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Herbal Treatment of Oligomenorrhea with *Sesamum indicum* L.: A Randomized Controlled Trial

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Abstract

Background: Oligomenorrhea (defined as infrequent menstrual flow at intervals of 36 days to 6 months or 5–7 cycles in a year) is mostly managed with hormone therapy; however, there is an increasing demand for alternative medicine treatments in this field. This study is designed to evaluate the efficacy of Sesamum indicum L. in inducing menstrual bleeding in women with oligomenorrhea. **Materials and Methods:** A single-blind clinical trial was performed on 56 cases of oligomenorrhea, admitted to Beheshti hospital clinic. Patients randomly received treatment for a week either in the sesame or progesterone group and then were followed for 8 weeks. Menstrual bleeding occurrence, waiting period, volume of blood flow, severity of pain, uterus temperament, menstruation in the next episode and side effects were assessed by interview. **Results:** Twenty-seven patients (mean age 29.42 ± 8.99 years) and 29 patients (mean age 26.63±5.63 years) were enrolled in the sesame and progesterone groups, respectively. Seventy and two percent and 93.10% of the patients in the sesame and progesterone groups experienced menstrual bleeding (P=0.012) on an average of 10.38 and 11.88 days (P>0.05) respectively. Volume of blood flow and severity of pain were not increased in both groups. Fifty percent and 6% of the patients in the sesame and progesterone groups experienced on-time menstruation in the next (drug-free) episode of menstruation, respectively (P= 0.016).**Conclusion:** Although the rate of bleeding following sesame consumption was lower than progesterone-treated group, it seems that the response rate is high enough to suggest more assessments in the future; moreover, in the sesame group, the rate of menstruation in the next drug-free episode was significantly higher than the progesterone group. Therefore, sesame, as a well-tolerated, partially effective choice in inducing and maintaining regular bleeding, could be considered in the patients who are not suitable candidates for hormone therapy.**[GMJ.2016;5(3):114-121]**

Keywords: Oligomenorrhea; Sesamum indicum; Progesterone; Menstruation

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Introduction

Oligomenorrhea (defined as infrequent menstrual flow at intervals of 36 days to 6 months or 5–7 cycles in a year) has a prevalence of approximately 10.2% among women of reproductive age [1, 2]. Oligomenorrhea is often associated with polycystic ovarian syndrome (PCOS) [2] which is the most common endocrine disorder in women [3]. Hormone therapy as the main treatment of oligomenorrhea; however, the results of a study on infertile women with PCOD revealed that only 25.6% of them had good compliance to this treatment [4].

According to Iranian traditional medicine (also is called as Humoral, Unani or Persian traditional medicine), normal menstruation is an indicator of healthy normal reproductive organ [5-7].

Menstruation is a physiological function of women during their reproductive age [5-8]. One of the most influential Iranian physicians, Avicenna (980 – 1037 A.D) in his famous book, Canon of Medicine, describes oligomenorrhea under the title of "Ehtebas Tams" [8]. He believes that it is necessary to treat patients with oligomenorrhea to avoid complications that may occur because of cessation of menstrual bleeding as a major excretory pathway [8]. The humoral medicine scholars have explained several treatments for oligomenorrhea which includes lifestyle modification, herbal medicine therapies and invasive methods like cupping [6, 8]. Based on traditional medicine texts particularly "Canon of Medicine", "Al-Havi" (Rhazes 865–925 A.D), and Makhzan al Advia (Aghyli, 18th A.D), Sesamum indicum L. (sesame) is one of the medicinal herbs that can induce menstrual bleeding with ignorable side effects [6-11].

Sesame , a member of the Pedaliaceae, is one of the oldest oilseed crops, growing widely in tropical and subtropical areas [12]. This herb is revealed to play a major role in health promotion; there are many evidence for the antioxidant activity, antiproliferative activity, lowering cholesterol level, increasing hepatic fatty acid oxidation enzymes, antihypertensive effects, and neuroprotective effects against hypoxia or brain damage [13].

The use of 50 g sesame seed powder daily for 5 weeks in the postmenopausal woman has been shown to positively affected sex hormones, antioxidant status, and blood lipids [14].

In the traditional medicine, sesame has been reported as a useful remedy for oligomenorrhea treatment, fetus abortion, increasing the sexual tendency and sperm count [6-8]. Sesame is known as "Konjed," is a common component of the Middle East diet. In the traditional medicine clinics, sesame is commonly prescribed for oligomenorrhea treatment. Many physicians and patients believe that this herb is a suitable alternative for hormonal drugs in this field. However, its effect on menstruation has not been scientifically evaluated yet. The aim of the present study is to compare the efficacy of sesame and the common hormonal oligomenorrhea treatment (Medroxy Progesterone) in inducing bleeding in women with oligomenorrhea.

Materials and Methods

Patients

This clinical trial was carried out among 56 women with oligomenorrhea. Oligomenorrhea was defined as postponement of menstrual bleeding for at least 14 days, with history of at least two episodes of menstrual bleeding postponement during the past year. Exclusion criteria included any anatomical abnormality or gynecological neoplasia, a positive pregnancy test, breastfeeding, sesame allergy or history of severe unusual drug reactions towards herbs, and intake of any chemical or herbal hormonal products in the previous two months. Physical and gynecological examinations, ultrasonography of uterus and ovaries, and pregnancy test were performed at the beginning of the study. Demographic and baseline data, medical history and any concomitant medications were also recorded.

Preparation the Sesame seeds

Laboratory tests on sesame seeds from four sources were performed; as a results, the seeds from Morvarid-No company were approved for usage in the study. In this sample, total ash (6.1-6.15 %), water soluble ash (1.15-

1.25 %), oil amount (34/100 grams), mucilage amount (0.34/ 100 grams), gum amount (0.34/ 100 grams), oil fraction rate (1.471), total number of aerobic bacteria (4.65*103/ gram), total amount of fungi (2.6*103/gram), contamination with Pseudomonas aeruginosa, Staphylococcusaureus, Salmonella sp. and Eschericiacoli (zero) were within acceptable range [15]. The seeds were stored in the temperature of 2-5 C°.

Study Design and Data Collection

Patients were allocated randomly into two groups: the progesterone group (29 patients) received Medroxy Progesterone 5 mg tablets (Iran Hormon Company, Iran) twice daily for 7 days. In the sesame group (27 patients), sesame was prescribed for patients at a dose of 60 g once daily for 7 days. Patients were educated to prepare the drug as follow: "60 g powdered sesame to be boiled in 400 cc water for 4 minutes, then filtered and be drunk warm." The patients in both groups were followed by telephone calls every week after receiving the drug. Data on drug intake (yes/no), method of preparing the drug product (correct/ incorrect), the length of drug intake (days), vaginal bleeding and the delay before bleeding initiation, dysmenorrhea and any complications of medications were recorded.

The primary outcome measure was the occurrence (yes/no) of bleeding after receiving the drug. A bleeding episode was defined as bleeding if it occurred within two weeks after consumption of sesame or progesterone. The delay before bleeding initiation was also recorded and compared between groups.

The temperament of uterus organ was diagnosed based on a standard questionnaire [16] that contains 12 questions with a Likert scale of 1 to 7 for each question. The questions were filled out by the physician based on history and physical exam. The sum of scores in the first 9 questions (which includes questions about odor, hotness, amount of hairs, hair growing speed, the touch heat, color of the vaginal discharge, libido, the vaginal discharge viscosity and the vaginal feeling during coitus) as an indicator of hotness score and the sum of scores in the last 3 questions (which includes questions about amount of vaginal discharge, the wetness and the texture of the cervix) as the indicator of wetness score were represented. The volume of bleeding flow in the existing menstruation compared to the past episodes was also assessed via interview.

Ethical Issue

All participants provided written informed consent. The research protocol was in accordance with the Helsinki declaration of 1975, as revised in 2000 and the Ethics Committee of Shahid Beheshti University of Medical Sciences approved the protocol (code: 143; 12.1.2013). The research protocol was registered with the Iranian Registry of Clinical Trials (IRCT ID: IRCT2013072014072N1).

Statistical Analysis

Statistical analysis was performed using SPSS 16 software. Comparisons between two groups were carried out by the student t-test for numerical and by the chi-square in the case of categorical data. The statistician was blinded about the treatment groups. All tests in the exploratory analysis were carried out two-sided and a result with a P value <0.05 was explained as significant.

Results

Demographic Characteristics

Fifty- six women were enrolled in the study. Twenty-seven of them were known cases of PCOD. Twenty-seven patients (mean age 29.42± 8.99 years) and 29 patients (mean age 26.63± 5.63 years) were enrolled in the sesame and progesterone groups, respectively (P>0.05). Mean height and weight were 160.85±6.71 cm and 67.37±18.76 kg in the progesterone and 160.14±7.81 cm and 65.28±19.49 kg in the sesame group, respectively (P>0.05). The main reason for dropping out of the study was due to unpleasant taste of sesame (1 person), or a failure to follow up (1 person in the progesterone group). The mean body mass index (BMI) was 25.25± 6.5 in the sesame and 25.77± 6.08 in the progesterone groups. The t-student test revealed that there was no significant difference between the sesame and progesterone groups in term of age, weight, and BMI (P>0.05).

Menstruation on Treatment

Eighteen (72%) of the patient experienced bleeding after received the sesame. In the progesterone group, the rate was 27 (93.10%) which was significantly higher than the sesame group (P=0.012). The BMI was lower in the patients that had positive response to the treatment in both groups compare to those who did not respond the treatment (24.40± 6.63 and 26.66 ± 6.65 in sesame group with positive and negative response to treatment, respectively;25.34± 5.68 and 37.2 in the progesterone group with positive and negative response to treatment, respectively). The diagnosing of the temperament of the uterus organ was done for both groups that showed a lower score of hotness and wetness in the patients who had a positive response to the treatment compare to those who did not experience bleeding after sesame use (3.83± 0.75 vs. 4.25± 0.83 for hotness and 2.62± 0.45 vs. 2.16± 0.78 for wetness). The difference was not statistically significant though (P>0.05).

In the progesterone group, the scores were 3.89± 0.81 vs. 4.55± 0.0 for hotness (P>0.05) and 2.39± 0.77 vs. 4.66± 0.0 for wetness (P=0.009) in the groups with positive and negative response to treatment respectively.

Patients in the progesterone group experienced bleeding on an average of 11.88 days after the treatment initiation, while this time was shorter (10.38 days) in the sesame group (P>0.05).

Sonographic Findings

The sonography was performed to evaluate the relationship between endometrial thickness and response to treatment. 26 (46%) of the patients showed the signs of PCOS in sonographic evaluation. The mean endometrial thickness in the sesame group was 6.87± 0.33 and 8.22± 0.23 mm in the patients who had positive and negative response to treatment ,respectively (P>0.05). In the progesterone group the thicknesses were 7.27± 0.83 and 4± 0.0 mm in the patients who had positive and negative response to treatment ,respectively (P>0.05).

Volume of Menstrual Flow and Pain

Volume of menstrual flow and the pain compare to the past episodes were compared between sesame and progesterone groups which was not significantly different between the two groups (P>0.05). The data of amount of menstrual bleeding and the pain is shown in Table-1.

Safety and Tolerability

Sesame was well tolerated by the patients. 4 patients reported that they are very satisfied using sesame compare to hormonal drugs (vs. nobody in the progesterone group). There were no serious adverse reactions in the patients. The most unpleasant report in the sesame group was hotness feeling and hot mal-temperament in 5 patients (20%). In the progesterone group, the most unpleasant report increased in dysmenorrhea compares to the last menstrual episodes in 6 patients (20%). Two patients reported that they are unsatisfied with progesterone therapy and do not like to use it

Table 1. Volume of Blood Flow and Severity of Pain in Sesame and Progesterone Groups.

Variable		Progesterone group N(%)	Sesame group N(%)
Volume of bleeding flow	More than past episodes	5 (23.8%)	5 (27.7%)
	Less than past episodes	2 (0.95%)	4 (22.3%)
	Equal to past episodes	14 (66.6%)	9 (50%)
	Unacceptable report	4	11
Severity of pain	More than past episodes	4 (19%)	6 (31.5%)
	Less than past episodes	0 (0%)	0 (0%)
	Equal to past episodes	17 (80%)	13 (68.4%)
	Unacceptable report	4	10

in the future (vs. nobody in the sesame group). The adverse reactions reported by the patients in both study groups showed in Table-2.

Follow-up Results for the Next Menstruation Episodes

Fifteen patients in the progesterone and 8 in the sesame group were followed successfully for two months. Others were excluded from this analysis because of several reasons that mainly included using any hormonal drugs (including progesterone) or herbal treatments. In the progesterone group, 14 out of 15 patients (93.3%) reported that they did not have menstruation in the next episode without using the medication. One (6.6%) patient experienced on time menstruation in the next episode without using medication.

In the sesame group, 4 (50%) patients reported on time menstruation for the next (drug-free) episodes compare to the progesterone group(P=0.016).

One of these patients reported having 6 months of on time, regular menstruation following one episode of Sesame treatment. Three (37%) patients had menstruation with 10 days delay and one (12%) patient reported to have no menstruation in the next episode without using medication.

Discussion

Sesame, a common part of Mediterranean diet is an important herb mentioned in the humoral medicine for oligomenorrhea treatment; although this is widely used in the traditional medicine university clinics, no clinical trial has evaluated and approved its therapeutic effect. The present study is the first comprehensive assessment of menstruation upon S.indicum L. use compare to the common hormonal treatment. The authors had previously conducted a pilot study on sesame efficacy for oligomenorrhea treatment, which showed positive results in the induction of uterus bleeding; however, the important limitation of this pilot study was the lack of control group [17]. Our results showed that the mean BMI was lower in the patients that had a positive response to the treatment in both groups compare to those who did not respond the treatment. This is in accordance with our expectations from previous studies [18, 19]. Also, a high rate (46%) of the patients showed the signs of PCOS in the sonographic evaluation that is in agreement with other studies that represent PCOS as the main etiology of the oligomenorrhea [20].

The main results of the current study were that 72% of the patients experienced bleeding

Table 2. The Frequency of Adverse Reactions Reported by the Patients in Both Study Groups.

Sign/ symptom	Sesame group (n=25) N(%)	Progesterone group (n=22) N(%)
Dysmenorrhea	4(16)	6(27.7)
Nausea	1(0.04)	1(4.5)
Headache	1(0.04)	1(4.5)
Depression	0(0)	2(9)
Mood irritability	0(0)	2(9)
Spotting	0(0)	14.5)
Hirsutism	0(0)	2(9)
Obesity	0(0)	3(13.6)
Acne	4(16)	2(9)
Breast tenderness	0(0)	1(4.5)
Hot flashes/ hotness feeling	5(20)	1(4.5)
Thirst	2(8)	0(0)
Dyspepsia	1(0.04)	0(0)
Sweating	2(8)	0(0)
Hot mal-temperament	5(20)	0(0)

following sesame consumption. Although this rate is significantly lower than the rate of bleeding following hormonal treatment, it seems that the response rate is high enough to suggest more assessments in the future. Moreover, the patients were satisfied using this herbal medicine compared to the progesterone.

Papadakis *et al*. in a study on Wistar rats receiving sesame for 8 weeks, reported that the levels of enterolignans (i.e. enterolactone and enterodiol, which are the end metabolites of lignans in mammals and express strong phyto-estrogenic activity) were increased dramatically in the plasma of the rats receiving sesame [21]. In the same experiment on Wistar rats supplied for 8 weeks with a diet rich in sesame, Anagnostis *et al*. evaluated the expression of estrogen receptors (ERalpha and ERbeta) in the uterus tissue [22]. Significant increase in the expression of ERbeta was seen, while no statistically significant change was observed in the expression of ERalpha in the uterus. Therefore, a shift of ERalpha: ERbeta in favor of ERbeta was evident [22]. The authors suggested that this effect is attributed to the lignans present in the pericarp which exert phyto-estrogenic activity [22].

Another study by Mahabadi *et al*. was designed to examine the effect of a sesame seed regimen on the testicular structure and sex hormones in adult rats [23]. The findings revealed that sesame seed intake improves the testicular parameters (the mean number and motility of sperms in the epididymis, the number and volume percentage of epithelial cells, lumen and interstitial space as well as the diameters of the tubules), fertility, sperm production and LH level in male rats [23].

Moreover, Wu *et al*. in his study proposed decrease in dehydroepiandrosterone sulfate (DHEAS) , and increase in the sex hormone-binding globulin (SHBG) () level after sesame intake; However this study could not show any decrease in serum estrogen level after sesame intake [14].

In another study, Asghary *et al*. evaluated the blood fibrinogen and factor XII levels in rabbits divided into different groups with normal, hyper cholesterol and sesame diets. The results showed that the blood fibrinogen and factor XII7 were decreased in groups that had sesame seed or oil in their diet [24]. This result is noteworthy as the PCOS is a foremost pathology in the oligomenorrhea and several studies of women with PCOS have shown dysregulation of the homeostatic system [25-27]. For instance, Manneras-Holm *et al*. demonstrated that women with PCOS have high circulating concentrations of plasminogen activator inhibitor-1 activity and fibrinogen after adjustment for age and BMI [28]. The effects of sesame on coagulation factors should be considered as a possible mechanism in oligomenorrhea treatment.

In the field of oligomenorrhea treatment, a similar study with another herbal remedy was recently done by Mokaberinejad *et al*. They designed a clinical trial to assess the effect of Mentha longifolia L. in inducing bleeding in women with secondary amenorrhea and oligomenorrhea [29]. The most of the women in the drug group experienced bleeding during the first cycle (68.3% vs. 13.6% in the placebo group; $P < 0.001$) [29]. In our study, the length of treatment was shorter (once daily for a week vs. three times a day for two weeks) and the response rate in our drug group was higher. In our study, no serious side effect was observed, while the treatment of oligomenorrhea in the conventional medicine is mostly based on empiric hormone therapy that is evident to have adverse effects and complications [30, 31].

The high rate of menstruation in the next menstrual cycle without treatment is also remarkable. In our study, 50% compare to 6% of the patients experienced on-time menstruation in the next drug-free episode in the sesame and progesterone groups, respectively. According to the traditional medicine viewpoint, the high rate of regular menstruation following one episode of Sesame treatment is due to the treatment of the uterus male temperament.

The temperament evaluation results showed that the patients with a “colder” uterus temperament showed a better response to the treatment. According to the humoral medicine textbooks, the sesame is a drug of hot temper and can be an effective therapy for the cold temper disease [6-11]. Moreover, the oligomenorrhea is usually considered as a cold

temper disease so that sesame can be an effective treatment for oligomenorrhea. These findings are in harmony with Mokabberinejad *et al*. survey that showed that Mentha longifolia L., a herb of hot temper, is more efficient in the treatment of oligomenorrhea in patients with cold temper uterus [29]. These evidence suggest conducting more research in the field of uterus organ temperament.

Based on traditional medicine theories, we expected to have a better response to treatment in both groups with higher endometrial thickness. The sonography data showed that patients with thicker endometrium had a better response to progesterone therapy (although the data was not statistically significant); however, we could not find a positive relation between endometrial thickness and response to sesame. This result is probably due to insufficient sample size and we suppose to see different results in future studies with larger sample size.

Due to the beneficial effects of *S. indicum* L., besides its safety, availability, and low cost; it is recommended to plan more clinical trials with larger sample size to evaluate its therapeutic effect. If the result of stronger studies would approve the effects shown in the current study, *S. indicum* L is an excellent choice for treatment of patients with oligomenorrhea. A significant benefit of using this herb especially for PCOS patients is that these patients, on one hand, can get free of the long list of the hormonal therapy side effects, and on the other hand to stay protected from menstruation cessation complications. Before designing therapeutic protocols, it is also necessary to organize further large randomized studies to determine appropriate dosages and duration of treatment and the reliability of *S. indicum* L. as a good option for the cessation of menstruation.

Conclusion

Finally, the effects of sesame in inducing bleeding and maintaining regular menstruation in patients with oligomenorrhea are promising and propose more studies for further assessment.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article. This work was financially supported by Shahid Beheshty University of Medical Sciences.

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