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A Comparison of the Effect of Ajwain (*Trachyspermum ammi* (L.) Sprague) and Mefenamic Acid for Alleviating the Symptoms of Primary Dysmenorrhea: An Open-Label Randomized Controlled Trial

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Abstract

Trachyspermum ammi (L.) Sprague (commonly known as ajwain) contains ingredients that attenuate menstrual problems, especially cramping. In this study, we evaluated the impact of ajwain on the pain intensity in a sample of Iranian female college students with primary dysmenorrhea (PD) in comparison to mefenamic acid (MFA). This study was an open-label, randomized, parallel-group clinical trial conducted in the university dormitories in Tehran, Iran, from September 2018 to May 2019. Seventy patients were randomly assigned to two groups of ajwain and MFA. The participants in the ajwain group were treated with a 500 mg ajwain capsule three times a day for seven days, from the 26th cycle day to the 3rd day of the menstrual cycle, for three consecutive cycle periods. The other group received MFA capsules with the first dose of 500 mg and then 250 mg every eight hours, if necessary, from the first day of the menstrual cycle. The two groups were compared in terms of the pain intensity by the visual analog scale (VAS) in pre-intervention cycle and three consecutive cycles during the study. Maximum pain intensity, mean pain, and duration of pain after the intervention were significantly reduced in both groups. The mean VAS score significantly decreased in the ajwain group compared to the MFA group post-intervention ($p < 0.02$). Moreover, passing blood clots was significantly reduced in the ajwain group ($p < 0.03$). The findings of this study suggest that ajwain may be effective in pain relief in PD without adverse effects.

Keywords: Primary dysmenorrhea; Pain relief; Traditional medicine; Persian Medicine; *Trachyspermum ammi*

Introduction

Dysmenorrhea or menstrual pain is a common gynecological disorder affecting about 75% of women with menstrual cycles and is an especially common health issue in women of university age [1-3]. Primary dysmenorrhea (PD) is described as suprapubic region cramps during the menstrual cycles with no specific pathologic reasons [2,4,5]. Pain commences one or two days before or at the onset of the menstrual flow and gradually subsides within 72 hours with the end of blood flow [6]. Menstrual pain can frequently occur with more symptoms, including heavy menstrual bleeding, premenstrual mood disturbances, irritability, fatigue, nausea/vomiting, headaches, dizziness, weakness, lower backache, and diarrhea [1,6,7]. Dysmenorrhea can considerably diminish the quality of life and

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cause restrictions in normal daily activities, such as absenteeism from class and work, which may lead to reduced occupation and education efficiency, particularly in subjects with severe pain [1,5,8]. The etiology of PD is related to an overproduction of prostaglandins (PGs) in the uterine during the ovulatory cycle [3,6,8]. Two endometrial PGs (PGF2α and PGE2) are involved in the pathogenesis of dysmenorrhea, which leads to uterine contractions and ischemia. The role of PGF2α is more pronounced in this disorder [6,9]. Accordingly, non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment, which may be considerably effective in pain management. NSAIDs can inhibit cyclooxygenase enzyme that is responsible for the conversion of arachidonic acid to PG [10]. About 30% of women with PD withdraw from these treatments because they often have side effects in long-term administration, including neurological, gastrointestinal and hematological adverse effects. Moreover, they have limited efficacy in some situations [1,5,6,8,9]. Although oral contraceptive pills (OCPs) are recommended as another treatment in the management of PD, the majority of young women generally do not seek hormone therapy to reduce pain. Moreover, OCPs are often ineffective in the management of PD and have associated adverse events, including nausea, headaches, and weight gain [5,11]. Therefore, the use of complementary and alternative medicine (CAM) therapies, such as medicinal herbs, has been considered among patients with PD [5,6,8]. There is promising evidence to support the use of herbal medicines and their secondary metabolites for PD. Some of these herbs effectively reduce the severity of pain and also shorten the duration of pain [12,13].

Trachyspermum ammi (L.) Sprague (commonly known as ajwain) is native to Egypt, Iraq, Iran, Afghanistan, Pakistan, and India. It is classified as an aromatic spice with a pleasant taste, which is used both in diet and in traditional medicine (TM) for thousands of years [14,15]. Ajwain has been recommended in Persian Medicine for the treatment of various illnesses, especially menstrual complications, either solely or in combination [16]. Thymol is a phenolic monoterpene compound and is mainly found in the ajwain, which inhibits menstrual cramping [17]. This plant has revealed immunomodulatory, antioxidant, antinociceptive, antispasmodic, and anti-inflammatory activities [17-19]. In an animal study, it was shown that aqueous extract of ajwain has an anti-inflammatory activity similar to ibuprofen and can diminish the expression of genes involved in the inflammatory process more than ibuprofen [19]. Moreover, this plant has a carminative effect and has been used for alleviating fatigue, nausea, vomiting, and abdominal cramps [14]. Therefore, ajwain has the potential to affect other symptoms associated with PD. However, there is inadequate clinical evidence regarding the effectiveness of ajwain on PD; thus, this study was designed to evaluate the impact of ajwain on pain relief in female students with PD.

Materials and Methods

Study design

This open-label, randomized, parallel-group clinical trial was performed from September 2018 to May 2019. The study protocol was reviewed and approved by the Medical Ethics Committee of Iran University of Medical Sciences [Code: IR.IUMS.REC1397056] and registered in the Iranian Registry of Clinical Trials [registration code. IRCT20180805040697N1]. At the beginning of the study, the objectives and details of the study were explained to all enrolled participants and then they provided written informed consent.

Study participants

The study population was comprised of the female students with PD who were living in university dormitories in Tehran, Iran. Those subjects meeting the following criteria were enrolled in the study: (1) age >18 years old; (2) moderate to severe dysmenorrhea (Grades 2 and 3) based on a verbal multidimensional scoring system [20], and (3) regular menstrual cycle of 28 ± 3 days. The exclusion criteria were (1) known or suspected allergy to ajwain, (2) a history of abdominal or pelvic surgery, (3) irregular menstrual cycles, (4) history of secondary dysmenorrhea, (5) use of intrauterine device (IUD) or OCPs, (6) pregnancy or suspected pregnancy at the time of enrollment, and those who may have a birth plan during the trial period, (7) breastfeeding women, (8) any contraindication to NSAIDs usage, (9) use of any medication for dysmenorrhea, and (10) improper use of medication.

Interventions

The intervention group (n = 35) received 500 mg of ajwain capsule three times daily from the 26th day to the 3rd day of their cycles up to one week. The control group (n = 35) received MFA capsules with the first dose of 500 mg and then 250 mg every eight hours, if necessary, from the onset of menstruation. Both groups received the medications for three consecutive cycle periods. Demographic characteristics, including age, height, weight, body mass index (BMI), menarche, dysmenorrhea onset, length of the menstrual cycle, menstrual bleeding length, and marital status were recorded at the beginning of the study. Pain intensity was assessed by visual analog scale (VAS) in pre-intervention cycle and three consecutive cycles during the study. In addition, the severity of dysmenorrhea was recorded based on the verbal multidimensional scoring system before the intervention. Also,

the menstrual bleeding loss (MBL) and the passage of clots were determined with a pictorial blood loss assessment chart (PBLAC) in the cycle before entering the study and the last intervention cycle. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown in figure 1.

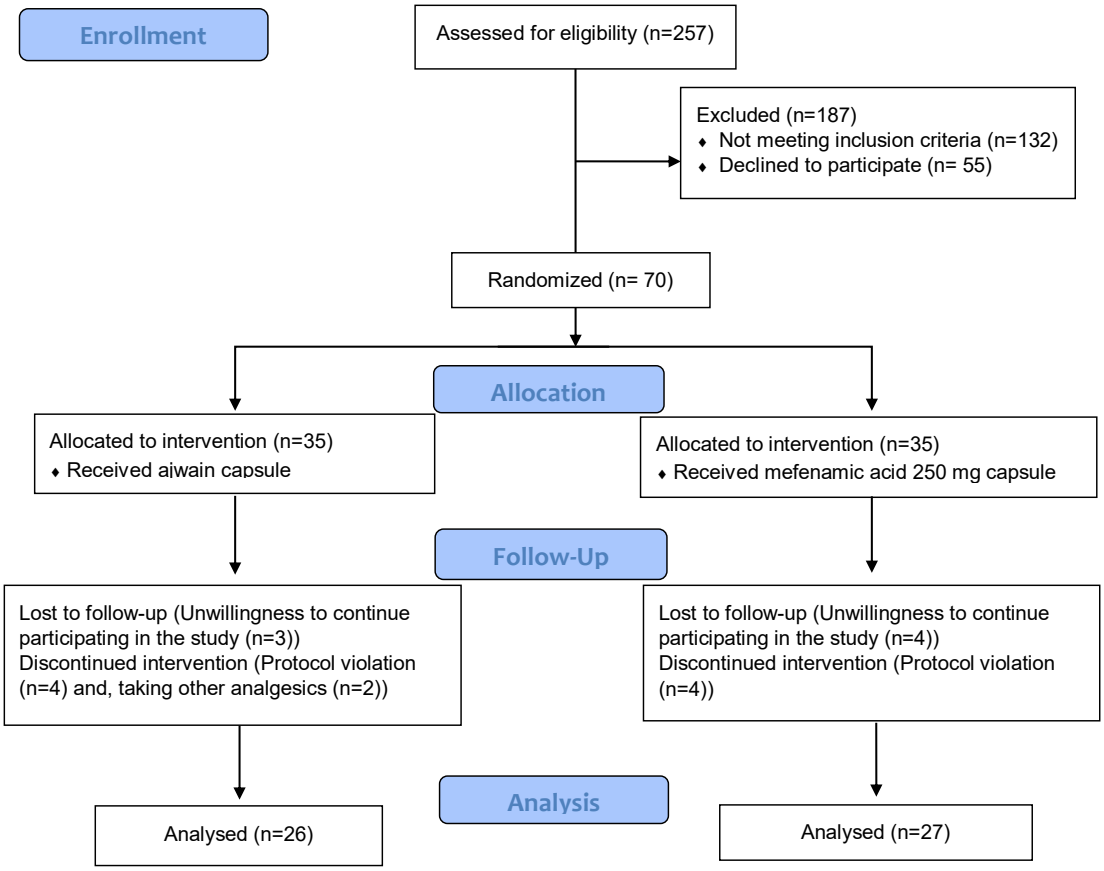

Figure 1. CONSORT flow diagram of enrollment of the participants, allocation, intervention, follow up, and analysis

Plant material

Dry fruit of *Trachyspermum ammi* (L.) Sprague was purchased from a local spice market in Tehran, Iran. The plant material was identified and authenticated by a botanist in the herbarium center of the faculty of pharmacy, Tehran University of Medical Sciences, Tehran, Iran (Voucher number: PMP-1736).

Randomization

Each patient who met all the inclusion criteria was enrolled in the study and randomly assigned to the ajwain group or MFA group in a 1:1 ratio. For randomization, we used block randomization by a random numbers table.

Outcomes

The primary outcome was the change in the pain intensity compared with the baseline. Secondary outcomes were the maximum pain intensity, mean pain, duration of pain, length of the menstrual cycle, menstrual bleeding length, and passing blood clots. Safety was regularly assessed by monitoring possible adverse events in each cycle.

Statistical Analysis

Quantitative variables were presented as mean ± standard deviation (SD). Qualitative variables were reported in the form of percentage. For comparison of the mean pain reduction between the two groups, repeated measures ANOVA was done using the Statistical Package for the Social Sciences software, version 16.0 (SPSS Inc. Chicago, IL, USA). Paired t-test was also considered for the comparison of other symptoms' scores at the beginning and the end of the study in each group. A

p value of less than 0.05 ($p < 0.05$) was considered statistically significant. We used repeated measure analysis and the significance of Mauchly's Test of Sphericity was less than 0.05, so we used Greenhouse-Geisser correction.

Results

A total of 70 patients with moderate to severe PD were enrolled in the study (Figure 1). Finally, 53 patients completed the study and were included in the analysis (26 patients in ajwain group and 27 patients in the MFA group). The mean age (± SD) in the ajwain and MFA groups were 25.80 ± 5.69 and 25.14 ± 5.79, respectively ($p = 0.678$). The two groups were similar in terms of BMI ($p = 0.162$), menarche ($p = 0.532$), age at onset of dysmenorrhea ($p = 0.591$) and length of the menstrual cycle ($p = 0.085$), days of menstrual bleeding ($p = 0.480$), mean of the pain ($p = 0.160$), MBL (0.998), and passing blood clots (0.393). The patients in the MFA group had higher education and this difference was statistically significant between the two groups (Table 1). Patients in the MFA group used an average of two capsules per day during the study.

The comparison of menstruation characteristics between the ajwain and MFA groups during the study is shown in table 2. Maximum pain intensity, mean pain, and duration of pain after the intervention were significantly reduced in both groups. There was a significant difference in the mean pain between the two groups over time, which was lower in the ajwain group compared to the MFA group. At the beginning of the study, the mean pain and duration of pain were not significantly different in the two groups from each other. While, pain intensity in the ajwain group was more than the MFA group and this difference was statistically significant (Table 2). The mean VAS score significantly decreased in the ajwain group compared to the MFA group post-intervention ($p < 0.02$). Furthermore, pain intensity and duration of pain were not significantly different between the groups at the end of the study. There were no significant differences between groups in terms of menstruation characteristics, including length of the menstrual cycle, menstrual bleeding length, and MBL. However, passing of clots was 24.96 ± 44.89 and 22.44 ± 32.66 in the ajwain and MFA groups post-intervention. The passing blood clots was significantly reduced in the ajwain group post-intervention ($p < 0.03$).

Administration of ajwain affected other PD-related symptoms among patients, including amelioration in bloating (2 patients), gastroesophageal reflux disease (GERD) (1 patient), constipation (2 patients), nausea (4 patients), low back pain (1 patient), diarrhea (1 patient), acne (1 patient), abdominal cramps (1 patient), and urinary frequency (1 patient).

Moreover, in the ajwain group, some complications also occurred in a few patients such as acne in one patient, constipation in one patient, and spotting before the onset of bleeding in two patients. In the MFA group, three patients reported stomach pain, one of them experienced constipation and two patients reported bloating following medication.

Discussion

In this open-label, randomized, parallel-group clinical trial, we attempted to compare the pain intensity in female college students with PD treated with either ajwain or MFA. The findings of the research revealed that the mean VAS score significantly decreased in the ajwain group in each of the three cycles compared to the MFA group post-intervention. The ajwain also led to a significant reduction in clot passage comparing the condition of patients before the intervention.

To the best of our knowledge, the present study was the first clinical trial on the effect of ajwain on PD. However, there are several other plants, which have been investigated for their effects on PD. Some of them, such as *Foeniculum vulgare* Miller, *Zingiber officinale*, *Thymus vulgaris* L., *Anethum graveolens* L., *Rosa damascena* Mill. and *Valeriana officinalis* L.,

Table 1. The baseline clinical/socio-demographic information of the study participants

Variable	Ajwain group, mean ± SD	MFA group, mean ± SD	p value
Age (years)	25.80 ± 5.69	25.14 ± 5.79	0.678
BMI (kg/m^2)	22.27 ± 3.86	20.93 ± 3.01	0.162
Age of menarche (years)	13.54 ± 1.42	13.30 ± 1.38	0.532
Age at onset of dysmenorrhea	15.04 ± 2.08	14.70 ± 2.39	0.591
Length of the menstrual cycle	28.69 ± 2.18	27.63 ± 2.22	0.085
Menstrual bleeding length	6.38 ± 1.6	6.70 ± 1.66	0.480
Mean of the pain	3.58 ± 1.54	3.00 ± 1.39	0.160
Menstrual bleeding loss (cc)	182.92±145.60	182.80±142.47	0.998
Passing blood clots	34.20±53.71	23.40±32.26	0.393

Abbreviations: SD, standard deviation; MFA, mefenamic acid; BMI, body mass index

Table 2. Comparison of menstruation characteristics between the ajwain and MFA groups during the study

Menstruation characteristics						RMANOVA[a]	
		Onset	First cycle	Second cycle	Third cycle	Time	Time*group
Mean pain	Ajwain group	3.58 ± 1.54	2.03 ± 1.09	1.96 ± 1.19	1.83 ± 1.12	0.001<	0.02
	MFA group	3.00 ± 1.39	2.40 ± 1.17	2.26 ± 1.29	2.19 ± 1.38		
	p value[b]	0.16	0.12	0.38	0.30		
Pain intensity	Ajwain group	8.76 ± 1.58	6.03 ± 2.61	6.03 ± 2.56	6.00 ± 2.62	0.001<	0.27
	MFA group	7.92 ± 1.20	6.81 ± 1.79	6.37 ± 2.00	6.03 ± 1.97		
	p value[b]	0.035	0.10	0.59	0.96		
Duration of pain	Ajwain group	22.00 ± 16.21	12.38 ± 13.32	10.65 ± 11.17	10.23 ± 10.71	0.001<	0.05
	MFA group	14.88 ± 14.74	8.22 ± 6.94	8.14 ± 9.07	7.92 ± 6.95		
	p value[b]	0.10	0.16	0.37	0.36		

Abbreviations: MFA, mefenamic acid
[a] Repeated Measure ANOVA
[b] Independent t-test

have been effective in reducing PD, but no significant difference has been reported compared to the control group (Ibuprofen or MFA) [21-26]. In this study, the effect of ajwain on reducing the mean pain was significant compared to MFA. Also, some other plants that were examined in separate trials, such as *Vitex agnus-castus*, *Matricaria chamomilla* L., and *Salix alba* L. were more effective than the control group, and there was a significant difference consistent with this study [27-29].

PD is caused by myometrial ischemia, which occurs as a result of prolonged and intermittent uterine contractions. The severity of these contractions is related to the concentration of PG produced by the primary precursor of arachidonic acid in the secretory endometrium [30]. Arachidonic acid, a precursor of PG, is produced by the effect of the enzymatic lysosomal enzyme phospholipase A2 on cell wall phospholipids [9]. The mechanism of action of NSAIDs is to inhibit cyclooxygenase activity, an enzyme that converts arachidonic acid to PG. In various studies, the anti-inflammatory effect of ajwain has been investigated and one of the effective mechanisms is to reduce the production of PG [31].

Thymol is the main ajwain essential oil constituent, which is a polyphenol compound with antiseptic, antiflatulent, antifungal, and antibacterial activities [32]. Thymol also has antioxidant and anti–inflammatory properties, and reduces C-reactive protein (CRP), interleukin1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), TNF-β, and matrix metalloproteinase 9 (MMP9) levels [33]. This plant contains isomerism of thymol, called carvacrol, which has the same anti–inflammatory properties [34]. Several mechanisms have been reported for the anti-inflammatory effect of carvacrol, including the decreased activation of the enzyme cyclooxygenase 2 [35], as well as reduction of its gene expression [36]. Moreover, ajwain has a carminative effect and has been used for alleviating fatigue, nausea, vomiting and abdominal cramps [14]. Therefore, this plant has the potential to affect other symptoms associated with PD.

Limitations of the study

This study has some limitations. One of them is the relatively small sample size of the study. So, it is recommended to carry out studies with larger sample sizes with a multi-center clinical approach. Second, ajwain fruits have a strong aromatic smell, which could not be masked; accordingly, this study was designed a non-blind trial and the participants in the study were not "blind" to the interventions. Another limitation of this study was the relatively low willingness of participants to participate in the study until the end of the three menstrual periods, which resulted in a long time to reach the desired sample size.

Conclusion

The ajwain may be considered an effective and safe complementary modality in relieving PD. Moreover, owing to pharmacologic activities of this plant on gastrointestinal ailments, this plant may be possibly used for those who do not tolerate NSAIDs due to digestive problems. Furthermore, ajwain has therapeutic potential for women who pass clots during their menstrual cycles.

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ical Sciences.

Data Availability

Data and material from this trial are available upon reasonable request and approval by the corresponding author.

Conflict of Interests

There was no conflict of interest in this study.

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