Taiwanese Journal of Obstetrics & Gynecology 58 (2019) 227–233

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Effect of eryngo (*Eryngium caucasicum Trautv*) on primary dysmenorrhea: A randomized, double-blind, placebo-controlled study

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ARTICLE INFO

Article history:
Accepted 8 August 2018

Keywords:
Dysmenorrhea
Herbal medicine
Women

ABSTRACT

Objective: This study strove to investigate the safety and effectiveness of Eryngo in the treatment of primary dysmenorrhea.
Materials and methods: The researchers conducted a blinded, randomized, trial design on 169 women, 15–30 years of age, who had been diagnosed with primary dysmenorrhea at Babol University of Medical Sciences. Subjects were randomly assigned to receive 5 ml syrup of Eryngo, placebo, or Ibuprofen (200 mg) three times a day (15 ml/day), from one day prior to the onset of bleeding for five days. The degree of dysmenorrhea was reported by two measures; Visual analogue scale (VAS), as a primary outcome, and the assessment of dysmenorrhea severity (VMS), as a secondary outcome at 4 menstrual cycles: at pretreatment phase, at the first menstrual cycle, at the second menstrual cycle, and the third menstrual cycle without drug.
Results: The reduced peak-pain differed by the treatment length in women treated for two menstrual cycles: 4.2 (1.0) cm in the Eryngo group, 4.3 (0.0) cm in the Ibuprofen group, and 0.9 (0.1) cm in the placebo group ($P < 0.0001$). No serious side effects were reported in all groups under study. According to the results, minor side effects did not increase in the Eryngo group when compared with the placebo group.
Conclusion: Eryngo relieved dysmenorrhea as effectively as Ibuprofen did. Thus, Eryngo could be regarded as a new herbal remedy for the treatment of dysmenorrhea. However, in order to prescribe Eryngo as herbal remedy, rigorous research studies are required to establish its efficacy by investigating its chemical, pharmacologic, and therapeutic properties.

Introduction

Dysmenorrhea, also known as painful menstruation, is one of the most common gynecological symptoms among women of reproductive age [1–3]. Relying on its clinical presentation, it could be divided into two types: primary and secondary dysmenorrhea. The initial presentation of primary dysmenorrhea could be within 6–12 months after menarche, and is usually associated with normal ovulatory cycles [4]. Dysmenorrhea, also known as cramps, often accompanies other symptoms such as lower back and sacral back pain. It is generally assumed that there is no identifiable pelvic pathology in primary dysmenorrhea [5].

The prevalence of primary dysmenorrhea is 38.3%–100% among Iranian menstruating women, which could vary according to the population as well as the duration of the study [6]. Primary dysmenorrhea is also one of the most prevalent factors for absenteeism from work among young women in the world [7].

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https://doi.org/10.1016/j.tjog.2019.01.011

It is assumed that the cause for primary dysmenorrhea is not totally unknown, but excess production and the release of prostaglandins (PGs) in the uterine tissue could be regarded as the two most suggested causes for primary dysmenorrhea [8].

Research findings have demonstrated that PGs can stimulate uterine contractions and increase vasopressin release, which could result in ischemia and pain [9]. A quick look at the existing literature indicates that there are a number of complementary alternative medicines which could be used to treat menstrual symptoms. It is also worth noting that the focus of these suggested medicines is mostly on the reduction of PG production and the relief of the cramping pelvic pain. It is evident that both non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCPs) have the same effect on PGs and uterine contractions. It is, nevertheless, believed that NSAIDs and OCPs are the most commonly used therapeutic modalities for the management of primary dysmenorrhea, although some kinds of primary dysmenorrhea do not respond to NSAIDs or oral contraceptives. In addition, research findings indicate that these medications can trigger some side effects including indigestion, headaches and drowsiness in female patients [9]. In the same vein, many women were found to have preferred herbal or natural therapy as alternatives, which could be due to the side effects of chemical drugs or patients' personal beliefs [10].

In order to find a more reasonably tangible result, researchers have investigated numerous traditional, complementary treatments such as herbal, supplement, dietary therapies, behavioral interventions, acupressure, message, and aromatherapy [11].

Eryngo (Gharsaneh) (Qersaanna), for instance, is a perennial species that has been distributed and cultivated in the vicinity of Alborz Mountains and the shore sides of the Caspian Sea, which are both located in Iran [12]. The aerial parts of this herbal plant are used as an additive flavor in food. Its fresh leaves, in particular, are used as a mixture in fish and chicken stuffing [13].

Based on Traditional Iranian Medical texts books, Eryngo possesses the following characteristics: It can be used as an emmenagogue, it can increase lactation and sweating, it is carminative, it is used as an aromatic agent and a fragrant, it can decrease edema and inflammation, it can promote digestion, and it can also remove phlegm (*balgham*) from the digestive system. Drinking and embrocating of Eryngo oil can also alleviate back pain and reinforce sexual strength [2,3]. It is worth mentioning that all species of Eryngo (*Eryngium caucasicum*) enjoy almost the same temperament (*Mizaj*) (warm and dry) and properties.

In 1735, Reogh referred to it as a diuretic, emmenagogue, antiflatulence, and kidney obstruction eliminator in his book [14]. Furthermore, Eryngo is widely used to treat asthma, bronchitis, hypochondriac, and epigastric pain. It appears that the root of this plant is diuretic, effective on kidney and bladder stone, and peripheral edema. Chinese doctors also treat cough, malaria, and animal poisoning by Eryngo [15]. The root is also used as diuretic and analgesic for rheumatoid arthritis patients [16].

Research findings have demonstrated that all parts of Eryngo including the dried leaves, root, blossom, and stem are anti-oxidant [17], Reno-protective [13], and have scavenging activity [18] properties.

Recent studies have demonstrated that its chemical composition mainly consists of phenols and flavonoids. Phenolic compounds include a large group of aromatic secondary herbal metabolites. These compounds have shown varieties of biological effects both in vitro and in vivo. Flavonoids, for instance, can affect antimicrobial, antineoplastic, antioxidant, hypolipidemic, anti-platelet aggregation, anti-prostaglandins and anti-inflammatory activities. The biochemical effects of Flavonoids can act through the inhibition of a number of enzymes such as aldose reductase, phosphodiesterase, Ca+2-ATPase, xanthine oxidase, lipoxygenase and phospholipase A_2, etc. Some kinds of Polyphenols and flavonoids can also have a regulatory role on different hormones such as estrogens and thyroid hormone [19–21]. It is worth mentioning that, according to the Physician's Desk Reference report (PDR), there is no side effect for this herb, and that it is widely used as a main ingredient in local cuisine in various parts of world as well as in Iran. Given the wide applications of this plant, this study was conducted to evaluate the effect of Eryngo on primary dysmenorrhea.

Materials and methods

This study was a randomized, double-blind, placebo-controlled trial attempt to investigate the effect of Eryngo on primary dysmenorrhea. It was approved by the ethics committee of Babol University of Medical Science (protocol number: 2697), and was also registered in Iranian Registry of Clinical Trials (IRCT ID: IRCT2015082823789N1). The study protocol was performed based on the declaration of Helsinki. Through advertisements in university dormitories and high schools in Babol, a total number of 260 young women, with complaints about painful menstruation, were selected for the study, which was conducted between January 2016 and March of 2017.

The inclusion criteria for this study were as follows: The participants had to be non-pregnant. They had to be at least 15–30 years of age. They had to have regular menstruation (interval 21–35 days), with bleeding duration between three and seven days in the last 6 months. There had to be no pelvic abnormality and no history of pelvic surgery. The initial onset of painful menstruation had to be 1–2 years after the menarche. The painful menstruation for these patients had to be between eight and 72 h. The score of painful menstruation, according to the verbal multidimensional scoring system (VMSS), had to be more than grade one (moderate and sever). On the other hand, the patients who were professional athletes or pregnant, had a history of taking OCP, had medicinal or herbal sensitivities, were diagnosed to have secondary dysmenorrhea or mild dysmenorrhea, had irregular menstruation, had severe causes of stress such as family disputes or the death of parents, and did not take any medication regularly were excluded from the study.

A total number of 260 eligible women completed the VMSS, and were screened through inclusion/exclusion criteria. 212 women who met the criteria were included in the study and signed the informed consent. 183 women were confirmed to have primary dysmenorrhea, which was determined through an abdominal ultrasonography on pelvic and abdominal areas after ruling out organic diseases. Finally, a total of 169 young women with complicated data were randomly divided into three groups receiving syrup of Eryngo, syrup of Ibuprofen, or syrup of placebo based on the blocked randomization with a block size of 6 for the three groups *(A, B, C)*. At first, blocks containing 6 of 3 treatments (syrup of Eryngo, syrup of Ibuprofen, and syrup of placebo) were written with different possible combinations, each one was assigned a number. Then, each block was given a number using the random number table. Medications in the same shape (syrup) in three groups were also given to the biostatisticians to be assigned a 5-digit code to each. After the coding procedure, the syrups were given to the investigator. The researcher was unaware of the contents of the syrups, and the identities of the syrups were available only to the biostatisticians. To hide it, the biostatisticians, as mentioned in the randomization section, provided blocks of 6 with different combinations containing three syrups (two syrup from each group). Then, he replaced the name of each syrup with a 5-digit number, sealed the envelopes and gave one number to each

envelope. Then, using the random number table, the envelopes were given to the researcher randomly. It should be noted that both the researchers and participants were blinded to the whole process (double-blind) (Fig. 1).

We purchased Ibuprofen syrup from Soha pharmaceutical company, and Eryngo syrup was made by researchers of this study. The freshly-harvested plant was purchased from a field in a village in Babol, Mazandaran, Iran in the fall of 2015. Plant was confirmed scientifically by a professor of pharmacognosy in the school of Pharmacy at Shahid Beheshti University of Medical Sciences. Voucher specimen of the plant in number of SBMU-8075 is deposited in the of faculty of Traditional Medicine at Babol University of Medical Sciences and the school of Pharmacy at Shahid Beheshti University of Medical Sciences. Then, 10 kg were bought from the same farm for the main drug in the same time. The plant was cleaned, washed and dried at room temperature. The total phenolic content of aqueous extract of *E. caucasicum* was determined by the folin ciocalteu method. The total flavonoid content of hydro alcoholic, water and ethanolic extracts was measured by the aluminum chloride spectrophotometer assay.

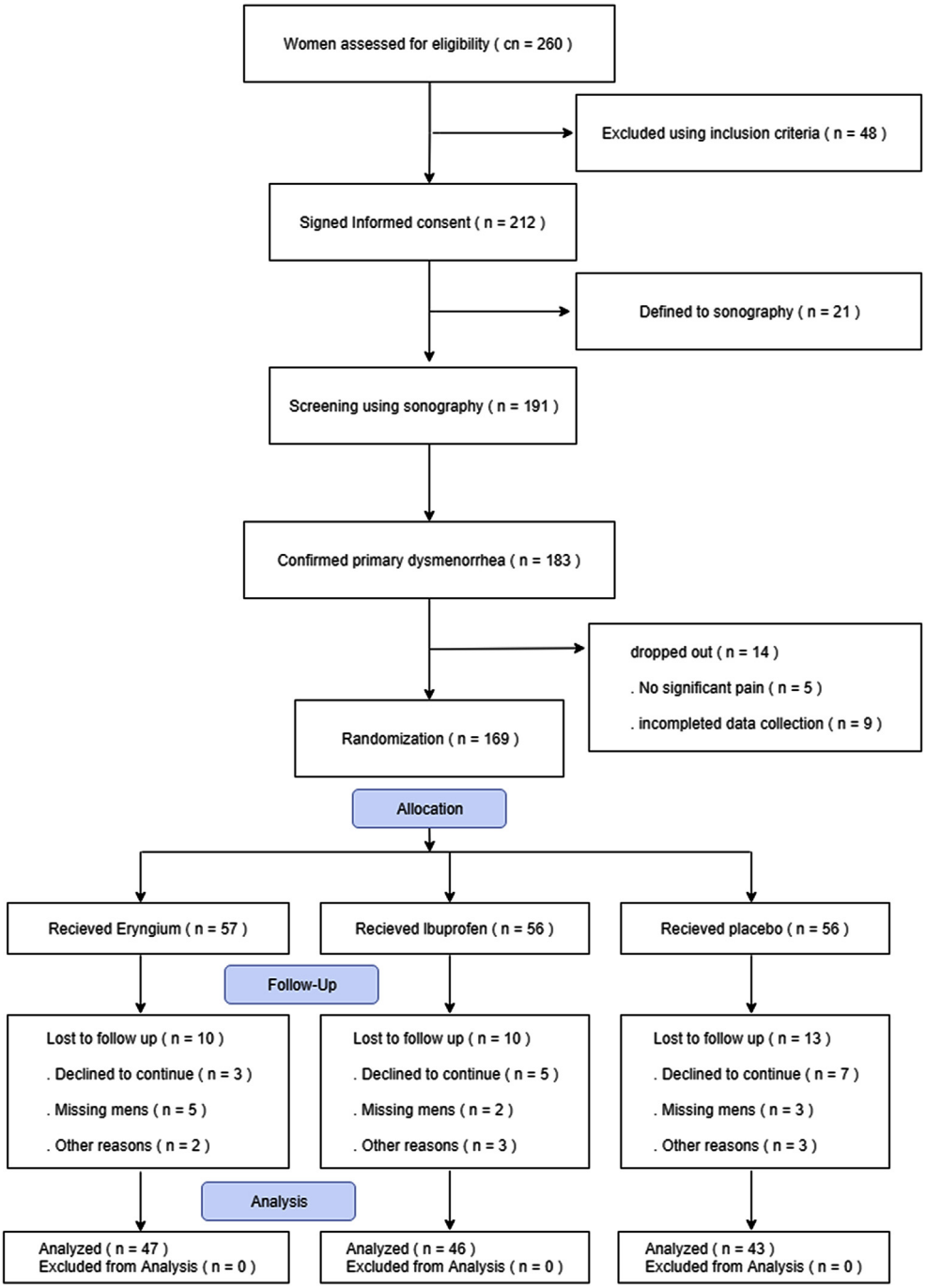

Fig. 1. Consort Fellow diagram of the participants.

The bottles of syrup for the Eryngo plant and the placebo were purchased from the same company. The bottles were sealed and secured, with a band at the interface by Soha pharmaceutical company. Eryngo and placebo syrup were prepared based on USP (United State Pharmacopeia) simple syrup method (66.7%). Standardization, physicochemical and microbial evaluation of Eryngo syrup was done by school of pharmacy at Shahid Beheshti University. The volume of each bottle of syrup approximately was 100 ml. We determined the dosage, 5 ml syrup three times a day (15 ml/day), from one day before the onset of bleeding for five days, during 2 menstrual cycles.

A baseline questionnaire including: age, age at menarche, cycle length, the length of menstrual pain, duration of bleeding in every menstrual cycle, and the number of days with painful menstruation were completed by all subjects. Then, they were also asked to report the degree of dysmenorrhea by two measures: visual analogue scale (VAS), as a primary outcome, and the assessment of dysmenorrhea severity (VMS), as a secondary outcome at 4 menstrual cycles: at pretreatment, at the first menstrual cycle, at the second menstrual cycle, and the third menstrual cycle without drug. During the study, the subjects were not allowed to take any analgesic medication, except for Acetaminophen to endure the pain in case the need arose.

The VAS is a scale for measuring dysmenorrhea score with a score from 0 (no pain) to 10 (severe pain), usually a 10 cm straight horizontal line (Huskisson EC). The VAS was classified based on the score of the pain as mild (1–3), moderate (4–7), and sever (8–10). The VMS symptom scale is a scale for assessing the pain with a range 0 (no pain) to 3 (severe pain) by verbal scale (Andersch B).

In addition, the participants were also asked to report the possible side effects of drugs such as any skin problems (eczema and getting blisters), gastric irritation (esophageal reflux, nausea and vomiting), and menstrual disorders (amenorrhea, menorrhagia and spotting) during each cycle. They should report the number of consumable Acetaminophen tablets during the intervention. At the end of the treatment, we conducted two simple questions to seek the participants' general attitude towards the treatment. Our aim was to check whether the participants were satisfied with the medical treatment, or whether they advised this medical treatment to other people.

To the best of our knowledge, there is no published data available on the effect of Eryngo on primary dysmenorrhea. But the statistical calculation of the required sample size was inspired by a study by Cao et all's previous clinical trial on a traditional drug for primary dysmenorrhea, which reported that the traditional drug could relieve the menstrual pain 2 cm by VAS (Cao et al., 2010).

Considering 80% power, $\alpha = 0.05$, and the reduction of 2 score in pain between two drugs and 10% dropout rate, 30 samples were selected for each group based on the inclusion criteria.

The collected data were analyzed by the SPSS software (SPSS version 21 for windows). The demographic and baseline characteristics of the subjects were elucidated by descriptive statistics. The follow up variables (before and after intervention) were analyzed by Repeated Measure Analyses of Variance and GEE model. The data were analyzed according to the intention-to-treat (ITT) analysis. The number-needed-to-treat (NNT) was calculated through obtaining the severity of pain (mild severity) on the second menstrual. All analyses were employed using two-tailed hypothesis testing with the level of significance set at 0.05. This study was published based on CONSORT checklist. The accepted level of significance for all analysis was $P < 0.05$.

Result

The total phenol content of the extract of *E. caucasicum*, based on the Gallic acid standard, was on the routine in 35 μg/ml or 9.72% of herbal extract. The total flavonoid content in the extracts was determined based on the routine in 27 μg/ml or 7.5% of herbal extract. The total phenol and flavonoid were determined and the amounts were 9.72 mg and 7.5 mg in 100 ml of Eryngo syrup (a bottle of syrup).

The mean age and body mass index (BMI) of the participants were 19.5 ± 5.0 years and 21.6 ± 3.8 kg/m^2, respectively. Among the participants, the mean age at menarche was 12.6 ± 1.2 years, their mean menstruation duration was 6.9 ± 1.3 days, and their menstrual cycle length was 29.1 ± 5.4 days. The base line data, the menstruation duration, and the menstrual cycle length in the three groups were similar (Table 1).

The main outcome was the change in peak-pain intensity according VAS (Fig. 2). The peak-pain, based on VAS of the three groups, was significantly reduced at the first and second menstrual cycles when compared with that of the pretreatment cycle ($P < 0.0001$). However, the reduced peak-pain varied by the length of the treatment for women treated for two menstrual cycles: 4.2 (1.0) cm in the Eryngo group, 4.3 (0.0) cm in the Ibuprofen group, and 0.9 (0.1) cm in the placebo group ($P < 0.0001$). The reduction of VAS score was more than 4 cm in both groups, Eryngo and Ibuprofen groups, whereas it was less than 1 cm in the placebo group.

Table 1
Baseline characteristics and menstruation characteristics of the subjects (n = 169).

	Eryngo (n = 48) Mean ± SD	Ibuprofen (n = 46) Mean ± SD	Placebo (n = 43) Mean ± SD
Age (years)			
≤25	35 (74.5)	41 (89.1)	35 (81.4)
>25	12 (25.5)	5 (10.9)	8 (18.6)
BMI (kg/m^2)			
<25	40 (85.1)	34 (73.9)	35 (81.4)
≥25	12 (26.1)	8 (18.6)	7 (14.9)
Age at menarche (years)			
≤12	26 (55.3)	23 (50.0)	16 (37.2)
>12	21 (44.7)	23 (50.0)	27 (62.8)
Duration of Menstrual bleeding (days)			
3–5	9 (19.1)	8 (17.4)	2 (4.7)
6–10	38 (80.9)	38 (82.6)	41 (95.3)
length of Menstrual cycle			
21–27	13 (27.7)	12 (26.1)	18 (41.9)
28–30	23 (48.9)	18 (39.1)	18 (41.9)
31–35	11 (23.4)	16 (34.8)	7 (16.3)

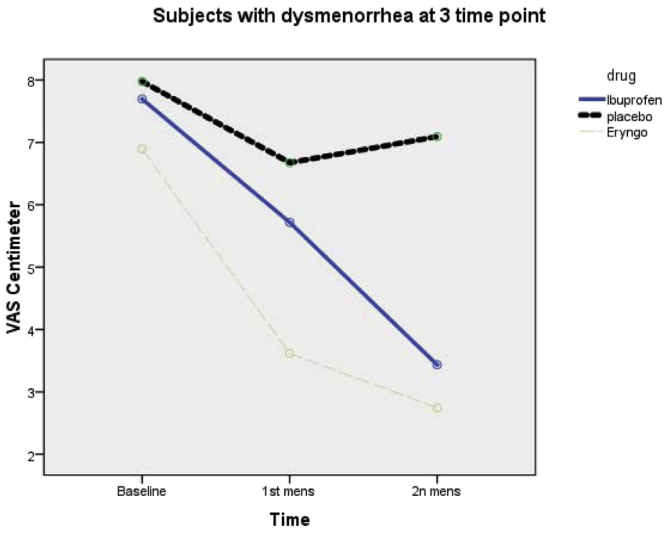

Fig. 2. Changes in the mean VAS score of peak pain from the pretreatment cycle to cycle 2 for the three groups.

Table 2
Comparison of the severity[a] pain score of primary dysmenorrhea based on VAS[b] from the pretreatment cycle to cycle 2 for the three groups.

		Eryngo (n = 48) N (%)	Ibuprofen (n = 46) N (%)	Placebo (n = 43) N (%)	P-value
Pretreatment Cycle	moderate	27 (57.4)	21 (45.7)	14 (32.6)	0.061
	sever	20 (42.6)	25 (54.3)	29 (67.4)	
The first menstrual cycle	mild	24 (51.1)	9 (19.6)	2 (4.7)	<0.0001
	moderate	9 (40.4)	26 (56.5)	27 (62.7)	
	sever	4 (8.5)	11 (23.9)	14 (32.6)	
The second menstrual	mild	34 (72.3)	25 (54.3)	1 (2.3)	<0.0001
	moderate	11 (23.4)	21 (45.7)	24 (55.8)	
	sever	2 (4.2)	0 (0.0)	18 (41.9)	

[a] The pain as mild (1–3), moderate (4–7), and sever (8–10).
[b] Visual Analogue Scale.

At the follow-up cycle (without drug), the decreased pain intensity was persisted in both groups. The Eryngo and the Ibuprofen groups were still both lower at the pretreatment cycle while there was an increase in the placebo group.

At the pretreatment cycle, 57.4% and 42.6% of the Eryngo group, 45% and 54.3% of Ibuprofen group, and 32.6% and 67.4% of placebo group experienced moderate and severe pain, respectively. The pain severity decreased after the intervention in the Eryngo group and Ibuprofen group. Based on the criteria of severity of pain on the second menstrual in Eryngo group, Ibuprofen, and placebo group, 72.3% (34 patients from 57), 54.3% (25 patients from 56), and 2.3% (1 patients from 56) had complete mild dysmenorrhea on the second menstrual, respectively (Table 2). Based on the criteria of severity of pain on the second menstrual, the numbers needed for the treatment (NNT) for both Eryngo and Ibuprofen groups, compared with the placebo group, were approximately 1.5 and 2, respectively. It should be stated that the NNT for Eryngo with Ibuprofen in this study was calculated to be approximately 6.

The results of the GEE model has also demonstrated that the pain intensity, which was significant between the three groups at different times, can change according to VMS criteria ($P < 0.0001$). At pretreatment cycle, the difference in pain intensity, according VMS criteria, was not significant between the Eryngo and Ibuprofen groups, but the difference was significant between the Eryngo and placebo groups. In the first menstrual cycle, the pain decreased, which was significantly higher in the Eryngo group compared with those of other groups. In the first menstrual cycle, the decreased pain intensity in the Ibuprofen group was higher compared with those of other groups. It should be noted that in the Eryngo group, there was a significant difference between the pretreatment cycle and the first menstrual cycle, while the difference between the first menstrual cycle and the second menstrual cycle was not significant. But there was a significant difference between the pretreatment and the second menstrual cycle. In the Ibuprofen group, there was no significant difference between the intervention times. There was a significant difference between the first month and the pre-intervention period, and there was also no significant difference between the first menstrual and the second menstrual cycles. Thus, despite the significant difference in the pain intensity between the three groups before and after the intervention, there was a significant difference in pain intensity in the second menstrual cycle. Also, there was a significant difference between Eryngo and Ibuprofen groups (Table 3).

No serious side effects were reported in all groups. Out of 136 subjects, five of them experienced such minor side effects as gastric reflux, nausea, vomiting, and menorrhagia, and the differences between the three groups were not statistically significant. The follow-up survey included questions about the general attitude of participants toward the drugs.

Having participated in Eryngo, Ibuprofen, and placebo groups, 70.2%, 39.4% and 7.0% of participants were fully satisfied with the treatment, and 89.4%, 84.7%, and 37.2% of participants in each group recommended the treatment to others, respectively ($P = 0.0001$) (Table 4).

Table 3
Comparison of the pain intensity of primary dysmenorrhea based on VMS[a] from the pretreatment cycle to cycle 2 for the three groups.

	Eryngo (n = 48) Mean ± SD	Ibuprofen (n = 46) Mean ± SD	Placebo (n = 43) Mean ± SD	P-value
Pretreatment Cycle	2.2 ± 0.58^{Ba}	2.4 ± 0.85^{Cab}	2.7 ± 0.50^{Bb}	<0.0001
The first menstrual cycle	1.3 ± 0.75^{Ab}	1.7 ± 1.06^{Bc}	2.2 ± 0.70^{Aa}	<0.0001
The second menstrual	1.0 ± 0.78^{Ab}	0.76 ± 0.6^{Ac}	2.23 ± 0.75^{Aa}	<0.0001
P-value	<0.0001	<0.0001	<0.0001	

Similar superscripted lowercase letters in each row indicate no significant difference between drugs at different times in the level of = α 0.05.
The same superscripted capital letters in each column indicate no significant difference between different times in each group in the level of = α 0.05.
[a] Verbal Multidimensional Scoring System.

Table 4
Comparison of post treatment of client satisfaction among participants with primary dysmenorrhea.

	Eryngo (n = 48)	Ibuprofen (n = 46)	Placebo (n = 43)	P-value
Dissatisfied	4 (8.5)	2 (4.3)	34 (79.0)	0.0001
Satisfied	10 (21.3)	30 (65.3)	6 (14.0)	0.0001
Very satisfied	33 (70.2)	14 (30.4)	3 (7.0)	0.0001
Presented to others	42 (89.4)	39 (84.8)	16 (37.2)	0.0001
No presented to others	5 (10.6)	7 (15.2)	27 (62.8)	0.0001

Discussion

This study was the first experimental attempt investigating the effect of Eryngo on menstrual pain among Iranian women. It was also the first trial of a documented Eryngo formula, conducted as rigorously as those for synthetic drugs. The implementation of the study demonstrated its feasibility in Iran (northern Region of Iran), where the consumption of Eryngo, as a mixture in fish and chicken, is usual.

Eryngo may also provide an effective clinical medicine for women with primary dysmenorrhea. Study findings have depicted that women had an average decrease of more than 4 cm in pain after taking 2 cycles of Eryngo, which was a clinically meaningful change in pain intensity.

It is worth mentioning that the peak-pain improved after two cycles of Eryngo and Ibuprofen, and it persisted to the follow-up cycle. We observed a greater decrease in pain intensity after the consumption of Eryngo or Ibuprofen compared with the placebo. The findings of this study are consistent with the results of a similar study by Yeh et al., indicating the therapeutic effects of Four-Agents-Decoction on the pain intensity of dysmenorrhea. In general, treatment with a combination of drugs, containing more than one herb, can have more side effects and lower immunity when compared with those made from only one herb [22]. It appears that Eryngo could be a favorable herbal medicine for women who prefer to take herbal remedies and do not like to take combined oral contraceptive pills or NSAIDS.

Women participating in this study expressed their satisfaction with the Eryngo treatment, and reported that they were interested in taking Eryngo. Further studies are needed to investigate the safety, the efficacy, and the potential side effects of this herb in treatment of primary dysmenorrhea.

According to the results, adverse effects such as gastric symptoms or disturbed menstruation did not increase in the Eryngo group compared with that of the placebo group. Our regimen for this formula appears safe. We collected daily pain score reports using the pain VAS and the pain VMS. Our self-reported VAS pain score was appropriate for evaluating the effectiveness of the intervention. In addition, we used the pelvic ultrasonography to confirm the primary dysmenorrhea, which was an enhanced method to achieve a rigorous clinical trial of herbal medicine.

This study, however, had some limitations on recruitment. The participants were recruited from among high school or university students. The individuals were not selected from among patients in gynecology clinics because very few patients with primary dysmenorrhea refer to these clinics in Iran. Another limitation of the study is that we did not examine the mechanism of Eryngo, and that how it can affect dysmenorrhea. It should be noted that the potential biological function of Eryngo on dysmenorrhea is unknown. In Traditional Iranian Medical textbooks, it is mentioned that Eryngo can work as a digestive tonic and have a carminative effect; therefore, it can be speculated that it could be the result of eryngo effect on the digestive system [19]. NSAIDs can alleviate the pain of menstrual cramps by affecting the prostaglandin levels [22]. But the relationship between Eryngo and prostaglandins level has not been examined exactly yet. Eryngo is typically studied in treating asthma, bronchitis, hypochondriac and epigastric pain as a diuretic, emmenagogue, anti-flatulence and kidney obstruction eliminator, and a nervous system tonic [3,14,17], Reno-protective [13], scavenging activity [18] properties. Although it is beyond the scope of the current study, the pharmacokinetics of Eryngo and its possible effect(s) on prostaglandin inhibition require further investigations.

Conclusions

This study strove to present the beneficial role of Eryngo in alleviating the menstrual pain among women in Iran. However, at pretreatment phase, although we precisely used the randomization process, there was a significant difference in pre-treatment VMS and VAS scores between the groups. There is also “selection bias” in this study, which could be due to the fact that some subjects did not complete the study or may have lost the follow-up phase. Since our patients were familiar with Eryngo flavor, especially in high dosage (therapeutic dosage), it could not be completely masked (only “partially similar flavor”). However, we supposed that this type of bias would be the same for all the three groups. Therefore, patients with severe dysmenorrhea who were assigned to the placebo group may have been more likely to quit the study compared to subjects in other groups. The difference between the three groups at the pretreatment phase could not be important due to the fact that the pain severity was similarly moderate to severe in all the three groups at pretreatment phase. Eligible women had to have moderate or severe dysmenorrhea based on the inclusion criteria, which excluded women with mild dysmenorrhea from the study. Therefore, we analyzed data according to the intention-to-treat (ITT) analysis. The number needed to treat (NNT) was calculated for two stages (completed and remaining subjects). This is an important assessment to understand the true benefits of one intervention over another one (control group). With no intention and with intention, Eryngo had a NNT of 1.5 and 1.7, and Ibuprofen had a NNT of 2 and 2.3 (very good), respectively. This could mean that around approximately 2 patients needed to be treated with the Eryngo or Ibuprofen in order for one to get the benefits (the ideal NNT is one).

Such a clinical trial is needed to be conducted at the international level to reach more tangible results. If an herbal remedy is effective, it will need quality assurance so as to ensure that the product has the expected effects. To prescribe Eryngo as an herbal remedy, Iran Pharmacopeia Convention requires establishing its efficacy by investigating its chemical, pharmacologic, and therapeutic properties through rigorous research studies. In addition, Eryngo needs to be standardized, although the standardization of herbal remedies is difficult.

Conflict of interest

The authors revealed no conflict of interest.

Acknowledgements

The authors acknowledge the assistance of Iranian high school students for their participation in this study as well as the financial support of Babol University of Medical Sciences.

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