THE EFFECTS OF METHYLTESTOSTERONE IN SURGICALLY MENOPAUSAL WOMEN USING HORMONE REPLACEMENT THERAPY

L. Safdarian, S. Azari

Department of Gynecology and Obstetrics, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- In a double blind, parallel-group, clinical trial, we compared the effects of conjugated estrogen with estrogen plus methyltestosterone in surgically menopausal women. In this study, 251 women were randomly assigned to one of the two regimens: 1- conjugated estrogen 0.625 mg/day+placebo. 2- conjugated estrogen 0.625 mg/day+methyltestosterone 1.25 mg/day (E+A group). Study parameters were psychologic, urinary and sexual symptoms, lipid profile, liver function test (LFT) and side effects. Significantly greater improvement in psychologic, urinary and sexual symptoms was observed in the E+A group. (P<0.002). Changes in hairgrowth were similar in both groups. No clinically significant side effects were seen except body mass index (BMI) which was more increased in E+A group, but its changes were in normal limit. (no obesity, no overweight was seen) (p<0.002). Changes in LFT were similar in both groups. LDL was increased only in E+A group, but HDL rising was higher in estrogen alone group, in contrast, triglyceride and cholesterol levels were increased in E+A group more than other groups (p<0.002), but the changes were in normal limit. As compared to estrogen alone, E+A significantly improved menopausal symptoms in surgical menopause without added side effects.

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Key Words: Surgical menopause, androgen, estrogen, lipids, side effect, menopausal symptoms.

INTRODUCTION

Bilateral oophorectomy leads to an abrupt fall in circulating levels of estrogen and testosterone, the first menopausal symptom is hot flush, then vaginal and urinary tract atrophy takes place a few months later (1-6). Hormone replacement therapy (HRT) can decrease these problems, especially E+A therapy (7-11).

Correspondence:
L. Safdarian, Department of Gynecology and Obstetrics, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +9821 84902421, E.mail: lsafdarian@yahoo.com

The enhanced effectiveness of E+A therapy was first reported by Burger et al (12) and again recently by Regestein in 2001 (13). E+A therapy has better effects on energy level and menopausal symptoms (8,14-15). An increased chance of overall improvement may be predicted by specific pretreatment measures (13). CNS is the main target for sex steroid hormones, androgens produce effects via special receptor or conversion to estradiol (16,17). At McGill University, E+A therapy begins in Recovery Rooms (if not contraindicated) (18). In recent years, many outside studies accomplished about androgenic benefits in surgical menopause, but such studies were not shown in Iran, so we determined to assess profits of added standard dose of methyltestosterone in surgical menopause in our country.

MATERIALS AND METHODS

Since October 2000 to January 2002, 251 surgically menopausal women, at least 3 months after surgery, underwent HRT in our randomized, double blind clinical trial in Gynecologic clinic/Shariati Hospital. They were randomly assigned to one of the two treatment regimens.

A- Conjugated estrogen 0.625 mg/day + placebo (equal with methyltestosterone 1.25 mg)

B- Conjugated estrogen 0.625 mg/day + methyl-testosterone 1.25 mg/day. Women aged 46-52 years. Exclusion criteria included any previous cancer,endometriosis, thrombo-phlebitis, hyper-triglyceridemia, liver and gallbladder disease, uncontrolled diabetes and hypertension, single women, treatment with estrogen and progesterone in the previous 12 weeks, use of psychotropic drugs in previous 4 weeks, dependence on alcohol, tobacco or illicit drugs (1,8,19). Menopausal symptoms were evaluated at baseline and every monthly visit. Psychologic symtoms (hot flush, sweat, inability to concentrate, nervousness, irritability, excitability, feeling of depression, trouble sleeping, tired feeling, forgetfulness), sexual symptoms (reduction of libido,

dyspareunia, vaginal dryness), number of coitus per week, urinary symptoms (dysuria, frequency, stress incontinency) were assessed. (2) Also, symptoms were scored on a 0-5 scale (0 = never, 1 = sometimes, 2= tolerable, 3 = many but continue to working, 4= severe- inability to concern, 5= very severe– intolerable) (20). Facial hair growth was assessed at baseline and at third month of treatment using a modified Ferriman-Gallway Scale. (1991) Facial hair growth at third month was considered unchanged if the total hirsutism score then remained within ± 1 unit of the base (19). Physical examination, BMI, vital signs, lipid profile and LFT, pelvic and breast examination, concomitant medication and recording of adverse effects were done at baseline and at third month of treatment.

Mamogram and other laboratory tests were also done at baseline (1,19). Randomizing and blinding of women and drugs were done on the basis of random numbertable by Aburaihan Pharmaceutical Company, also drugs were prepared in this company.

Data were analyzed by chi-squared, T test, and repeated measurement.Total treatment duration for each person was 3 month.

RESULTS

Both groups were parallel with regard to mean age, BMI, and duration of menopause (Table 1).

Table 1. summary of demographic features

Feature	E	E + A
No.	120	120
Age (yr)	48.17 ± 0.14	48.15 ± 0.13
BMI (kg/m^2)	25 ± 0.16	25.03 ± 0.18
Duration of menopause (mt)	7.02 ± 2.13	7.04 ± 2.15

Values are given as mean ± SE mean

96% of 251 women completed 3 month of treatment. 4 women discontinued treatment due to being single and 7 women discontinued due to emigration. They were excluded from the study. Menopausal symptoms were improved in both groups at 3 months, with significantly greater improvements in E+A group ($p<0.002$) (data shown in Fig. 1, 2, 3, 4). Among two treatment groups, facial hirsutism scores remained the same in 98.3% of women, worsened in 1.7% over 3 months. There was no significant difference in the hirsutism scores between the treatment groups (Fig. 5). As shown in table 2, there were differences between groups with respect to any lipid parameter at baseline.

Levels of LDL were increased only in E+A group, but HDL rising was higher in estrogen alone group, in contrast, triglyceride and cholesterol levels were increased in E+A group more than the other group, ($p<0.002$) but the changes were in normal limit. There was no significant difference in LFT between groups (data in table 3), also no difference was observed in adverse events including acne, hoarseness, headache, and mean blood pressure, but BMI was more increased in E+A group, but its changes were with in normal limits (no obesity and no overweight was shown) ($p<0.002$) (Table 4, 5).

Table 2. The effects of treatment on lipid profile changes in all treated patients

	E (n=120)	E+A (n=120)	P
HDL cholesterol (mg/dl)			0.001
At baseline	46.85 ± 0.79	47.26 ± 0.77	
At end point	52.60 ± 0.53	48.85 ± 0.70	
LDL cholesterol (mg/dl)			0.001
At baseline	109.29 ± 0.90	109.49 ± 0.92	
At end point	101.22 ± 1.06	110.65 ± 0.86	
Total cholesterol (mg/dl)			0.001
At baseline	200.94 ± 0.43	200.45 ± .39	
At end point	200.95 ± 0.96	203.85 ± 0.41	
Triglyceride (mg/dl)			0.001
At baseline	183.13 ± 1.17	184.04 ± 1.15	
At end point	184.40 ± 1.20	200.86 ± 0.58	

Values are given as mean ± SE mean

Table 3. The effects of treatment on liver function test changes in all treated patients

	E (n=120)	E + A (n=120)	P
SGOT (mg/dL)			0.315
At baseline	25.02 ± 2.49	24.99 ± 2.51	
At end point	25.90 ± 1.88	25.60 ± 1.40	
SGPT (mg/dL)			0.369
At baseline	25.04 ± 2.51	25.03 ± 2.52	
At end point	26.10 ± 1.56	25.90 ± 1.65	
ALKP (mg/dL)			0.381
At baseline	100.50 ± 2.91	103.12 ± 2.59	
At end point	101.00 ± 0.86	101.40 ± 0.88	
BILL (mg/dL)			0.992
At baseline	0.56 ± 0.03	0.61 ± 0.02	
At end point	0.60 ± 0.04	0.65 ± 0.02	

Values are given as mean ± SE mean

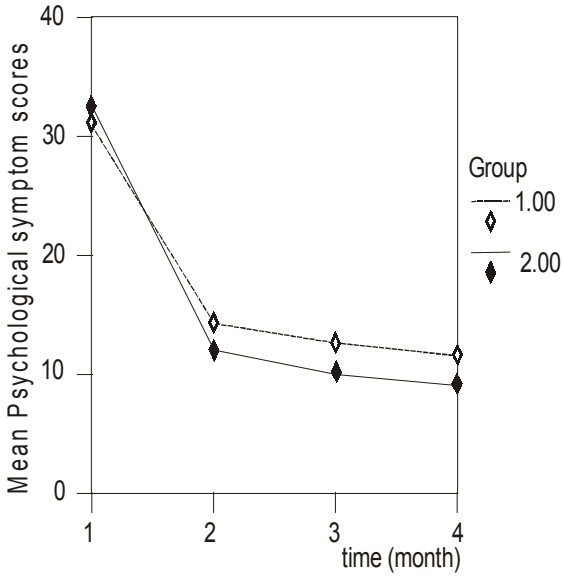

Fig. 1. Mean psychological symptom scores. The treatment groups are: Estrogen alone group (◊), Estrogen + Androgen group (♦)

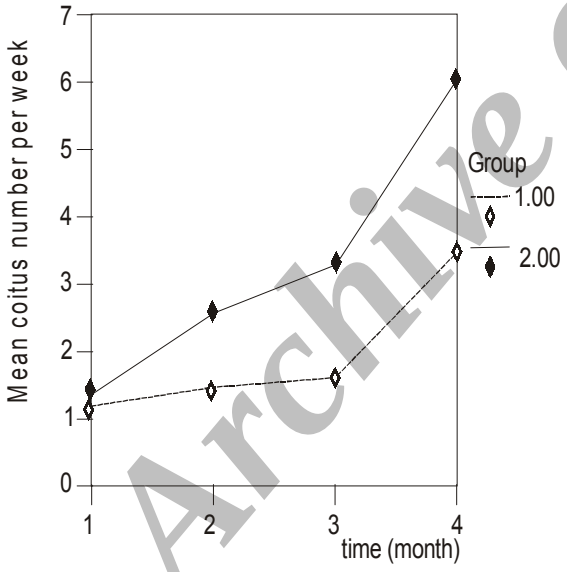

Fig. 2. Mean coitus number per week. The treatment groups are as figure 1.

Table 4. Frequency of side effects in all treated patients

Side effect	E (n=%)	E + A (n=%)	P
headache	16 (13.3 %)	25 (21%)	0.052
Acne	16 (13.3 %)	25 (21%)	0.052
hoarseness	0	0	–

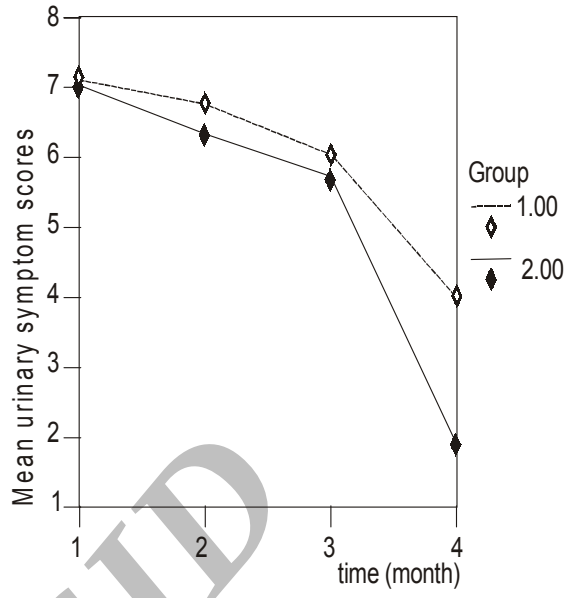

Fig. 3. Mean urinary symptom scores. The treatment groups are as figure 1.

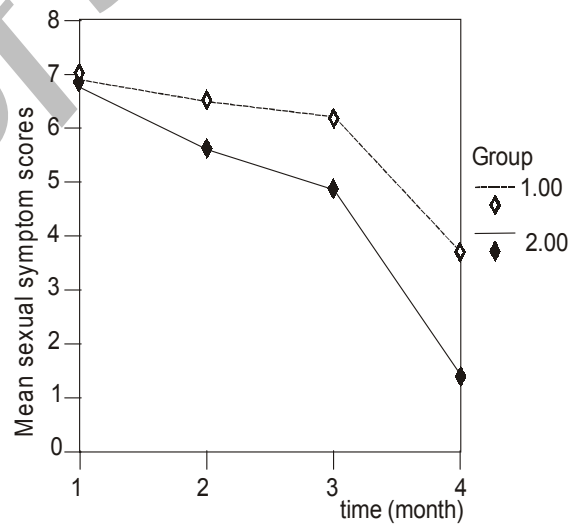

Fig. 4. Mean sexual symptom scores. The treatment groups are as figure 1.

Table 5. The effects of treatment on BMI and MBP changes in all treated patients

	E (n=120)	E+A (n=120)	P
MBP			0.381
At baseline	93.41 ± 0.64	93.53 ± 0.66	
At end point	93.66 ± 0.66	93.70 ± 0.64	
BMI			0.001
At baseline	25.00 ± 0.16	25.03 ± 0.18	
At end point	24.98 ± 0.15	25.54 ± 0.18	

Values are given as mean ± SE mean

DISCUSSION

The menopausal symptoms in surgically menopause are unresponsive to estrogen alone (22,23). Similar to previous studies, psychologic symptoms were significantly improved by both groups at all visits, beginning as early as one month after initiating treatment, but urinary and sexual symptoms were improved later on third month of therapy, in this study. Menopausal symptoms in E+A group were improved more than the other group. The superior efficacy of androgens on menopausal symptoms was reflected to the anabolic and energizing properties, furthermore, the presence of androgen receptors in hypothalamus, pituitary and limbic system allows for the possibility that this hormone may exert its effects on behavior centrally (8,24). Similar to other studies, no clinically significant side effects were seen, in this study and the changes were in normal limits with standard dose of methyltestosterone (19,25). This treatment (E+A) in low dose is safe in surgical menopause, and it must be associate with appropriate nutrition and regular exercise (1,7).

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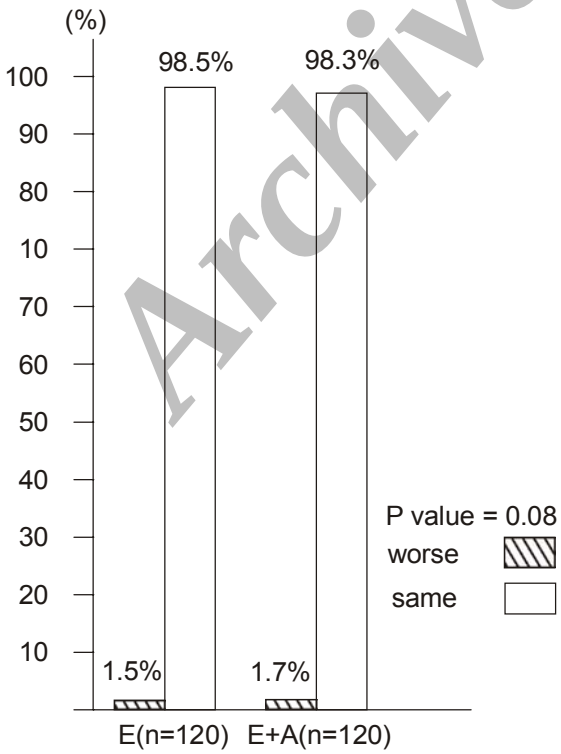

Fig. 5. Hirsutism scores assessed with a modified Ferriman-Gallway scale at month 3 of treatment

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