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Comparison of the Effects of *Crocus Sativus* and Mefenamic Acid on Primary Dysmenorrhea

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ABSTRACT

Background: In previous studies, extract of 3 herbs, celery, fenugreek and saffron was effective on primary dysmenorrhea. However, the health effects of saffron alone on primary dysmenorrhea have not been yet studied. The aim of this double blind, single center clinical trial is to examine the effects of saffron on primary dysmenorrhea pain in women aged 18-27 years old.

Methods: One hundred eighty patients were randomly divided into three groups. Group 1 received saffron capsules three times per day for three days of menstrual period for three consecutive menstrual cycles. Group 2 received mefenamic acid, and group 3 has received identical placebo. Visual Analogue Scale (VAS) has been recorded at baseline and after each menstrual period.

Results: In saffron group VAS was reduced from 6.8 to 3.6, 3.4, and 3 in 3 consecutive months. This effect was significantly greater than mefenamic acid and placebo (P:0.0001).

Conclusions: It was found that the effect of saffron in reducing pain is more than mefenamic acid and far more than placebo.

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Introduction

Primary dysmenorrhea or menstrual pain is a pain occurring one to two days before the menstruation in the absence of pathologic pelvic disorder. It might last for two to three days (1). 50-70% of women are reported to develop the primary dysmenorrhea (1,2). It usually begins before the age of 20 and almost always begins 6-12 months after the first menstruation cycle. If the pain begins 3 years after the first menstrual period (menarche), or dysmenorrhea occurs with periods without ovulation, secondary reasons must be sought (2).

Dysmenorrhea is a common gynecological disorder affecting approximately 50% of women with regular menstrual cycles (3,4). Over 10% of women have severe symptoms requiring rest. They are also incapacitated in daily activities, so that they are not able to manage the daily activities in each menstrual cycle for one to three days due to severe uterine cramps (5,6). Dysmenorrhea is the most common gynecological complaint among adolescents and young women (7).

Studies showed that 45% of women had medium-to-severe dysmenorrhea. In the United States, almost 60% of adults reported dysmenorrhea during menstruation

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and 14% regularly skipped school. Menstrual problems, including dysmenorrhea are more common among smokers (8,9).

Various methods have been proposed to treat the primary dysmenorrhea including non-steroidal anti-inflammatory drugs, birth control pills or supportive therapies such as acupuncture. Although chemical drugs are widely used in the treatment of primary dysmenorrhea, none has been specifically used for this purpose (1). The use of herbal medicines has recently been on the rise used for treating primary dysmenorrhea due to concerns about chemical drugs (1,2).

Women with primary dysmenorrhea traditionally used herbs to alleviate their symptoms. They used medicinal herbs regardless of proper time and dose (1). The study by Khoda Karami et al., (1) compared the effect of SCA (Saffron, Celery seeds and Anise) and mefenamic acid on primary dysmenorrhea. They randomly assigned 180 women aged 18-27 into three similar groups. The first group received mefenamic acid and the second group received SCA and the last group placebo. The results showed that pain and bleeding reduction were greater among the patients receiving SCA than mefenamic acid or placebo.

According to the studies, saffron with the scientific name of Crocus Sativus has been used in folk medicine due to regulatory and pain-killing properties for treating dysmenorrhea (10). It is made up of Crocin glycoside, Crostin, Picrocrocin, and essential oil (11). The studies on the effect of Saffron, Celery and Fenugreek show positive effects on treating primary dysmenorrhea (12). However, no studies have been carried out on saffron alone in the treatment of primary dysmenorrhea. Therefore, we studied the effectiveness of saffron in primary dysmenorrhea.

Patients and methods

This study is a randomized double-blind clinical trial, which was approved by the Ethics Committee of the Pharmaceutical Sciences Branch, Islamic Azad University, Tehran-Iran (IAUPS) (Code: R.IAU.PS.REC.1395.8), and submitted in the Iranian Registry of Clinical Trials (Registration Code: IRCT2016081329327N1). All participants were given written consent form.

The population consisted of 180 female students of Islamic Azad University, Pharmaceutical Sciences Branch, diagnosed with primary dysmenorrhea. Diagnosis was made based on current guidelines by an OB-GYN specialist (13). In order to demonstrate a significant difference between saffron and placebo groups using VAS, the estimated sample size was calculated to be 51 patients per group. A study with such a sample size would have a power of 95% at a 0.05 significance level. The sample size was rounded up to 60 per group. Pain severity was assessed by patient reported Visual Analogue Scale (VAS) at baseline, and after three days of treatment for three menstrual cycles. Saharkhiz Saffron ® (Tehran, Iran) was used in this study and validated by a botanist and then analyzed by HPLC with UV detector at three wavelengths (250 nm, 308 nm, and 440 nm). It contained 30±0.07 mg Crocin, 13.2±0.05 mg Picrocrocin, and 0.1±0.01 mg Safranal in each 100 mg Saffron powder.

The participants were randomly assigned in to three groups (60 patients in each group), randomization was done using an online random sequence generator (available at www.random.org). Group I received Mefenamic acid 250 mg capsules. Group II received Saffron 30 mg capsules and group III received Placebo capsules. Mefenamic acid, placebo and empty capsules were purchased from Amin Pharmaceutical Company (Isfahan, Iran). Empty capsules were filled by Saffron using a manual capsule filling machine, microcrystalline cellulose was used as excipient. All groups received their treatment in identical containers which was coded according to each group by an independent person. The researchers and patients were blinded about the groups.

In this study, patients received 3 capsules per day for three days during three consecutive menstrual cycles, according to each group protocol. Statistical analysis was done using a repeated measure ANOVA test by SPSS software.

Results

One hundred eighty patients aged 18-27 years were enrolled. The mean age of the participants was 22.4 years in placebo group, 22.5 years in mefenamic acid group, and 22.7 years in Saffron group (P: 0.87).

In this study, three patients (1.7%) were excluded due to non-adherence (2 in placebo group, 1 in mefenamic acid group), 4 (2.2%) left the study due to the need for concomitant pain killers (3 in placebo group, 1 in mefenamic acid group), and one patient (0.6%) left the study due to sensitivity to saffron (mild pruritus and red skin, which was resolved after saffron was discontinued without any treatment). No other complications were reported.

Figure 1 shows VAS at the first of the study and after each treatment in 3 consecutive menstrual cycles. VAS was 6.9 in placebo group, 7 in mefenamic acid group, and 6.8 in Saffron group (P:0.9) After each treatment, mean VAS was 5.9, 5.9, 5.8 in placebo group; 4.6, 4.4, and 3.9 in mefenamic acid group; and 3.6, 3.4, and 3 in Saffron group, respectively (P:0.0001).

Discussion

In this study Saffron significantly reduced dysmenorrhea pain. Several studies have been conducted to examine the effect of herbal medicines on treating dysmenorrhea. In the study by Mirabi et al., (14) a total of 50 unmarried women with primary dysmenorrhea (age, 18–25 years) received *Hypericum Perforatum* herbal tea three times a day for

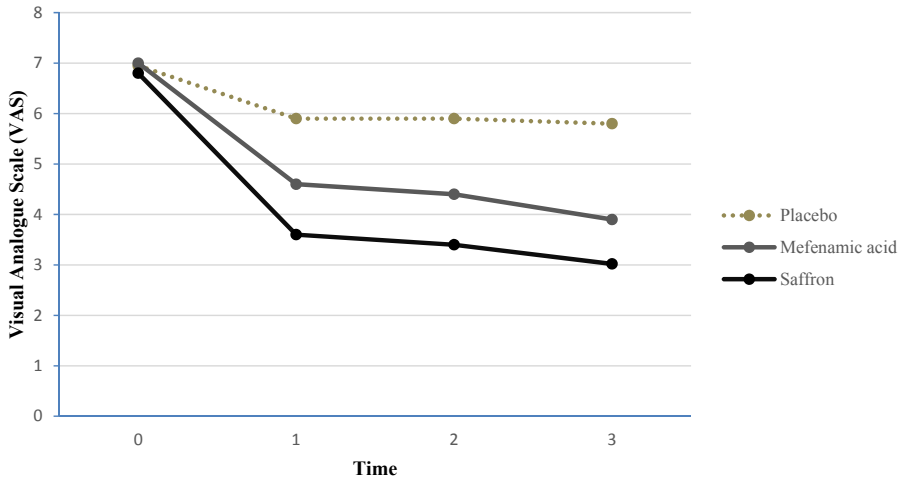

Figure 1. Visual Analogue Scale (VAS) at the first of the study and after each treatment. Baseline VAS was 6.9 in Placebo group, 7 in Mefenamic acid group, and 6.8 in Saffron group (P:0.9) After each treatment, mean VAS was 5.9, 5.9, 5.8 in Placebo group; 4.6, 4.4, and 3.9 in Mefenamic acid group; and 3.6, 3.4, and 3 in Saffron group, respectively (P:0.0001).

three days during two subsequent menstrual periods. The severity and duration of pain were significantly reduced after medication. The total multidimensional verbal scale scores for systemic manifestations associated with dysmenorrhea did not show significant difference between groups.

The study by Simber et al., (15) examined the effect of PAC (Anise, Celery and Saffron) and mefenamic acid on postpartum pain. A total of 108 women aged 28.5±5.5 were randomly assigned into two groups after delivery. One group received 500 mg PAC capsule (60.1 mg Anise, 16.1 mg Celery, 4.1 mg Saffron, and 419.7 mg Lactose) and the other group received 250 mg mefenamic acid capsule. The results showed that PAC was more effective than mefenamic acid. The authors concluded that this finding may be due to the relaxant and anti-spasmodic effects of the PAC on the smooth muscle cells.

In a study of Khoda Karami and colleague (1) effects of SCA (Saffron, Celery seeds and Anise) and mefenamic acid on primary dysmenorrhea was compared. The results showed that pain and bleeding reduction were greater with SCA than mefenamic acid and placebo. All of these effects can be attributed to the reduction of prostaglandin synthesis by SCA acting as an antispasmodic and anti-prostaglandin. This study used a three herb combination to treat dysmenorrhea pain, but in our study, we used only saffron (one of three aforementioned ingredients) to evaluate its effect as a sole component.

According to the study by Hosseinzadeh et al., (16) saffron have anti-inflammatory, antispasmodic and emmenagogue effects. Although the exact mechanism is yet to know. Due to these effects and according to our findings saffron can be used as an effective dysmenorrhea treatment. Further studies are needed to investigate which saffron constituent is more effective for dysmenorrhea pain.

In conclusion, saffron capsules showed a significant effect on alleviating dysmenorrhea pain. Whether this effect could be seen beyond three cycles is yet to know, thus lengthier trials are needed.

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