INTRODUCTION

Menopause is an evolutionary female stage that is experienced by all women at an older age and exposes women to a wide range of variations. According to the World Health Organization (WHO), menopause occurs 12 months after amenorrhea and between the ages of 45 and 55 years [1].

Menopause and lower estrogen levels during menopause are associated with some side effects that can affect a woman's quality of life and weaken her health and well-being. The symptoms that women experience during this period include night sweats, osteoporosis, vaginal dryness, dyspareunia, moral fluctuations, joint pain, palpitations, sleep disturbances, restlessness, and urinary symptoms [2,3].

Hot flashes and night sweats are the most common and annoying consequences that can affect enjoying work and social activities, leisure time, mood, concentration, communication with others, sexual activity, enjoyment of life, and the quality of life. The word “hot flash” describes the sudden onset of redness of the scalp, neck, and chest, which is accompanied by a feeling of intense heat in the body and occasionally ends in severe sweats. These symptoms are more frequent at night and cause night sweats and sleep disorders [4].

During menopause, the production of hormones from the ovaries stops, resulting in a significant reduc-
Effect of Evening Primrose Capsule in Postmenopause

The circulating estrogen level. A clinical study evaluated the effects of complementary therapies on the treatment of menopausal symptoms [5]. A hormone replacement therapy with estrogen and progesterone is the treatment which is currently used to alleviate the symptoms of hot flashes and sweating in postmenopausal women. The complications of hormone therapy at this age include negative effects on lipids and lipase activity, increased risk of stroke, breast and endometrial cancer, thromboembolic disorders, liver and Alzheimer's problems. Like all other chemical treatments, this treatment is contraindicated in some people and others are not satisfied with its use [6].

According to the WHO, 80% of the world's population uses herbal compounds for treatment [7]. Medicinal herbs as alternative therapies, and estrogenic herbs, among them, are the most desirable treatments for reducing and treating menopausal symptoms in postmenopausal women [8]. Phytoestrogens are estrogen-like compounds present in plant products that are found in the bile, urine, semen, stool, and the blood of humans or animals. The evening primrose oil is one of the most important plant phytoestrogens. This plant belongs to the family Onagraceae, which has various effects on menopausal vasomotor symptoms, symptomatic relief of psoriasis and premenstrual syndrome, and the inhibition of platelet aggregation [9,10]. According to some studies, evening primrose is effective in relieving the symptoms of menopausal vasomotor. Given the above-mentioned introduction, the present study aimed to investigate the effect of the evening primrose oil capsule on hot flashes and night sweats in postmenopausal women.

MATERIALS AND METHODS

Study design

This randomized clinical trial was performed in health centers of Hamadan from May 2018 to April 2019.

Determination of sample size

The required values for determining the sample size were calculated according to a study by Sadeghi et al. [11] according to the following formula:

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

The minimum required sample size in each group was 85 and a total of 170 people were examined in this trial.

Participants

Inclusion criteria included at least a year after the last menstrual cessation, no acute and chronic illnesses, no herbal medication since three months before the intervention, no previous allergy to medicinal herbs, affliction from or a history of breast cancer and genital cancers. Exclusion criteria included acute illnesses during the follow-up and inappropriate drug use during the follow-up that was monitored by the researcher using the weekly telephone follow-up.

Permission was obtained from the Hamadan Health Center and the Ethics Committee of Hamadan University of Medical Sciences to conduct a research project (No. IR.UMSHA.REC.1396.822), and the written informed consent was obtained from all patients. A total of eight clinics were randomly selected from comprehensive health centers in Hamadan and assigned to intervention (n = 4) and control (n = 4) groups. Eligible women signed a study consent form. Both groups were randomly allocated to four blocks (Fig. 1). It should be noted that each participant was then given a closed packet based on the sequence containing either evening primrose oil or a placebo. The drugs were placed in some opaque closed pockets and then coded for sequencing sequences, respectively. The present study was single-blind, and the researcher was to the study. First, medicines were coded and then delivered by someone who did not know about the types of medication.

Instruments

The researcher-made demographic questionnaire and the hot flash and night sweat questionnaire were completed by the researcher. Wiklund Vasomotor Symptom Subscale score was used to measure hot flashes and night sweats. This instrument was developed by the U.S. Food and Drug Administration. The volunteers could report the duration, severity, and frequency of hot flashes during 24 hours per week. For each hot flash, a mark was recorded in the special column after its occurrence.

The intensity of hot flashes was classified into mild (a score of 1), moderate (2), and severe (3) grades representing a sense of heat without sweating, a sense of heat with sweating, and a sense of heat with sweating and intervention with normal activities, respectively. The

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duration of hot flashes was also less than 30 seconds, 30–60 seconds, 1–3 minute(s), 3–5 minutes, and more than 5 minutes and was recorded quantitatively. The intensity of night sweats was classified into mild, moderate, and severe degrees. The first one indicated that the night sweat did not wake you up although you found that your clothes or bed were wet when you woke up for another reason. Moderate and severe degrees demonstrated that night sweat woke you up, but not enough to do anything for and it woke you up and you took measures to solve it. All the above-mentioned cases were included in a table for conveniently completing hot flash registration forms. The reliability of the tool was reported in other studies [12,13]. On this scale, the intensity of night sweats was categorized into mild, moderate, and severe degrees. The form was given to volunteers to complete in case of night sweats in the morning and after a night sleep.

Intervention
The intervention was in the form of evening primrose oil and placebo consumption twice daily. The evening primrose oil is available in 1,000 mg soft capsules in a medicine container with a brochure in a cardboard box in pharmacies (group A). The control group (group B) received a placebo. The 1,000 mg evening primrose oil, which was produced by Barij Essence Pharmaceutical Company (Mashhad Ardehal, Iran), was used twice a day for eight weeks for treating hot flashes and night sweats. North America is considered as the main source of this plant, and then it has been transferred to other areas from this region. An oil called ‘huiledon-ager’ is obtained from the seeds of this plant. The oil is greenish-yellow and is composed of various acids such as palmitic (6.5%), stearic (1.5%), oleic (11%), linoleic (72%), alpha-linoleic, gamma-linolenic, and arachidonic acids. The oil is valuable due to its drying properties and the existence of gamma-linolenic acid. Several agents also contribute to the prostaglandin biosynthesis in this oil. The placebo capsule was also produced similar to the first drug and given to eligible participants. Correct drug use was monitored weekly by the telephone. Questionnaires were completed by participants in both groups before and eight weeks after the study.

Statistical analysis
The data were analyzed using Stata 13 (StataCorp, College Station, TX, USA). The distribution of quantitative variables was checked using histogram, central-dispersion indices, and the Shapirovilk test. In addition, an independent t-test and Mann–Whitney test were used to compare quantitative demographic and obstetric variables with a normal distribution and quantitative variables with an abnormal distribution, respectively. Further, chi-square and Fisher’s exact tests were applied to compare variables that were classified into groups. The transformation was used since the distribution of the duration, number, and severity of hot flashes was not normal. Accordingly, the distribution of duration and the severity of flushing using square transformation, along with the number of flushing by applying inverse square root transformation became near nor-
mal. Data analysis related to the main outcome of the study was performed by ANOVA/ANCOVA test, and back-transformation was utilized to report the means in the table. Finally, the data were reported in the original scale. Moreover, Fisher’s exact and chi-square tests were employed to compare the number and severity of sweating, comorbid symptoms, and sleep disturbance along with night sweats. The significance level was considered 0.05.

RESULTS

Based on the results (Table 1), the mean age of the participants and the mean age of the onset of menopause were 54.7 ± 4.8 years and 55.9 ± 5.2 years, as well as 48.6 ± 5.3 years and 50.1 ± 4.8 years in intervention and placebo groups, respectively. The mean duration of menopause was also higher in the placebo group compared to the intervention group. The majority of participants in both groups had primary education and more than 90% were housewives. The comparison of the body mass index status among the two groups indicated that approximately half of the individuals were overweight. There was no statistically significant difference between the two groups regarding demographic characteristics and the two groups were homogeneous ($P > 0.05$).

By controlling the effect of pre-intervention scores, the results showed that the duration and frequency of hot flashes between the two groups were not statistically significant. However, the comparison of the two groups in terms of the severity of hot flashes revealed that the mean ± standard deviation was 1.9 ± 1.7 and 2.1 ± 1.7 in the intervention and placebo groups, respectively, and this decrease was statistically significant ($P = 0.03$). Conversely, a Cohen’s $d$ value of 0.13 indicated that the intervention was not effective in reducing the severity of hot flashes (Table 2).

Based on the comparison of the frequency and intensity of night sweats in the pre-intervention phase, no statistically significant difference was found between the two groups. After the intervention, 27.5% of partic-

| Table 1. Comparison of some demographic characteristics in groups |
|---------------------------------------------------------------|
| Variable                      | Evening primrose oil group | Placebo group | Test statistics | $P$ value |
| Age (y)                      | 54.7 ± 4.8                | 55.9 ± 5.2    | −1.51          | 0.13*     |
| Age of the onset of menopause (y) | 48.6 ± 5.3                | 50.1 ± 4.8    | −1.07          | 0.28*     |
| Duration of menopause (y)    | 6.0 ± 5.9                 | 7.0 ± 5.0     | −1.63          | 0.10*     |
| Parity                       | 3 (3, 5)                  | 4 (3, 5)      | −0.54          | 0.59*     |
| No. of children alive        | 3 (2, 4)                  | 4 (3, 5)      | 0.22           | 0.82*     |
| Education                    |                            |              | 0.89           | 0.93*     |
| Illiterate                   | 16 (18.8)                 | 14 (16.9)     |                |           |
| Primary                      | 34 (40.0)                 | 33 (39.8)     |                |           |
| High school                  | 15 (17.6)                 | 18 (21.7)     |                |           |
| Diploma                      | 15 (17.6)                 | 15 (18.1)     |                |           |
| Academic                     | 5 (5.9)                   | 3 (3.6)       |                |           |
| Occupation                   |                            |              | 0.38           | 0.53*     |
| Employed                     | 5 (6.0)                   | 7 (8.4)       |                |           |
| Unemployed                   | 79 (94.0)                 | 76 (91.6)     |                |           |
| Body mass index              |                            |              | 0.46           | 0.79*     |
| 18.5–24.9 kg/m²              | 17 (20.0)                 | 16 (19.5)     |                |           |
| 25–29.9 kg/m²                | 49 (57.6)                 | 44 (53.7)     |                |           |
| ≥ 30 kg/m²                   | 19 (22.4)                 | 22 (26.8)     |                |           |

Data are presented as mean ± standard deviation, median (Q1, Q3), or number (%).
In the variables with total number less than 85, there was missing data and the participants did not answer the question.
BMI: body mass index.
*Independent t-test; †Mann–Whitney; ‡chi-square test.

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participants in the intervention group reported no sweating. Contrarily, about 40% of those in the placebo group reported high rates of night sweats during a week. Additionally, nearly 2.5% and 47.5% of participants of the intervention group had severe and mild sweating, respectively. However, 9.6% of people in the placebo group reported mild sweating. These differences were statistically significant (Table 3).

### DISCUSSION

The results of this study indicated that evening primrose oil had no significant effect on relieving the symptoms of hot flashes although it was effective in improving night sweats.

The evening primrose oil capsule is a drug with phytoestrogenic properties. Its mechanism in improving hot flashes and night sweats is unclear although it may act as an estrogen agonist, and antagonist and through interaction with the estrogen [14] receptor. Phytoes-
trogens act as agonists or antagonists of the estrogen receptor and can provide stronger estrogenic effects when the estrogen level is low in the environment and it, in fact, compensates for the lack of androgen 17 beta-estradiol in menopause. For this reason, many women use phytoestrogenic family herbs as a supplement and hormone replacement therapy in menopause to improve the symptoms of this period [15].

Based on the findings of the present study, this herbal drug did not affect the severity, duration, and frequency of hot flashes, but it was effective on the frequency and severity of night sweats. Different studies evaluated the effect of phytoestrogenic plants on hot flashes in postmenopausal women. In their study, Farzaneh et al. [16] investigated the frequency, severity, and duration of hot flashes in treating 45–59 years old women using the evening primrose oil capsule and found that flashing attacks diminished after six weeks. In this regard, Motaghi Dastenaie et al. [17] indicated the significant effect of the evening primrose oil on reducing hot flashes in postmenopausal women compared to women taking the placebo. They also suggested that herbal compounds could be used as complementary therapies in treating menopausal symptoms instead of some hormonal therapies. The reason for the discrepancy in the results of this study with those of other studies regarding the effect of the drug on reducing hot flashes may be due to the lower dosage of the drug in our study. In the study of Mehrpooya et al. [18], the evening primrose oil affected the severity of hot flashes in menopause while having no significant effect on its frequency. In another study, Low Dog [19] reported that the evening primrose oil was not effective in relieving menopausal vasomotor symptoms. The results of the above-mentioned studies are in line with those of our study.

In a systematic review study, Yousefi et al. [20] concluded that the consumption of evening primrose oil is effective in reducing the severity and frequency of sweating in menopause. Another systematic study by Mahboubi [21] highlighted the beneficial effects of the evening primrose oil on menopausal vasomotor symptoms. The findings of these studies corroborate with the results of the present study. Similar to the other study [22], our findings showed another effect of herbal medicines in treating the symptoms of diseases. One of the limitations of our study is the small sample size, which reduces the generalizability of the results.

In general, the results of the present study indicated that the evening primrose oil was effective in reducing the frequency and severity of night sweats although it had no significant effect on the relief of hot flash symptoms. Therefore, this herbal medicine can be useful in relieving some menopause-associated symptoms.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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