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Comparison the effect of manhae supplement with hormone therapy on frequency and intensity of hot flashes in postmenopausal women

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Abstract

Introduction: In recent years, many treatments have been used for hot flashes. Non-hormonal methods have the utmost attention and applied by the most women with hot flashes due to their high acceptability and limited side effects. The aim of this study was to compare the effect of Manhae and hormone replacement therapy (HRT) on hot flashes in postmenopausal women.

Materials & Methods: In this single blind randomized controlled trial, 72 eligible postmenopausal women recruited randomly. The Manhae group was treated with Manhae (850 mg daily) and HRT group was treated with (0.312 mg conjugated estrogen plus 2.5 mg medroxyprogesterone daily). Two groups followed-up for 12 weeks. Data was analyzed using SPSS software and Repeated Measure, t-test and Chi – Square test were used to compare changes in the frequency and intensity of hot flashes in two groups.

Results: After 12 weeks intervention, significant differences were not observed between two groups in the frequency of hot flashes ($p= 0.73$), however, significant differences were observed between two groups in intensity of hot flashes ($p< 0.001$), when HRT could reduce intensity of hot flashes better.

Conclusion: Manhae and hormone replacement therapy have similar effects on reducing the frequency of hot flashes, but the most significant effect of hormone therapy on reducing the intensity of hot flashes was evident. Manhae appears to be somewhat effective in reducing frequency of hot flashes in women who HRT is contraindicated.

Key words: Menopause, Hot flashes, Manhae supplement

Introduction

Menopause is one of the crucial stages in the life of women and appropriate treatment of its symptoms has a particular medical and psychological importance (1). Hot flashes are a common problem among postmenopausal women (2). This term refers to the sudden onset of redness of head, neck and chest with a feeling of intense heat in the upper body, which sometimes ends with profuse sweating (3). Due to declining estrogen levels, approximately 80% of postmenopausal women are experiencing hot flashes until three months after natural or surgical menopause (4-5). Hot flashes can affect the professional and social activities, the joy and the quality of life (6).

The most common conventional treatment is hormone replacement therapy or HRT (1) , which can reduce the hot flashes by 70-80% (7). Despite the many benefits that HRT produces, it can lead to complications such as heart attacks, coronary artery disease, stroke and thromboembolic events, as well as breast cancer (8). Alternative therapies should be used for the women who have contraindications to hormone (3).

Although, many women are not prohibited to use hormones, they do not like this approach and prefer to resort to natural treatment methods with less complications (9). People basically tend to conventional medicine when they are affected by a disease or have an injured part of body. However, when their goal is to improve the health, they turn to alternative cares, in order to treat chronic disorders, or to deal with lifestyle related issues

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(10). For this reason, the use of hormone therapy in women is less than 20 percent (11). Since the non-hormonal mechanisms play a role in the pathophysiology of hot flashes (12). Different therapies are in common usage e.g. alpha-2 adrenoceptors, Veralipride, Phenobarbital, oral Bromocriptine and Naloxone, vitamin K, mineral supplements, Belladonna alkaloids, along with the relievers for mild pain and tranquilizers or antidepressants such as Venlafaxine, and isoflavones or phytoestrogens such as soy and Black cohosh(3). In addition, various studies suggest the use of supplements such as folic acid, Omega-3, vitamin E, Oxtongue to reduce or control hot flashes. (13-16).

Given the huge number of women who reach menopause each year and due to their physical and psychological problems associated with menopause, it is necessary to find safe and effective treatments for its complications. Manhae supplement is a combination of fish oil (containing Omega-3 fatty acids), vitamin E, folic acid, citrus extract (containing flavonoids) and oxtongue (containing gamma-linolenic acid).

Considering that other studies have examined in detail the composition of this product, but of the best of researcher's knowledge, there is lack of studies to consider the effect of whole product for reducing complications of menopause. The primary aim of this study was to compare the effects of the Manhae supplement with HRT on hot flashes in postmenopausal women.

Materials and Methods

This study is a single blind randomized controlledtrial. Subjects were selected from postmenopausal women referring to the Health Care Center No. 1, located in the East area of Ahvaz, Iran during 2011-12. Based on a pilot study conducted on 15 subjects the sample size was determined to be 36 women in each group. The data used to calculate the sample size was the mean of hot flashes in the week before treatment and week 12th after treatment in Manhae group. Inclusion criteria were including; basal literacy, experiencing at least four mild, moderate or severe hot flashes per day, 1-5 year passed from last menstruation, age 45 -55 years and BMI 19.8-29. Exclusion criteria were including; known chronic diseases, history of breast diseases, abnormal mammograms, cervical, uterine and ovarian abnormalities diagnosed by ultrasound or Pap smear; abnormal menopause caused by radiotherapy or surgery, having special diet, use of herbs and supplement to relieve hot flashes, and smoking during treatment. A written informed consent was obtained from all participants and necessary trainings were provided on how to record the symptoms and how to consume supplements or HRT. Given the risks of hormone therapy, blood pressure, weight and height were measured to check the health situation of the contributors; also tests of blood glucose, LDL, HDL, T3, T4, TSH, SGPT, SGOT, cholesterol, triglycerides, Pap smear, mammogram and ultrasound were requested. Then they were entered the study after giving bill of health.

Study tools were included; demographic questionnaire, weekly record checklist for the frequency and intensity of hot flashes in the time of recruitment and 12 weeks after treatment, thermometer, scales and meters. Content validity was used to check the validity of the questionnaire and checklist. Reliability tests were conducted in a pilot study, and Cronbach's alpha was calculated at 0.98. The samples were randomly divided into two groups of Manhae therapy and hormone therapy. Then, treatment was conducted over 12 weeks.

Women in the Manhae group were requested to take one capsule with breakfast every day and women in the HRT group requested to take 0.312 mg conjugated estrogen plus 2.5 mg medroxyprogesterone daily.

Each Manhae capsule (Ponroy Vitarmonyl Industries, ordered by Nutrisante laboratory in France) includes 80 mg of Omega-3, 85 mg of citrus extract (containing flavonoids), 135 mg of Oxtongue oil, 10 mg of vitamin E, and 0.18 mg of

folic acid. According to the pharmaceutical brochure of the manufacturer, minimum effective dose of Manhae was prescribed. In addition, the minimum effective dose cited in the endocrinology references was also considered as the dose of HRT (3). The subjects requested come to clinic nine times during the study as follows; one week before treatment, and 1, 2, 3, 4, 6, 8, 10 and 12 weeks after treatment. In the weekly checklist form, the frequency and intensity of hot flashes were recorded. Intensity of hot flashes were considered mild (sensation of heat without sweating), moderate (sensation of heat with sweating, without interfering with daily work) and severe (sensation of excessive heat with sweating, with interfering with daily activities), which were scored 1, 2 and 3 respectively(17).

In weekly checklist form, the frequency and intensity of hot flashes, as well as any possible side effects were recorded by contributors. Final checklist form for the frequency and intensity of hot flashes included a summary of information related to the weekly forms, which was separately completed by the researcher for each sample, as follows:

The mean daily frequency of hot flashes was equal to the frequency of hot flashes per week divided by 7. In addition, the mean daily intensity of hot flashes was calculated on the basis of the intensity of hot flashes in a week divided by the frequency of hot flashes.

Once the data were collected, they were entered into a computer and analyzed using SPSS software. Repeated Measures and t-tests, were utilized to compare changes in the frequency and intensity of hot flashes and Chi-square test was used to assess differences between categorical variables in both groups.

Ethical considerations

The initial plan of the study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences with code No. u-91116.

Results

A total of 60 women completed the trial . Six women were excluded for the fear of potential side effects, four women because of using other remedies for hot flashes, and two women for irregular use of medication.

The mean age of subjects was 50.48 ± 2.75 years. Most of them were married (88.33%), had completed primary education (75%), were housewives (91.66%) and in a good economic situation (91.67%). No significant difference was found between two treatment groups in terms of demographic variables (Table 1).

In addition, the two groups had no significant difference in the frequency (p=0.179) and intensity (p=0.328) of hot flashes before treatment. The mean frequency and intensity of hot flashes before treatment in Manhae group were 5.66 ± 1.44 and 2.47 ± 0.37 respectively, while in HRT group, it was 6.16 ± 1.43 and 2.36 ± 0.48, correspondingly.

Twelve weeks after treatment, the mean frequency of hot flashes between the two groups showed no significant difference (p=0.73). The within study of Manhae group showed that the mean frequency of hot flashes declined from 5.66 in the week before treatment to 3.86 in the 12th week of treatment (p=0.0001); and there was no significant difference in the mean frequency of hot flashes between the week before treatment and the second week of treatment (p=0.096). However, a significant decrease was observed at beginning of the third week, compared to the week before treatment (p=0.029). The within group study of the HRT also showed that the mean frequency of hot flashes decreased from 6.16 in the week before treatment to 2.72 in the 12th week of treatment (p=0.0001); and the mean frequency of hot flashes in the week before treatment has no significant difference with that in the first week of treatment (p=0.187). However, compared to the week before treatment, it showed a significant decrease from the beginning of the second week, (p=0.024). At the end of the 12th week of treatment, the mean

improvement in frequency of hot flashes in Manhae and HRT groups was 31.9% and 56.15% respectively (p=0.0001)(Figure 1).

After 12 weeks of treatment, there was significant difference between the intensity of hot flashes in Manhae and HRT groups (p=0.001). In the within group study of Manhae, the mean intensity of hot flashes decreased from 2.47 in the week before treatment to 2.08 in the 12th week of treatment (p=0.0001); and the mean intensity of hot flashes between the week before treatment and the 4th week of treatment showed no significant difference (p=0.103); but compared to the week before treatment, there was a significant decrease from the sixth week of treatment (p=0.006). In the within group study of the HRT, the mean intensity of hot flashes reduced from 2.36 in the week before treatment to 1.41 in the 12th week of treatment (p=0.0001), and that in the week before treatment had no significant difference with that in the first week of treatment (p=0.304), but the mean in the second week of treatment was significantly lower than that in the week before treatment (p=0.03). At the end of the 12th week of treatment, the mean improvements in the intensity of hot flashes in Manhae and HRT groups were 15.126% and 38.86% respectively (p=0.0001)(Figure 2).

Table 1: Demographic characteristics of women in two study groups

Demographic characteristics		Manhae group n=30 Mean ± SD Or Number (%)	HRT group n=30 Mean ± SD Or Number (%)	p-value
Age(Years)		50.37 ± 2.76	50.6 ± 2.77	0.745
Duration of menopause(month)		25.8 ± 8.66	26.83 ± 8.37	0.642
BMI(kg/m^2)		26.15 ± 1.99	25.46 ± 1.99	0.725
Blood pressure	Systolic	114.33 ± 8.58	112.33 ± 6.79	0/312
	Diastolic	72.33 ± 5.68	72 ± 4.07	0.795
Marital Status	Married	27 (90)	26 (86.66)	
	Unmarried	3 (10)	4 (13.33)	0.688
Number of Pregnancies	0 , 1	1 (3.33)	1 (3.33)	
	2	2 (6.66)	1 (3.33)	
	3	4 (13.33)	6 (20)	0.538
	≥ 4	23 (76.66)	22 (73.33)	
Educational level	Primary education	23 (76.66)	22 (73.33)	
	High school	6 (20)	6 (20)	0.837
	University education	1 (3.33)	2 (6.66)	
Occupation	Employed	28 (93.33)	27 (90)	
	Housekeeper	2 (6.66)	3 (10)	0.640
Economical level	Good	27 (90)	28 (93.33)	0.640
	Not favorable	3 (10)	2 (6.66)	

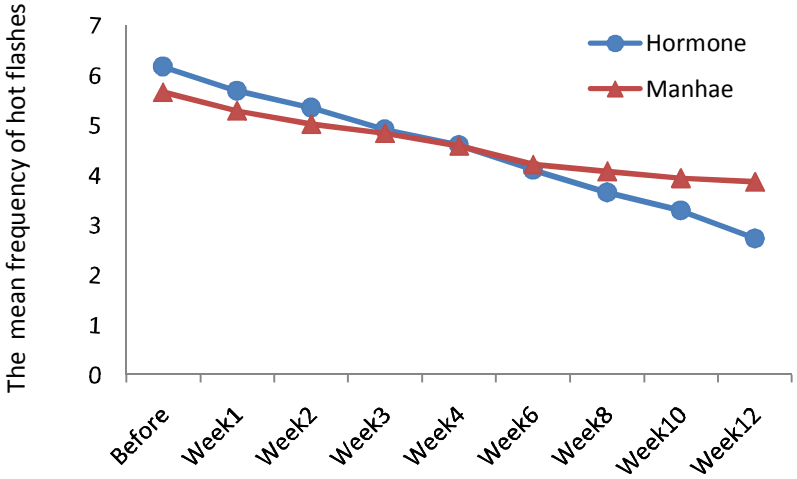

Figure 1: The mean frequency of hot flashes in Manhae and HRT groups

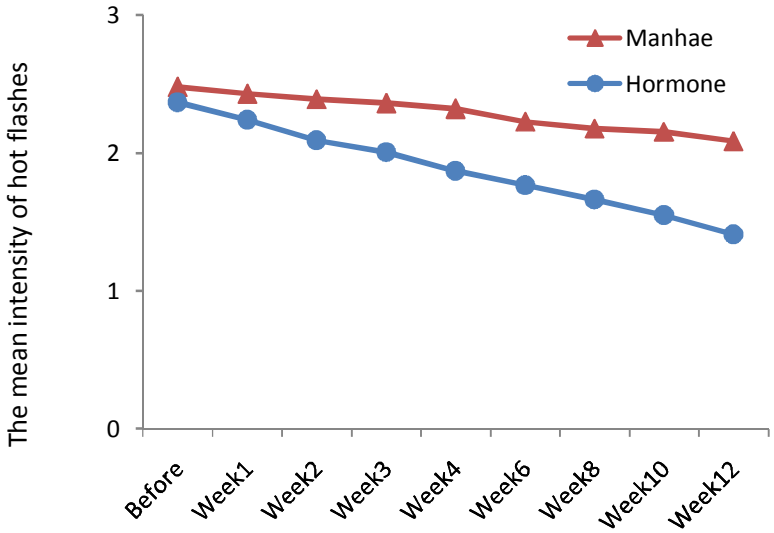

Figure 2: The mean intensity of hot flashes in Manhae and HRT groups

Discussion

The results showed that the mean frequency of hot flashes after treatment in both Manhae and hormone therapy groups had no significant difference, and that Manhae, like hormone, seems able to reduce the frequency of hot flashes in postmenopausal women. Despite a significant decrease in the intensity of hot flashes in both treatment groups, there was significant difference between two groups, and hormone was more effective in reducing the intensity of hot flashes, compared to Manhae. Due to the lack of access to clinical studies about the effects of Manhae on hot flashes, the studies that have separately examined the compounds of Manhae on hot flashes are mentioned below.

In a study entitled "the effect on hot flashes of a soy isoflavone extract alone and with the Omega-3 in postmenopausal women'' by Campagnoli et al., the frequency of hot flashes after treatment with isoflavones in combination with and without Omega-3 was reported to be reduced by 38.5% and 20%, respectively. According to this study, Omega 3-fatty acids could reduce hot flashes using their influence on neuronal membranes or the modulation of the neurotransmitter function and the serotoninergic system (14). These results with a slight difference are consistent with an improvement of 31.9 percent in the frequency of hot flashes in Manhae group. These differences may be due to the moderate and severe hot flashes used in the study of Campagnoli et al, while the present study recruited the mild hot flashes as well.

Norepinephrine and serotonin control the thermoregulatory area in hypothalamus, and endorphin plays a key role in regulating the release of norepinephrine. Therefore, the factors that increase endorphin levels are expected to reduce the release of central norepinephrine and decrease the hot flashes. Vitamin E may reduce hot flashes through its influences on the levels of endogenous opioids (15). The present study is consistent with the study by Ziaei et al, on "the effect of vitamin E on hot flashes in postmenopausal women". Within group comparison in their studies showed that the mean frequency of hot flashes after nine weeks of treatment (including wash out period) significantly decreased, and the reduction in the group treated with vitamin E was higher than that with placebo (18).

According to a study that was performed by Sherief et al, about the effect of folic acid supplement on the occurrence of hot flashes and plasma levels of 3-methoxy-4-hydroxy phenyl glycol (major metabolite of norepinephrine in brain) after four weeks of treatment, the number of women who reported improvement in hot flashes was significantly higher, and the plasma levels of 3-methoxy-4-hydroxy phenyl glycol in the treatment group was lower. The results of this study showed that folic acid may help to reduce hot flashes by reduction of central noradrenergic activity (13), which is consistent with reduction in hot flashes in Manhae group in the present study.

Within group comparison shows that the frequency and intensity of hot flashes in the HRT group have decreased since the beginning of the second week of treatment, which is consistent with the study of Fawad et al, about the effect of HRT on vasomotor symptoms in postmenopausal women (19). In their study, reducing the frequency and intensity of hot flashes in the HRT group has been significant in the second week, which is consistent, with a little difference, with the study of Michell regarding pros and cons of hormone therapy. Both frequency and intensity of hot flashes in Michell's study reduced in the third week of the treatment (20). It seems likely this difference is due to higher age of the participants in this study (mean age of 63.2 years) compared to our study (mean age of 50.6 years in the HRT group). Therefore, the subjects in Michell's study maybe were more hypo-estrogenic than those in the present study.

Compared to the effect of Manhae supplement and hormone therapy on the intensity of hot flashes, there is significant difference between

both groups, which is consistent with the results of the study of Biglia et al, on non-hormonal treatment of hot flashes with Gabapentin and vitamin E, in which there was significant different between the intensity of hot flashes in both groups(21).

Side effects evaluation of Manhae supplement and hormone therapy during treatment showed that the major complications in Manhae group were gastrointestinal ones, which is consistent with the study by Moghaddam et al, in "the effects of Omega-3 on vasomotor dysfunction in postmenopausal women" (22). In the HRT group, the most common side effect was headache, which is consistent with Compston's study entitled "the risks and benefits of HRT" (23). In present study, HRT improved the average time of hot flashes by 56.15%, which is consistent with some studies in Iran (24), but is lower than other studies in which the decrease was 70-80% for the HRT (7). According to the results of this study and previous studies, the response to hormone therapy appears to be affected by various factors that may require further evaluation in future studies.

This was a single blined randomized controlled trial that carried out with intense follow-up and for the first time in Iran. The limitations of this study include the data relating to the frequency and intensity of hot flashes and possible side effects, which were collected from individual reports. Thus, this information may exposed to the recall biase.

Conclusion

Manhae supplement and hormone therapy have similar effects on reducing the frequency of hot flashes, but compared to Manhae, HRT had more significant effect on reducing the intensity of hot flashes. It seems that the Manhae supplement can be somewhat effective in reducing the frequency of hot flashes and is recommended as a choice to reduce hot flashes for those who have contraindications to hormone or do not tend to use hormones for any reason.

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