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Original Study

Effect of *Achillea Millefolium* on Relief of Primary Dysmenorrhea: A Double-Blind Randomized Clinical Trial

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A B S T R A C T

Introduction: Primary dysmenorrhea occurs in as many as 50% of postmenarche women and is characterized by a particularly intense pain that is localized in the abdominal inferior quadrants and radiates to the inner thigh. This study assessed the effectiveness of *Achillea millefolium* on relief of primary dysmenorrhea.
Materials and Methods: The clinical trial was conducted at Islamic Azad, Toyserkan Branch in western Iran from July 10 to November 18, 2013. It consisted of female students from the university who had primary dysmenorrhea. The subjects were randomly divided into 2 equal groups and were given either placebo or *A millefolium* in teabag form for 3 days in 2 menstruation cycles. They graded the severity of their pain by using a visual analog scale.
Results: The severity of pain in the 2 groups was compared using *t* test. The mean change in pain score in the *A millefolium* group was significantly greater than that in the placebo group at 1 month ($P = .001$) and 2 months ($P < .0001$) after treatment.
Conclusion: A millefolium is effective in minimizing the pain severity in primary dysmenorrhea.
Key Words: Achillea millefolium, Primary dysmenorrhea

Introduction

Menstrual pain that occurs in the absence of visible organic pelvic origin is called primary dysmenorrhea.[1] In general, it begins within 6-12 months after menarche.[2] More than half of all postmenacheal women complain of dysmenorrhea at least once during their lifetime.[1] It is characterized by a particularly intense pain that is localized in the abdominal inferior quadrants and radiates to the inner thigh. This symptom begins many hours before menstruation or contemporaneously at the beginning of the same.[3] There is no clarity about its ethnopathogenesis.[2]

An abnormal increase in the contractible uterine activity is observed in the women with dysmenorrhea. This situation is due to an elevated production of prostaglandins E2 and F2α in the uterus.[2]

Evidence of efficacy supports the use of pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) or oral contraceptives to alleviate menstrual pain. However, pain relief may be inadequate for some women, or side effects may not be well tolerated.[4] Complementary and alternative medicine treatments for dysmenorrhea that have been studied include transcutaneous electrical nerve stimulation, acupuncture, acupressure, spinal manipulation, behavioral interventions, and herbal and dietary therapies.[5] *Achillea millefolium* is an herbal drug that has traditionally been used for the relief of menstrual pain in Iran.[6]

A millefolium is a member of the Asteraceae family and has been used in folk medicine for hundreds of years in many countries ranging from Europe to Asia.[7] Inhibition of both $CaCl_2$-induced contractions may indicate that the spasmolytic compound included in the ethanol extract is not a specific receptor antagonist. Furthermore, because we deal directly with the total extract, there may be > 1 spasmolytic compound involved. It is well known that some flavonoids can act as spasmolytic agents by relaxing smooth muscles in various parts of the mammalian body.[8]

A millefolium has been traditionally used to treat inflammatory and spasmodic disorders.[9]

It is used in hemorrhoids, headaches, bleeding disorders, diabetes mellitus, influenza, eczema, and menstrual disorders.[10] This herb is available in shops in Iran.

Studies in this field are limited; only 1 study in Iran showed that the use of *A millefolium* decreased the pain and bleeding duration of menstruation,[6] and there is no published report on the effect of *A millefolium* on relief of primary dysmenorrhea. Therefore, the aim of this study was to determine the effect of *A millefolium* on relief of primary dysmenorrhea.

Patients and Methods

This double-blind randomized clinical trial was conducted from July 10 to November 18, 2013, with female students from Islamic Azad University, Toyserkan Branch in the west of Iran. After approval from the Research Ethics Committee of Islamic Azad University, written informed

The authors indicate no conflicts of interest.

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consent was received from all students. Inclusion criteria for all students were as follows: 19 to 23 years of age; single; a history of regular menstrual cycles for the previous 3 months ranging from 25 to 30 days; no ongoing hormonal treatment; no use of other medication that alleviates menstrual pain, pain score >3 on the visual analog scale (VAS); and no clinical history of major psychological problems. Ultrasound was performed to rule out secondary dysmenorrhea. In this study, pain score <3 indicated mild dysmenorrhea, 4-6 indicated moderate dysmenorrhea, and >6 indicated severe dysmenorrhea. Cases of mild dysmenorrhea were excluded.

According to calculations performed to find differences ~30% in pain scores and pain reduction according to 95% power scale and significance level of .05, the sample size of 92 subjects in this study was justified. Anticipating a 5% loss to follow-up, we increased the sample size to a maximum of 96, or 48 students in each group.

The eligible students were randomly assigned to 2 groups using the balance block randomization method. For this work, we prepared 4 sheets of paper, writing on 2 sheets "A" for "*A millefolium*" and on 2 sheets "P" for "placebo." The sheets were pooled, placed in a container, and randomly drawn 1 at a time for each patient without replacement until all 4 sheets were drawn. The 4 sheets were then placed back into the container, and this action was repeated until the sample size was reached. The allocations remained concealed during the study. For this purpose, the random allocation was conducted and labeled by a pharmacologist, so that neither the students nor the distributer, who elevated the effect of the interventions, were aware of the administered drugs, until the data were analyzed and the labels were decoded.

The flower heads of *A millefolium* were selected, completely dried in the shade, and turned into fine powder. Teabags were prepared with 4 g of *A millefolium* powder.[11] These stages were done by a pharmacologist. Tea was prepared by pouring boiling water onto the teabag containing *A millefolium* powder; the teabags were seeped for 10 minutes, and then the tea was used. Participants in the experimental group were taught how to use teabags and were asked to drink tea from first menstrual period day to the third menstrual day, for a total of 2 cycles. The participants drank 3 teacups of *A millefolium* in morning, noon, and night with each meal (a teabag in 300 mL of hot water per teacup) for 3 days every month.

Participants in the placebo group received teabags of placebo (starch) made according to the *A millefolium* method. The teabags of *A millefolium* and placebo were packed in similar packages and given to a person (B.F.) for distribution who had no information about the package contents, so neither this person nor the students were aware of the package contents.

A VAS was used to quantify the changes in severity of dysmenorrhea.

The subjects were asked on their first visit to grade the severity of their dysmenorrhea by marking an asterisk corresponding to their perceived state on a 10-cm vertical line, ranging from 0 ("no pain") to 10 ("pain as bad as it can be"). To obtain an objective measurement, the VAS

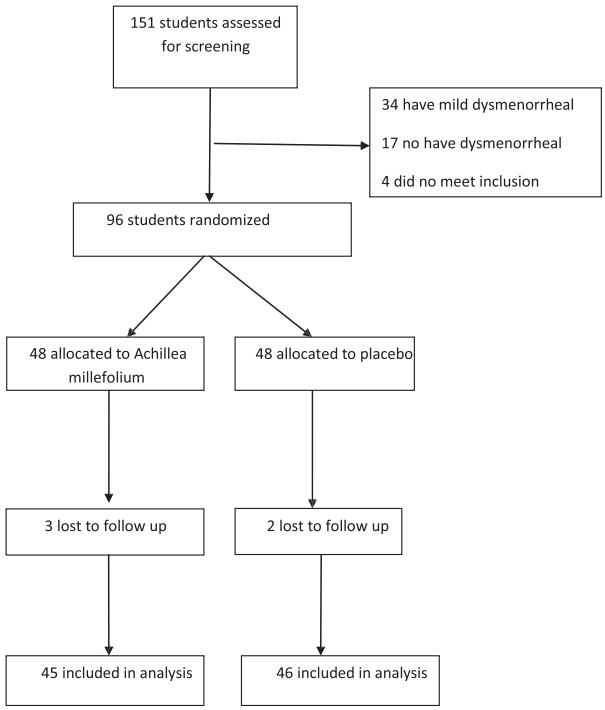

Fig. 1. Flowchart of progress through the trial.

markings were measured in centimeters on the first, second, and third days of each cycle in 2 groups. The mean pain scores for each subject were then calculated.

The severity of pain in the 2 groups was compared using *t* test. All hypothesis tests were 2-sided, and *P*-values <.05 were considered statistically significant. SPSS Version 16.0 was used for statistical analyses.

Results

Of 96 students identified, 3 students in the *A millefolium* group and 2 students in the placebo group did not return for follow-up and were excluded from the study. The analysis was based on data from the remaining 91 students, including 45 in the *A millefolium* group and 46 students in the placebo group (Fig. 1).

The mean age of menarche was 13.61 ± 3.5 years (range 10-15 years), the mean duration of menstruation was 5.92 ± 1.82 days, and the mean age of students was 21.51 ± 5.53 years (range 19-23 years). Differences in baseline characteristics of the 2 groups were not statistically significant (Table 1).

Table 2 shows the severity of pain in the 2 groups as compared using *t* test. The mean change in pain score (baseline minus average post-therapy pain score) in the *A*

Table 1
Characteristics of Participants by Treatment Group

Characteristics	Placebo group (n = 46, mean ± SD)	*Achillea millefolium* group (n = 46, mean ± SD)
Age (yr)	20.37 ± 6.0	21.66 ± 5.77
Menarche age (yr)	14.37 ± 2.91	13.09 ± 1.88
Body mass index (kg/m^2)	21.87 ± 1.70	21.53 ± 1.22

Table 2
Change in Pain Scores by Treatment Group

Characteristics	Before of use (Mean ± SD)	0 to 1 mouths* (Mean ± SD)	0 to 2 mouths* (Mean ± SD)
Type of treatment			
Achillea millefolium (n = 45)	7.40 ± 1.84	1.17 ± 1.04	1.87 ± 1.32
Placebo (n = 46)	7.78 ± 1.88	0.52 ± 0.62	0.75 ± 0.87
P value	.1	.001	<.0001
Intent-to-treat analysis			
A millefolium (n = 48)	8.25 ± 1.73	1.02 ± 0.84	1.59 ± 1.81
Placebo (n = 48)	7.91 ± 1.47	0.22 ± 0.59	0.41 ± 0.79
*t-test *P* value	.25	.001	<.0001

* Baseline minus post therapy.

millefolium group was significantly greater than that in the placebo group at 1 month ($P = .001$) and 2 months ($P < .0001$) after treatment. Table 2 presents data for before and 1 and 2 months after intervention in the 2 groups, placebo and *A millefolium*. No students in this trial had any side effects after *A millefolium* use.

Discussion

This study was a randomized double-blind controlled trial conducted to compare the efficacy of *A millefolium* and placebo for the relief of primary dysmenorrhea. The results of this randomized trial showed that *A millefolium* may be an effective nonpharmacological alternative for students with primary dysmenorrhea, with evidence of symptom improvement 1 and 2 months after beginning the treatment. This plant is a widely available species that is used in Iranian folk medicine to treat diverse diseases including inflammation, pain of menstruation, and gastrointestinal disturbances.

In Iran, only 1 relevant study was performed, and it showed that the use of *A millefolium* was effective in decreasing pain and bleeding duration of menstruation,[6] but there is no study on the effect of *A millefolium* for the relief of primary dysmenorrhea.

Results obtained by Karamenderes et al[11] support the idea that total extract of *Achillea nobilis* subsp. *sipylea* exhibits antispasmodic activity on rat duodenum, probably by inhibiting calcium influx. Further, the hypotensive effect of the crude extract and fractions could be associated with high levels of artemetin, a methoxylated flavonoid previously identified in *A millefolium*.[8]

A study was performed in 2012 at 2 preuniversity centers in Iran to compare the effects of *Valeriana officinalis* and mefenamic acid on primary dysmenorrhea.[12] Students were randomly grouped into 2 groups, each enrolling 54 students. Participants in study group of *V officinalis* were given capsules of 250 mg every 8 hours in the first 3 days of menstruation for a 2-month period, and students in the mefenamic acid group were given capsules of 250 mg in similar way as the study group. Data were gathered via questionnaire in 3 groups (ie, data before any clinical intervention and 1 and 2 months after clinical intervention). The mean pain score for the *V officinalis* group decreased from 7.08 ± 1.01 to 3.68 ± 1.32, and that in the mefenamic acid group decreased from 7.68 ± 1.21 to 3.06 ± 1.67. There was no statistically significant difference between the 2 groups, and both *V officinalis* and mefenamic acid were found to be effective for primary dysmenorrhea.

Iranians prefer to use traditional methods rather than more modern methods to treat gynecological disorders. This study showed that *A millefolium* is effective in relieving the severity of pain. Therefore, this herb can be an alternative of NSAIDs. Most NSAIDs in long-term therapy show severe adverse effects.[1] Health care providers should consider *A millefolium* to be an effective treatment for women with primary dysmenorrhea.

The main limitation of the present study was the small sample size of the study groups. If the sample size were large enough, the difference between the trial groups could be indicated more clearly with less possibility of random error. Also, our study was conducted in single adolescents and may not be generalized to females outside that age range.

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