



Efficiency of peppermint oil in the treatment of patients with irritable bowel syndrome

İrritabl bağırsak sendromlu hastaların tedavisinde nane yağının etkinliği

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ABSTRACT

Aim: The purpose of our study is to examine the effect of mint oil, which is used together with the classical agents we use in the treatment of irritable bowel syndrome (IBS), on the success of treatment.

Methods: Patients diagnosed with IBS based on the ROME IV criteria were included in our study. The patients were randomized and divided into two groups as the medication only group and the medication+peppermint oil group. A questionnaire called IBS symptom severity scoring system (IBS-SS) to measure the symptom severity of the IBS patients and IBS quality of life measurement questionnaire (IBS-36), consisting of 36 questions, was applied to both groups. At the end of 12 weeks, the IBS-SS and IBS-36 questionnaires were repeated in both groups to evaluate the response to treatment.

Results: The change in IBS-SS scores from the beginning to the 3rd month was significant in both the medication group and the medication+peppermint group ($p<0.001$). According to IBS-SS the median change from the beginning to the 3rd month was 62.5 for the medication group, this difference was 85 for the medication+peppermint group. The difference was statistically significant ($p<0.001$). According to the IBS-36 the median change from the beginning to the third month was 35.5 for the medication group, this difference was 45.5 for the medication+mint oil group. The difference was statistically significant ($p<0.001$).

Conclusion: The use of peppermint oil together with classical drugs in the treatment of IBS will increase the success of the treatment.

Keywords: constipation; diarrhea; irritable bowel syndrome; plant oils

ÖZET

Amaç: Çalışmamızın amacı iritabl bağırsak sendromu (İBS) tedavisinde kullandığımız klasik ajanların yanında kullanılan nane yağının tedavi başarısına olan etkisini araştırmaktır.

Yöntem: Çalışmamıza ROMA IV kriterlerine göre İBS tanısı koyduğumuz hastalar dâhil edilmiştir. Hastalar randomize edilerek yalnızca ilaç kullanılacak grup ve ilaç + nane yağı kullanacak grup olmak üzere ikiye ayrılmıştır. Her iki gruba IBS semptom skorlama sistemi (IBS-SS) isimli İBS hastalarında semptom şiddetini ölçmeye yarayan anket ve 36 sorudan oluşan İBS hayat kalitesi ölçüm anketi (IBS-36) uygulanmıştır. 12 haftanın sonunda tedaviye alınan yanıtları değerlendirmek için her iki gruba İBS-SS ve İBS-36 anketleri tekrarlanmıştır.

Bulgular: Gruplar İBS-SS açısından değerlendirildiğinde; ilaç grubunda da, ilaç + nane grubunda da başlangıçtan 3. aya kadar İBS-SS skorlarındaki değişim anlamlıdır ($p<0.001$). İlaç grubunda başlangıçtan 3. Aya kadar değişim medyan 62.5 iken ilaç + nane grubunda bu fark 85'tir. Aradaki fark istatistiksel olarak anlamlıdır ($p<0.001$). İBS-36'ya göre ilaç grubunda başlangıçtan üçüncü aya kadar medyan değişim 35.5 iken, ilaç+nane yağı grubunda bu fark 45.5'tir. Fark istatistiksel olarak anlamlıydı ($p<0.001$).

Sonuçlar: İBS tedavisinde nane yağının klasik ilaçlar ile birlikte kullanımı tedavi başarısını arttıracaktır.

Anahtar kelimeler: konstipasyon; diyare; iritabl bağırsak sendromu; bitki yağları

Introduction

Irritable bowel syndrome (IBS) is a highly prevalent disease characterized by recurrent abdominal pain and changes in bowel habits, significantly affecting quality of life (Drossman, Camilleri, Mayer & Whitehead, 2002). Prevalence rates of IBS vary between 1.1% and 45%, based on population studies from countries worldwide (Lovell & Ford, 2012). IBS is diagnosed based on symptoms, and a distinction is made between the following subtypes of IBS: IBS with pain or discomfort and predominant constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (IBS-U) (Enck et al., 2016). There are many factors thought to be the cause of the disease in the etiology such as altered visceral sensitivity, functional brain alterations, bowel motility and secretory dysfunctions, and somatic and psychiatric comorbidities. Furthermore, gastrointestinal abnormalities such as immune activation, microbial imbalance, impaired mucosal

functions, nerve sensitization, post-infectious plasticity, altered expression and release of mucosal and immune mediators, and altered gene expression profiles have been associated with IBS. However, the pathogenesis has not been clearly determined, and therefore, there is no definitive treatment that works for every patient. The general approach in this regard is to keep the patient's symptoms under control and to increase the quality of life (Wu, 2010).

Complaints can be controlled by using a combination of several drugs in the treatment guide, based on the symptoms and the severity of the symptoms. Since classical methods in the treatment of IBS are often not completely successful, complementary therapies, especially herbal medicines, are widely preferred in the treatment of IBS (Wu, 2010).

Peppermint oil, with its scientifically proven antispasmodic, anti-inflammatory, antimicrobial, and anxiolytic effects, is accepted as a promising treatment option for IBS, a difficult

and complex disease that is hard to treat. Guideline recommendations regarding the use of peppermint oil in IBS treatment are currently based on prior studies showing highly favorable results in terms of abdominal pain reduction and global improvement of symptoms (Weerts et al., 2020). In studies on the effectiveness of peppermint oil in the treatment of IBS patients, the placebo and peppermint oil were compared in general. In this study, unlike other studies, we aimed to assess the effectiveness of peppermint oil, which we used together with the classical treatment agents, and to reveal whether it provides additional benefit by a synergistic effect when it is used as a combination treatment.

Methods

This study is a single-center and cross-sectional study. For the power analysis of the study, "A Novel Delivery System of Peppermint Oil Is an Effective Therapy for Irritable Bowel Syndrome Symptoms" taken as reference (Cash, Epstein & Shah, 2016). It was observed that the IBS scores between the placebo group and the peppermint oil group were approximately 0.50 and standard deviations were approximately 0.7 each. It was determined that it would be appropriate to include a minimum of 32 patients per group, with a type 1 error of $\alpha=0.05$ and the power of the study being 80%. Sampling was calculated using MedCalc® Statistical Software version 20.027 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022).

Patients between the ages of 18-65, who applied to the departments of internal medicine and general surgery of Istanbul Medipol University and were diagnosed with IBS (IBS-C, IBS-D, IBS-M and IBS-U) according to the ROME IV criteria after being evaluated by a physician of internal medicine and general surgery, were included in the study.

The patients were informed about the content of the study and their written consent was obtained in this regard.

Inclusion Criteria

- Between the ages of 18 and 65
- IBS diagnosis according to ROMA IV criteria

Exclusion Criteria

- Under 18 or over 65
- Hypo-hyperthyroidism
- Acute or chronic infection
- Presence of malignancy
- Inflammatory bowel disease
- Lactose intolerance
- Use of any medication that will affect bowel movements

Examinations

First, detailed medical history of patients was obtained and physical examination was performed for the study. Laboratory tests including complete blood count, kidney function tests, serum electrolytes, C-reactive protein, erythrocyte sedimentation rate, thyroid function tests, and fecal occult blood were performed on all patients participating in the study. Anti-endomysium and anti-gliadin antibodies were tested for celiac disease for diarrhea-dominant patients, and stool microscopy was examined for infectious gastroenteritis. Blood samples of the patients were taken between 08:00 and 10:00 h on an empty stomach. Endoscopic screening was performed on patients over 50 years of age who had alarm symptoms.

As a result of these examinations, 2 patients were diagnosed with hypothyroidism, 1 patient with colon cancer, 1 patient with inflammatory bowel disease, 3 patients with infectious

gastroenteritis, and 1 patient with lactose intolerance, and these patients were, therefore, excluded from the study.

Randomization

The patients were randomized to form two parallel groups according to the order of arrival, with the first patient in the medication group, the second patient in the medication + peppermint oil group.

The patients were informed about not using any medication that may affect the gastrointestinal system throughout the study period. The quality of life for "beginning" specific to IBS was measured with the IBS-36 questionnaire.

IBS 36

36 questions specific to IBS were asked to the patients about their quality of life, which they were asked to answer considering the last 2 months. Each question was given an answer ranging from 0 (never) to 6 (always), expressing how often the problem in the question was encountered. The level of quality of life for the pre-treatment period was measured by summing the scores of the answers (for this questionnaire with a maximum of 216 points, higher scores indicate worsening in the quality of life) (Groll et al, 2002).

IBS-SS

The global severity of the symptoms was measured using the IBS symptom scoring (IBS-SS) system. The patients were asked 5 questions, which were answered between 0 and 100 points, and the total symptom severity was calculated over a maximum of 500 points. Based on the calculated scores, the symptoms of the patients were classified as in remission (0–74), mild (75–174), moderate (175–299), and severe (>300) (Francis, Morris & Whorwell, 1997).

Intervention

Antispasmodic otilonium bromide (40 mg) + antiflutane simeticone (80 mg) combination was used in 3x1 posology for the medication group. In addition to this treatment, mint oil capsule (small intestine-release) in 3x1 posology standardized over 1.8 cineole containing medical peppermint oil, each of which is 112.84 mg, was used for the medication + mint oil group. Otilonium bromide + simeticone combination is recommended to be taken half an hour before meals, and small intestine-released peppermint oil capsule is recommended to be taken 30-90 minutes before meals (Cash et al., 2016) For this reason, only the drug-administered group was told to take the drug half an hour before meals. The group using medication + peppermint oil was told to use peppermint oil capsules one hour before meals and medication half an hour later.

In chronic recurrent diseases, keeping the treatment period long reduces the risk of recurrence after the drugs are stopped. Therefore, treatment in IBS patients should continue for 3-6 months. In our study, the patients were followed up and treated for 12 weeks. At the end of 12 weeks, the IBS-36 and IBS-SS questionnaires were re-applied to both groups. It was analyzed whether there was a difference in symptom severity and quality of life for the medication only group and the medication + peppermint oil group compared to the beginning. The groups were first assessed within themselves, and it was analyzed whether there was a difference in symptom severity and quality of life for the medication + peppermint oil group compared to the medication only group. Correlation of the data was assessed in order to reveal the correlation between the data obtained from the IBS-36 and IBS-SS questionnaires and to verify the reliability of each measurement method with the other.

Statistical Analysis

Continuous variables were described using descriptive statistics. (mean, standard deviation, minimum, median, and maximum) The conformity of continuous variables with normal distribution was examined by the Shapiro Wilk test. Examination of the correlation between 2 continuous variables that did not fit the normal distribution was carried out with the Mann Whitney u test. The variation between two continuously dependent variables that did not fit the normal distribution was examined using the Wilcoxon Signed Rank test. The correlation between 2 continuous variables that did not fit the normal distribution was examined using the Spearman Rho Correlation Coefficient. The statistical significance level was set at 0.05. The MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2021) program was used for the analyses.

Ethical considerations

Approval was obtained by the local ethics committee for the study (Istanbul Medipol University, Clinical Research Ethics Committee Number: 10840098-772.02-4095, Date: 19.08.2021) and it was carried out in accordance with the Helsinki Declaration principles.

Results

76 patients who met the criteria were included in the study. A total of 8 patients discontinued the study during the 12-week period. The study was completed with a total of 68 patients, 31 males and 37 females. The patients were divided into 2 groups, 34 in the medication group and 34 in the medication + peppermint oil group. There was no significant difference between the two groups in terms of the mean age and sex of the patients (p= 0.902, p= 1.00, respectively) (Table 1). According to the IBS-SS results of the groups; the change in IBS-SS scores from the beginning to the third month in the medication group was statistically significant (p<0.001). The change in IBS-SS scores from the beginning to the third month in the medication + peppermint group was statistically

significant (p<0.001). While the median change from the beginning to the third month was 62.5 for the medication group, this difference was 85 for the medication + peppermint oil group. The difference was statistically significant (p<0.001) (Table 2).

Table 1. Distribution of demographic data

Variables	Medication	Medication + Mint	All patients	p
Gender, n (%)				
Male	16 (47.1)	15 (44.1)	31 (45.6)	1.00*
Female	18 (52.9)	19 (55.9)	37 (54.4)	
Age, Mean±SD	38.2±15.6	38.7±14.7	38.4±15.1	0.902**
Median (min-max)	36 (18-65)	37.5 (18-64)	36 (18-65)	

*Yates Continuity Correction

**Mann Whitney U test

According to the IBS-36 results of the groups; the change in IBS-36 scores from the beginning to the third month in the medication group was statistically significant (p<0.001). The change in IBS-SS scores from the beginning to the third month in the medication + peppermint oil group was statistically significant (p<0.001). While the median change from the beginning to the third month was 35.5 for the medication group, this difference was 45.5 for the medication + peppermint oil group. The difference was statistically significant (p<0.001) (Table 3). If the correlation of the data obtained from the IBS-SS and IBS-36 questionnaires is examined; it can be seen that there is a significant correlation between IBS-SS and IBS-36 scores in terms of beginning and post-treatment changes (r= 0.857, p<0.001 and r= 0.717, p< 0.001, respectively) (Table 4).

Table 2. Assessment of IBS-SS

IBS-SS	Medication			Medication + Mint		
	Beginning (n=34)	3rd Month (n=34)	Difference	Beginning (n=34)	3rd Month (n=34)	Difference
Mean±SD	251.0±83.5	185.4±66.9	-65.6±25.4	253.7±81.6	163.4±57.3	-90.3±31.9
Median (min-max)	230 (120-450)	165 (80-340)	-62.5 (-125-(-25))	240 (140-460)	162.5 (70-290)	-85 (-140-(-40))
p*	<0.001			<0.001		

Wilcoxon Signed Rank test

Table 3. Assessment of IBS-36

IBS-36	Medication			Medication + Mint		
	Beginning (n=34)	3rd Month (n=34)	Difference	Beginning (n=34)	3rd Month (n=34)	Difference
Mean±SD	159±19.9	124.7±16.5	-34.3±9.6	161.2±19	114.2±14.7	-47±10.1
Med (min-max)	161 (131-198)	127.5 (102-152)	-35.5 (-61-(-2))	165.5 (130-193)	116 (81-138)	-45.5 (-67-(-30))
p*	<0.001			<0.001		

Wilcoxon Signed Rank test

Discussion

Irritable bowel syndrome (IBS) is a disease with a very high prevalence and significantly affects the quality of life. The ROME IV criteria based on the patient symptoms is used for the diagnosis (Mearin & Lancy, 2012). Inflammatory bowel diseases, celiac, fructose/lactose intolerance, infective colitis should be considered for the differential diagnosis, and additional tests can be planned if necessary (Begtrup et al., 2013). Especially patients aged >50 years, patients with a family history of colon cancer, patients with rectal bleeding without a disease such as hemorrhoids or anal fissures, patients with anemia and weight loss should be subjected to further examinations (Ford & Bercik, et al., 2013). Anti-diarrheal medicines can be used for the diarrhea-predominant group, and laxatives can be used for the constipation-predominant group. Smooth muscle antispasmodics are preferred for abdominal pain cases. Probiotics, antibiotics (rifaximin), antidepressants, antiflatulants are also among the treatment options in this respect (Borowiec & Fedorak, 2007; Ford & Moayyedi et al., 2014; Ford & Quigley et al., 2014; Pimentel et al. 2011).

In our study, we used a combination of otilonium bromide + simeticone, which has antispasmodic and antiflatulent effects, as the classical treatment. Peppermint oil is a widely used agent for gastrointestinal tract diseases. In the literature, placebo-controlled studies examining the effect of peppermint oil on IBS have proven that peppermint oil is an effective and good option in the treatment of this disease (Pittler & Ernst, 1998; Ford & Talley et al. 2008; Khanna, MacDonald & Levesque, 2014). In this study, we aimed to show whether peppermint will provide additional benefit with a synergistic effect when used together with an agent that we use in our routine treatments. For the assessment of a disease with abstract features such as IBS, we obtained comparable concrete data using objective measurement methods such as symptom severity score and quality of life questionnaire. According to the results we obtained with a randomized and controlled prospective study design, we observed that there was a significant decrease in symptom severity and a significant increase in quality of life for our patients who used the treatment regularly for 12 weeks for the medication-only group.

This suggests that one of the reasons for the failure of IBS treatment may be that patients do not use their prescribed medication in the appropriate posology and for the appropriate duration. In the group using the medication with peppermint oil, the severity of symptoms decreased much more, and the quality of life increased much more. Considering that the etiology of IBS includes motility disorders, visceral hypersensitivity, intestinal inflammation, previous gastrointestinal tract infections, microflora changes, bacterial overgrowth, food sensitivity, stress and psychological disorders, mint oil seems to be an ideal treatment option.

Peppermint oil with menthol as the active ingredient is obtained from fresh mint leaves via steam distillation (Kearns, Chumpitazi, Abdel-Rahman, Garg & Shulman 2015). The recommended dose is 250-750 mg (Grigoleit & Grigoleit, 2005). In our study, we used about 340 mg of peppermint oil on daily basis. The benefit of peppermint oil in functional gastrointestinal disorders such as IBS has been attributed primarily to its antispasmodic effect. In vitro studies on animals have proven that peppermint oil reverses acetylcholine-induced contraction through calcium channel blocker and antagonizes

serotonin-induced contraction (Hills & Aaronson, 1991). It reduces visceral pain when administered orally or intraperitoneally (Adam et al., 2006). Many studies have demonstrated the strong antimicrobial/antifungal/antiviral effectiveness of the peppermint oil (Kamatou, Vermaak, Viljoen & Lawrence, 2013).

It reveals its anti-inflammatory effect by suppressing the generation of inflammatory mediators from monocytes (Juergens, Stober & Vetter, 1998). In studies conducted on animals, it has been proven that menthol has a dose-dependent anxiolytic effect via dopamine pathways (Umezue, 2009). Very few side effects related to the use of mint oil have been reported in the literature. Although it is thought that it may increase the symptoms of gastritis and reflux, the enteric-coated formulations used today minimize this risk. Pulegone and its metabolite menthofuran found in peppermint oil have been considered potentially toxic at high doses. The amount of pulegone varies depending on how mint is grown, when it is harvested, and how it is processed (Rios-Esteva, Turner, Lee, Croteau & Lange, 2008). The European Medicines Agency reported that the use of peppermint oil in therapeutic doses does not cause liver toxicity for humans (European Medicines Agency, 2016).

Table 4. Examination of correlation between IBS-SS and IBS-36

IBS-SS and IBS-36	r	p*
Beginning IBS-SS x IBS-36	0.857	<0.001
3rd Month IBS-SS x IBS-36	0.717	<0.001

*Spearman's Rho Correlation Coefficient

Limitations

Our study is a single-center study conducted on 68 patients, and there is a need for multi-center studies with more patients on this subject. In our study, 340 mg of peppermint oil was applied daily to all of our patients who used peppermint oil; in this context, it would be useful to conduct studies that reveal how different doses will have an effect.

Conclusion

In our study, we found that there was a decrease in symptom severity and an increase in quality of life with regular use of conventional drug therapy for 12 weeks in IBS patients. In addition, we found that the small intestine-released peppermint oil capsule used alongside conventional drug therapy both reduced the severity of symptoms more and increased the quality of life more than the group using only medication. We did not encounter any side effects related to the use of peppermint oil in our study.

Peppermint oil, which has antispasmodic, anti-inflammatory, antimicrobial and anxiolytic effects, is observed to be an ideal treatment option for IBS, which is a difficult disease to treat due to its complex etiopathogenesis. Peppermint oil has no observed obvious side effects, on the contrary, it reduces the severity of the symptoms of the disease and increases the quality of life. Its use alone or in combination with the classical medicines we use in the treatment of IBS will increase the success of the treatment.

Conflict of Interest

There is no conflict of interest.

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Ethics Committee Approval

This study was approved by Ethics committee of Istanbul Medipol University (Approval No: E-10840098-772.02-4095 date: 27/08/2021).

Informed Consent

Written consent was obtained from the patients included in the study, in order to use the information collected by filling out a questionnaire before and after the treatment in a scientific study.

Peer-review

Externally peer-reviewed.

Author Contributions

E.Y.: Concept, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Writing Manuscript

G.Y.: Literature Search, Design, Supervision, Critical Review, Writing Manuscript.

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