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Alimentary Tract

Peppermint oil (Mintoil®) in the treatment of irritable bowel syndrome: A prospective double blind placebo-controlled randomized trial

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Abstract

Introduction. The use of peppermint oil in treating the irritable bowel syndrome has been studied with variable results probably due to the presence of patients affected by small intestinal bacterial overgrowth, lactose intolerance or celiac disease that may have symptoms similar to irritable bowel syndrome.

Aim. The aim of the study was to test the effectiveness of enteric-coated peppermint oil in patients with irritable bowel syndrome in whom small intestinal bacterial overgrowth, lactose intolerance and celiac disease were excluded.

Methods. Fifty-seven patients with irritable bowel syndrome according to the Rome II criteria, with normal lactose and lactulose breath tests and negative antibody screening for celiac disease, were treated with peppermint oil (two enteric-coated capsules twice per day or placebo) for 4 weeks in a double blind study. The symptoms were assessed before therapy (T_0), after the first 4 weeks of therapy (T_4) and 4 weeks after the end of therapy (T_8). The symptoms evaluated were: abdominal bloating, abdominal pain or discomfort, diarrhoea, constipation, feeling of incomplete evacuation, pain at defecation, passage of gas or mucus and urgency at defecation. For each symptom intensity and frequency from 0 to 4 were scored. The total irritable bowel syndrome symptoms score was also calculated as the mean value of the sum of the average of the intensity and frequency scores of each symptom.

Results. At T_4, 75% of the patients in the peppermint oil group showed a >50% reduction of basal (T_0) total irritable bowel syndrome symptoms score compared with 38% in the placebo group ($P < 0.009$). With peppermint oil at T_4 and at T_8 compared with T_0 a statistically significant reduction of the total irritable bowel syndrome symptoms score was found (T_0: 2.19 ± 0.13, T_4: 1.07 ± 0.10*, T_8: 1.60 ± 0.10*, *$P < 0.01$ compared with T_0, mean ± S.E.M.), while no change was found with the placebo.

Conclusion. A 4 weeks treatment with peppermint oil improves abdominal symptoms in patients with irritable bowel syndrome.

Keywords: Double blind trial; Irritable bowel syndrome; Peppermint oil; Placebo

1. Introduction and aim

The symptoms of the irritable bowel syndrome (IBS) are represented by recurrent episodes of abdominal distension and bloating, abdominal pain and altered bowel habits with constipation, diarrhoea and urgency to defecate [1]. These symptoms, however, do not exclusively characterize this disease and may be found with similar intensity and frequency in patients with lactose intolerance (LI), syndrome of small intestinal bacterial overgrowth (SIBO) and celiac disease (CD) [2,3]. SIBO and LI are associated with increased gas production, which may sometimes trigger abdominal discomfort and bloating which are also considered also the cardinal symptoms in IBS [4,5]. Furthermore, a high prevalence of celiac disease has been observed in patients with bloating and diarrhoea and positive H2-lactose breath test. In these patients the symptoms related to lactase deficiency seem to be the only manifestation of celiac disease [6]. Basing themselves on these data, some authors suggest that these diseases should

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be previously excluded in clinic therapeutic trials with investigational drugs that affect IBS [7]. Peppermint oil has been tested in children [8] and adults [9] with IBS, with conflicting results. A recent meta-analysis on this topic concluded that the role of peppermint oil has not yet been established beyond a reasonable doubt [10]. Among the various possibilities of applying this therapy, the potential inclusion of patients with the above-cited diseases should be taken into account.

The aim of the study was, therefore, to test the effectiveness of pH-dependent, enteric-coated, peppermint oil in patients with symptoms indicative of IBS in whom SIBO, LI and CD have been excluded.

2. Materials and methods

Patients with symptoms indicative of IBS that met the Rome II criteria [11] were investigated. All patients had a negative lactose breath test for lactose intolerance (a positive test required an increase in breath hydrogen >20 ppm within 90 or 180 min after an oral ingestion of <20 g lactose powder diluted in 150 ml tap water) and a lactulose breath test for bacterial overgrowth (a positive test required two distinct peaks >20 ppm of breath hydrogen within 90 min after 6 g lactulose diluted in 150 ml tap water). Both tests were performed during the month preceding the study. A stool test for ova and/or parasites, occult stool blood, blood test for full count, liver function tests, tissue transglutaminase and anti-endomysium antibodies for CD had to be in the normal range. Abdominal ultrasound and total colonoscopy were performed when required by clinical symptoms. The exclusion criteria were: age under 18 and over 80 years, previous surgery on the abdomen except appendectomy, inflammatory bowel disease, colonic diverticular disease, intestinal neoplasia, systemic disease, thyroid disease and chronic assumption of medication that could interfere with intestinal motility, secretion and sensation.

The study was approved by the ethical committee of G.d'Annunzio University.

2.1. Protocol

The study was a randomized, double blind, placebo-controlled study. Peppermint oil and a placebo were prepared in enteric-coated, gastro-protected capsules which do not dissolve during their passage through the stomach and which only dissolve when there is intestinal pH of 7.0 or higher. Each capsule was filled with 225 mg of peppermint oil and 45 mg of Natrasorb, a particular starch that absorbs oils in solid powder (Mintoil® Cadigroup, Rome, Italy), while the placebo contained 225 mg of maltodextrin with mint flavour (Cadigroup, Rome, Italy). Each patient admitted to the study was randomly given two capsules of peppermint oil or placebo twice a day, for 4 weeks, on the basis of data from a computer-generated list. The capsules were administered 1 h before meals in order to guarantee low gastric pH which prevents an untimely capsule dissolution with the release of peppermint oil into the stomach.

The symptoms score data were collected by two researchers (G.C. and M.S.), following an intensity and frequency scale from 0 to 4 – intensity: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable; frequency: 0 = absent, 1 = once per month, 2 = once per week, 3 = twice per week, 4 = ≥ three times per week. Symptoms were made note of at the beginning of the trial, at the end of the trial (4 weeks later) and 4 weeks after the end of the trial. The symptoms evaluated were the following: abdominal bloating or distension, abdominal pain or discomfort, diarrhoea (>3 defecation/day, constipation (<3 stools/week), pain at evacuation, urgency of bowel movement, sense of incomplete evacuation and passage of gas or mucus**.** A total IBS symptoms score was also calculated as follows: (a) a mean score for each symptom was obtained for each patient adding the relative intensity and frequency scores and halving this value; (b) the mean scores of the eight symptoms were summed for each patient and divided by 8, obtaining a total IBS mean score for every patient. The collection of symptoms was performed at entry (T_0), at the end of treatment (T_4) and 4 weeks after the end of treatment (T_8). Remission of IBS symptoms was defined as a ≥50% improvement of the overall IBS symptoms score from baseline T_0 to T_4 and T_8.

2.2. Statistical analysis

The sample size was calculated assuming a mean difference between groups on the basis of the total change of the total IBS symptoms score before and after the treatment of 1.0 or greater points (with a standard deviation = 1.0), which was considered a clinically relevant difference. With $\alpha = 0.05$, $\beta = 0.80$ and considering a 10% value of withdrawals and dropouts, a minimum number of 25 patients was therefore required in each group.

Two sets of populations were identified for the purpose of assessing the effectiveness, namely, the "intention to treat" (ITT) group and "per protocol" (PP) group. The χ^2-test was used to compare the percentage of patients with remission of the IBS symptoms in the group of peppermint oil versus that of the placebo. The Student's *t*-test for paired data was used to test the changes in the symptoms score between T_0 and T_4 and T_8 within the group with peppermint oil and within the group with the placebo. The Mann–Whitney *U*-test (two-tailed) was used to compare the symptoms score between peppermint oil and the placebo at T_0, T_4 and T_8. A *P*-value ≤0.05 was considered statistically significant. Data are presented as mean ± S.E.M.

3. Results

3.1. Characteristics at baseline

Fifty-seven patients, who satisfied the inclusion criteria, were studied: 28 taking peppermint oil and 29 taking a

Table 1
Distribution of IBS symptoms among patients with IBS taking peppermint oil or placebo.

Total patients	Peppermint oil (No. 24)	(%)	Placebo (No. 26)	(%)	P^*
Abdominal pain or discomfort	24	100	26	100	n.s.
Bloating or distension	22	92	24	89	n.s.
Diarrhoea	18	75	20	74	n.s.
Constipation	6	25	6	26	n.s.
Feeling of incomplete evacuation	12	50	16	59	n.s.
Urgency	12	50	16	59	n.s.
Pain at evacuation	12	50	10	38	n.s.
Pass of gas or mucus	14	58	15	60	n.s.

* χ^2-test.

placebo. At T_8, 4 weeks after the completion of the treatment period, three patients in the peppermint oil group and three patients in the placebo group did not return for the final control examination. These patients were excluded from the study. One patient in the peppermint group withdrew due to intense heartburn after taking the medication. The data from fifty patients, therefore, were available for comparison. Twenty-four patients were in the peppermint oil group (18 women, 6 men; mean age 42, range 22–58) and 26 patients (20 women and 6 men; mean age 40, range 20–60) in the placebo group. The two groups were balanced regarding smokers/non-smokers and the consumption of alcohol (72% of patients in the peppermint oil and 75% in the placebo group did not smoke, and 83% and 88%, respectively, drank less than 15 g of ethyl alcohol per day). The two groups were well balanced regarding the baseline symptoms in terms of the percentage of patients with the presence or absence of a specific symptom (Table 1) and basal symptoms score (Fig. 1).

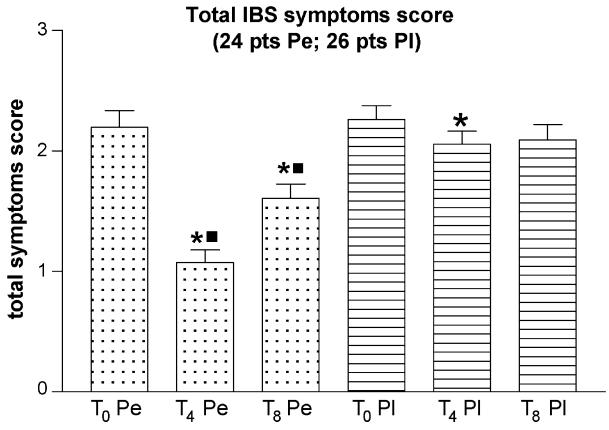

Fig. 1. Total IBS symptoms score (mean ± S.E.M.) before (T_0), after 4 weeks of treatment (T_4) with peppermint oil (Pe) or placebo (Pl) and after 4 weeks of wash out (T_8). (*) $P < 0.05$ vs. T_0 (*t*-test); (■) $P < 0.05$ vs. placebo (Mann–Whitney *U*-test).

3.2. Response to treatment

At the end of the 4 weeks of treatment (T_4) and of the subsequent 4 weeks (T_8), a statistically significant higher number of patients in the peppermint oil group had a ≥50% reduction in the mean total IBS symptoms score versus the placebo group at both ITT and PP analyses (Table 2).

The variation of the total IBS symptoms score computed at T_0, T_4 and T_8 is described in Fig. 1. It may be observed that in the group treated with peppermint oil there was a statistically significant improvement in total IBS symptoms score ($P < 0.01$) at T_4, with a persisting beneficial effect at T_8 ($P < 0.05$) too. In the placebo group there was a reduction in the total IBS symptoms score at T_4 ($P < 0.05$) with a return falling within the baseline values at T_8 (Fig. 1). In the peppermint oil group all the symptoms evaluated were significantly reduced at T_4 and at T_8, while in the placebo group, diarrhoea, pain and bloating improved significantly at T_4 (Fig. 2).

The Mann–Whitney *U*-test used to compare the peppermint oil group with the placebo group, showed a statistically significant lower total IBS symptoms score in the peppermint oil group in comparison with that of the placebo at T_4 and T_8 (Fig. 1). The same test also showed that the score of each symptom evaluated was significantly lower at T_4 in the peppermint oil group in comparison with the placebo group (Fig. 2).

Table 2
Number of patients with ≥50% reduction of total IBS symptoms score at T_4 and T_8

	PP		P^*	ITT		P^*
	Peppermint oil	Placebo		Peppermint oil	Placebo	
T_4	75%(18/24)	38% (10/26)	9	64%(18/28)	34% (10/29)	2
T_8	54%(13/24)	11% (3/26)	1	46%(13/28)	10% (3/29)	2

* χ^2-test.

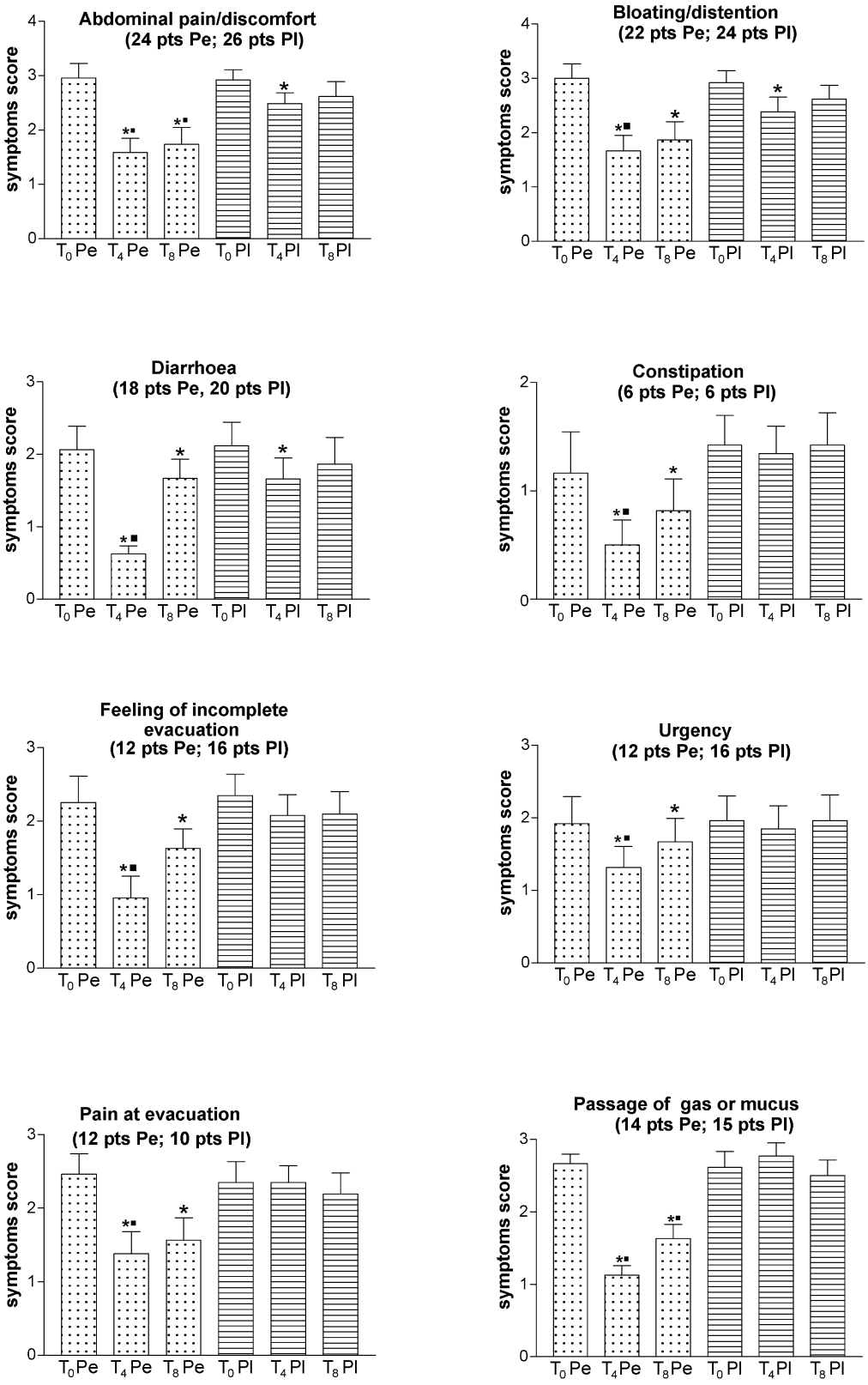

Fig. 2. Mean value between intensity and frequency of IBS symptoms (mean ± S.E.M.) before (T_0), after 4 weeks of treatment (T_4) with peppermint oil (Pe) or placebo (Pl) and after 4 weeks of wash out (T_8). (*) $P < 0.05$ vs. T_0 (*t*-test); (■) $P < 0.05$ vs. placebo (Mann–Whitney *U*-test).

4. Discussion

This study shows that, in patients with IBS, treatment with enteric-coated capsules of peppermint oil given twice a day for 4 weeks is more effective than placebo in reducing abdominal symptoms related to IBS than a placebo. The beneficial effect of peppermint oil also lasts for 1 month after the therapy in more than 50% of treated patients.

Several types of therapy are available for IBS treatment and include bulking agents, prokinetics, antispasmodics, 5-HT agonists and antagonists, smooth muscle relaxants and antidepressants. However, most studies are hampered by poor methodology and inconclusive findings [12]. Furthermore, complementary and alternative medical therapies and practices such as hypnotherapy, forms of herbal therapy and certain probiotics are widely employed in the treatment of IBS. The absence of truly randomized placebo-controlled trials for many of these therapies has limited meaningful progress in this area [13].

So far, few studies have shown a beneficial effect of peppermint oil on symptoms of IBS both in adults and in children. A critical review and meta-analysis published in the American Journal of Gastroenterology [10] analysed five double blind, placebo-controlled trials. Two trials did not demonstrate significant differences between peppermint oil versus placebo in patients with IBS [14,15], while the other three found a significant difference [16–18]. Several methodological limitations were identified and the conclusion of these authors was that, despite the apparently positive results of the published trials, the role of peppermint oil in the treatment of IBS was far from being established. Since then, two more trials have been published on this topic: one in children and the other in adults. In the first trial in the adult population from Taiwan [9] some relief in the severity of symptoms was recorded in 79% of the patients treated with peppermint oil with significant differences from the placebo group. In the second study on children [8] affected by IBS a general improvement in the symptoms was found in 76% of the patients treated with peppermint oil compared with 19% of those receiving the placebo. However, symptoms such as abdominal distension and gas production remained unchanged. The lack of the effectiveness of peppermint oil on such symptoms found in this study may be explained by the presence of patients affected by LI or SIBO that may account for 5–50% of patients with IBS, according to recent studies [19,20].

In our study the improvement in IBS symptoms observed in the group treated with peppermint oil may be due to the relaxing effect of peppermint on the intestinal smooth muscle obtained by the interference of menthol with the movement of calcium across the cell membrane [21]. Furthermore, the antispasmodic effect of peppermint oil could explain both the reduced diarrhoea present in the majority of our patients through a prolongation of oro-caecal transit time [22] but also of the constipation present in the rest of the group. In fact, antispasmodics in fact may decrease the functional obstruction caused by increased phasic colonic contractions that may be present in constipation [23].

Constipation and related symptoms including bloating, abdominal distension, difficulty at evacuation, pain at evacuation and the feeling of incomplete evacuation also improved in our patients. Since these symptoms may be related to abnormal intestinal gas production [24,25] an action on enteric bacteria for peppermint oil may be suggested. Peppermint oil has an intrinsic antibacterial activity in vitro and in vivo, and it has been shown that it is able to reduce the intestinal hydrogen production in patients with bacterial overgrowth [26]. Its influence on the enteric flora presumably persists beyond the therapeutic period, an effect that may explain why the positive effect of peppermint oil on IBS symptoms was still present in more than half of our patients 1 month after the end of therapy. Indeed, a similar effect has been recorded in a recent study with probiotics in IBS [27].

In this study the therapeutic trial lasted 4 weeks, which is normally considered too short a period for the observation of a condition such as IBS, which is, by definition, chronic and intermittent. In the present study, however, the total IBS symptoms score calculated at the end of the 4 weeks of treatment with peppermint oil is strikingly reduced in comparison with the placebo. This suggests that a longer period of therapy is unlikely to produce a more positive response. On the contrary, since after treatment the beneficial effect was lost in about 50% of the patients, it may be also suggested that a longer period of therapy may be required if an improvement in symptoms is to be maintained.

The placebo effect in the present study is in the range of all similar studies in IBS. It must be underlined that the specific improvement that has been recorded with the placebo on diarrhoea and bloating in our study may be due to the intrinsic effect of maltodextrin, the principal component of our placebo capsule that has been shown to be effective in children with infectious diarrhoea [28].

Three patients in each group left their group during the study due to reasons not linked to the treatment. One patient in the peppermint oil group refused to continue the study due to prolonged heartburn and a minty taste in his mouth. This side-effect, already recorded in previous studies [8,17], may be due to the incorrect assumption of the capsule (patient chewing the capsule) or due to the capsule dissolving too early into the stomach, causing oesophageal reflux of gastric juice mixed with menthol.

In summary, this study shows that patients with IBS may benefit from a 4-week treatment with enteric-coated peppermint oil. The improvement in the symptoms lasts longer than the therapeutic period in almost half of the treated patients. These data suggest that when peppermint oil is administered for a short 4-week period, it is safe and effective for patients with IBS.

Further studies, however, with longer therapeutic periods will be required before the definite impact of peppermint oil therapy in IBS can be established.

Practice points

- Consider that in IBS symptoms such as abdominal discomfort or pain, bloating, constipation or diarrhoea are present also in lactose intolerance, small intestinal bacterial overgrowth and celiac disease.
- Perform in every patients with a suggested diagnosis of IBS a lactose, glucose or lactulose breath test and dosage of the antibody to tissue transglutaminase.
- Most of the available substances suggested for the treatment of IBS is devoted towards the reduction of a specific symptom such as constipation, diarrhoea and bloating or pain, and their therapeutic effect is limited to a short period of time.

Research agenda

- The therapeutic choice for IBS includes bulking agents, prokinetics, antispasmodics, 5-HT agonists and antagonists, smooth muscle relaxants, antidepressants, hypnotherapy, some forms of herbal extract and certain probiotics. Controlled clinical trials with a clear-cut evidence of a real efficacy of these substances are few and most of them are hampered by poor methodology and inconclusive findings.
- IBS may be due to altered intestinal microflora, excessive intestinal smooth muscle motility, reduced bowel wall compliance and enhanced pain perception. The search of a substance that may act on one or more of these cited points may be beneficial in the treatment of the disease.

Conflict of interest statement

None declared.

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