



Effectiveness of Treatment with Chamomile on Menstrual Function, Dysmenorrhea and Premenstrual Syndrome in Patients with Polycystic Ovary Syndrome

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Article Type	ABSTRACT
Research Paper	Background and Objective: Polycystic ovary syndrome is one of the most common endocrine disorders, whose symptoms usually begin immediately after the first menstrual period. Previous studies found a significant relationship between dysmenorrhea, premenstrual syndrome and polycystic ovary syndrome. The aim of this study is to investigate the effect of chamomile on dysmenorrhea and premenstrual syndrome in patients with polycystic ovary syndrome. Methods: This clinical trial was conducted on 70 patients diagnosed with polycystic ovary syndrome based on Rotterdam criteria referring to a clinic in Mashhad. Patients were randomly assigned to two groups. The first group received two 500 mg chamomile capsules per day and the second group received two placebo capsules per day for three months. The response to treatment in premenstrual syndrome, dysmenorrhea and oligomenorrhea was evaluated using the Visual Analogue Scale and DSM-IV premenstrual syndrome diagnosis questionnaire. Findings: The mean age of the patients in the intervention group was 25.43 ± 5.58 and in the placebo group was 28.06 ± 5.71 years. The rate of improvement in women with premenstrual syndrome (16.6%), dysmenorrhea (50%) and oligomenorrhea (26.7%) was higher in chamomile group compared to placebo. There was no statistically significant difference in body mass index between the chamomile group (25.17 ± 4.95) and the control group (25.57 ± 6.7). Conclusion: Based on the results of this study, chamomile improved the symptoms of oligomenorrhea in patients with polycystic ovary syndrome and showed positive effects on dysmenorrhea and premenstrual syndrome. Therefore, chamomile can be used as a simple, low-cost therapy in the treatment of polycystic ovary syndrome patients. Keywords: Chamomile, Dysmenorrhea, Premenstrual Syndrome, Polycystic Ovary Syndrome, Testosterone, Oligomenorrhea.

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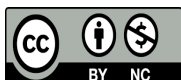
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Introduction

Polycystic ovary syndrome is the most common endocrine disorder (1) and the most common cause of infertility due to lack of ovulation in women, and about 2 to 26% of women suffer from it (2). Rotterdam diagnostic criteria for polycystic ovary syndrome include: menstrual cycle disorders (amenorrhea, oligomenorrhea), clinical or biochemical hyperandrogenism, or ultrasound symptoms of polycystic ovary, after ruling out other diseases. Other diseases that cause a phenotype similar to polycystic ovary syndrome include: congenital adrenal hyperplasia, adrenal and ovarian neoplasm, Cushing's syndrome, hypo or hypergonadotropic disorders, hyperprolactinemia and thyroid disease. The ultrasound criterion for diagnosing polycystic ovary syndrome is the presence of 12 or more follicles with a diameter of 2-9 mm or an increase in ovarian volume (10 ml or more) even in one ovary (3, 4). The occurrence of polycystic ovary syndrome is the result of genetic (5) as well as environmental or multi-causal factors (6). Polycystic ovary syndrome symptoms often begin immediately after the first menstrual period (7). Due to the considerable prevalence of menstrual cycle disorders, different methods have been proposed to regulate the menstrual cycle including: taking birth control pills, metformin, progestins, and weight loss, each of which has side effects. For example, metformin has side effects such as digestive disorders and lactic acidosis. On the other hand, it is preferably not used in patients with underlying liver and kidney disorders or congestive heart failure. These cases reduced the acceptance of the use of these medicines (8).

Treatments for hyperandrogenism and polycystic ovary syndrome include: weight loss, birth control pills, medroxyprogesterone acetate, gonadotropin-releasing hormone agonists, glucocorticoids, ketoconazole, spironolactone, cyproterone acetate, flutamide, cimetidine, finasteride, and insulin sensitizers (9). Chamomile with the scientific name *Matricaria chamomilla* has anti-inflammatory properties (10). Among other properties of chamomile, we can mention anti-diabetic properties and regulation of menstruation (11). Chamomile flowers contain the essential oil of Anthemine (12), tannin, phytosterol, and also a bitter substance called Anthemique Acid (13). The findings of a systematic review reported a significant relationship between the level of anxiety and depression and polycystic ovary syndrome (14). A study showed a significant relationship between dysmenorrhea and polycystic ovary syndrome and suggested that dysmenorrhea should be managed and treated in these patients (15).

Various herbal treatments were shown to be effective on dysmenorrhea (16). The studies carried out on chamomile show that chamomile is effective in relieving menstrual pain (17, 18). The findings of a systematic review showed that chamomile can be used as a suitable herbal medicine for the treatment of women with PMS (19). Based on literature review, no study has yet addressed the effectiveness of chamomile on dysmenorrhea and premenstrual syndrome in women with polycystic ovary syndrome. Considering the high prevalence of dysmenorrhea and premenstrual syndrome and the relationship between dysmenorrhea and polycystic ovary syndrome and the side effects of chemical drugs, and the general interest in using herbal medicines, the present study was conducted to investigate the effect of chamomile on menstrual function, dysmenorrhea, and premenstrual syndrome. Menstruation in women with polycystic ovary syndrome has been discussed to take a step towards improving the quality of life in patients with polycystic ovary syndrome.

Methods

After approval by the Ethics Committee of Mashhad University of Medical Sciences with the code IR.MUMS.fm.REC.1396.444 and registration in the Clinical Trial Registration Center with the code IRCT20170315033085N3, this randomized clinical trial was conducted on 70 patients with polycystic ovary

syndrome. Considering that no study has been conducted investigating the effect of chamomile on polycystic ovary syndrome, the sample size was determined as 31 people in each group considering the initial assumption that chamomile has a 20% effect in the intervention group compared to the control group, and considering $\alpha=0.05$ and $\beta=0.2$ using PASS software. Considering the drop-out of about 10% of the samples, 35 people were considered for each group. The diagnosis of polycystic ovary syndrome in this study was based on the Rotterdam criteria. According to this criterion, it is necessary to have at least two of the three criteria (Rotterdam criteria): 1. Low ovulation or no ovulation (in the form of oligomenorrhea and amenorrhea). 2. In vitro hyperandrogenemia (increased level of circulating androgens) and clinical hyperandrogenemia (hirsutism, obesity). 3. Following the detection of polycystic ovaries in ultrasound, the diagnosis of PCOS was confirmed after ruling out secondary causes of hyperandrogenism, including hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and androgen-secreting ovarian tumors (20).

Patients with polycystic ovary syndrome according to the Rotterdam criteria, history of normal puberty, thyroid test in the normal range (0.5-5), suffering from dysmenorrhea, and age range of 18 to 35 years were included in the study. In case of using sex steroids at the moment or in the last two months (such as birth control pills, hormone therapy, androgenic drugs), using chemical or herbal drugs, using cigarettes or hookah, having a recent history of surgical treatment for polycystic ovary syndrome and treatment for polycystic ovary syndrome, patients were excluded from the study.

After introducing himself/herself to the participants, the researcher explained the objectives of the research and its steps. Then the participants entered the study voluntarily. The researcher considered compliance with ethical issues as well as the confidentiality of information according to Declaration of Helsinki. The subjects could withdraw from the study if they were not willing to continue. First, written consent was completed by all participants in the study. Then, questionnaire number one including demographic variables was completed for the participants. On the 3rd to 5th day of menstruation, patients with amenorrhea were asked to refer to the clinic of Imam Reza Hospital (after daily administration of 10 mg/dL of progesterone for 7 days) for transvaginal ultrasound. Patients referred to women's clinics of teaching hospitals with ultrasound and biochemical test results. If polycystic ovary syndrome was confirmed, dysmenorrhea severity questionnaire and premenstrual syndrome temporary diagnosis questionnaire were provided to the participants before and after the intervention.

The severity of dysmenorrhea was assessed using the Visual Analogue Scale (VAS), which is an accurate tool to evaluate the intensity of menstrual pain. This tool is like a 10 cm ruler, where number 0 indicates that there is no pain and number 10 is considered severe pain (21). People with dysmenorrhea severity greater than 4 were included in the study.

Premenstrual syndrome diagnosis questionnaire, which is based on Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), includes 11 options and if at least 5 of the 11 symptoms are present, a person is diagnosed with premenstrual syndrome. The reliability and validity of the questionnaire was measured and confirmed in a previous study, and its reliability was reported as 0.82 using Cronbach's alpha (22). Height was measured standing without shoes with a measuring tape mounted on the wall with an accuracy of 0.5 cm. Weight was measured with a scale (Seka, Germany), without shoes and with light clothes, with an accuracy of 0.1 kg. Body mass index was obtained by dividing weight (in kilograms) by height (in meters squared).

Chamomile capsule is available in the pharmaceutical market of Iran, which is prepared from the hydroalcoholic extract of the *Matricaria chamomilla*. Each capsule contains 500 mg of standardized chamomile extract based on 1.2% Apigenin. The placebo tablet was made by Faculty of pharmacy in Mashhad. Medicines were placed in envelopes and numbered by a person unrelated to the research.

Chamomile tablets (product of Gol Darou Company) and placebo, which were completely similar in appearance, were placed in two envelopes A and B. The organizers of the plan and the patients were unaware of the contents of the envelope. Therefore, it can be said that the study was conducted in a double-blind manner. The control group received a similar capsule (same color, same shape and same size) as the capsule of the intervention group, which contained starch. Then the patients were randomly assigned into intervention and control groups by a random allocation list that was prepared using an application. The medicines were given to the patients by the researcher's helper based on the checklist. The first group of 35 people received 2 capsules containing 500 mg chamomile per day for 3 months, and the second group of 35 people received 2 placebo capsules per day for 3 months. For controlling medicine consumption, it was ensured that they took the medicines and completed the questionnaire through face-to-face visits or phone calls at the end of each month. People's questions were answered and the questionnaires were completed before the intervention and at the end of the intervention.

The recorded data were analyzed by SPSS 23. The characteristics of the studied people were presented by descriptive statistical methods, including central indices, dispersion and frequency distribution in the form of tables. To compare the quantitative variables between the two groups, if the data were normally distributed, the independent t-test was used; otherwise, the Mann-Whitney test was used. To compare qualitative variables between two groups, chi-square test and Fisher's exact test were used, and $p < 0.05$ was considered significant.

Results

Seventy people were initially included in the study. In the chamomile group, 2 people were excluded from the study due to gastrointestinal complications and 3 people were excluded from the study due to incomplete use of medicine. In the placebo group, 5 people were excluded from the study due to incomplete drug use. The mean age of the patients in the intervention group was 25.43 ± 5.58 and in the placebo group was 28.06 ± 5.71 . Body mass index before treatment was 25.28 ± 4.98 in the intervention group and 25.58 ± 5.98 in the placebo group. Mean age, body mass index, marital status, history of pregnancy and history of infertility in two groups did not show significant difference before treatment (Table 1).

Table 1. Comparison of demographic and fertility characteristics in placebo and intervention groups

Variable	Placebo group Number(%)	Intervention group Number(%)	p-value
Marital status			
Married	15(50)	18(60)	0.436
Single	15(50)	12(40)	
Pregnancy history			
Yes	7(46.7)	8(44.4)	0.898
No	23(53.3)	22(55.6)	
History of infertility			
Yes	2(13.3)	3(16.7)	>0.99
No	28(86.7)	27(83.3)	

After treatment, the number of people with dysmenorrhea, premenstrual syndrome, and oligomenorrhea did not show a statistically significant difference between the intervention and placebo groups. Although the rate of recovery in women with premenstrual syndrome (16.6%), dysmenorrhea (50%) and oligomenorrhea (26.7%) was higher in the chamomile group compared to the placebo, no statistically significant difference could be found between the chamomile and placebo groups regarding the mentioned parameters. In chamomile group, the number of people suffering from premenstrual syndrome (46.6%), dysmenorrhea (50%), oligomenorrhea (30%) was significantly reduced ($p < 0.05$). In the comparison of body mass index before (25.28 ± 4.98) and after treatment (25.17 ± 4.95), no significant difference was observed. Furthermore, no statistically significant difference was observed between the two groups. Testosterone showed a statistically significant decrease in both placebo ($p = 0.005$) and chamomile ($p = 0.001$) groups. The comparison between the two groups was not statistically significant (Table 2).

Table 2. Comparison of clinical symptoms before and after treatment in placebo and intervention groups

Characteristics	Placebo group (n=30)	Intervention group (n=30)	p-value
Premenstrual syndrome [Number(%)]			
Before treatment	17(56.7)	22(73.3)	0.176
After treatment	8(26.7)	8(26.7)	>0.99
Intragroup p-value	0.004	<0.001	
Dysmenorrhea [Number(%)]			
Before treatment	9(30)	23(76.7)	<0.001
After treatment	9(30)	8(26.7)	0.7
Intragroup p-value	>0.99	<0.001	
Testosterone (95% CI)			
Before treatment	17(20-64)	30 (58-110.85)	0.346
After treatment	8.5(20.62)	16.5 (25-57.9)	0.894
Intragroup p-value	0.005	0.001	
Body mass index (Mean$\pm$SD)			
Before treatment	25.58 $\pm$ 5.98	25.28 $\pm$ 4.98	0.831
After treatment	25.58 $\pm$ 6.7	25.17 $\pm$ 4.95	0.777
Intragroup p-value	0.89	0.24	
Oligomenorrhea for more than 35 days [Number(%)]			
Before treatment	18(60)	19(63.3)	0.07
After treatment	17(56.7)	10(33.3)	0.069
Intragroup p-value	0.99	0.049	

Discussion

In the present study, clinical symptoms such as premenstrual syndrome, dysmenorrhea and oligomenorrhea and chemical parameters of testosterone decreased significantly after treatment in the chamomile group. However, no statistically significant difference was observed in any of these chemical and clinical parameters between the two groups.

The results of a study by Heidary et al., who investigated the effect of chamomile on women with polycystic ovary syndrome, showed that the level of testosterone decreased significantly in the treatment group (23). In the present study, testosterone also showed a statistically significant decrease. A study among Korean women showed that the morphology of polycystic ovary syndrome as one of the criteria of this syndrome plays a key role in causing menstrual pain. Furthermore, this study suggests that patients with polycystic ovary syndrome should be under active monitoring for rapid management of dysmenorrhea (16). In a cross-over clinical trial, Modarres et al. compared the effect of chamomile with Mefenamic acid on 80 students with dysmenorrhea. The intensity of menstrual pain in chamomile group was significantly reduced after two cycles of treatment. However, this reduction was more significant in the chamomile group compared to Mefenamic acid (24). In another study by Karimian et al., consumption of 250 mg of chamomile every 8 hours for 2 cycles significantly reduced the severity of primary dysmenorrhea compared to pre-treatment stage. However, no significant statistical difference was observed between Mefenamic acid and chamomile. That is, both medicines had reduced the pain to the same extent. The control group in both above studies was Mefenamic acid (18). The present study is consistent with the previous two studies. In line with the present study, in a study by Jenabi et al., the effect of consuming two cups of chamomile tea every day for a week before menstruation and the first 5 days of menstruation was investigated for three cycles. After one month of tea consumption, pain, anxiety and emotions in the chamomile group was significantly reduced compared to the control group (25).

In a study by Samadi et al., the use of a mixture of fennel, chamomile and ginger among 90 students with dysmenorrhea showed that there was a significant relationship between the improvement of symptoms and pain intensity before and after consumption of this mixture (26). The present study is in line with the study of Samadi et al. The results of a study by Najafi Mollabashi et al. showed that chamomile was more effective than placebo in relieving the symptoms of premenstrual syndrome (27).

The mechanism of action of chamomile in reducing dysmenorrhea in the present study can be attributed to the anti-inflammatory effects of chamomile, whose anti-inflammatory effects are mostly due to the compounds matricin (alkaloid) and bisabolol (alkaloid) and its oxides (10). Chamomile extract leads to the interruption of cyclooxygenase, thus stopping the production of prostaglandins and leukotrienes (28). In addition, chamomile has antispasmodic effects, which is attributed to the apigenin (active plant substance) present in it (29). In fact, chamomile is used as an antispasmodic and anti-inflammatory agent. Its antispasmodic property can control menstrual cramps and also reduce the possibility of premature birth.

One of the limitations of this study is that it was not possible for the researchers to evaluate the research units with transvaginal ultrasound, laparoscopy or hysteroscopy, smear and pelvic examination (due to the singleness of the research units) to rule out secondary dysmenorrhea. The findings of the study relied on the reporting of samples, which was beyond the control of the researchers. From the physiological point of view, since the pain tolerance threshold is different in different people, the feeling of symptoms associated with primary dysmenorrhea is different in different people, and thus the reaction and feeling of reduction of symptoms after using drugs will also be different (30). Genetic differences and differences in diet are factors affecting dysmenorrhea, which were beyond the control of the present study. It is also suggested to study on a larger sample size.

Based on the results of this study, chamomile improved the symptoms of oligomenorrhea in patients with polycystic ovary syndrome and showed positive effects on dysmenorrhea and premenstrual syndrome. Therefore, chamomile can be used as a simple, low-cost measure in the treatment of patients with polycystic ovary syndrome.

Conflict of interest: The authors declare that there is no conflict of interest.

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