Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 14, No. 5, 2023 (pp. 1-10)

RESEARCH ARTICLE WWW.JOCMR.COM

Investigating the Effect of Fennel on the Severity of Primary Dysmenorrhea: a Clinical Trial with a Triple-Blind Control Group

Ataollah Ebrahim Najafabadi[1*],Behzad Jaybashi [2],Roya Hemmatpour [3],mehrdad fojlaley[4] , Fernando maldonado lopes[4]

1- Doctorate in traditional medicine ,department of medicine ,Technofest institute of technology university (TITU) ,Belgium
2- PhD in traditional medicine ,Technofest institute of technology university (TITU) ,Belgium
3- PhD in traditional medicine ,Technofest institute of technology university (TITU) ,Belgium
4- Professor at Technofest institute of technology university (TITU) ,Belgium
5- Corresponding author : Ataollah Ebrahim Najafabadi

Abstract

Aim: This clinical trial investigated the effect of fennel on reducing the severity of primary dysmenorrhea in women.

Methods: This study was a clinical trial with a triple-blind control group. The number of samples was 63 women aged 15-25 years. They were selected from the Farhangian Clinic using a convenience sampling method. To measure the severity of primary dysmenorrhea, the visual analog scale (VAS) was used. The clients were screened by a gynecologist and obstetrician. Participants were evaluated at baseline, cycle 1, and cycle 2 in fennel and placebo groups. Data were analyzed using the MANOVA test in SPSS26 software.

Results: The results revealed that the mean severity of pain in the experimental and placebo groups at baseline did not differ from each other ($P>0.05$). However, the results showed that the severity of pain in the fennel group ($F=6.430$, $P<0.05$) was reduced compared to the placebo group in cycle 1. The results also revealed that the severity of pain in the fennel group ($F=5.548$, $P<0.05$) was reduced compared to the placebo group in cycle 2.

Discussion: The results revealed that fennel can reduce the severity of pain of primary dysmenorrhea compared to placebo. Thus, health professionals are recommended to use fennel to reduce the severity of primary dysmenorrhea due to its low side effects and high impact on reducing primary dysmenorrhea.

Introduction

Dysmenorrhea or painful menstruation is one of the most common problems in women. It may occur two or more days before the onset of menstruation and continue up to three days after bleeding [1]. It is associated with pain caused by muscle spasms in the lower abdomen and may spread to the back and thighs. It can be followed by some symptoms including nausea, vomiting, diarrhea, confusion, fatigue, weakness, and chest pain [2]. Also, studies have indicated that dysmenorrhea is associated with mental disorders such as anxiety and depression [3, 4]. It has two primary and secondary origins. Primary dysmenorrhea is painful menstruation in the absence of confirmed pelvic diseases. It usually begins one to three years after the first menstruation. Recent studies suggest that it is due to the overproduction of prostaglandins [5, 6, 7, 8]. Its secondary type is associated with the occurrence of painful bleeding due to pelvic diseases such as endometriosis, adenomyosis, pelvic inflammatory disease, etc. [9]. A study reported the prevalence of dysmenorrhea at 73.8%. Also, the rate of primary dysmenorrhea was 63.3% and the rate of secondary dysmenorrhea was 10.5% [10].

Keywords: Fennel, Primary dysmenorrhea, Severity of pain, Herbal medicines

DOI: 10.5455/jcmr.2023.14.05.1

Other studies have reported the prevalence of primary dysmenorrhea at 41.7% to 80.9% [11, 12, 13, 14, and 15]. Several methods have been used to treat primary dysmenorrhea, including pharmaceutical methods such
as non-steroidal anti-inflammatory drugs [16, 17, 18, and19] and non-pharmacological methods such as therapeutic exercise [20], abdominal stretching exercises [21], meditation [22], massage therapy [23], and acupuncture [24]. The use of herbal medicines to reduce the severity of dysmenorrhea has increased in recent years due to their low side effects and availability [25].

Fennel is another plant that plays a role in reducing the pain and duration of primary dysmenorrhea. Fennel is an herbaceous and aromatic plant. It belongs to the Umbelliferae family. It grows in many regions of Europe, the Mediterranean, Asia, and Iran. It is one of the native plants of these regions [26, 27]. The root, leaf, and fruit parts of fennel are used [28]. This plant has antibacterial [29], antifungal [30], anti-inflammatory, and antioxidant [31] properties. Several studies have indicated that the fennel plant is effective in reducing the pain of primary dysmenorrhea. A study reported that fennel reduces the severity of primary dysmenorrhea better than Tarhana [32]. Another study also reported that fennel reduced pain in PRIMARY DYSMENORRHEA better than placebo [33]. Another study compared chamomile and fennel in early dysmenorrhea and showed that fennel was more effective than chamomile on fatigue and lethargy, but chamomile has a better effect on abdominal pain, pelvic pain, depression, and anger [34].

Motavalli & Shahbazzadegan [35] showed that gelofen and fennel equally reduce pain in PRIMARY DYSMENORRHEA. Another study revealed that fennel reduces the pain, symptoms, and length of the menstrual period [36]. A meta-analysis and systematic review reported that fennel significantly reduced the severity of dysmenorrhea [37]. Also, a study revealed that fennel cannot reduce systemic symptoms associated with primary dysmenorrhea and is not different from placebo [38]. The mechanism of the action of fennel may be due to the structural similarity of Anthole found in fennel with dopamine, which binds to dopamine receptors and reduces pain, and improves other associated symptoms [39].

Moreover, fennel causes pain-relieving effects in the uterus by inhibiting prostaglandins [40]. The mechanism of action of fennel is similar to that of NSAIDs [41]. This result led to conducting several studies to compare the effectiveness of fennel with mefenamic acid in reducing dysmenorrhea. The results of these studies suggest that fennel is as effective as mefenamic acid in reducing primary dysmenorrhea [37, 42, and 43]. Although there is nowadays an increasing tendency to use medicinal plants to reduce primary dysmenorrhea among women, a few studies have examined the effect of fennel on primary dysmenorrhea and they have reported conflicting results. Thus, the present study investigated the effect of fennel in reducing the severity of primary dysmenorrhea.

Methods

This triple-blind clinical trial was conducted on 63 women with mild, moderate, and severe primary dysmenorrhea. The number of samples was initially considered to be 30 people for each group based on the study by Zeraati et al. [44]. In the initial screening, 84 women with primary dysmenorrhea from the FarhangianClinic were included in the study. The inclusion and exclusion criteria of the study included informed consent, not using contraceptive pills and analgesics, regular menstrual cycles with intervals of 21-35 days, menstrual bleeding without clot removal (light and moderate bleeding), suffering from dysmenorrhea, not suffering from kidney and liver diseases, allergy to herbal medicines, allergy to fennel during the study, and unwillingness to cooperate.

According to the inclusion and exclusion criteria, 63 people were randomly placed in the control or placebo (n=31) and fennel (n=32) groups. To measure the severity of pain, a visual analog scale (VAS, which was a 100-mm ruler, was used. VAS reliability was obtained at 0.9 [45, 46]. This scale was completed during three menstrual periods (baseline, cycle 1, and cycle 2). At baseline, only the VAS scale was given to the participants. In cycle 1 and cycle 2, the capsules of the two groups were prepared uniformly in similar packages. Medicines had no name but had a code. They were prescribed by a colleague (midwife) who was not aware of the code. Statistical analyses were performed by another colleague who did not have any knowledge about the studied groups. The patients did not have any knowledge about their groups and the evaluator did not have any knowledge about their groups. For the fennel intervention group, Fennelin Barij capsules produced by Barije Essence Pharmaceutical Company with a health code of 861961910785578 were used. Each capsule contains 30 mg of Foeniculum vulgare, which is standardized to 21-27 mg of Anthole per capsule.

Other compounds were fenchone, methylchavicol, and estragole. The dose used in this study was one every 4 hours on the first three days of menstruation. Based on the previous studies, the capsules of the placebo group contained 250 mg of sugar [47]. Participants took 4 capsules every day during the first three days of their period. The data obtained from the questionnaires were analyzed by a statistician who did not have any knowledge about the experimental and placebo groups. Data were analyzed in SPSS26 Software. First, mean and standard deviation were obtained in descriptive statistics. Then, MANOVA and LSD tests were used. Chi-squared test was used to observe the difference in the demographic characteristics of the groups.

Results

The results revealed that the mean (standard deviation) age of the placebo and fennel groups is 20.32 (0.413) and 21.06 (0.406) respectively. The age of onset of menstruation in these groups was

12.70 (0.218) and 12.56 (0.219) respectively. The results of the chi-square also revealed that the experimental and placebo groups did not differ from each other regarding body mass, as shown in Table 1. The mean (standard deviation) of the severity of pain in the placebo and fennel groups at baseline was 56.83 (19.375) and 57.31 (18.861), respectively. The mean (standard deviation) of the severity of pain in the placebo and fennel groups in cycle 1 was 52 (17.281) and 40.15 (19.670), respectively, and the mean (standard deviation) of the severity of pain in the placebo and fennel groups in cycle 2 was 53.51 (18.226) and 42.09 (20.177), respectively, as shown in Table 2.

A multivariate analysis of variance (MANOVA) test was used to examine the hypothesis. One of the presumptions of MANOVA is the homogeneity of the covariance matrix. For this purpose, Box's M test was used. Its results are presented in Table 3. As shown in Table 3, the correlation between the studied variables is homogeneous. Since the observed F related to this test is not statistically significant at the p<.050 level, the presumption of homogeneity of the covariance matrix has been fulfilled.

Levene's test was used to examine the presumption of homogeneity of error variance. Based on the results of Table 4, the presumption of homogeneity of error variance has been fulfilled (p>0.05). Due to the normality of the data, Pillai's Trace test was used, the results of which are presented in Table 7. Based on Table 5, the observed F is significant at the p<.050 level. Table 6 reports the results of comparing the placebo and fennel groups at baseline, cycle 1, and cycle 2. According to the results of Tests of Between-Subjects Effects, fennel significantly reduced the severity of pain in the experimental group compared to the placebo group in Cycle 1 and Cycle 2 (P<0.05). The results also showed that the severity of pain between the two groups at baseline did not differ significantly from each other (P>0.05). Diagrams 2, 3, and 4 show these changes.

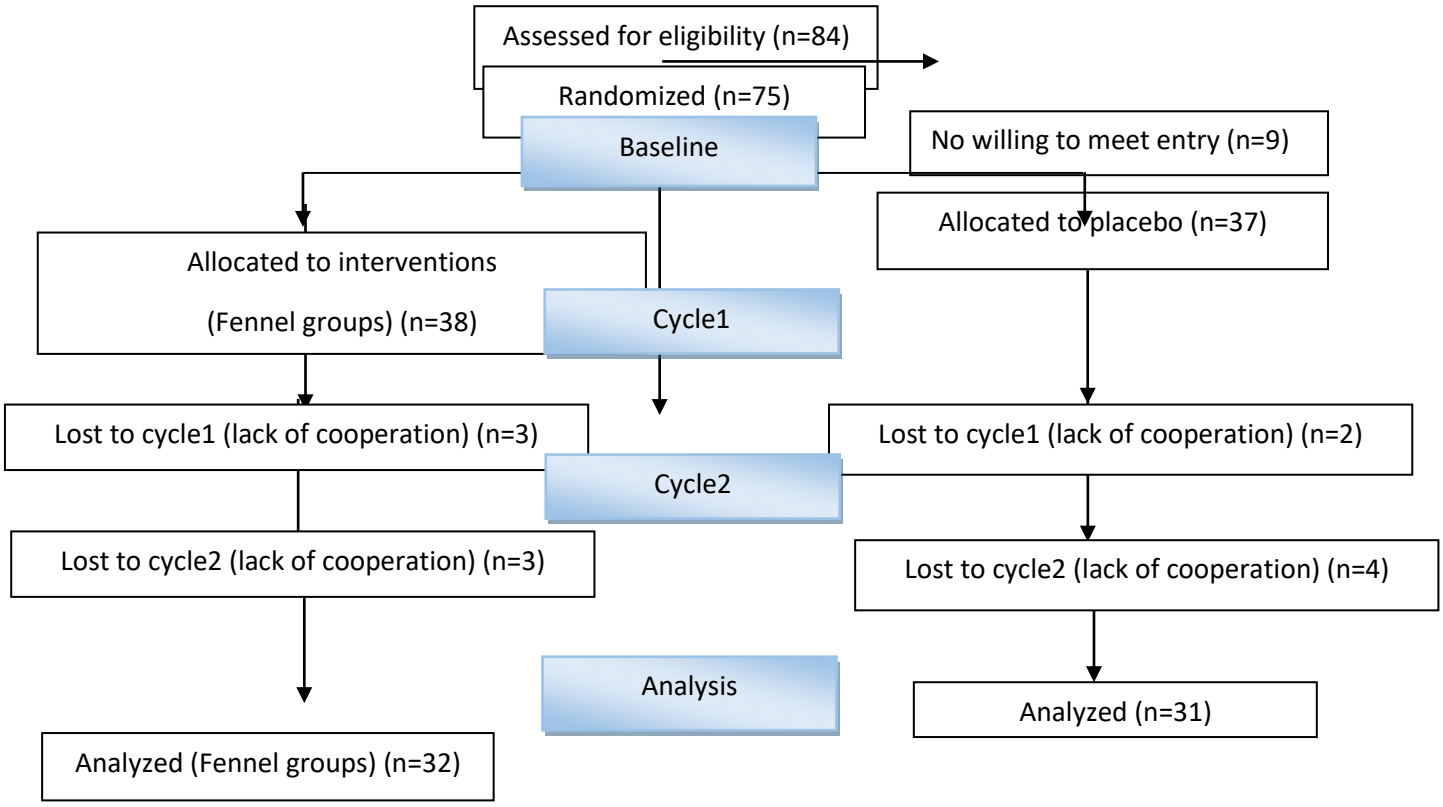

Diagram 1: Random allocation of samples in two experimental and control groups

Table1 :Chi-square tests

		group		Chi-square	p
		placebo	fennel		
Body mass	Underweight	5	3		
	Normal range	9	14	3.850	0.921

	Overweight	10	11		
	Obese	7	4		
Total		31	32		

Table 2: Descriptive Statistics

	group	Mean	Std. Deviation	N
baseline	placebo	56.8387	19.37541	31
	fennel	57.3125	18.86187	32
cycle1	placebo	52.0000	17.28198	31
	fennel	40.1563	19.67004	32
cycle2	placebo	53.5161	18.22612	31
	fennel	42.0938	20.17721	32

Table 3: The results of Box's M test

Box's M	**F**	**df1**	**df2**	**sig**
2.459	3.88	66	26882.239	0.887

Table 4: Levene's Test of Equality of Error Variances

		Levene Statistic	df1	df2	Sig.
baseline	Based on Mean	.053	1	61	.819
cycle1	Based on Mean	.771	1	61	.383
cycle2	Based on Mean	.437	1	61	.511

Table 5: Multivariate Tests

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	.932	269.994	3.000	59.000	.000	.932	809.982	1.000
group	.152	3.519	3.000	59.000	.020	.152	10.558	.756

Table 6: Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power
Corrected Model	baseline	3.535	1	3.535	.010	.922	.000	.010	.051
	cycle1	2208.765	1	2208.765	6.430	.014	.095	6.430	.704
	cycle2	2054.396[c]	1	2054.396	5.548	.022	.083	5.548	.640
Intercept	baseline	205178.646	1	205178.646	561.476	.000	.902	561.476	1.000
	cycle1	133727.496	1	133727.496	389.295	.000	.865	389.295	1.000
	cycle2	143938.396	1	143938.396	388.739	.000	.864	388.739	1.000
group	baseline	3.535	1	3.535	.010	.922	.000	.010	.051
	cycle1	2208.765	1	2208.765	6.430	.014	.095	6.430	.704
	cycle2	2054.396	1	2054.396	5.548	.022	.083	5.548	.640
Error	baseline	22291.069	61	365.427					
	cycle1	20954.219	61	343.512					
	cycle2	22586.461	61	370.270					
Total	baseline	227552.000	63						
	cycle1	156379.000	63						
	cycle2	168070.000	63						
Corrected Total	baseline	22294.603	62						
	cycle1	23162.984	62						
	cycle2	24640.857	62						

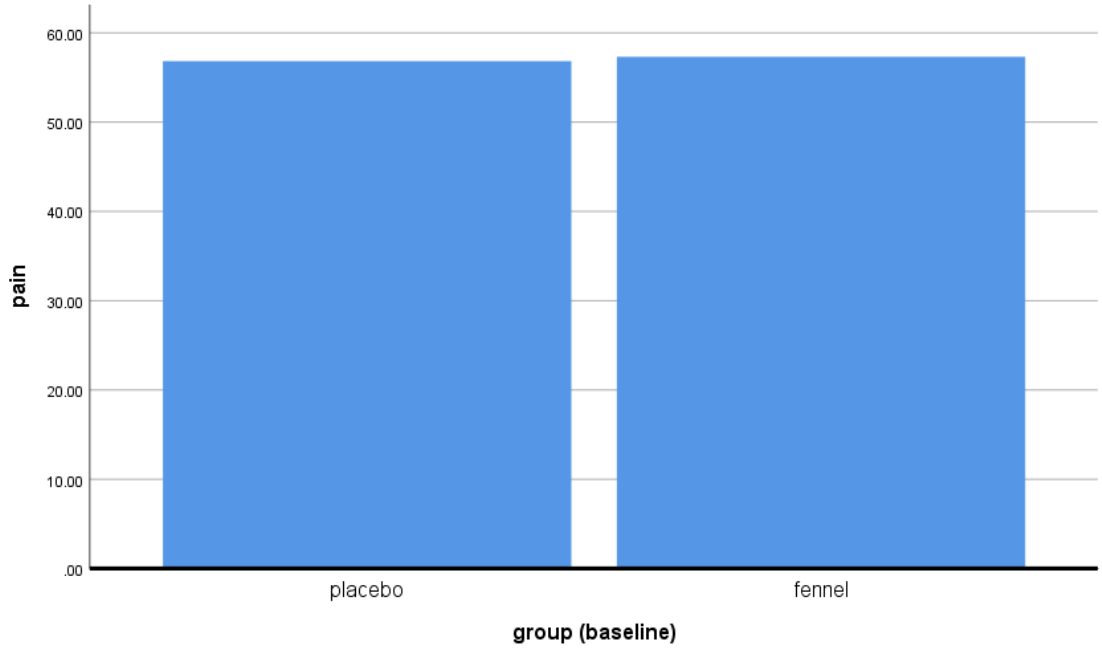

Diagram 2: pain severity in the experimental and control groups at baseline

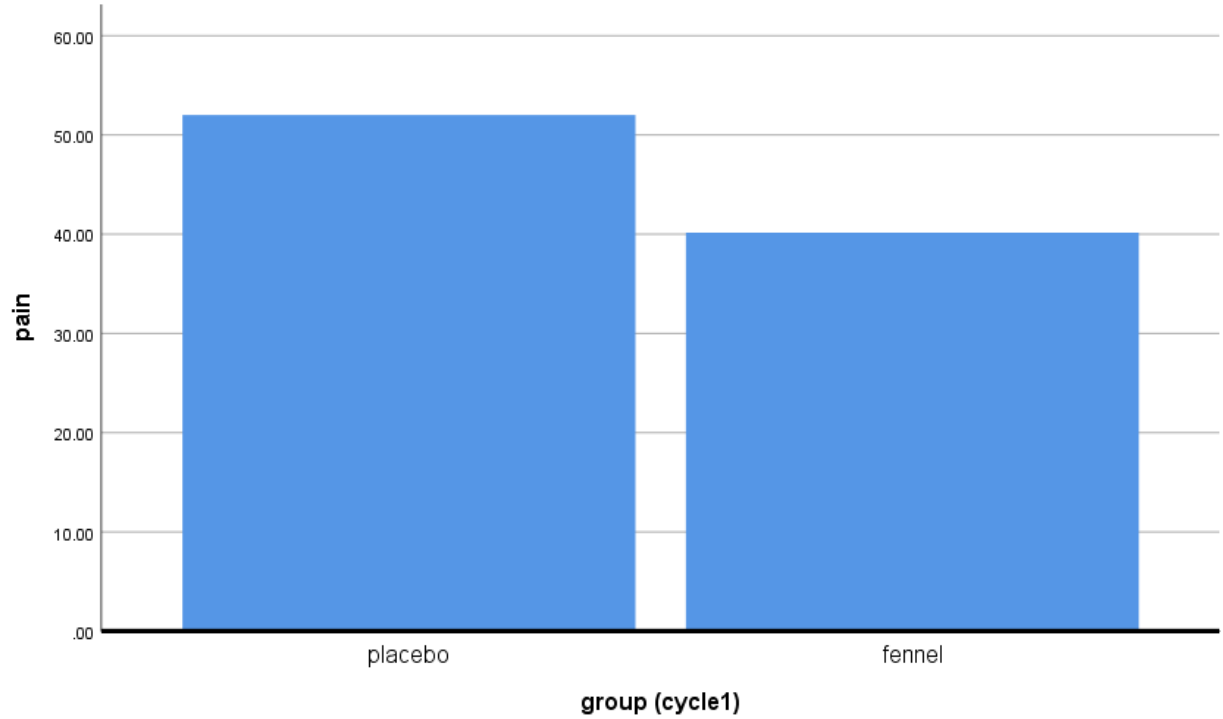

Diagram 3: pain severity in the experimental and control groups in Cycle 1

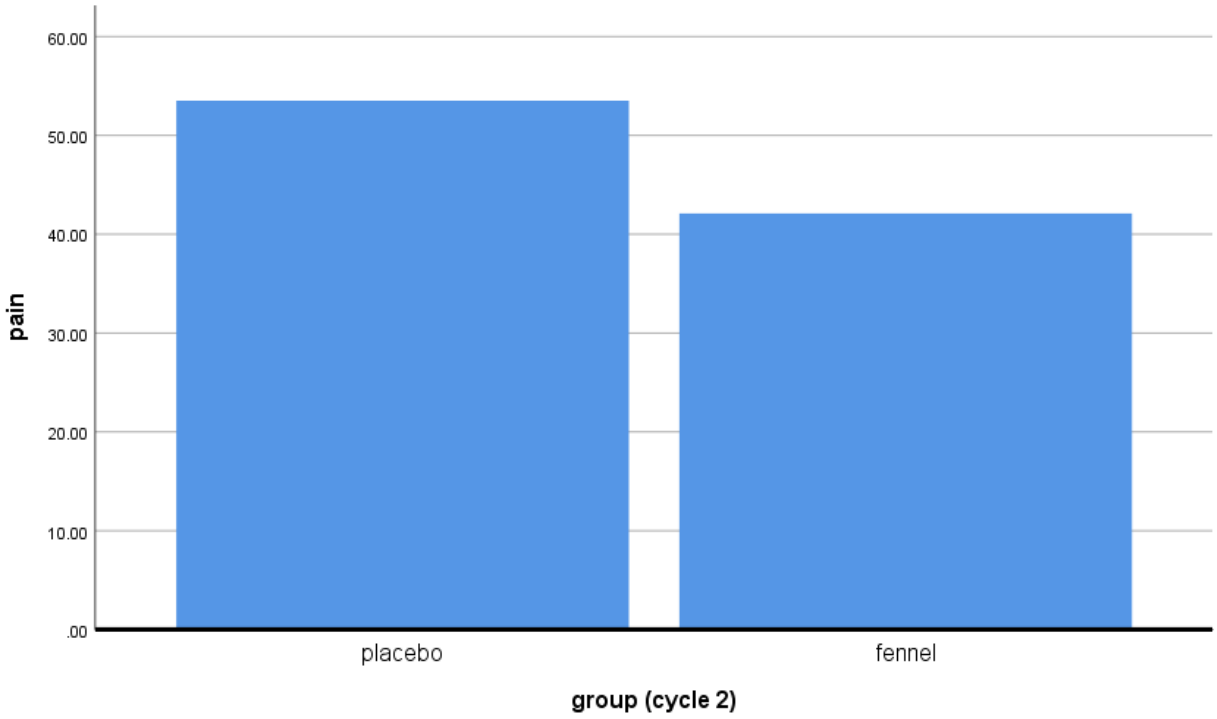

Diagram 4: pain severity in the experimental and control groups at Cycle 2

Discussion and Conclusion

The results revealed that fennel, compared to placebo, significantly reduces the severity of dysmenorrhea in cycles 1 and 2. These results are consistent with those of other studies [48, 32, 33, 35, 42, and 49]. Although the definite cause of primary dysmenorrhea is unknown, an accepted theory about its cause is the overproduction of prostaglandins [50]. Thus, its treatment should be planned in reducing the production of prostaglandins [51]. Also, the use of a drug that has antispasmodic properties is effective in reducing pain since prostaglandin causes uterine smooth muscles to contract and cause colic pain [52]. The results revealed that the severity of dysmenorrhea after treatment was significantly different in the two groups, so fennel extract reduced the severity of dysmenorrhea. The possible mechanism of action of fennel may be secondarily related to its spasmolytic, which is due to the structural similarity of Anthole found in fennel with dopamine, which binds to dopamine receptors and reduces pain [39, 53]. Moreover, according to the studies conducted in this regard, fennel essential oil can inhibit uterine smooth muscle contractions caused by oxytocin and prostaglandin E2, and thus, it can reduce pain [54].

Xu et al. (2020) showed that the duration and severity of pain were reduced in the intervention group compared to the control [48]. Abdollahi et al. (2018) showed that in Cycle 1 after treatment, the use of fennel increased menstrual bleeding in the intervention group compared to the control group. However, it had no significant effect on menstrual bleeding in cycle 2 after treatment [55]. Bokaie, M., Enjezab et al. (2017) examined one of the side effects of fennel. They studied 59 female students and showed that fennel did not cause a significant difference in the overall level of menstrual bleeding compared to the control group. [56].

Delaram & Sadeghian (2007) showed that both plants can reduce the severity of dysmenorrhea. However, fennel showed a better performance than Tarhana [32]. A systematic review and meta-analysis in 2020 revealed that fennel is as effective as conventional drug treatments in reducing primary dysmenorrhea. Also, 3 studies investigated its adverse side, and only one study reported a partial adverse side [49]. Another study by Momenzadeh et al. (2017) reported that the reduction in the severity of pain in one month was significant in both intervention groups. However, no significant difference was observed between mefenamic acid and fennel in reducing pain and they reduced the pain equally [57].

Research limitations

The present study investigated the severity of pain in women with primary dysmenorrhea. One of the limitations of the present study was the lack of investigation of other symptoms related to primary dysmenorrhea and related variables such as duration and severity of bleeding. Thus, it is recommended to investigate the mentioned factors in future studies. Also, the use of a convenience sampling method and examination of dysmenorrhea women in a clinic in Tehran makes it difficult to generalize the results to other women. Therefore, it is necessary to conduct more studies in this field to increase the generalizability of the data.

Conclusion

The present study investigated the effect of fennel on the severity of primary dysmenorrhea. The results revealed that fennel can reduce pain in women with primary dysmenorrhea compared to placebo. This study suggests that women with primary dysmenorrhea can benefit from fennel as an effective and safe treatment. However, more studies with a higher sample size are needed to investigate the variables of this study.

References

1- Rahnama P, Montazeri A, Huseini HF, Kianbakht S, Naseri M. Effect of Zingiber officinale R. rhizomes (ginger) on pain relief in primary dysmenorrhea: a placebo randomized trial. BMC complementary and alternative medicine. 2012 Dec;12:1-7.

2- Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiologic reviews. 2014 Jan 1;36(1):104-13.

3- Gagua T, Tkeshelashvili B, Gagua D, Mchedlishvili N. Assessment of anxiety and depression in adolescents with primary dysmenorrhea: a case-control study. Journal of Pediatric and adolescent gynecology. 2013 Dec 1;26(6):350-4.

4- Balık G, Üstüner I, Kağıtcı M, Şahin FK. Is there a relationship between mood disorders and dysmenorrhea?. Journal of Pediatric and adolescent gynecology. 2014 Dec 1;27(6):371-4.

5- Fajrin I, Alam G, Usman AN. Prostaglandin level of primary dysmenorrhea sufferers. Enfermería Clínica. 2020 Mar 1;30:5-9.

6- Li X, Guo S, Chen Z, Ren K, Zhang H, Yu S, Yang S. Regulation of mild moxibustion on uterine vascular and prostaglandin contents in primary dysmenorrhea rat model. Evidence-Based Complementary and Alternative Medicine. 2021 Jul 10;2021.

7- Dawood MY, Khan-Dawood FS. Clinical efficacy and differential inhibition of menstrual fluid prostaglandin F2α in a randomized, double-blind, crossover treatment with placebo, acetaminophen, and ibuprofen in primary dysmenorrhea. American Journal of Obstetrics and Gynecology. 2007 Jan 1;196(1):35-e1.

8- Dawood MY, Khan-Dawood FS. Differential suppression of menstrual fluid prostaglandin F2a, prostaglandin E2, 6-keto prostaglandin F1a, and thromboxane B2 by suprofen in women with primary dysmenorrhea. Prostaglandins & other lipid mediators. 2007 Feb 1;83(1-2):146-53.

9- Mohamed EA, Ahmed Attia A, Hassan Omran AA, Elsayed Afifi HA. Traditional practices self-reported by nursing students to relieve dysmenorrhea. Egyptian Journal of Health Care. 2020 Mar 1;11(1):176-90.

10- Abreu-Sánchez A, Parra-Fernández ML, Onieva-Zafra MD, Ramos-Pichardo JD, Fernández-Martínez E. Type of dysmenorrhea, menstrual characteristics and symptoms in nursing students in Southern Spain. InHealthcare 2020 Aug 26 (Vol. 8, No. 3, p. 302). MDPI.

11- Karout S, Soubra L, Rahme D, Karout L, Khojah HM, Itani R. Prevalence, risk factors, and management practices of primary dysmenorrhea among young females. BMC women's health. 2021 Dec;21:1-4.

12- Hu Z, Tang L, Chen L, Kaminga AC, Xu H. Prevalence and risk factors associated with primary dysmenorrhea among Chinese female university students: a cross-sectional study. Journal of Pediatric and adolescent gynecology. 2020 Feb 1;33(1):15-22.

13- Hashim RT, Alkhalifah SS, Alsalman AA, Alfaris DM, Alhussaini MA, Qasim RS, Shaik SA. Prevalence of primary dysmenorrhea and its effect on the quality of life amongst female medical students at King Saud University, Riyadh, Saudi Arabia: a cross-sectional study. Saudi medical journal. 2020 Mar;41(3):283.

14- Fernandez H, Barea A, Chanavaz-Lacheray I. Prevalence, intensity, impact on quality of life and insights of dysmenorrhea among French women: A cross-sectional web survey. Journal of Gynecology Obstetrics and Human Reproduction. 2020 Dec 1;49(10):101889.

15- Ortiz MI. Primary dysmenorrhea among Mexican university students: prevalence, impact, and treatment. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010 Sep 1;152(1):73-7.

16- Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception. 2010 Mar 1;81(3):185-96.

17- Dawood MY. Nonsteroidal anti-inflammatory drugs and changing attitudes toward dysmenorrhea. The American Journal of Medicine. 1988 May 20;84(5):23-9.

18- Budoff PW. Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA. 1979 Jun 22;241(25):2713-6.

19- RAO KA, CHANDRA S, KASTURE PN. Role of Prostaglandins in Pathogenesis of Dysmenorrhea and Place of Mefenamic Acid and Dicyclomine in its Management. Indian Journal of Clinical Practice. 2022 Mar;32(10).

20- Carroquino-Garcia P, Jiménez-Rejano JJ, Medrano-Sanchez E, De La Casa-Almeida M, Diaz-Mohedo E, Suarez-Serrano C. Therapeutic exercise in the treatment of primary dysmenorrhea: a systematic

review and meta-analysis. Physical therapy. 2019 Oct 28;99(10):1371-80.
21- Murtiningsih M, Solihah L, Yuniarti S. the Effect of Abdominal Stretching Exercise on Dysmenorrhea in Adolescent Girls. Journal of Maternity Care and Reproductive Health. 2019 Sep 12;2(3).
22- Widyanata KA, Putra IG, Daryaswanti PI, Febianingsih NP. Physical Activity and Meditation to Reduce Primary Dysmenorrhea in Adolescents. In8th International Nursing Conference on Education, Practice and Research Development in Nursing (INC 2017) 2017 Apr (pp. 40-42). Atlantis Press.
23- Azima S, Bakhshayesh HR, Kaviani M, Abbasnia K, Sayadi M. Comparison of the effect of massage therapy and isometric exercises on primary dysmenorrhea: a randomized controlled clinical trial. Journal of Pediatric and adolescent gynecology. 2015 Dec 1;28(6):486-91.
24- Woo HL, Ji HR, Pak YK, Lee H, Heo SJ, Lee JM, Park KS. The efficacy and safety of acupuncture in women with primary dysmenorrhea: a systematic review and meta-analysis. Medicine. 2018 Jun;97(23).
25- Gomathy N, Dhanasekar KR, Trayambak D, Amirtha R. Supportive therapy for dysmenorrhea: Time to look beyond mefenamic acid in primary care. Journal of Family Medicine and Primary Care. 2019 Nov;8(11):3487.
26- Díaz-Maroto MC, Pérez-Coello MS, Esteban J, Sanz J. Comparison of the volatile composition of wild fennel samples (Foeniculum vulgare Mill.) from Central Spain. Journal of agricultural and food chemistry. 2006 Sep 6;54(18):6814-8.
27- Taherian A, Dehghanina M, Vafaei A, Sadeghi H, Miladi Gorgi H. Effects of aqueous extract of the fruit of Foeniculum vulgar on neurogenic and inflammatory pain in mice. SJKU 2007; 12 (2) :29-36
28- Mahdavi S, Alizad M, Sajadi P, Baleghi M. A Study of the Antioxidant and Antimicrobial Effects of Ethanolic Extract of Fennel (Foeniculum vulgare Mill) Seeds. J Babol Univ Med Sci 2017; 19 (5) :32-38
29- Diao WR, Hu QP, Zhang H, Xu JG. Chemical composition, antibacterial activity, and mechanism of action of essential oil from seeds of fennel (Foeniculum vulgare Mill.). Food control. 2014 Jan 1;35(1):109-16.
30- Zeng H, Chen X, Liang J. In vitro antifungal activity and mechanism of essential oil from fennel (Foeniculum vulgare L.) on dermatophyte species. Journal of Medical Microbiology. 2015 Jan;64(1):93-103.
31- Rafieian F, Amani R, Rezaei A, Karaça AC, Jafari SM. Exploring fennel (Foeniculum vulgare): Composition, functional properties, potential health benefits, and safety. Critical Reviews in Food Science and Nutrition. 2023 Feb 2:1-8.
32- Delaram M, Sadeghian Z. The Comparison of Echinophora-Platyloba and Fennel effects on Primary Dysmenorrhea. Avicenna J Clin Med 2011; 18 (1) :42-47
33- moslemi L, Aghamohammadi A, Bekhradi R, Zafari M. Comparing the Effects of Vitamin E and Fennel Extract on Intensity of Primary Dysmenorrhea. J Mazandaran Univ Med Sci 2012; 22 (88) :103-107
34- Yazdani M, Shahrani M, Hamedi B. Comparison of fennel and chamomile extract and placebo in treatment of premenstrual syndrome and dysmenorrheal. Hormozgan Medical Journal. 2004 Apr 15;8(1):57-61.
35- Motavalli, R., Shahbazzadegan, S. Comparative study of the effects of fennel with Gelofen on the severity of primary dysmenorrhea: A randomized clinical trial. *The Iranian Journal of Obstetrics, Gynecology and Infertility*, 2018; 21(7): 36-42.
36- Ghodsi Z, Asltoghiri M. The effect of fennel on pain quality, symptoms, and menstrual duration in primary dysmenorrhea. Journal of pediatric and adolescent gynecology. 2014 Oct 1;27(5):283-6.
37- Shahrahmani H, Ghazanfarpour M, Shahrahmani N, Abdi F, Sewell RD, Rafieian-Kopaei M. Effect of fennel on primary dysmenorrhea: a systematic review and meta-analysis. Journal of Complementary and Integrative Medicine. 2021 Jun 1;18(2):261-9.
38- Motavalli R, Mousazadeh T. Effect of Fennel on Reduction of Symptoms Associated with Pain in Primary Dysmenorrhea. JHC 2019; 21 (1) :26-33.
39- Zarei Amand H, Vahidi Rad Z, Vahidi Rad M, Eneam M, Vahidi Rad M, Vahidi Rad AH. Foniculum vulgare: review of pharmaceutical features. International Journal of Medical Investigation. 2016 Dec 10;5(4):132-138
40- Tarko A, Fabová Z, Kotwica J, Valocký I, Alrezaki A, Alwasel S, Harrath AH, Sirotkin AV. The inhibitory influence of toluene on mare ovarian granulosa cells can be prevented by fennel. General and Comparative Endocrinology. 2020 Sep 1;295:113491.

41- Cimolai N. The potential and promise of mefenamic acid. Expert review of clinical pharmacology. 2013 May 1;6(3):289-305.
42- Modaress Nejad V, Motamedi B, Asadi pour M. Comparison between the Pain-Relief Effect of Fennel and Mefenamic Acid on Primary Dysmenorrhea. JRUMS 2006; 5 (1) :1-6
43- Nazarpour S, Azimi H. Comparison of therapeutic effects of Fennelin and Mefenamic Acid on Primary Dysmenorrhea. J Mazandaran Univ Med Sci 2007; 17 (61) :54-61
44- Zeraati F, Shobeiri F, Nazari M, Araghchian M, Bekhradi R. Comparative evaluation of the efficacy of herbal drugs (fennelin and vitagnus) and mefenamic acid in the treatment of primary dysmenorrhea. Iranian journal of nursing and midwifery research. 2014 Nov;19(6):581.
45- Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith C. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. The Journal of rheumatology. 1990 Aug 1;17(8):1022-4.
46- Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). Arthritis care & research. 2011 Nov;63(S11):S240-52.
47- Davdabady Farahani M, vakilian K, Seyyedzadeh Aghdam N. Comparison of Ginger and Valerian on the Severity of Primary Dysmenorrhea: a Randomized Triple Blind Clinical Trial. cmja 2013; 3 (2) :494-50
48- Xu Y, Yang Q, Wang X. Efficacy of herbal medicine (cinnamon/fennel/ginger) for primary dysmenorrhea: a systematic review and meta-analysis of randomized controlled trials. Journal of International Medical Research. 2020 Jun;48(6):0300060520936179.
49- Lee HW, Ang L, Lee MS, Alimoradi Z, Kim E. Fennel for reducing pain in primary dysmenorrhea: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2020 Nov 10;12(11):3438.
50- Chan WY, Dawood MY, Fuchs F. Prostaglandins in primary dysmenorrhea: comparison of prophylactic and nonprophylactic treatment with ibuprofen and use of oral contraceptives. The American journal of medicine. 1981 Mar 1;70(3):535-41.
51- Fajrin I, Alam G, Usman AN. Prostaglandin level of primary dysmenorrhea sufferers. Enfermería Clínica. 2020 Mar 1;30:5-9.
52- Moura LS, Carvalho Jr RN, Stefanini MB, Ming LC, Meireles MA. Supercritical fluid extraction from fennel (Foeniculum vulgare): global yield, composition and kinetic data. The Journal of supercritical fluids. 2005 Oct 1;35(3):212-9.
53- Charles DJ, Charles DJ. Fennel. Antioxidant Properties of Spices, Herbs and Other Sources. 2013:287-93.
54- Ostad SN, Soodi M, Shariffzadeh M, Khorshidi N, Marzban H. The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. Journal of ethnopharmacology. 2001 Aug 1;76(3):299-304.
55- Abdollahi NG, Mirghafourvand M, Mollazadeh S. The effects of fennel on menstrual bleeding: a systematic review and meta-analysis. Journal of Complementary and Integrative Medicine. 2018 Sep 1;15(3).
56- Bokaie, M., Enjezab, B. The Effects of Oral Fennel Extract on the Intensity of Menstrual Bleeding in Relieving Dysmenorrheal: A Randomized Clinical Trial. *Community Health Journal*, 2017; 8(1): 55-62.
57- Momenzadeh, F., Toghiri, M. A., Taghizadeh, M., Mahlioji, M., Rafiee, F. Comparison the Effect of Fennel and Mefenamic Acid on Severity of Primary Dysmenorrhea. *The Iranian Journal of Obstetrics, Gynecology and Infertility*, 2017; 20(4): 44-49.