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Original Article

A Double-Blind, Randomized Controlled Trial of Soy versus Estrogen in Alleviating Post-Menopausal Vasomotor Symptoms

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Abstract :
Introduction: Estrogen therapy has long been prescribed to treat menopausal symptoms. It has been extensively studied, and it is the most consistently effective therapy for vasomotor symptoms. Soy has been investigated, mainly over the past 10 years, because of their potential effects on the health of postmenopausal women.
Objectives: To compare the efficacy of soy and estrogen in alleviating post-menopausal vasomotor symptom
Study Design: Randomized controlled trial.
Materials & Methods: A total of 122 post-menopausal women, 40 to 65 years of age were included. Patients on hormone replacement therapy, tamoxifen or receiving chemotherapy/radiation therapy or taking any dietary supplements were excluded. Then selected patients were placed randomly into Group A (estrogen) & Group B (soy), by using lottery method. Patients were called for follow up after 12 weeks and data was collected of the number of hot flushes average per day and efficacy.
Results: The mean age of women in group A was 52.82 ± 6.08 years and in group B was 52.09 ± 6.90 years. The mean hot flushes/day in group A was 2.56 ± 1.19 and in group B was 2.85 ± 1.25. There was 50% post-treatment reduction in hot flushes as compare to number of hot flushes average per day at pre treatment in 57 (93.44%) patients in Group A (Estrogen) while in Group B (Soy), it was seen in 46 (75.41%) patients with p-value of 0.006.
Conclusion: This study concluded that use of estrogen therapy was more effective in alleviating post-menopausal vasomotor symptom compared to soy therapy.
Keywords: Menopause, flushes, estrogen, soy

Introduction

The World Health Organization defines menopause as the permanent natural cessation of menstruation for one year due to the loss of ovarian follicular activity.[1] The median age of menopause is 51 years**,** but it may sometimes occur earlier (before the age of 40) for surgical, autoimmune, genetic, iatrogenic and idiopathic reasons.[2] Menopause occurs due to changes in the levels of female sex hormones, decreases in the circulating levels of estrogen and progesterone, and concomitant increases in the levels of follicle-stimulating hormone and luteinizing hormone. The initial years of menopause are often accompanied by vasomotor symptoms such as hot flushes and night sweats.

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Hot flushes are typically experienced as a feeling of intense heat with sweating and rapid heartbeat, and may typically last from two to thirty minutes for each occurrence. The frequency, severity, and duration of vasomotor symptoms vary according to the population.[3] Menopause related symptoms have a negative effect on the quality of life of postmenopausal women.[4]

Gold standard treatment for postmenopausal symptoms is Hormone Replacement Therapy.[5] Hormone Replacement Therapy is recommended for vasomotor symptoms, treatment of vaginal atrophy and prevention of osteoporosis but it may be associated with various side effects including fluid retention, bloating, breast tenderness or swelling, nausea, leg cramps, headache, indigestion.[6] Estrogen therapy has long been prescribed to treat menopausal symptoms. It has been extensively studied, and it is the most consistently effective therapy for vasomotor symptoms.[7] Estrogen is a steroid hormone which is derived from the androgenic precursors and rostenedione and testosterone by means of

aromatization. Estrogens affect many different systems, organs, and tissues, including the liver, bone, skin, gastrointestinal tract, breast, uterus, vasculature, and central nervous system. These effects appear to become most prominent during times of estrogen deficiency, such as the menopausal transition. Soy has been investigated, mainly over the past 10 years, because of their potential effects on the health of postmenopausal women. Even though some clinical studies have demonstrated the efficacy of soy in reducing the frequency and severity of hot flushes, soy foods have been adopted as a natural alternative to hormone therapies because the soybean contains nutritionally relevant amounts of isoflavones.[8] Isoflavones have been demonstrated to reduce both the severity and the frequency of menopause-related vasomotor symptoms.[9]

Our hospital provides medical care for a wide area, so we have decided to perform this study to assess the treatments for post-menopausal problems in shape of vasomotor symptoms in the patients presenting in gynaecology outpatient department and to study the effect of estrogen and soy therapy for the relief of vasomotor symptoms in our general population. This study would also pave the way for our doctor community to select the right treatment for postmenopausal vasomotor symptoms for our local population.

Materials & Methods

This randomized controlled trial was done from January 2015 to December 2015. After approval from local ethical committee, 122 cases of postmenopausal women having hot flushes defined as reporting 4 hot flushes average per day presented to the OPD Department of Obstetrics & Gynaecology, Abbas Institute of Medical Sciences, Muzaffarabad were selected. Patients with hormone replacement therapy, surgically induced menopause (oophorectomy), tamoxifen or receiving chemotherapy/radiation therapy or planned antineoplastic chemotherapy/ radiation therapy, renal failure and taking any dietary supplements for the treatment of hot flashes were excluded. Informed, written consent was taken. At study entry baseline demographics were recorded. Randomization was performed by block design. Randomization was 1:1 for Estrogen group or Group-A and Soy group or Group-B.

Data was collected about the years since menopause and no. of hot flushes average per day before the start of treatment in both groups. Group A was allocated to treatment with estrogen as Premarin 0.3 mg one tablet daily for 12 weeks whereas the Group B was given Soy as tablet 35 mg daily for 12 weeks. All the patients were kept blinded about the type of medicine. Medicines was provided to them without strips in plain air-tight glass bottles and a list was made to identify the nature of medicines and was kept hidden from the patients and data recorders. Patients were asked to write down the numbers of hot flushes daily in a diary. Patients were called for follow up after 12 weeks and data was collected of the No. of hot flushes average per day and efficacy (number of hot flushes average per day at post-treatment reduced to 50% as compare to number of hot flushes average per day at pre treatment).

Data was analyzed with statistical analysis program (SPSS version 20.0). Frequency and percentage was computed for qualitative variables like age groups and efficacy. Mean ± SD was presented for quantitative variables like age, No. of Hot Flushes average per day and years since menopause. Efficacy was compared between the both groups and chi square was applied as test of significance. P-value ≤0.05 was taken as significant.

Results

Age range in this study was from 40 to 65 years with mean age of 52.46 ± 6.49years.Majority of the patients 61 (50.0%) were between 51 to 60 years of age (Table I). Mean duration of menopause was 11.08 ± 6.28 years. The mean hot flushes/day in group A was 2.56 ± 1.19 and in group B was 2.85 ± 1.25.

There was 50% post-treatment reduction in hot flushes as compare to number of hot flushes average per day at pre treatment in 57 (93.44%) patients in Group A (Estrogen) while in Group B (Soy), it was seen in 46 (75.41%) patients with p-value of 0.006 (Table II).

Table-I: Age distribution for both groups (n=122)

Age (years)	Group A (n=61)		Group B (n=61)		Total (n=122)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
40-50	23	37.70	25	40.98	48	39.34
51-60	31	50.82	30	49.18	61	50.0
61-65	07	11.47	06	9.84	13	10.66
Mean ± SD	**52.82 ± 6.08**		**52.09 ± 6.90**		**52.46 ± 6.49**	

Table II: Comparison of Efficacy between both Groups (n=122)

		Group A (n=61)		Group B (n=61)	
		No. of Patients	%age	No. of Patients	%age
EFFICACY	Yes	57	93.44	46	75.41
	No	04	6.56	15	24.59

P value is 0.006 which is statistically significant.

Discussion

Hot flashes are the most common menopausal symptom in North America and Europe; up to 70% of women are affected. The average duration of hot flashes is 6 months to 5 years, although 20% of women continue with symptoms into their 70s and 80s. Estrogens are effective in decreasing the frequency and severity of these symptoms and are commonly used as a positive control in clinical trials. However, the management of menopause has changed considerably since the publication of the Women's Health Initiative (WHI) trial results in 2002.[10] This report showed estimated hazard ratios (HRs) for chronic heart disease CHD, 1.29 (1.02-1.63); breast cancer, 1.26 (1.00-1.59); stroke, 1.41 (1.07-1.85); pulmonary embolism PE, 2.13 (1.39-3.25); colorectal cancer, 0.63 (0.43-0.92); endometrial cancer, 0.83 (0.47-1.47); hip fracture, 0.66 (0.45-0.98); and death due to other causes, 0.92 (0.74-1.14). Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index.[10]

This randomized controlled study has compared the efficacy of soy and estrogen in alleviating post-menopausal vasomotor symptom. Mean age of patients in our study was 52.46 ± 6.49years. The mean age of women in group A (estrogen) was 52.82 ± 6.08 years and in group B (soy) was 52.09 ± 6.90 years. Majority of the patients 61 (50.0%) were between 51 to 60 years of age. These results were very much comparable with study of Fawad et al[7] who had found a mean age of 53 years with majority of patients between 50 to 60 years of age. Vitolins et al[11] in his study had also found the mean age of 55 years in menopause women which is also much comparable to our study. Similarly, Nahas et al[12] in his study has also found the mean age of 55 years.

In our study, there was 50% post-treatment reduction in hot flushes as compared to number of hot flushes average per day at pretreatment in 93.44% patients in Group-A (Estrogen) while in Group-B (Soy), it was seen in 75.41% patients. So, Efficacy was 93.44% in Group-A (Estrogen) and 75.41% in Group-B (Soy) with p-value of 0.006. In a recent systematic review shows that estrogen therapy can expect a 75% reduction in the frequency of hot flushes and an 87% reduction in their severity.[13] Fawad et al reported 80% women with hot flushes got complete relief when treated with estrogen therapy. Vitolinset al[11] has reported the treatment failure in 2.9% for Estrogen therapy and 18.4% for Soy therapy. [7]

In a recently done randomized controlled trial by Borah BK[14], it was found that hot flashes were reduced significantly in 82.75% women in estrogen group in comparison to 26.92% women only in soy group. Estrogen alone markedly improves the frequency and severity of vasomotor symptoms as demonstrated by many randomized trials.[15] Estrogens, which are available in oral, transdermal, vaginal ring and topical forms, are effective in up to 90% of women with vasomotor symptoms.[16] The benefit is dose-related and even low doses of estrogens are often effective.[17,18]

In a study from Australia, 58 postmenopausal women ages 30–70 years were randomized to receive soy flour or wheat flour over 12 week. It was seen that vasomotor symptoms decreased in both groups with no significant difference between them.[18]

According to Utian et al [19], vasomotor symptoms in surgical menopause can be reduced upto 80% with estrogen. In another study done in Canada, out of 99 women, 87 women who completed the trial, there was no significant difference in the frequency and severity of hot flashes between treatment groups.[20] In a double-blind randomized controlled trial of low-dose hormone therapy, Carmignani treated symptomatic postmenopausal women with either a regimen of 1mg estradiol and 0.5mg norethisterone acetate, daily dietary soy supplementation containing 90 mg of isoflavone, or placebo for 16 weeks and reported that patients who received soy supplementation and hormone therapy had a 49.8% and 45.6% reduction in hot flushes, respectively.[21]

In a previous double-blind, placebo-controlled study of 50 postmenopausal women with contraindication for conventional hormone therapy, the author demonstrated alleviation of vasomotor symptoms in 44% of the postmenopausal women using soy germen versus a 10% decrease with placebo.[21] In the US, 82 women with irregular menses or in amenorrhea for at

least 12 months were randomized in a cross-over design between 2 diet sequences: therapeutic lifestyle changes diet with soy or without soy.[22] Soy nut ingestion was associated with a 45% decrease in hot flashes in women with >4.5 hot flashes/d at baseline ($P < 0.001$) and a 41% decrease in those with ≤4.5 hot flashes/d. When hot flashes were assessed by the menopausal symptom quality of life questionnaire, the group consuming soy nuts reported a 19% decrease in vasomotor score ($P = 0.004$).

Crisafulli A et al[23] evaluated the effects of the phytoestrogen genistein (an isoflavone), estrogen – progesterone HRT, and placebo on hot flushes in postmenopausal women and reported a 22% daily reduction in hot flushes in the genistein group after 12 weeks of treatment when compared with placebo, and a 53% reduction after 12 weeks when compared with placebo in the HRT group. In another study[12], total relief of hot flushes occurred in 36.8% of the women on soy isoflavone. This rate is modest when compared to the 77% reduction reported in a meta-analysis of trials using estrogen therapy.[24] Another systematic review and meta-analysis done by Bolanos-Diazetal et al[25] concluded that hormone therapy and soy interventions are efficacious in reducing flushes in post menopausal women compared to placebo; however using indirect comparison, they found a statistically significant different between HT and soy extracts in their respective effects on hot flushes.

Conclusion

This study concluded that efficacy of estrogen therapy (93.44%) was more in alleviating post-menopausal vasomotor symptoms as compared to soy therapy (75.41%). So, we recommend that estrogen therapy should be used as primary treatment in women for relief of post-menopausal vasomotor symptoms in order to reduce their morbidity.

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