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Original Article

Clinical Effects of Fennel Essential oil on Primary Dysmenorrhea

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Abstract

Dysmenorrhea is among the most common gynecological complaints. There are several mechanisms which initiate dysmenorrhea. Therefore, different compounds can be employed to control its symptoms. NSAIDs such as ibuprofen are highly used in modern medicine to relieve the pain in short-term therapy. This method is not acceptable for long-term therapy due to side effects. Our previous data showed that Fennel essential oil (FEO) could reduce the frequency and intensity of contraction of rat uterus in isolated organ models. Furthermore, the use of FEO is strongly recommended in traditional medicine for the relief of dysmenorrhea symptoms. Clinical study of FEO in primary dysmenorrhea showed that the essence reduces pain and some of following sequelae side effects noticeably.

Keywords: Primary dysmenorrhea; Fennel; Essential oil; Traditional medicine.

Introduction

Dysmenorrhea is a common complaint in women. Half of the girls have experienced mild pain during their menstrual cycles; however, only 10% required complete bed rest for 1-3 days and are unable of doing their normal activities. This has become social and economical problems for those affected women (1). Dysmenorrhea is classified into primary and secondary according to the pathogenicity. Menstrual pain that occurs in the absence of visible organic pelvic origin is nominated primary dysmenorrhea (2); It usually occurres during adolescence, within three days of menarche (3). Primary dysmenorrhea usually appears within 1-2 years of menarch, when ovulatory cycles are established. The disorder affects younger women but may persist into forties (4). It is shown that the pain associated with this disorder is caused by hypercontractility of uterine muscle, subsequent reduction in blood flow and concomitant uterine ischemia (5, 6). The pain of primary dysmenorrhea usually begins a few hours prior to or just after the onset of a menstrual period and may last as long as 48-72 hours. The pain is labor-like with suprapubic cramping and may be accompanied by lumbosacral back ache, pain radiating down the anterior thight, nausea, vomiting, diarrhea, and rarely syncopal episodes (4). Despite thorough studies conducted about reasons of dysmenorrhea, it is still unsolved. However, most symptoms can be explained by the action of uterine prostaglandins, particularly $PGF_{2\alpha}$. During endometrial sloughing, the disintegrating cells release $PGF_{2\alpha}$ as menstruation begins. $PGF_{2\alpha}$ stimulates myometrial contractions, induces ischemia and sensitizes nerve endings (2). The clinical evidence for this theory is quite strong. Women with severe dysmenorrhea have a higher level of $PGF_{2\alpha}$ in their menstrual fluid and NSAIDs, which act through prostaglandin synthetase inhibition, have been found to be

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effective for the treatment of primary dysmenorrhea (7). In addition to NSAIDs including mefenamic acid and ibuprofen, hormone-based drugs such as oral contraceptives, electrical stimulation, vitamins and other complementary foods have been used to manage dysmenorrheal (8-11).

Most of the above-mentioned agents are smooth muscle relaxant. In spite of their effectiveness, side effects of these drugs in long-term therapy limit their clinical uses (12, 13). Fennel (foeniculum vulgare mill) is a well-known umbeliferous plant. The seeds of this plant have been claimed to be a promoter of menstruation, alleviate the symptoms of female climacteric, and increase libido (14). The use of FEO in the treatment of pediatric colic and some respiratory disorders has been previously reported due to its anti-spasmodic effects (15). Seeds of fennel are used in Iranian folk remedies for the treatment of dysmenorrhea. In this study the clinicals aspect of FEO were evaluated in the patients.

Experimental

Patients

Not married out-patients females aged 17-25 years showing following conditions participated in the study; 1) suffering from primary dysmenorrheal (diagnosis of primary dysmenorrhea was based on the patient's history, physical and gynecological examinations and uterine sonography. Severity of dysmenorrhea was classified based on Andersch & Milsom's verbal multidimensional scoring system (16)) 2)having history of regular menstrual cycle ranging from 25 to 32 days (mean 29 days), 3) do not take oral contraceptives and 4) having no other disease.

Study procedure

A randomized, double blind study comparing FEO 1% and 2% with placebo, according to a 3 period crossover design was carried out on eligible patients that randomly allocated to 1 of the 6 treatment sequences according to the randomization list (17). Patients were carefully instructed to use the trial medicine and fill in the assessment form properly. 0.3-1 ml of FEO (1% and 2% v/v obtained from Brij Essence Company) was administered used for intestinal colic pain (15). The trial medicines were administered as soon as pain feeling. All subsequent doses were taken on "as needed" basis, depending on the pain severity. These doses were not administered at intervals less than 4 h. Serial assessment of pain intensity (0 = nil, 1= mild, 2 = moderate, 3 = severe) on verbal rating scales (18) was made by the pain baseline after 1,2,3 and 4 h following the first dose. Rescue medication (usual therapy for the patient symptoms) was permitted after 1 h of administration, if the trial medication was not effective to control the symptoms. If no relief of pain was provided (17), assessment of pain and systemic symptoms including headache, dizziness, diarrhea, faint, mood change, tiredness, nausea and vomiting was carried out by a symptom chart. Patients have been asked to rate the menstrual cramp and systemic symptoms (19) at four stages. The global assessment of efficacy at the end of each treatment period was classified as excellent, good, fair and poor. Prospective charting of bleeding was used for the assessment of menstruation. Rate of bleeding (0 = none, 1= mild, 2 = moderate, 3 = heavy with clots) was daily recorded in the chart (4).

Statistical analysis

Using Friedman non-parametric test, statistical significance of differences between results was assessed. Severity of dysmenorrhea was rated by a categorical scoring method (19). In this method, each symptoms was scored as follows; pain=10, headache=10, faint=6, nausea and vomiting=6, diarrhea=5, dizziness=4, mood change=4 and fatigue=2.

Results

Sixty people were chosen between total volunteers. The range of age in this group was 17-25 years with average ± sd of 21.05 ± 0.24. Thirty percent of this people had grade 2 intensity of primary dysmenorrhea and the rest had grade 3. They were allocated in one of the 6 treatment sequences randomly. During period of treatment, four individuals in the placebo group, two in 1% FEO treated group and one in 2% FEO treated group were rejected from the treatment program. Six people in first two groups discontinued the protocol due to unsatisfactory therapeutic response and one

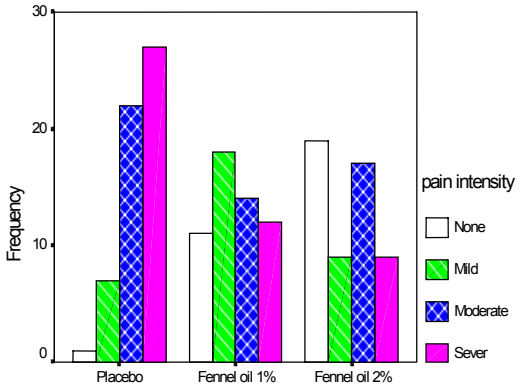

Figure 1. Frequency of different pain intensity in the three groups under study. Statistical significance was observed between treated and placebo groups. (p<.05).

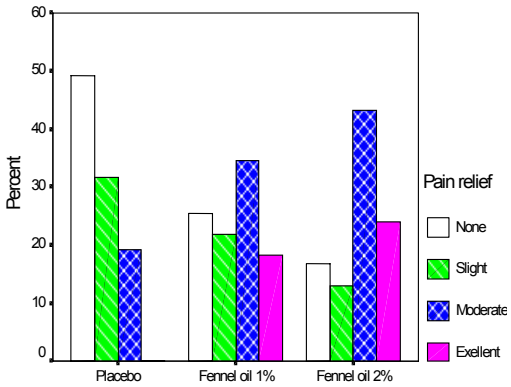

Figure 2. Global patient self-assessment of pain relief in the three groups.

person in the latter group discontinued due to poor tolerability.

Table 1 shows the percent of prevalence of pain, fatigue, nausea, vomiting, diarrhea, headache, change mood and faint. Severity of these symptoms was scored from 0 to 3 on verbal rating scales. As it is observed in this table, the severity of pain in treated groups decreased significantly ($p<0.05$). Statistical significance was not observed for other symptoms, however, at least one of them is in the borderline (fatigue $p=0.08$; dizziness $p = 0.3$; diarrhea $p = 0.9$; headache $p = 0.5$; faint $p = 0.85$, mood changes $p = 0.47$). Also figure1 shows the frequency of different pain intensity in the three groups under study. Statistical significance was observed between treated and placebo groups ($p<0.05$). Table 2 shows the mean of dysmenorrhea severity based on scoring system in the three groups under study. Mean of dysmenorrhea severity has decreased from 46.684 ± 2.965 in placebo group to 28.019 ± 2.876 and 30.073 ± 2.571 in FEO 2% and 1% groups respectively. A significant difference was observed between two treated groups, and placebo ($p<0.05$). Furthermore, table 2 shows the mean of total bleeding during menstruation based on prospective chart of bleeding. The average total bleeding in the treated groups was significantly higher than that observed in the placebo group ($p<0.01$), but it was not significant between treated groups. In treated groups, intake of trial dose significantly decreased the intensity of pain at different times ($p<0.05$). Figure 2 shows self-assessment efficacy of patients. As it is shown in this figure, the evaluation of treatment is significantly improved in the treated groups compared with placebo, but it was not different between treated groups. In the placebo group, 66.7% of patients needed to use other medication to relief symptoms, but in 1% and 2% FEO treated groups, 41.8% and 39.9% of

Table 1. Frequencies of dysmenorrhic pain and adverse event based on verbal rating score.

Adverse Effect	FEO Doses	Placebo				FEO 1%				FEO 2%			
	severity	0	1	2	3	0	1	2	0	0	1	2	3
Abdominal Pain		1.70	12.3	38.6	47.4	20.0	32.7	25.5	21.8	35.2	16.7	31.5	16.6
Fatigue		12.3	36.8	38.6	12.3	23.7	40.0	32.7	3.6	33.3	44.5	18.5	3.7
Diarrhea		71.9	12.3	12.3	3.5	76.4	23.6	0	0	81.5	18.5	0	0
Dizziness		17.5	31.6	35.1	15.8	18.2	43.6	38.2	0	18.5	50	29.6	1.9
Headache		59.7	26.3	10.5	3.5	78.2	18.2	1.8	1.8	66.7	25.9	5.6	1.8
Mood Change		29.8	26.3	29.8	14.1	32.7	27.3	34.5	5.5	40.7	27.8	24.1	7.4
Nausea/Vomiting		49.1	19.3	21.1	10.5	80.0	14.5	3.7	1.8	68.5	20.3	5.6	5.6
Faint		52.6	19.4	14	14	58.2	23.6	10.9	7.3	61.1	18.5	14.8	5.6

0=none, 1=mild, 2=moderate, 3=severe

Statistical significance was observed for pain ($p<0.05$) and not for other symptoms.

Table 2. Mean of dysmenorrhea severity based on categorical scoring method and total bleeding during menstruation based on prospective charting of bleeding.

	Placebo	Doses 1%	Fennol 2%
Main of dysmenorrhea severity	46.684 ± 2.965	30.073±2.571	28.019±2.876
Main of total bleeding	10.333 ± 0.327	11.345±0.335	10.611±0.358

Statistical significance was observed between treated and placebo groups ($p<0.05$).

patients needed to use other medications, respectively.

Discussion

Primary dysmenorrhea is the most common gynecological problem in menstruating women and common cause of absenteeism. It is accounted for 600 million lost hours and 2 billion dollars lost productivity annually (2). Because of high prevalence of dysmenorrhea and its economical and social complication, several studies have been conducted for the treatment of dysmenorrhea.

Since exaggerated myometrial contraction is an important factor in the pathogenesis of dysmenorhea, its treatment is associated with uterine muscle relaxation (20). NSAIDs, which act through inhibition of prostaglandins synthesis, are highly effective. Prostaglandins are responsible for the painful uterine contractions of primary dysmenorrhea. Various reports show successful pain relief with nitric oxide and calcium antagonists that are smooth muscle relaxants and inhibit uterine contractions (12, 20). These drugs exert side effects when administered over a long period. In order to overcome this problem, several studies have been designed to find new agents with less adverse effects. One of the good candidates is FEO. It has been previously reported that FEO inhibits spasms in smooth muscles of intestinal tract and due to this effect; it is used as a remedy for the treatment of colic in infants (21). Our previous study demonstrated that FEO could inhibit uterine contractions induced by oxytocin and prostaglandin E_2 (22).

Present study shows that FEO can decrease pain intensity in the treated groups. The major component of FEO is anethole that has shown estrogen like activity in ovariectomized rats (23). It has been reported that injection of estrogens in rats evokes complete abolition of uterine motility (24). The mechanism of action of FEO may be related to this effect. Some of the patients did not show any improvement of pain. It may be related either to the absorption and metabolism of FEO in individuals or to the pathological source of dysmenorrhea. As it is mentioned earlier, the etiology of uterine hypercontractility in dysmenorrhea is not well understood and may result in ovarian steroids, cervical obstruction, pituitary hormones and prostaglandins. Therefore, the cause of dymenorrhea may be different and some of them did not respond to FEO. The results in table 1 indicate that the symptoms accompanying with pain decrease, but this reduction is not statistically significant. It has been reported that systemic symptoms of dysmenorrhea are related to systemic effects of prostaglandins, but NSAIDs could not suppress these symptoms completely. Furthermore, it has been claimed that some other factors get involved in these symptoms (25). One of the mechanisms which describes this phenomen, is direct effect of FEO on uterine muscle rather than its effect on the released mediators. The results of our previous work may confirm this hypothesis (22). Results showed that the total bleeding in treated groups significantly increased. This effect may be due to the muscle relaxation. Well known NSAIDs that are used for the relief of pain in dysmenorrhea are mefenamic acid, ibuprofen, indomethacin and naproxen with average efficacy of 90%, 60%, 68% and 62%, respectively (26). Most of these NSAIDs in addition to prostaglandin inhibition effects have direct muscle relaxation activity. The present study showed that the efficacy of 2% FEO in pain relief is 67.4%. This efficacy is comparable with the efficacy of usual NSAIDs.

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