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Comparative evaluation of raloxifene versus estrogen: Progestin on symptomatology, endometrium, and lipid profile in postmenopausal women

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ABSTRACT

The objective of the study was to evaluate the effects of raloxifene and estrogen progesterone (E + P) combination on symptoms, endometrium, and lipid profile in postmenopausal women. Ninety healthy postmenopausal women were enrolled and allocated to three groups namely E + P, raloxifene, and controls. These groups were given 0.625 mg conjugated estrogen and 2.5 mg medroxyprogesterone, 60 mg raloxifene and no therapy, respectively. Symptomatology and lipid profile were evaluated at 3, 6, and 12 months. Endometrial thickness was evaluated at 6 and 12 months, and endometrial biopsy was repeated at 12 months. The demographic profile of the women in the three different groups was comparable. In addition, the symptomatology, lipid profile, mean endometrial thickness, and endometrial biopsy categorization were comparable. E + P and raloxifene were equally effective in improving the postmenopausal symptoms and lipid profile. E + P had stimulatory effect on the endometrium, whereas raloxifene was found to be neutral.

Key Words: E + P, endometrial thickness, raloxifene

INTRODUCTION

Improved social conditions and new developments in medical science have led to increased life expectancy of women. The menopause constitutes a watershed in a women's life. Falling estrogen level commonly results in a spectrum of unpleasant symptoms such as hot flushes and night sweats, sleep disturbances, vaginal dryness, and depression. In the long term, absolute estrogen deficiency leads to generalized atrophy of skin, lean body mass, bone mass, and a rapid increase in the incidence of coronary heart disease. Hormone, replacement therapy (HRT) is the most frequently used in the relief of postmenopausal symptoms, but none of the larger trials has evaluated its effect on the quality of life and postmenopausal symptomatology. In addition, use of HRT is associated with increased risk of breast cancer, endometrial cancer, ovarian cancer, and gall stones.[1] During the last decade, a novel class of agents called selective estrogen receptor modulators (SERMs) have been identified. Raloxifene is a commonly used SERM. Like estrogen, it has potential to reduce osteoporosis and various markers of cardiovascular risk in menopausal women, but without deleterior effects such as endometrial and breast stimulation.[2,3] Safety of raloxifene has been studied in postmenopausal women in early studies. There are not many studies from Indian population.[4] This study was undertaken to evaluate the comparative effects of raloxifene versus estrogen progestin on endometrium, lipid profile, and symptomatology in postmenopausal women.

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MATERIALS AND METHODS

Ninety healthy postmenopausal women in the age group 40-60 years attending medical education and research (PGIMER) were enrolled in the study and randomly allocated to three groups (group I: HRT; group II: raloxifene; group III: controls). Women who had undergone hysterectomy or had postmenopausal bleeding, uncontrolled hypertension, diabetes, and prior cerebro accident were excluded.

Informed consent was obtained from the enrolled

women. The subjects were evaluated for somatic symptoms such as headaches and dizzy spells, vasomotor symptoms such as hot flushes and night sweats, symptoms such as breast tenderness and symptoms related to depressed mood such as feeling sad, having lost interest in things, and other symptoms related to memory, anxiety, sexual behavior according to the Women's Health Questionnaire (WHQ). Each participant was asked to respond with one of the four possible answers, "yes, definitely," "yes sometimes," "no, not much," and "no, not at all," based on her current feelings. For directional consistency in the calculations, each response was assigned to a four-point scale with one considered the best condition and four the worst. For certain items, the scoring was reversed as some items were phrased positively and some negatively.

Complete general physical examination was carried out including breast examination. Routine investigations such as hemoglobin, urine-albumin, sugar; blood sugars-fasting, post breakfast; mammogram, ultrasound gall bladder, bone densitometry, and lipidogram were performed. The lipidogram was performed after an overnight fast and analyzed for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. A baseline pelvic ultrasound for uterus, tubes, and adnexa, including a transvaginal ultrasound for endometrial thickness was done, double endometrial thickness from one myoendometrial junction to the other myoendometrial junction was measured, and a baseline endometrial biopsy was taken. Endometrial biopsy was classified according to Blaustein's classification of postmenopausal endometrial biopsy. Eligible women were randomly allotted to three groups: raloxifene or HRT or contest using a computer-generated random number sequence. Patients in the raloxifene group were instructed to take 60 mg tablet daily. Those in the HRT group were asked to take 0.625 mg of conjugated estrogen and 2.5 mg of medroxy progesterone daily. Women who did not take either therapy were the controls. Symptomatology and lipid profile were evaluated at 3, 6, and 12 months. Transvaginal endometrial thickness was evaluated at 6 and 12 months, and endometrial biopsy was performed at 12 months [Tables 1-4].

Table 1: Comparison of symptomatology at 12 months in the three groups

Symptom group	Group I	Group II	Group III	*P* value	I versus II *P* value
Depressed mood	11.45 ± 3.8	12.70 ± 4.5	11.95 ± 3.5	0.63	0.37
Somatic	11.63 ± 2.6	11.73 ± 3.8	15.50 ± 4.9	0.004	0.92
Memory and concentration	4.26 ± 1.5	4.41 ± 2.0	4.77 ± 1.7	0.64	0.80
Vasomotor	3.31 ± 1.2	2.82 ± 0.9	4.47 ± 1.5	0.01	0.19
Anxiety and fear	5.38 ± 1.7	5.86 ± 2.4	6.21 ± 2.5	0.52	0.53
Sexual	5.23 ± 1.4	5.66 ± 3.3	6.22 ± 2.4	0.51	0.77
Menstrual	5.2 ± 10	5.5 ± 1.9	6.3 ± 2.7	0.22	0.56
Sleep	5.05 ± 1.4	5.20 ± 2.3	5.00 ± 1.4	0.93	0.82
Perceived attractiveness	3.53 ± 1.9	4.25 ± 2.5	3.42 ± 1.4	0.48	0.44
Overall score	60.37 ± 13.9	58.00 ± 20.9	66.76 ± 13.9	0.50	0.82

Table 2: Comparison of lipid profile at 12 months in the three groups

Variable	Group I	Group II	Group III	*P* value	I versus II *P* value
Total cholesterol (mg/dL)	187.58 ± 37.3	174.80 ± 21	210.48 ± 34.1	0.004	0.22
LDL cholesterol (mg/dL)	107.32 ± 27	99 ± 18	118.40 ± 29.3	0.07	0.30
HDL cholesterol (mg/dL)	53.53 ± 11.4	57.80 ± 8.2	48.48 ± 9.2	0.01	0.21
Triglycerides (mg/dL)	129.47 ± 43.8	103.13+ 42.0	121.52 ± 32.3	0.14	0.08

Table 3: Comparison of endometrial thickness (mm) in the three groups: at 6 and 12 months of therapy

ET thickness, mm	Group I	Group II	Group III	*P* value	Group I versus II *P* value
At 6 months	3.83 ± 1.71	4.08 ± 1.39	3.07 ± 1.25	0.09	0.62
At 12 months	3.64 ± 1.21	4.22 ± 0.9	3.33 ± 1.20	0.06	0.14
Baseline to 6 months	0.47 ± 2.4	-0.45 ± 0.9	-	-	0.12
Baseline to 12 months	0.60 ± 0.9	-0.35 ± 0.8	-	-	0.004

Table 4: Comparison of endometrial biopsy in the three groups at 12 months of therapy

Variable	Group I (*N* = 18)	Group II (*N* = 16)	Group III (*N* = 27)	*P* value
Normal benign	17 (94)	16 (100)	26 (96)	0.80
Benign stimulatory	1(6)	0	1 (4)	0.80
Benign abnormal	0	0	0	-
Premalignant	0	0	0	-
Malignant	0	0	0	

Figures in parenthesis are in percentage

Statistical Analysis

The results obtained were analyzed by applying unpaired *t*-test for evaluation of intergroup variance, and intragroup significance was assessed by paired *t*-test.

RESULTS

The demographic profile (mean age of enrollment, mean age at menopause, mean duration of menopause, and the mean BMI) of the women in the three different groups was comparable. The mean age of the women in the study population was 52.66 ± 6.33 years. The age at menopause was varying from a minimum of 37 years to a maximum of 55 years, and the mean age of menopause was 47.11 ± 4.13 years. The mean duration of menopause was 5.42 ± 4.67 years with a range from 1 year to 20 years. At baseline the symptomatology, the lipid profile, the mean endometrial thickness, and the endometrial biopsy categorization were comparable except for the total cholesterol which was higher in the controls. Both estrogen progestin (group I) and raloxifene (group II) were equally effective on the postmenopausal symptoms as assessed by the WHQ. There was no difference between the two groups in any of nine domains (depressed mood, somatic symptoms, memory/concentration, anxiety/fear, sexual, menstrual, sleep, vasomotor, and perceived attractiveness) of WHQ at all times of evaluation. Both raloxifene (group II) and estrogen progestin (group I) were equally effective in decreasing the total cholesterol, LDL cholesterol, and increasing the HDL cholesterol except for the mean drop in cholesterol levels which was significantly higher in estrogen progestin group (7.5%) at 3 months compared to raloxifene group (1.3%). The increase in the endometrial thickness was significantly higher with the use of estrogen progestin in comparison to raloxifene at 12 months of therapy. The mean endometrial thickness increased by 0.47 ± 2.4 mm from the baseline at 6 months and by 0.60 ± 0.9 mm from the baseline at 12 months in estrogen progestin group. In the raloxifene group, there was a decrease in endometrial thickness from the baseline by 0.45 ± 0.9 mm and by 0.35 ± 0.8 mm at 6 months and 12 months of follow-up, respectively.

In the estrogen progestin subgroup, there was an improving trend in the symptomatology related to vasomotor symptoms depressed mood, somatic symptoms, and sexual symptoms. The mean total cholesterol showed a declining trend, and the decline reached statistical significance only at 6 months of therapy (a decline of 12.36 ± 15 mg/dL from the baseline). The decline in LDL cholesterol was significant at all points of evaluation. The HDL showed a rising trend, and the rise was significant at 3 months (8.25 ± 11.3 mg/dL, $P = 0.02$) and at 12 months (5.68 ± 9.9 mg/dL, $P = 0.02$). Triglycerides did not show any significant trend over time. In the raloxifene group, there was an improving trend in the symptomatology related to depressed mood, somatic symptoms, and vasomotor symptoms. Over time the mean total cholesterol showed a declining trend at 6 months of therapy, the LDL cholesterol showed a significant decline from the baseline at all points of evaluation, and the HDL showed a rise at 3 months (3.14 ± 5 mg/dL, $P = 0.03$) and at 12 months (6.15 ± 5.3 mg/dL, $P = 0.01$).

DISCUSSION

To alleviate the postmenopausal problems and to ensure a better quality of life, various therapeutic regimes have been tried. Of these regimes, the most frequently used has been a combination of estrogen and progestin (HRT). The use of estrogen progestin has decreased after the release of the women's health initiative (WHI) results.[5] Raloxifene is a new drug in the armamentarium for the management of postmenopausal problems. There are very few studies on the comparative effects of raloxifene and estrogen progestin on postmenopausal symptomatology, lipid profile, and endometrium, and showing variable results. As raloxifene has been recently launched in the Indian market, we designed this study to evaluate the comparative effects of raloxifene versus estrogen progestin on symptomatology, lipid profile, and endometrium.

The results of our study show that both estrogen progestin and raloxifene were equally effective on the

postmenopausal symptoms as assessed by the WHQ. There was no difference between the two groups in any of eight domains (depressed mood, somatic symptoms, memory/concentration, anxiety/fear and sexual sleep, vasomotor and perceived attractiveness) of WHQ at all times of evaluation. Similar to the observation in a study comparing raloxifene and continuous combined HRT on 1008 healthy postmenopausal women,[6] there was no difference between the groups for four of the nine domains (somatic, anxiety/fear, sleep, and perceived attractiveness). The differences seen in various domains in different studies and this study possibly suggest that there is a variable effect of raloxifene and estrogen-progestin on postmenopausal symptoms. On analysis of the symptomatology in the estrogen progestin group, we found an improvement in the vasomotor, somatic, sexual, and depressed mood symptoms. Estrogen improved the vasomotor symptoms at all times of evaluation, somatic symptoms at 6 months of therapy, depressed mood, and sexual symptoms at 12 months. Similar to our observation, Campbell and Whitehead[7] demonstrated that estrogen was significantly more effective than placebo in reduction of vasomotor symptoms including hot flushes and also in the Cochrane reviews of published, randomized controlled trials of HRT, HRT reduced vasomotor symptoms compared with placebo [relative risk (RR), 0.10; 95% CI, 0.6-0.19].[8] The improvements in the scores for sexual domain were similar to the study by Voss *et al*.[6] On in-group analysis, it was seen that raloxifene improved the scores in the depressed mood and somatic and sleep domains. The improvement in depressive symptoms was evident at all times of evaluation, whereas the improvement in sleep symptoms occurred at 3 months and the improvement in somatic symptoms occurred at 12 months. It was also noted that raloxifene improved the vasomotor symptoms at 6 months of therapy although no change from baseline was seen at 3 and 12 months. Similar to our results, in the study by Jarkova *et al*.,[9] the depressive symptoms improved with raloxifene at 3 and 12 months of therapy. In their study, there was also an improvement in the anxiety symptoms at 12 months. In contrast to our results, in the MORE study it was noted that the incidence of hot flushes was higher ($P < 0.001$) in women taking raloxifene 60 or 120 mg/day treatment (9.7% and 11.6%, respectively) than with placebo (6.4%) and similar to our observation raloxifene did not have any effect on the sexual symptoms.[10] As against the improvement of vasomotor symptoms in our study at all times of evaluation, in the study by Davies *et al*.,[11] hot flushes were more frequent ($P < 0.05$) during treatment with raloxifene than among those receiving HRT or conjugated equine estrogens.

Both raloxifene and estrogen progestin were equally effective in decreasing the total cholesterol, LDL cholesterol, and increasing the HDL cholesterol. However, the mean drop in cholesterol levels was significantly higher in estrogen progestin group (7.5%) at 3 months than the raloxifene group. In the HERS trial, similar to our results the LDL cholesterol decreased by 14% from baseline and HDL cholesterol increased by 8% from baseline at 12 months of therapy.[12] A few other studies have also shown significant beneficial effects on the lipid and coagulation particle 8a.

The increase in the endometrial thickness was significantly higher with the use of estrogen progestin when compare to raloxifene at 12 months of therapy.[13] In a study which compared raloxifene and estrogen progestin on endometrium, the mean endometrial thickness did not differ significantly at 1 or 2 years in the raloxifene group whereas in the HRT group the thickness increased by 0.5 mm at 1 year and 0.6 mm at 2 years.[14] In another study comparing uterine safety of raloxifene with HRT, the mean endometrial thickness in the HRT group increased by 1.2 mm from the baseline at 12 months which was significantly higher than that with raloxifene.[15] Among the patients in estrogen progestin group, we have noted a progressive increase in endometrial thickness from baseline and this was 0.47 mm at 6 months and 0.6 mm at 12 months. Only one patient at 12 months had biopsy showing proliferative endometrium. In the meta-analysis from the Cochrane database with continuous combined HRT, the odds ratio for endometrial hyperplasia was six times higher than placebo and it was 16 times higher for women taking unopposed estrogen for 36 months in the moderate doses.[16] In this study, raloxifene had no effect on the endometrium either at 6 or at 12 months of therapy. Similarly in the study by Dalmas *et al*., raloxifene when used for 24 months did not have any effect on endometrial thickness and so were the results of the study by Cohen *et al*.[17]

We have observed no significant change in the endometrial biopsy form baseline to end point in any of the three groups. In contrast to our findings, in the study by Fugere *et al*,[15] there were a significantly higher proportion of women with benign stimulatory endometrium in the combined continuous HRT group compared to the raloxifene group at 1 year and 2 year of therapy.[1] We could not pick up such differences probably due to the small sample size of our study.

When Goldstein *et al.*[18] compared the uterine effects of raloxifene and conjugated combined estrogen, proliferate endometrium was present in significantly higher proportion at 1 year of therapy, 39.8% of women in estrogen group as compared to 1.7% in the raloxifene group. The difference in the results on endometrial biopsy is possibly due to the use of combined HRT in our study. Progesterone is known to have a protective effect on the postmenopausal endometrium.

CONCLUSION

To conclude raloxifene and estrogen-progestin are equally effective in maintaining the quality of life and improving the lipid profile of postmenopausal women. Estrogen-progestin has a stimulatory effect on the endometrium whereas raloxifene has a neutral effect.

REFERENCES

1. Anderson GL, Judd HL, Kuntz AM, Barad DH, Beresford SA, Pettinger M, *et al*. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The Women's Health initiative Randomized Trial. JAMA 2003;290:1739-48.
2. Manson JE, Martin KA. Postmenopausal hormone replacement therapy. N Engl J Med 2001;345:34-41.
3. Clemett D, Spencer CM. Raloxifene: A review of its use in postmenopausal osteoporosis. Drugs 2000;60:379-411.
4. Abdullah KN, Raoof A, Raoof M. Effectiveness and safety of Raloxifene in postmenopausal females. J Coll Physicians Surg Pak 2005;15:266-9.
5. Kour D, Kapoor B, Sharma S, Mahajan A, Khajuria V. Comparative effects of raloxifene and HRT on serum lipids and fibrinogen in healthy postmenopausal women. J Obstet Gynecol India 2005;55:26-264.
6. Voss S, Quail D, Dawson A, Backstrom T, Aguas F, Erenus M, *et al*. A randomized, double blind trial comparing raloxifene HCl and continuous combined hormone replacement therapy in postmenopausal women: Effects on compliance and quality of life. BJOG 2002;109:874-85.
7. Campbell S, Whitehead M. Estrogen therapy and the menopausal syndrome. Clin Obstet Gynaecol 1977;4:31-47.
8. McLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes (Cochrane review). Update Software. Oxford: The Cochrane Library; 2002.
9. Jarkova NB, Martenyi F, Masanauskaite D, Walls EL, Smetnik VP, Pavo I. Mood effect of raloxifene in postmenopausal women. Maturitas 2002;42:71-5.
10. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, *et al*. The effects of raloxifene on risk of breast cancer in postmenopausal woman: Results from the MORE randomized trials: Multiple outcomes of raloxifene evaluation. JAMA 1999;281:2189-97.
11. Davies GC, Huster LJ, Lu Y. Adverse events reported by postmenopausal women in controlled trials with raloxifene. Obstet Gynecol 1999;93:558-65.
12. Hulley S, Grady D, Bush T, Furberg C, Hderrington D, Riggs B, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in post menopausal women: Heart and Estrogen progestin replacement study (HERS) Research group. JAMA 1998;280:605-13.
13. Dayspring T, Qu Y, Keech C. Effects of raloxifene on lipid and lipoprotein levels in postmenopausal osteoporotic women with and without hypertriglyceridemia. Metabolism 2006;55:972-9.
14. Research on the menopause. World Health Organ Tech Rep Ser 1981;670:1-120.
15. Fugere P, Scheele WH, Shah A, Strack TR, Glant MD, Jolly E. Uterine effects of raloxifene in comparison with continuous combined HRT in post menopausal women. Am J Obstet Gynecol 2000;182:568-74.
16. Neven P, Lunde T, Benedetti-Panici P, Tiitinen A, Marinescu B, de Villiers T, *et al.* A multicentre randomized trial to compare uterine safety of raloxifene with a continuous combined hormone replacement therapy containing oestradiol and norethisterone acetate. BJOG 2003;110:157-67.
17. Cohen FJ, Watts S, Shah A, Akers R, Plouffe L. Uterine effects of 3 year Raloxifene therapy in postmenopausal women younger than age 60. Obstet Gynecol 2000;95:104-10.
18. GoldsteinSR, Scheele WH, Srikanth K, Rajgopalan SK, Jennifer L, Wilkie B, *et al*. 12 months comparative study of raloxifene, estrogen and placebo on the post menopausal endometrium. Obstet Gynecol 2000;195:95-103.

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