Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?

H. Hassa[1], H.M. Tanir[1], T. Oge[2]

[1]Department of Obstetrics and Gynecology, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir
[2]Agrı Kadin Dogum ve Cocuk Hastanesi, Agri (Turkey)

Summary

Objective: To evaluate the short-term effects of two hormone therapy (HT) regimens and placebo on the Greene Climacteric Scale (GCS) of women with surgical menopause following six months of treatment. *Methods:* This 6-month, prospective, randomized, parallel-group, masked evaluator study compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (group I), 3.9 mg transdermal 17ß-estradiol patch applied every week (group II) and placebo (group III). Mean GCS before and after six months of treatment in each group was compared. *Results*: In groups I and II, vasomotor symptoms ($p < 0.005$, $p < 0.05$), somatic symptoms ($p < 0.05$, $p < 0.05$) and total score ($p < 0.005$, $p < 0.01$) significantly reduced from baseline values respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, vasomotor ($p < 0.05$), subscore and total score ($p < 0.05$) decreased significantly while other subscore reductions were not significant. *Conclusions:* Estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Additional larger prospective randomized studies need to be conducted in an aim to look at not only short-term but also long-term effects on climacteric symptoms, in comparison to both placebo arms and different dose and mode of HT use.

Key words: Surgical menopause; Greene Climacteric Scale; Hormone therapy; Placebo.

Introduction

Many psychological disturbances such as depressed mood, sleep problems, anxiety, irritability, and decreased libido that adversely affect the quality of life are attributed to early signs and symptoms of estrogen deprivation following surgical or natural menopause [1, 2]. We previously reported that intensity and frequency of urogenital symptoms and climacteric complaints based on the Greene Climacteric Scale (GCS) increased during menopausal transition [3].

Studies are quite conclusive as to whether hormone treatment (HT) improves the quality of life of menopausal women [4, 5]. As a measure for climacteric symptoms and complaints, the GCS has been introduced to meet the present accepted standards for psychological, somatic and vasomotor symptoms [6]. Taking the estrogen arm of the WHI study into consideration, although increased risk of stroke and no protective effect against breast and heart, estrogen still remains the most efficient way to alleviate climacteric complaints [7, 8].

The aim of this study was to evaluate the short-term effects of two HT regimens and placebo on the GCS of women with surgical menopause following six months of treatment.

Material and Methods

This 6-month, prospective, randomized, parallel-group, masked evaluator study conducted at the Department of Gynecology and Obstetrics Menopause Unit, Eskisehir Osmangazi University compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (CEE), a 3.9 mg transdermal 17ß-estradiol patch applied every week, and placebo. The local medical ethics committee approved the study and the tenets of the Declaration of Helsinki were followed.

Two-hundred and forty-seven women who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy due to benign gynecological conditions such as uterine myoma, benign adnexal mass, endometrial hyperplasia/polyp, endometriosis or intractable chronic pelvic pain were prospectively recruited into the study. Exclusion criteria were the presence of hypertensive disorders, previous history of gynecological or malignant disease, chronic liver, gallbladder, chronic renal, cardiac or endocrine diseases, current intake of medications known to affect coagulation, fibrinolysis, cigarette smoking, cerebrovascular or thromboembolic disease, self-admitted history of depression, history of psychotropic drug intake in the 6-12 weeks before the trial, chronic renal or liver disease, genital hemorrhage of undetermined origin and current intake of liver-enzyme inducing medication (barbiturates, phenytoin, rifampicin, carbamazepin). None of patients had been under HT before or after the operation. After obtaining a signed informed consent, systolic and diastolic blood pressure measurement, complete blood count, body mass indices (BMI, kg/m^2) basal blood liver function tests, fasting glucose levels and mammography were performed.

With regard to demographic characteristics, age, number of parity, gravidity, number of abortions, and living children were assessed prior to the study. Of the 247 women with surgical menopause, 83 women (group I) were randomly assigned to take 0.625 mg CEE (Premarin®, Wyeth, Istanbul, Turkey), 81 women (Group II) a 3.9 mg transdermal 17ß-estradiol patch applied every week (Climara®, Schering, Istanbul, Turkey) and 83 women (group III) received placebo. Randomization was obtained using a list of random numbers. HT was started after pathological examination of the specimen. All women completed questionnaires on aspects of quality of life assessed by the GCS with the same masked evaluator. During the study the investigator and the staff were masked to the treatment regimens.

Revised manuscript accepted for publication February 26, 2009

The GCS measured a total of 21 symptoms (Table 1) (6). Each symptom was rated by the woman herself according to its severity using a four-point rating scale: not-at-all (0); a little (1); quite a bit (2); extremely (3). Symptoms 1-11 address psychological symptoms divided in a measure of anxiety (symptoms 1-6) and depression (symptoms 7-11). Somatic symptoms are addressed in symptoms 12-18 and vasomotor symptoms in symptoms 19 and 20. Symptom 21 is a probe for sexual dysfunction. The total GCS is the sum of all 21 scores. Mean GCS before and after six months of treatment in each group was compared. Statistical analysis was performed by using SPSS for Windows, Version 13.0 (SPSS Inc, Chicago, IL, USA). Mean values are expressed as mean ± standard error of mean (SEM). Data were analyzed by the paired Student's t-test analysis. All tests were two-sided, and statistical significance was set a priori at $p < 0.05$.

Table 1. — *Items of the Greene Climacteric Scale [6]* [a].

Symptom
(1) Heart beating quickly or strong
(2) Feeling tense or nervous
(3) Difficulty in sleeping
(4) Excitable
(5) Panic attacks
(6) Difficulty in concentrating
(7) Feeling tired or lacking in energy
(8) Loss of interest in most things
(9) Feeling unhappy or distressed
(10) Crying spells
(11) Irritability
(12) Feeling dizzy or faint
(13) Pressure or tightness in head
(14) Parts of body feel numb
(15) Headaches
(16) Muscle and joint pain
(17) Loss of feeling in hands
(18) Breathing difficulties
(19) Hot flushes
(20) Sweating at night
(21) Loss of interest in sex

[a] Greene J.G.: "Constructing a standard climacteric scale". *Maturitas*, 1998, *29*, 25.

Results

Demographic characteristics of groups I, II and III are shown in Table 2. No statistically significant differences were observed between three groups. Although not depicted in Table 2, the level of education, occupational status, and percentage of women currently on regular exercise did not differ between the groups. Before HT, baseline GCS total score and subscores of both groups prior to HT were similar. As shown in Table 3, in group I and group II, vasomotor symptoms ($p < 0.001$, $p < 0.05$), somatic symptoms ($p < 0.05$, $p < 0.05$) and total score ($p < 0.05$, $p < 0.005$) significantly reduced from baseline values, respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, the vasomotor ($p < 0.05$) subscore and total score ($p < 0.05$) decreased significantly while other subscore reductions were not significant. Oral estrogen and placebo revealed statistically significant differences when compared with transdermal estrogen and oral estrogen in which reduced GCS subscores and total score statistically were nearly the same as placebo.

Table 2. — *Demographic characteristics of groups I, II and III (*mean ± SEM).*

Parameters parameters	Group I (n = 83) 0.625 mg oral CEE	Group II (n= 81) 3.9 mg transdermal 17β estradiol patch	Group 3 (n = 83) Placebo
Age (years)	49.7 ± 0.4	50.5 ± 0.9	50.4 ± 0.4
Number of gravidity (n)	4.4 ± 0.2	4.6 ± 0.3	4.4 ± 0.1
Number of parity (n)	2.9 ± 0.1	2.7 ± 0.1	2.8 ± 0.1
Number of abortion (n)	1.6 ± 0.1	1.9 ± 0.2	1.8 ± 0.2
Number of living children (n)	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.2
BMI (kg/m²)	28.3 ± 0.4	29.0 ± 0.7	27.9 ± 0.3

CEE: conjugated equine estrogen.

Discussion

This prospective, double-blind study has demonstrated that oral transdermal estrogen and placebo significantly improved vasomotor symptoms and total score. Taking all groups into consideration, anxiety, depression and sexual subscores statistically showed no improvement following six months of HT. In the present study oral CEE was found to be the most effective in vasomotor symptoms ($p < 0.001$). Although transdermal 17ß-estradiol and placebo are less effective than oral CEE in vasomotor symptoms, they also revealed statistically significant improvement ($p < 0.05$).

This clinical trial compared the short-term effects of 0.625 mg oral CEE, transdermal 17ß-estradiol and placebo on GCS scores in women with surgical menopause. The subject of this study was mostly a homogenous group with regard to obesity, occupation, level of education and state of regularly exercising and hysterectomy status. All of those factors have been proven to result in more climacteric symptom-free periods during postmenopause [9].

To confront climacteric complaints different treatment strategies have been established such as physical exercise, hormone therapy, tibolone, alternative remedies like antidepressants and herbal therapy [10-12]. Of them, different forms of HT such as the oral vs transdermal route or a low-dose continuous combination of estrogen+progesterone and tibolone were compared with each other or placebo in several studies [13-18]. Cohen *et al*. [13] examined the effect of short-term (4 weeks) use of transdermal 17ß-estradiol with placebo in 22 peri-postmenopausal women. The authors concluded that perimenopausal women may benefit from short-term use of an estradiol patch but did not obtain conclusive results on women with surgical menopause. Baksu *et al*. [14] through a randomized, double-blind interventional study has compared the effects of tibolone and transdermal estrogen therapy on climacteric complaints in women with surgical menopause following six months of HT. They concluded that both the transdermal estradiol patch and tibolone showed significant improvements in menopausal symptoms, depression and anxiety scores assessed by Kupperman's scales compared to the placebo group. Haines *et al*. [15] conducted a prospective, randomized, placebo-controlled study on the effect of 1 and 2 mg oral estradiol on menopausal symptoms, anxiety and depression symptoms of postmenopausal women (assessed by Kupperman's scale)

Table 3. — *Distribution of total GCS scores and mean subscores ± SEM of women with surgical menopause assigned to 0.625 mg oral CEE (group I), a 3.9 mg weekly transdermal 17β estradiol patch (group II) and placebo (group III) before and six months after the initiation of HT (*paired Student's t-test).*

Groups		Anxiety	Depression	Somatic	Vasomotor	Sexual	Total
Group I	Before	0.93 ± 0.04	0.91 ± 0.05	0.86 ± 0.03	1.42 ± 0.08	1.10 ± 0.11	0.96 ± 0.02
	After	0.94 ± 0.04	0.87 ± 0.04	0.74 ± 0.03	1.00 ± 0.08	1.90 ± 0.11	0.86 ± 0.02
	*p**	ns	ns	< 0.05	< 0.005	ns	< 0.005
Group II	Before	1.04 ± 0.04	0.90 ± 0.05	0.85 ± 0.04	1.54 ± 0.09	1.27 ± 0.11	1.1 ± 0.66
	After	0.95 ± 0.03	0.82 ± 0.03	0.74 ± 0.03	1.31± 0.07	1.43 ± 0.09	0.74 ± 0.50
	*p**	ns	ns	< 0.05	< 0.05	ns	< 0.01
Group III	Before	0.93 ± 0.04	0.82 ± 0.04	0.80 ± 0.04	1.56 ± 0.09	1.20 ± 0.11	1 ± 0.06
	After	0.94 ± 0.04	0.74 ± 0.04	0.78 ± 0.03	1.36 ± 0.07	0.92 ± 0.10	0.83 ± 0.06
	*p**	ns	ns	ns	< 0.05	ns	< 0.05

CEE: conjugate equine estrogen; ns = not significant.

over a 12-month study period and, finally concluded that there was a significant reduction in menopausal symptom scores in the 2 mg dose but not in the 1 mg dose compared to placebo.

Based on the results of our study, placebo seemed to be as effective as estrogen in alleviating the vasomotor complaints following six months of HT, a contradictory finding to published studies in the literature [13, 14, 16]. Different type of scales used, different ethnic populations and sample size, and various durations of hormone treatment may explain the discrepancies mentioned above. Whether this study has limitations such as sample size and short follow-up period, the different impact of two HT regimens and placebo on Greene Climacteric Scores remains to be elucidated.

To conclude, estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Further prospective randomized studies need to be conducted on a large case series with the aim of looking at not only short-term but long-term effects on climacteric symptoms in comparison to both placebo arms and different dose and mode of HT use.

References

[1] Breckwoldt M., Keck C., Karck U.: "Benefits and risks of hormone replacement therapy (HRT)". *J. Steroid Biochem. Mol. Biol*., 1995, *53,* 205.

[2] Session D.R., Kelly A.C., Jewelewicz R.: "Current concepts in estrogen replacement therapy in the menopause". *Fertil. Steril*., 1993, *59,* 277.

[3] Hassa H., Tanir H.M., Yildirim A., Senses T., Oge T., Mutlu F.S.: "Associated factors with urogenital score in natural and surgical menopause". *Maturitas*, 2005, *52,* 65.

[4] A decision tree for the use of estrogen replacement therapy or hormone replacement therapy in postmenopausal women: consensus opinion of The North American Menopause Society. *Menopause*, 2000, *7*, 76.

[5] Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause,* 2004, *11*, 11.

[6] Greene J.G.: "Constructing a standard climacteric scale". *Maturitas*, 1998, *29,* 25.

[7] Anderson G.L., Limacher M., Assaf A.R., Bassford T., Beresford S.A., Black H. *et al*.: "Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial". *JAMA,* 2004, *291*, 1701.

[8] Skouby S.O., Barlow D., Samsioe G., Gompel A., Pines A., Al-Azzawi F. *et al*.: "Climacteric medicine: European Menopause and Andropause Society (EMAS) statements on postmenopausal hormonal therapy". *Maturitas,* 2004, *48,* 19.

[9] Stadberg E., Mattsson L.A., Milsom I.: "Factors associated with climacteric symptoms and the use of hormone replacement therapy". *Acta Obstet. Gynecol. Scand*., 2000, *79,* 286.

[10] Mendoza N., Suarez A.M., Alamo F., Bartual E., Vergara F., Herruzo A.: "Lipid effects, effectiveness and acceptability of tibolone versus transdermic 17 beta-estradiol for hormonal replacement therapy in women with surgical menopause". *Maturitas,* 2000, *37*, 37.

[11] Chen L.C., Tsao Y.T., Yen K.Y., Chen Y.F., Chou M.H., Lin M.F.: "A pilot study comparing the clinical effects of Jia-Wey Shiau-Yau San, a traditional Chinese herbal prescription, and a continuous combined hormone replacement therapy in postmenopausal women with climacteric symptoms". *Maturitas*, 2003, *44*, 55.

[12] Ivarsson T., Spetz A.C., Hammar M.: "Physical exercise and vasomotor symptoms in postmenopausal women". *Maturitas,* 1998, *29,* 139.

[13] Cohen L.S., Soares C.N., Poitras J.R., Prouty J., Alexander A.B., Shifren J.L.: "Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report". *Am. J. Psychiatry,* 2003, *160,* 1519.

[14] Baksu A., Ayas B., Citak S., Kalan A., Baksu B., Goker N.: "Efficacy of tibolone and transdermal estrogen therapy on psychological symptoms in women following surgical menopause". *Int. J. Gynaecol. Obstet.,* 2005, *91,* 58.

[15] Haines C.J., Yim S.F., Chung T.K., Lam C.W., Lau E.W., Ng M.H. *et al*.: "A prospective, randomized, placebo-controlled study of the dose effect of oral oestradiol on menopausal symptoms, psychological well being, and quality of life in postmenopausal Chinese women". *Maturitas,* 2003, *44,* 207.

[16] Utian W.H., Shoupe D., Bachmann G., Pinkerton J.V., Pickar J.H.: "Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate". *Fertil. Steril*., 2001, *75,* 1065.

[17] Jirapinyo M., Theppisai U., Manonai J., Suchartwatnachai C., Jorgensen L.N.: "Effect of combined oral estrogen/progestogen preparation (Kliogest) on bone mineral density, plasma lipids and postmenopausal symptoms in HRT-naive Thai women". *Acta Obstet. Gynecol. Scand*., 2003, *82*, 857.

[18] Egarter C., Huber J., Leikermoser R., Haidbauer R., Pusch H., Fischl F., Putz M.: "Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints". *Maturita*s, 1996, *23*, 55-.

Address reprint requests to:
H. METE TANIR, M.D.
Eskisehir Osmangazi University School of Medicine
Department of Obstetrics and Gynecology
Perinatology Unit
Meselik Kampusu
26480 Eskisehir (Turkey)
e-mail: mtanir@superonline.com