289                     | 4.51            |
| Carvacrol     | 1137                 | 1294                     | 2.63            |
| Longifolene   | 1404                 | 1397                     | 5.47            |

**Eligibility Criteria**

**Patient characteristics**

This was a randomised, double-blind clinical trial study. This study was conducted at the Omid Chemotherapy Hospital of the Mashhad Medical University in Mashhad, Iran. The inclusion criteria were patients with any cancer diagnosis (colon adeno-carcinoma, breast cancer, colorectal cancer, oesophageal cancer, liver cancer, lung cancer, Hodgkins lymphoma, non-Hodgkins lymphoma, melanoma, nasopharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, sarcoma, stomach cancer, testicular cancer, and vaginal cancer), who were about to receive chemotherapy on an outpatient basis, and who were chemotherapy naïve. After the patients (or their guardians) signed informational consent forms, the patients received chemotherapy drugs (etoposide, ifosfamide, cisplatin, carboplatin, epirubicin, cyclophosphamide, adriamycin and/or irinotecan). Patients who were experiencing nausea and vomiting from causes other than chemotherapy reasons (i.e. intestinal obstruction, stomach cancer, pre-menstrual syndrome, motion sickness), or were deemed physically incapable of participating by the investigators, were excluded from the study.

The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences. Identified variables for patients included age, sex, nutritional status (body mass index [BMI]), diagnosis, chemotherapy regime, previous exposure to chemotherapy, prescribed antiemetic medication and nausea or vomiting in previous treatments.

Prior to each cycle, patients underwent a physical examination and a complete haematological and urinary evaluation to assure optimal conditions to receive treatment.

**Treatment plan**

During each cycle, patients received their normal antiemetic regimen (granisetron, dexamethason or metoclopramide) plus spearmint and peppermint capsules (containing two drops of each essential oil and filled with sugar) every four h. This was administered 30 minutes before the patients received their chemotherapy treatment, again four h after the first capsule and finally, four h later at home.

Patients or guardians received a self-applicable questionnaire to record the number of emetic events and the intensity of the nausea during the next 24 h period following chemotherapy.

Patients also underwent a complete physical evaluation on each day of their hospitalisation in order to identify any abnormal event. Evaluation of these results was performed by a blind investigator.
Statistical analysis

Statistical analysis included the Mann–Whitney U test or the Kruskal–Wallis test to compare the median value of emetic events for each day in both groups, as the assumptions for Student's t-test or ANOVA were not fulfilled. Risk analysis included a relative risk analysis, which was performed by comparing the incidence of the effect (presence of CINV in both groups. Pearson’s χ2 statistic was used to determine the association of nominal or ordinal variables. The Fisher’s exact test was performed when conditions were not met.

Results

The volatile oil from the *M. spicata* and *M. × piperita* were examined by GC and GC–MS. Thirteen compounds were identified in the essential oils of *M. × piperita* and 14 compounds in *M. spicata*, which were then evaluated for their preventive properties in CINV (Tables 1 and 2).

Fifty patients were analysed for each group. Clinical details of the patients are summarised in Table 3. No differences were found between treatment groups except for a greater proportion of normal weight in each group (Table 3).

Efficacy was assessed based on the number of emetic episodes (vomiting and retching), and intensity and duration of nausea.

Intensity of nausea was scored between 0 and 100: absent (0) severe (100) (Table 4).

| Table 3. Characteristics of patients |
|-------------------------------------|
| Control | Placebo | *M. × piperita* | *M. spicata* | p value* |
| Age 43±11 | 44±15 | 46±15 | 42±15 | 0.056 |
| ≤50 33 (66%) | 34 (68%) | 40 (80%) | 31 (62%) |
| >50 17 (34%) | 16 (32%) | 10 (20%) | 19 (38%) |
| Sex 0.274 |
| Male 16 (32%) | 14 (28%) | 14 (28%) | 22 (44%) |
| Female 34 (68%) | 36 (72%) | 36 (72%) | 28 (56%) |
| History of TM use 0.203 |
| Yes 26 (52%) | 21 (42%) | 28 (52%) | 17 (34%) |
| No 24 (48%) | 29 (58%) | 24 (48%) | 33 (66%) |
| Nutritional status 0.004 |
| Underweight 12 (24%) | 13 (26%) | 5 (10%) | 3 (6%) |
| Normal 37 (74%) | 30 (60%) | 41 (82%) | 37 (74%) |
| Obese 1 (2%) | 7 (14%) | 4 (8%) | 10 (20%) |
| Antiemetic treatment with chemotherapy |
| Granistron 29 (58%) | 37 (74%) | 29 (58%) | 34 (68%) | 0.253 |
| Dexamethasone or metoclopramide 21 (42%) | 13 (26%) | 21 (42%) | 16 (32%) |
| History of nausea in previous chemotherapy 32 (64%) | 25 (50%) | 29 (58%) | 33 (66%) | 0.36 |
| History of vomiting in previous chemotherapy 16 (32%) | 12 (24%) | 13 (26%) | 19 (38%) | 0.414 |

*Pearson’s χ² statistic or Fisher’s exact test.*
Table 4. Grades of nausea and vomiting

| Grade | Nausea | Vomiting |
|-------|--------|----------|
| 1     | Absent (scored 0) | Absent 1 episode/24 h |
| 2     | mild   | >3 episodes/24 h |
| 3     | moderate | 3-5 episodes/24 h |
| 4     | Severe (scored 100) | >5 episodes/24 h |

*Grading according to Reference [14].

Patients treated with *M. spicata* and peppermint were found to have a statistically significant reduction of the median emetic events during 24 h of treatment (acute phase) in which patients treated with placebo presented up to 1.8 emetic events versus 0.6 and 0.7 in the *M. spicata* and *M. × piperita*, respectively (p < 0.05) (Table 5).

The intensity of nausea was also significantly reduced in the *M. spicata* and *M. × piperita* groups during 24 h of treatment compared with placebo (p < 0.05) (Table 5).

Table 5. Summary of efficacy results (N = 50 in each group)

|                  | Control | Placebo | M. × piperita | M. spicata | p value* |
|------------------|---------|---------|---------------|------------|----------|
| Retching episodes | 3.1 ± 1.3 | 7.2 ± 2.3 | 2.4 ± 2.4     | 3.8 ± 1.2  | <0.0001  |
| intensity of nausea | 52.8 ± 20.7 | 14.6 ± 9.1 | 42.1 ± 22.7  | 43.9 ± 12.4 | <0.0001  |
| Vomiting episodes  | 1.1 ± 0.4 | 1.8 ± 0.9 | 0.7 ± 0.9     | 0.6 ± 0.3  | <0.0001  |

There was no statistical difference between spearmint and peppermint in controlling emetic events and intensity of nausea (p > 0.05).

None of the patients reported or presented any adverse effect during treatment with *M. spicata* and *M. × piperita*.

The cost of treatment with *M. spicata* and *M. × piperita* was significantly lower than with granisetron.

**Discussion**

Nausea and vomiting are still an obvious problem in patients receiving chemotherapy. On conditioning with more than 24 h of chemotherapy, patients are at risk for CINV throughout the entire treatment period. Aromatherapy is the inhaled use of essential oils for therapeutic or medical purposes. Ginger (*Zingiber officinale*), spearmint (*M. spicata*), and peppermint (*M. × piperita*) are recommended for their antiemetic and antispasmodic effects on the gastric lining and colon. Several studies show the efficacy of peppermint in reducing postoperative nausea and vomiting [6], chemotherapy-induced nausea [7], and colonic spasms during colonoscopy [8, 9] and after colostomy surgery [10].

Exposure to ionising radiation induces nausea and vomiting, such as in radiation accidents. Hence, plants with antiemetic activity (e.g. *Centella asiatica, M. × piperita, and Zingiber officinale*) have been evaluated for their ability to provide radiation protection [11–14]. Nevertheless, *M. × piperita* and *M. spicata* essential oils have not been fully analysed in populations.

In this study, we used spearmint and peppermint capsules (containing two drops of each essential oil every four h, filled with sugar, and administered 30 minutes before they received their chemotherapy treatment, again four h after first capsule and finally four h later in home) for all patients, independent of their age or weight. Furthermore, no significant side effects were found when increasing the dose.

Although it was not our aim to compare spearmint and peppermint, we found no difference between these two herbs in the control of vomiting in the first 24 h (p > 0.05).
Based on our results, we have concluded that the essential oils of spearmint and peppermint are less expensive, and a safe and effective therapeutic option for the treatment of chemotherapy-induced nausea and emesis in patients.

Acknowledgments

The authors would like to thank the Research Affairs of the Mashhad University of Medical Sciences for financially supporting this research.

References

1. Koeller J, Aapro M, Gralla R et al (2002) Antiemetic guidelines: creating a more practical treatment approach Support Care Cancer 10 519–22 DOI: 10.1007/s00520-001-0335-y PMID: 12324805
2. Lindley C, Bernard S and Fields S (1989) Incidence, duration of chemotherapy-induced nausea, vomiting in the out patient oncology population J Clin Oncol 7 1142–9 PMID: 2787480
3. Molassiotis A, Saunders MP, Valle J et al (2008) A prospective observational study of chemotherapy-related nausea, vomiting in routine practice in a UK cancer centre Support Care Cancer 16 2018 DOI: 10.1007/s00520-007-0343-7
4. Edris AE (2007) Pharmaceutical, therapeutic potentials of essential oils, their individual volatile constituents: A review. Phytother Res 214 308–23 DOI: 10.1002/ptr.2072
5. Anderson LA and Gross JB (2004) Aromatherapy with peppermint isopropyl alcohol or placebo is equally effective in relieving postoperative nausea J Post Anesth Nurs 191 29–35
6. Tate S (1997) Peppermint oil: a treatment for postoperative nausea J Adv Nurs 26 543–549 DOI: 10.1046/j.1365-2648.1997.t01-15-00999.x PMID: 9378876
7. Buckle J (2003) Clinical Aromatherapy: Essential Oils in Practice 2nd edn (Edinburg: Churchill Livingstone).
8. Asao T, Mochiki E, Suzuki H, Nakamura J, Hirayama I, Morinaga N et al (2001) An easy method for the intraluminal administration of peppermint oil before colonoscopy, its effectiveness in reducing colonic spasm Gastrointest Endosc 53 172–7 DOI: 10.1067/mge.2000.108477 PMID: 11174287
9. Leicester RJ and Hunt RH (1982) Peppermint oil to reduce colonic spasm during endoscopy Lancet 2 989 DOI: 10.1016/S0140-6736(82)90191-X PMID: 6127488
10. McKenzie J and Gallacher M (1989) A sweet smelling success Nurs Times 85 48–9 PMID: 2771679
11. Phillips S, Ruggier R and Hutchinson SE (1993) Zingiber officinale ginger – an antiemetic for day case surgery Anaesthesia 48 715–7 DOI: 10.1111/j.1365-2044.1993.tb07188.x PMID: 8214465
12. Meyer K, Schwartz J, Crater D and Keyes B (1995) Zingiber officinale ginger used to prevent 8-MOP associated nausea Dermatol Nurs 7 242–4 PMID: 7646942
13. Srivastava R, Shukla YN and Sushil K (1997) Chemistry, pharmacology of Centella asiatica: a review J Med Arom Plant Sci 19 1049–56
14. Krishnasamy M (2008) Cancer Nursing: Care in Context 2nd edn, ed J Corner and C Bailey (Oxford: Blackwell Science) pp 350–7