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Effect of Black Cohosh (Cimicifuga Racemosa) on Vasomotor Symptoms in Postmenopausal Women: A Randomized Clinical Trial

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ABSTRACT

Introduction: Hot flash is considered to be an early and common symptom of menopause. The present study aimed to determine the impact of black cohosh (Cimicifuga racemosa) on vasomotor symptoms in postmenopausal women. ***Methods:*** This was a randomized, double-blind, placebo-controlled clinical trial. This study was performed on 84 postmenopausal women. The participants were randomly divided into control and intervention groups. The participants of the intervention group received one black cohosh tablet per day and the control group received one placebo tablet per day for eight weeks. The severity of vasomotor symptoms and number of hot flashes were recorded during the pre-intervention phase, and 4 and 8 weeks after the intervention. The data were analyzed using repeated measures ANOVA and ANCOVA tests. The level of significance was considered lower than 0.05. ***Results:*** There was a significant difference between the two groups in terms of severity and number of hot flashes in weeks 4 and 8 by controlling the intensity of vasomotor symptoms and number of hot flashes before the intervention. Moreover, using repeated measures ANOVA, the intergroup comparison indicated a significant difference in bothgroups (the intervention and control groups) in terms of severity of vasomotor symptoms and number of hot flashes. ***Conclusion:*** According to the findings of the study, it seems that black cohosh can be used as an effective alternative medicine in relieving menopausal vasomotor symptoms.

Introduction

Menopause is a natural biological process that occurs with the permanent cessation of menstruation due to loss of ovarian activity. Mean age of menopause in the U.S. is 51.4 years, and in Tehran it has been reported between 46.8 to 50.2 years.[1,2] We now live in an era in which the population is ageing. Two-hundred years ago, only 30% of women could survive to experience menopause; however, currently 90% of women experience it.[3] According to the population and the Housing Census Center, the elderly population of Iran has tripled during 1976 to 2006. The elderly in Iran, which now constitute 7% of the population, are predicted to reach 33% of the population in 2030.[4] Thus, maintaining their health and welfare in this period is of high importance in terms of preventing socioeconomic losses in the current and future millennium.[5]

During menopause, ovarian follicles are decreased in the ovaries and thus the ovaries are no longer able to respond to pituitary hormones (i.e. FSH and LH). Consequently ovarian estrogen and progesterone production is stopped.

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The major consequences of menopause, including hot flashes, are mainly related to the decline in estrogen. Vasomotor symptoms are seen in 75% of premenopausal women. Such symptoms last 1 to 2 years after menopause, nevertheless, they may last for over 10 years in some women. They are followed with recurrent and transient flushing periods, sweating and feeling heat and usually are coincided with palpitation, anxiety, and sometimes with chills. The set of aforesaid symptoms are called hot flashes.[6-8] Hot flashes not only make women anxious in their workplace and impede their daily tasks, but also impair their sleep pattern, and cause difficulty in concentration and mood instability. If secondary mood and cognitive symptoms are related to the sleep disorder, and cause daytime fatigue, treating vasomotor symptoms will improve them.

Physiological mechanisms of hot flashes have not been identified yet. However, it appears to be a core event which probably begins in the hypothalamus, as a result, core body temperature increases the metabolic rate and skin temperature. This reaction causes peripheral vasodilatation and sweating in women. Noradrenergic, dopaminergic, or Serotogenic activity is likely to stimulate this core event. Increased LH secretion is often seen in every hot flashes attack.[3]

Hormone therapy is the standard treatment of vasomotor symptoms in postmenopausal women.[9] However, Women's Health Initiation showed that the risk of stroke, breast cancer, and cardiac diseases are enhanced in older women when using a combination therapy of estrogen-progesterone; therefore, there was a remarkable decline in use of hormone therapy.[10, 11] It has been shown that the effects of hormone therapy in alleviating postmenopausal signs and symptomsare less than expected.[12-14]

These reasons decreased the use of hormone therapy and increased the tendency toward using alternative therapies to relieve menopausal symptoms.[15] When a woman is not willing to use estrogen, or taking estrogen is contraindicated for her, other options and alternatives are also available; e.g. clonidine, which is a selective serotonin reuptake inhibitor (SSRI), gabapentin and bellergal. Although the mentioned medicines are effective in treating hot flashes, their use is limited due to their side-effects. Many postmenopausal women are interested in improving hot flashes by supplements and vitamins. Many of these therapies, which claim to relieve hot flashes, have rarely been investigated in controlled trials. Soya has been shown in some studies to reduce vasomotor symptoms, while other studies have indicated the opposite. Numerous studies also indicated that isoflavones and vitamin E had little effect on relieving hot flashes.[3] Black cohosh (Cimicifuga racemosa or Actaea racemosa) is one of the non-hormonal and herbal therapies.

Cimicifuga racemosa (Cimifuga racemosa) or the black cohosh, a member of the buttercup family, is a native herb of eastern North America. Black cohosh contains triterpene glycosides including ectoine, 27-deoxyactein, cimicifugoside, cytisine, N-methylcytisine, phenylpropan derivatives containing acid and a resinoid substance called cimicifugin, which encompass 25% to 50% of the rhizome materials.[16] The medicinal effects of the plant roots are related to the active component of the rhizome (triterpene glycosides).[17] The exact mechanism of black cohosh is still unknown. Nevertheless, some studies have found that black cohosh is linked to the estrogen receptor, and selectively inhibits LH secretion without affecting FSH.[16-18] The function mechanism of the black cohosh seems to be more serotogenic than estrogenic.[19-21] In Iran, black cohosh is supplied by Goldaru Pharmaceutical Company with the name of Cimifugol™ as coated tablets containing 6.5 mg dried extract of cohosh root and is equal to 0.12 to 0.18 mg of 27 deoxy ectoine.[22]

Some clinical trials have shown the effectiveness of black cohosh on reducing the severity and number of hot flashes, and some

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others have not.[23-26] In review studies, conducted investigations concerning the impact of black cohosh on relieving menopausal symptoms, such as hot flashes and vasomotor symptoms, were known to be unreliable due to lack of evidence, and accordingly further studies have been suggested.[27-29] In a review study by Hickey et al. and some other researches regarding black cohosh, it was considered to be a safe drug.[23,25,27,30] Very few side-effects have been reported in taking black cohosh; nausea, vomiting, headache, and dizziness.[27] If this drug is consumed as much as the recommended amount, it will be well tolerated and will not have major side-effects.[16,17,27]

Given the adverse impact of menopausal symptoms on somatic and mental quality of life of postmenopausal women and in order to maintain their health, we conducted the present study to take a step toward the health of women.

Materials and methods

This was a randomized, double-blind, placebo-controlled clinical trial. The aim of this study was to determine the impact of black cohosh on the severity of vasomotor symptoms and number of hot flashes in women referring to four health-care centers affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, which has the highest number of client referrals for family planning. The sampling started from the one with highest client referrals and continued until the completion of the desired sample size from the other three health-care centers. The target population included 45 to 60-year-old women who referred to the above mentioned centers. Through phone calls and with the help of the health records of women, who used to receive family planning services and have now reached the postmenopausal age, we invited those complaining about menopausal vasomotor symptoms and hot flashes, and were willing to participate in the study.

After gaining the approval of the Ethics Committee (Code 9061) of Tabriz University of Medical Sciences, sampling was done through convenience sampling method. Thus, women were selected who had the following inclusion criteria: no menstruation during the past 12 months, having normal BP [$^{60}/_{100}$ to $^{90}/_{140}$], obtaining a minimum score of 2 from the subscale of vasomotor symptoms severity, no history or existence of breast cancer, cervical cancer, abnormal vaginal bleeding, hepatic disease, depression, or hyperthyroidism, no use of hormonal drugs or herbal drugs to treat menopausal symptoms and/or psychiatric medication during the previous two months and during the study, no sensitivity to spices or seasoning and oil-bearing substances, no smoking and alcohol drinking, and literacy and ability to read and write for answering the questions.

The data collection method was face-to-face interviews and the tools included a demographic questionnaire, the vasomotor symptoms severity form as defined by the FDA, and Greene climacteric vasomotor subscale tool, which includes hot flash and night sweat severity scores. The scores for hot flashes were 1: mild, sensation of heat without sweating, 2: average, sensation of heat with sweating but no daily task dysfunction, and 3: severe, extra intense sensation of heat and sweating with daytime dysfunction. The scores for night sweating were 1: mild, they do not wake up for any reason and only wake up if they realize they are sweating, 2: average, they wake up due to heat and sweating but they do not need to do anything special, 3: severe, they wake up due to heat and sweating and need to change their cloths, open windows or get out of their bed (the minimum and maximum scores for the Greene vasomotor scale are 1 and 6, respectively).[31,32] The tools also included a form for recording the number of daily hot flashes (a researcher-designed form), and a form for recording the side-effects (dizziness, headache, nausea, and vomiting).

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The validity of the forms was confirmed by ten faculty members and test-retest was used for their reliability (r = 0.96). After explaining the study objectives to the participants, their vasomotor symptom severity score was calculated. All those who obtained a score of at least 2 from vasomotor symptom severity were selected and were examined by the researcher. Their blood pressure was recorded and they were examined in terms of rejecting uterine bleeding, history of breast or cervical cancer, hepatic disorders, depression, and hyperthyroidism. If they possessed the inclusion criteria a written consent form was obtained from them. The demographic questionnaire was completed through face-to-face interviewing. Then, they were asked to note their daily hot flashes for a week and return the form to the researcher. The participants were divided into two groups of black cohosh (n = 42), and placebo (n = 42) through 4 and 6 random block sampling method with allocation ratio of 1:1. Using a computer random numbers table, the sequence of allocation was identified. Sealed envelopes, similar in terms of size and shape, in sequence numbers of black cohosh or placebo tablets were used for allocation concealment. The placebo tablets were prepared in similar size, shape, and color of the black cohosh tablets in the School of Pharmacy, Tabriz University of Medical Sciences, Iran. The participants of both groups were instructed to take one tablet once a day after their dinner for eight weeks (n = 56 tablets). The researcher, her assistant, and the study participants remained blinded to the tablet allocation throughout the study.

Data collection was conducted in three phases (zero, 4, and 8 weeks after the intervention onset). The participants were asked to record the number of daily hot flashes (every 24 hours), and mark the potential side-effects on a checklist and return them to the researcher at weeks 4 and 8 after the intervention onset. The Greene climacteric vasomotor symptom subscale was completed by the researcher (i.e. week 4 and 8 after the intervention). Moreover, they were followed-up through phone calls once a week on how to take the medicine or other possible cases. The data were analyzed through repeated measures ANOVA for intergroup comparisons. ANCOVA test was also used to compare the severity of vasomotor symptoms and number of hot flashes before and after the intervention between the intervention and control groups by SPSS for Windows 13.0 (SPSS Inc., Chicago, IL, USA).

Results

This study was performed on 84 postmenopausal women in two intervention and control groups (n = 42 for each group). Data collection lasted for 6 months. No sample loss was observed during the study and all participants continued the study to the end.

The two groups were similar in terms of demographic and social characteristics. The mean age of the participants in both groups was approximately 51 years. Most of them were at the age range of 45 to 50 years. The majority of the participants had an education level higher than high-school degree. Most of them were housewives and married (both groups). 17% and 24% of the women in the intervention and control groups, respectively, did not exercise at all (Table 1).

There was no statistically significant difference between the two groups in terms of vasomotor symptoms before the intervention. In terms of severity of vasomotor symptomsin weeks 4 and 8, a statistically significant difference was found between intervention and control groups, when the baseline severity was taken into account. The results of repeated measures ANOVA, in intergroup comparison for severity of vasomotor symptoms, showed a statistically significant difference between the three time intervals (in both groups $p<0.001$) (Table 2).

There was no statistically significant difference between the intervention and control groups before the onset of intervention

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regarding the number of hot flashes. The number of hot flashes was significantly different between the two groups in weeks 4 and 8, when it was adjusted for number of hot flashes before the intervention. The results of repeated measures ANOVA in inter-group comparison showed a significant difference between the three time intervals for the number of hot flashes (In Intervention group: $p<0.001$, In Control group: $p=0.006$). (Table 3)

No side-effects were reported in any of the groups in this study.

Table 1. Comparison of the demographic characteristics of the study participants in intervention (black cohosh) and control groups (placebo)

Variables	Intervention group Mean (SD)	Control group Mean (SD)	Statistical indicators
Age (years)	51.47 (4.09)	51.76 (4.2)	t = 0.78, df = 82, p = 0.43
Length of menopause (months)	40.88 (31.7)	38.19 (35.7)	t = 0.71, df = 82, p = 0.71
Systolic BP	115.71 (13.5)	115.23 (8.6)	t = 0.19, df = 82, p = 0.84
Diastolic BP	79.28 (60.7)	77.38 (6.6)	t = 1.30, df = 82, p = 0.19
BMI	27.63 (3.64)	26.30 (2.97)	t = 1.83, df = 82, p = 0.07
Education	N (%)	N (%)	
Elementary	9 (21.4)	6 (14.3)	$\chi2 = 4.49$
Secondary	4 (9.5)	11 (26.2)	df = 3
High-school	20 (47.6)	19 (45.2)	p = 0.21
Academic	9 (21.4)	6 (14.3)	
Employment			
Housewife	33 (78.6)	33 (78.6)	$\chi2 = 0.22$
Employed	4 (9.5)	5 (11.9)	df = 2
Retired	5 (11.9)	4 (9.5)	p = 0.89
Income adequacy			
Yes	15 (35.7)	14 (33.3)	$\chi2 = 0.17$
No	3 (7.1)	4 (9.5)	df = 2
To some extent	24 (51.7)	24 (57.1)	p = 0.91
Exercise			
Never	7 (16.7)	10 (23.8)	$\chi2 = 0.71$
Sometimes	15 (35.7)	13 (31)	df = 3
Often	13 (31)	12 (38.6)	p = 0.87
Always	7 (16.7)	7 (16.7)	
Marital status			
Single	1 (2.4)	2 (4.8)	$\chi2 = 3.54$
Married	40 (95.2)	36 (85.7)	df = 3
Divorced	1 (2.4)	1 (2.4)	p = 0.31
Widow	0 (0)	3 (3.6)	
Total	42 (100)	42 (100)	

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Table 2. Mean severity of vasomotor symptoms in terms of follow-up time for intervention and control groups

	Intervention group Mean (SD)	Control group Mean (SD)	MD (95% CI)*	Statistical indicators
Pre-intervention (baseline)	4.04 (1.73)	3.59 (1.68)	0.45 (1.199, -2.90)	t = 1.21 df = 82 p = 0.22
† **4 weeks later**	1.83 (2.05)	2.64 (1.77)	-1.10 (-0.41, -1.79)	F = 10.09 df = 1 p = 0.002
† **8 weeks later**	0.76 (1.64)	2.45 (1.82)	-1.87 (-1.17, -2.57)	F= 28.44 df = 1 p < 0.001
Repeated measures ANOVA (Inter-group)	F = 82.78 df = 2 p < 0.001	F = 14.26 df = 2 p <0.001		

* Mean difference (95% confidence interval) † ANCOVA

Table 3. Mean number of hot flashes in terms of follow-up time for intervention and control groups

	Intervention group Mean (SD)	Control group Mean (SD)	MD (95% CI)	Statistical indicators
Pre-intervention (baseline)	5.90 (3.55)	5.11 (3.31)	0.78 (2.27, -0.70)	t = 1.05 df = 82 p = 0.29
*** 4 weeks later**	2.95 (3.24)	4.44 (3.22)	-2.06 (-1.17, -2.95)	F = 21.18 df = 1 p < 0.001
*** 8 weeks later**	1.07 (3.67)	3.92 (3.86)	-3.43 (-2.20, -4.66)	F = 30.89 df =1 p < 0.001
Repeated measures ANOVA(Inter-group)	F = 74.15 df = 1.58 p < 0.001	F = 6.67 df = 1.41 p = 0.006		

* ANCOVA

Discussion

The consumption of black cohosh in the present study (6.5 mg black cohosh dry root extract) once a day after dinner for 8 weeks caused a considerable decline in vasomotor symptoms severity and number of hot flashes compared with the placebo.

In a study titled "impact of cimicifugaracemosa dried ethanolic extract in menopausal disorders" conducted in Switzerland, [intervention (99cr extract of black cohosh) and control group (placebo)], 47% of the black cohosh group and 21% of the placebo group experienced a decrease in number of hot flashes which was statistically significant.[24] This was consistent with the present study.

In another study in Turkey titled "Black cohosh and fluoxetine in the treatment of postmenopausal symptoms", the monthly scores of hot flashes and night sweating significantly decreased in both groups. [33] However, this decline was much more significant in the black cohosh group at the end of month 6. There were 85% and 62% decline in the black cohosh and

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fluoxetinegroups, respectively.This study was consistent with the present study.

In a systematic review study, regarding the impact of black cohosh on menopausal symptoms, six trials with a total of 1163 pre- and postmenopausal women were included in the study.[30] In one of the trials in Germany, eighty 46 to 58-year-old women (pre- and postmenopausal) were divided into three double-blind groups which aimed to compare the impact of black cohosh, estrogen, and placebo on menopausal symptoms. One group received 2 tablets, containing black cohosh, every day. The other group received conjugated estrogens (0.625 mg), and the third group received placebo (two tablets every day for three months). Black cohosh significantly improved the studied criteria (time-dependent) in comparison with the placebo. The number of hot flashes declined from 5 times a day to less than once a day. However, no difference was seen between the placebo and conjugated estrogens. This study was consistent with the present study in terms of impact of black cohosh on reducing the number of hot flashes.

A study by Osmers et al. was published titled "efficiency and safety of isopropanolic black cohosh extract for climacteric symptoms".[23] The participants were randomly allocated into the groups receiving black cohosh (40 mg tablets), and matched placebo tablets for 12 weeks. The most significant effect was on hot flashes, which was in line with the present study.

Nevertheless, the results of some studies were contradictory to and inconsistent with the current study.

In a study performed in the Czech Republic the black cohosh extract had no significant effect on hot flashes.[34] This could be due to the difference in the type of black cohosh consumed.

In a study conducted in China, the failure of black cohosh, compared with Tibolone, was reported in relieving the menopausal symptoms. [35] The black cohosh dosage in that study was 40 mg. Their results were not in accordance with the present study which could be due to the different dosage of black cohosh and absence of a placebo group.

A study conducted in the U.S., titled "the effect of black cohosh on controlling hot flashes", measured the frequency and duration of hot flashes.[26] This was a cross-over study conducted in two 4-week periods for two groups of black cohosh and placebo. As a result, hot flashes decreased by 20% in the black cohosh group and 27% in the placebo group. This indicated the failure of black cohosh in comparison to the placebo. This study was not in accordance with the present study. The scoring tools were not mentioned and the results have been determined at the end of four weeks, which appears to be a short period for obtaining a reasonable result. In this study, black cohosh dosage was 20 mg equaled with 1 mg triterpene glycoside mixed with dicalcium phosphate, yeast, stearic acid, and magnesium. 16% of the participants in the 5th week, and 25% of them in the 9th week, discontinued the therapy and study due to lack of improvement. This inconsistency may be due to the above reasons.

In another study, conducted at the University of Illinois, Chicago, black cohosh and red clover[30], compared with placebo, could not reduce the frequency of vasomotor symptoms. This study was not in accordance with the results of the present study (the dosage of black cohosh was not mentioned). In this study, the participants were not similar in terms of race and body mass index (BMI) before the intervention. This may be the cause of the difference in their results.

No side-effects of black cohosh were seen in any of the above mentioned studies; which was in accordance with the present study.

Conclusion

Alternative hormonal therapy is still a standard treatment for menopause and vasomotor symptoms.[9] However, given the side-effects and serious risks of hormone therapy, the increased tendency of women

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toward using non-hormonal therapy and herbal therapies, the efficacy of black cohosh in this study and its safety, and based on the latest job description of midwives, approved by the Ministry of Health, allowing them to use herbal medicine, this herb can be proposed as an alternative option in relieving vasomotor and menopausal symptoms.[10,11,15]

It should also be mentioned that due to the 8 week time limit for examining the impact of black cohosh and since the effects of herbal medicines are identified in a longer period, it is recommended that this study be done in a 6-month follow-up and that the amount of LH and FSH hormones also be measured. We ignored to do so due to budget constraints.

Ethical issues

None to be declared.

Conflict of interest

The authors declare no conflict of interest in this study.

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