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ORIGINAL ARTICLE

Comparative Study of Low Dose Conjugate Equine Estrogen 0.3 mg *vs* Standard Dose Conjugate Equine Estrogen 0.625 mg as Hormone Replacement Therapy

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ABSTRACT

Introduction: Since menopause was related to variety of genitourinary, vasomotor, psychological and musculoskeletal changes, conjugated equine estrogen (CEE) was introduced for all menopause-related symptoms in various doses.

Materials and methods: It is a comparative study in which 100 postmenopausal women were selected (natural or surgical menopause) with one or more menopausal symptoms. All patients were randomly divided in two groups. Group A received 0.3 mg CEE and group B received 0.625 mg CEE, and both groups were compared with each other in various aspects.

Results: Both the groups were comparable to each other with respect to mean age, residence, type of menopause, total duration of menopause. Both the groups show comparable improvement in vasomotor, genitourinary and psychological symptoms and $p > 0.05$ which is not significant. On evaluation of bone mineral density (BMD), the group B showed significant improvement than group A ($p < 0.001$). Effect on endometrium was not significant.

Conclusion: Because of the complications of estrogen ± progestin, it should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risk for individual women.

Keywords: Conjugated equine estrogen, Medroxy progesterone acetate, Low dose hormone replacement therapy.

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INTRODUCTION

Ever since, menopause has been causally linked to several symptoms and disease processes. While the life expectancy has improved enormously the average age of menopause has not changed and hence a vast majority of women spend one-third of their lives in the state of estrogen deficiency. The long-term problems of menopause, therefore, are important to the present times. The world population together shows a rough mean menopausal age of 50 ± 5 years.[1]

Climacteric is the phase of weaning ovarian activity. During the climacteric period, women suffer from symptoms of vasomotor instability, such as hot flushes, night sweating, palpitations, insomnia, etc. Urogenital atrophy causes vaginal dryness, dyspareunia, itching, leukorrhea, urinary incontinence, frequency, urgency, nocturia and dysuria, etc. Other changes include skin laxity, dry lusterless skin, skeletal aches, pains and psychosomatic disturbances.

Estrogens are available in oral, parenteral, topical as well as vaginal forms. The most commonly prescribed oral estrogen preparation is conjugate equine estrogen (CEE) mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and 17β-dihydroequilin and various other estrogens extracted from urine of pregnant mares. Tablets for oral administration are available in 0.3, 0.45, 0.625, 0.9 and 1.25 mg strengths of conjugated estrogens.

After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by adrenal cortex to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, that is, estrone sulfate are the most abundant circulating estrogens in postmenopausal women. Estrogen acts to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

MATERIALS AND METHODS

The study was carried out on total 100 postmenopausal women with amenorrhea more than 6 months or had panhysterectomy at least 1 month back with one or more vasomotor symptoms, urogenital complaints or any psychological symptoms. Study duration was 1 year and approved by ethics committee of hospital. All women underwent full hematological profile as following:

- Complete blood count
- Renal function and liver function tests
- Lipid profile
- Pap smear with vaginal cytology
- Bone mineral density
- Transvaginal sonography
- Mammography.

Inclusion Criteria

- Vasomotor symptoms—hot flushes, night sweating, sleep disturbances.

- Genital symptoms—pain, dyspareunia, discharge, burning feeling, dryness in vagina.
- Urinary symptoms—dysuria, frequency, urgency, nocturia, incontinence.

Exclusion Criteria

- Patients with undiagnosed vaginal bleeding, genital neoplasia, breast neoplasia or history of carcinoma breast in family.
- Severe hypertriglyceridemia
- Cerebrovascular, cardiovascular and thromboembolic diseases
- Severe liver disease
- History of diabetes mellitus
- History of previous use of steroid, herpes and pelvic inflammatory disease, endometriosis
- History of epilepsy, migraine.

After obtained written consent from each subject, the patients were divided in two groups; each group had 50 patients.

Group A received oral-conjugated estrogen tablets 0.3 ± 2.5 medroxyprogesterone acetate (MPA) mg/day and group B received 0.625 mg/day ± 5 mg oral in natural menopausal cases.

Patients were evaluated after 1, 2 and 6 months of therapy. Chi-square test was used for comparison.

RESULTS

Maximum number of cases were between 45 and 55 years age group and duration of menopause was 6 to 12 months in both the groups.

Graph 1 shows distribution of patients according to degree of relief in vasomotor complaints. Hot flushes relieved 70% in group A and 74% in group B at 1 month, 90% in group A and 92% in group B at 6 months. Night sweats relieved 55% in group A and 57% in group B at 1 month and 70% in group A and 72% in group B at 6 months. Sleep disturbances relieved in 52% in group A and 53.2% in group B at 1 month and 72% in group A and 70% in group B at 6 months.

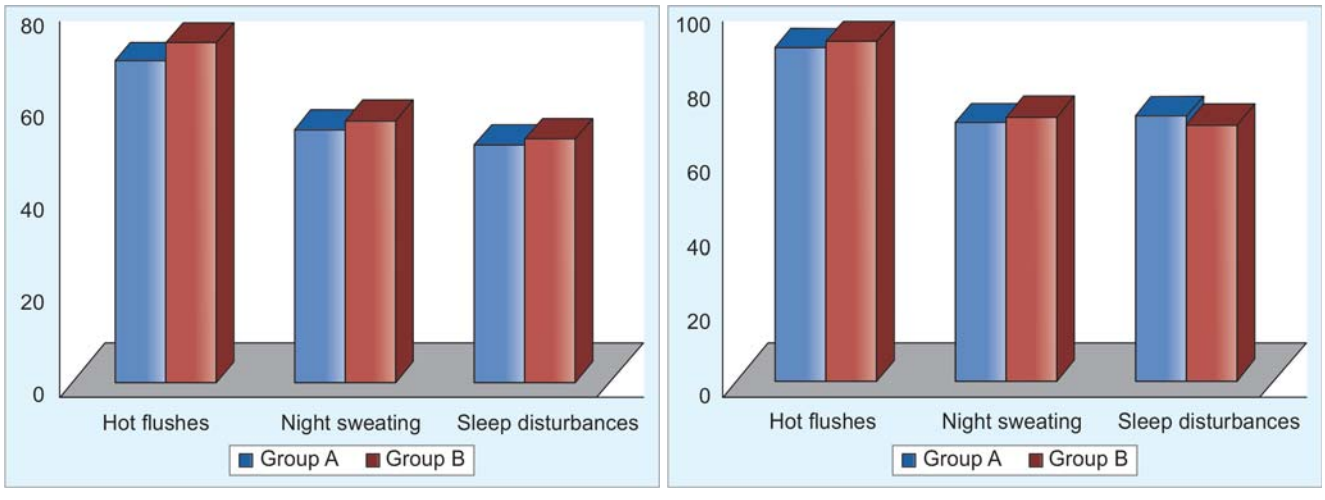
Graph 2 shows distribution of patient according to degree of relief in urinary symptoms. Around 65.4% patients of group A relieved in dysuria and 70% of group B at 1 month while 82.3% of group A and 85.6% in group B patient relieved at 6 months. A total of 63.2% patients of group A and 62% of group B patients were relieved in frequency at 1 month. 78.4% in group A and 80.5% in group B patient were relived in frequency at 6 month. A total of 54.2% of group A and 57.2% of group B got relief in urgency at 1 month and 68.5% of group A and 70.6% of group B were relieved at 6 months.

Incontinence was relieved in 40% of group A, 45% in group B at 1 month, and 94% in group A and 96.2% in group B patients at 6 months.

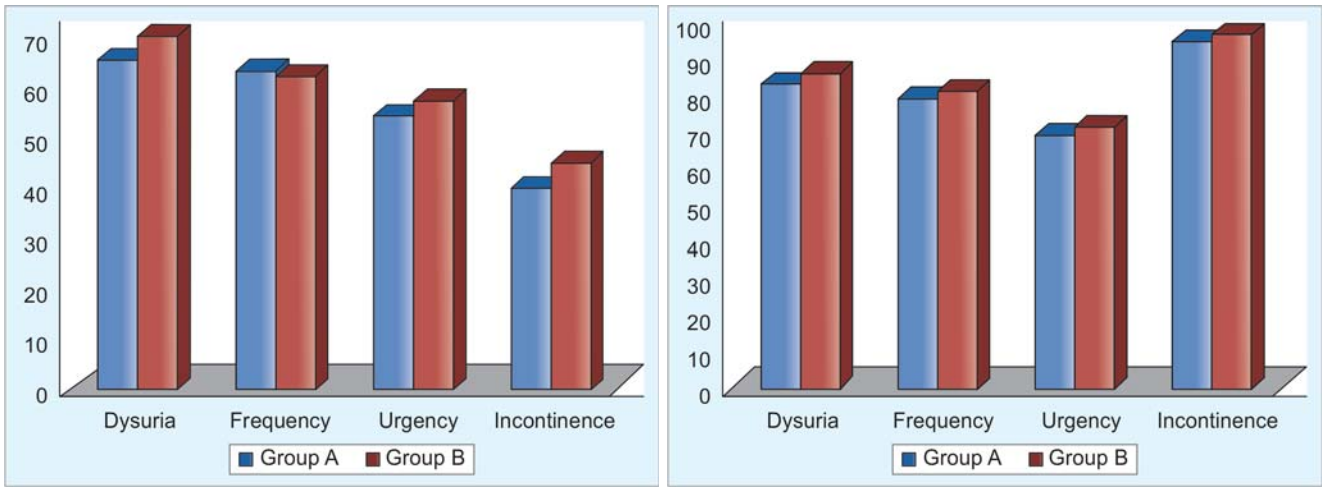
Graph 3 shows decrease in mean parabasal count from 88.4 to 22.2% at 6 weeks and 3.82% at 6 months in group A while from 85.6 to 20.4% at 6 weeks to 4.51% at 6 months in group B.

On evaluation by TVS for endometrial hyperplasia in both group, only two patients of group B show ET > 5 mm and other has endometrial thickness <5 mm; these two patients underwent endometrial biopsy in which simple hyperplasia was found.

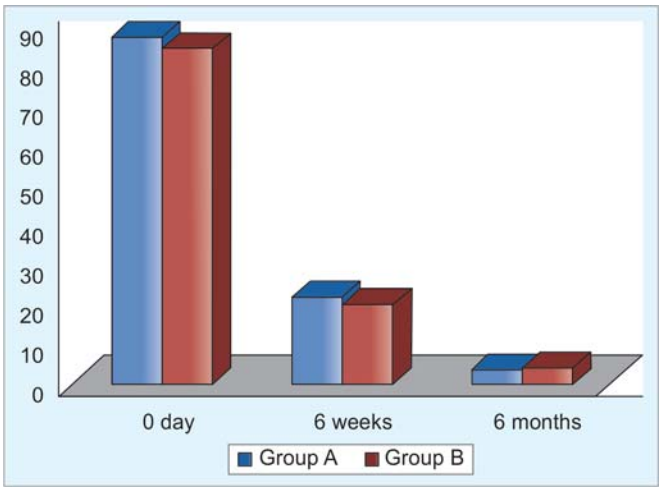
Table 1 shows increase in bone mineral density in L2 to L4 (1.14 ± 0.15 to 1.13 ± 0.36) at 6 months in group A *vs* (1.14 ± 0.16 to 2.28 ± 0.37) in group B. In results, independent sample 't' test was applied (t = 12.5 and p < 0.001) and found to be significant.



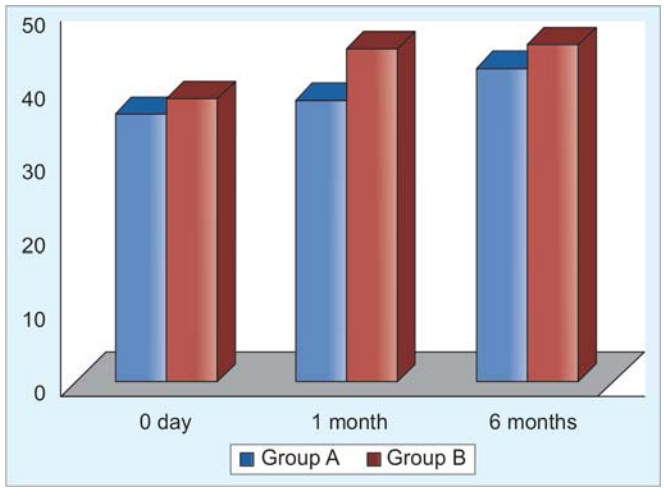
Graph 1: Distribution of cases according to relief in vasomotor symptoms in 0.3 and 0.625 mg CEE after 1 and 6 months (p > 0.05, not significant in both the groups)



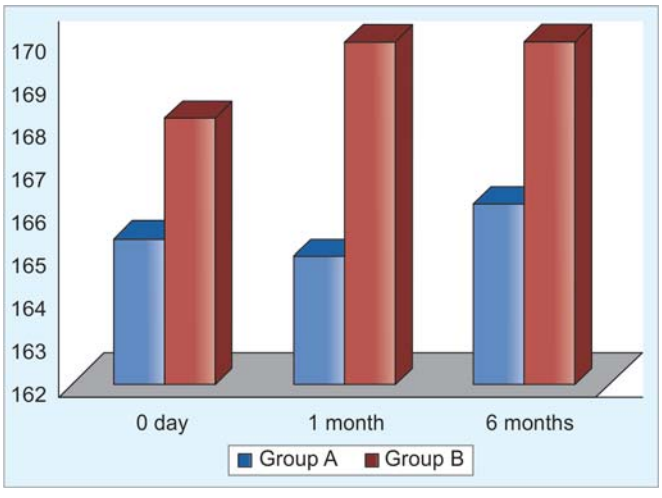
Graph 2: Distribution of cases according to relief in urinary complication after 1 and 6 months ($p > 0.05$, not significant in both the groups)



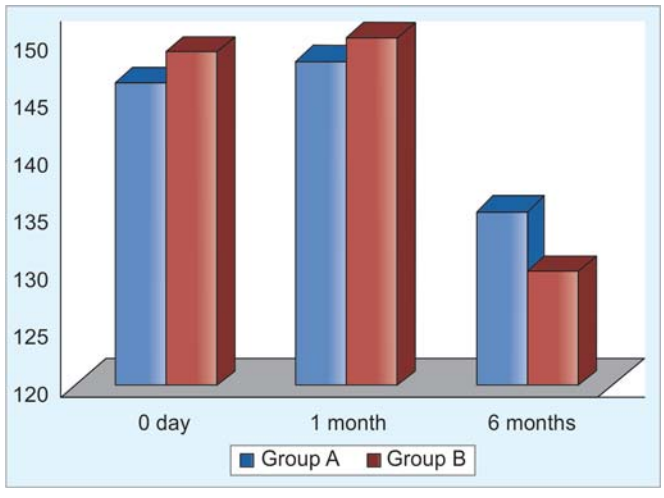
Graph 3: Effect on vulval and vaginal atrophy by vaginal maturation index (decrease in mean parabasal cell count) ($p > 0.05$, not significant in both the groups)



Graph 4: Comparison of HDL-C level which shows change from 38.2 to 45.0 mg/dl at 6 months in group B and 36.1 to 42 mg/dl in group A at 6 months



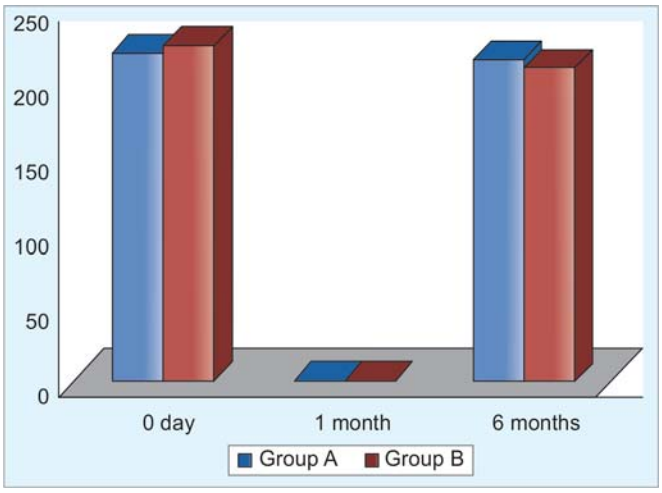
Graph 5: Serum TG level rises from 165.4 to 166.2 mg/dl in group A and 168.2 to 170 mg/dl in group B at 6 months



Graph 6: Serum LDL cholesterol level which decreases from 146.2 to 135 mg/dl in group A and 148.8 to 130 mg/dl in group B

Table 1: Percentage change in bone mineral density—comparison between 0.625 and 0.3 mg CEE at 6 months

	No. of cases	*Baseline g/cm^2 (mean ± SD)*	*Change from baseline (%) adjusted (mean ± SD)*
L2 to L4 BMD			
0.625 ± 5 mg	50	1.16 ± 0.16	2.28 ± 0.37
0.3 ± 2.5 mg	50	1.16 ± 0.15	1.13 ± 0.36



Graph 7: Total serum cholesterol decreases from 220 to 215.2 mg/dl in group A and 225 to 210.4 mg/dl at 6 months in group B

Graph 4 shows comparison of high density lipoprotein-cholesterol (HDL-C) level which shows change from 38.2 to 45.0 mg/dl at 6 months in group B and 36.1 to 42 mg/dl in group A at 6 months.

Graph 5 shows serum triglyceride (TG) level rise from 165.4 to 166.2 mg/dl in group A and 168.2 to 170 mg/dl in group B at 6 months.

Graph 6 shows serum Low density lipoprotein (LDL) cholesterol level which decrease from 146.2 to 135 mg/dl in group A and 148.8 to 130 mg/dl in group B.

Graph 7 shows total serum cholesterol decrease from 220 to 215.2 mg/dl in group A and 225 to 210.4 mg/dl at 6 months.

DISCUSSION

Both the groups were comparable with each other with respect to mean age, residence type of menopause and total duration of menopause. In our study, comparing improvement of vasomotor complaints and urinary complaints in both CEE groups by Chi-square test, p-value >0.05 was not significant and both groups were statistically comparable to each other. In the first year of the health and osteoporosis, progestin and estrogen (HOPE) study[2] shows similar results in improvement of vasomotor symptoms. There were no statistically significant difference between 0.625 and 0.3 mg group at any time period.

Results of vaginal maturation indexes at 6 months in both groups showing comparable results and $p > 0.05$ not significant.

To study the effect on endometrium, all patient had complete amenorrhea, only two patients of group B had endometrial thickenss >5 mm for which they underwent endometrial biopsy and came out to be simple hyperplasia. So, the difference in effect on endometrium was not significant in both the groups.

If we compare the effect of both groups on BMD at L2 to L4, it shows significant improvement in BMD in group B and less improvement in group A ($p < 0.001$) and found to be significant so 0.625 of CEE shows more improvement in BMD as 0.3 mg and results are comparable to HOPE study.[2]

On studying the effect on lipid profile and comparing with other studies by Schwartz Jill et al[3] and Sherwin BB,[4] it shows similar results. There is rise in HDL-C from 36.1 to 45 mg/dl.

Rise in TG level from 165.4 to 120 mg/dl and fall in LDL cholesterol from 146.2 to 130 mg/dl, but there is no significant difference in both groups.

CONCLUSION

An updated Cochrane database review[5] included 19 trials involving 41,904 women. In relatively healthy women, combined HRT leads to significant improvement in urogenital and psychological symptoms but significantly increase the risk of venous thromboembolism or coronary event (after l year use) stroke (after 3 years use), breast cancer and gallbladder diseases. The only statistically significant benefits of HRT were the decrease incidence of fractures.

Women need to be informed of the potential benefits and risks of all therapeutic options and care should be individualized based on women's need and preference. Based on current evidence therefore starting HRT at the early onset of the menopause and carrying on for a few years, apparently carries little risk in healthy women.

So, looking at all these complications estrogen with or without progestins should be prescribed at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. HRT is effective for preventing osteoporotic fractures, but the NAMS[6] recommends that hormone therapy for this purpose should be weighed against potential harm. So, in the past WHI era, HRT should be given in lowest possible dose and for shortest possible time to relieve symptoms.

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