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ORIGINAL ARTICLE

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Comparative effects of raloxifene and HRT on serum lipids and fibrinogen in healthy postmenopausal women

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OBJECTIVE(S): To evaluate and compare the effects of raloxifene and HRT on serum lipids, plasma fibrinogen, and drug tolerability in healthy postmenopausal women.

METHOD(S) : Effects of raloxifene (60mg/day) and HRT (conjugated equine estrogen 0.625mg and medroxy progesterone acetate 2.5mg daily) on serum lipids, plasma fibrinogen levels and drug tolerability were studied in 81 healthy postmenopausal women in prospective, randomized parallel designed study. Results obtained were analyzed by applying paired t test and unpaired t test. P value less than 0.01 was taken as significant..

RESULTS : At the end of 6 months, raloxifene and HRT lowered total cholesterol by 6% and 4.74% respectively. Levels of low density lipoproteins were reduced more with HRT (14.18%) than with raloxifene (8.18%). Triglyceride, very low density lipoprotein and high density lipoprotein levels were raised by HRT (11.05%, 11.02% and 24.37% respectively) but were not significantly altered by raloxifene. Raloxifene significantly lowered fibrinogen levels by 7% while HRT had no effect. The only significant adverse effect observed with raloxifene therapy was hot flashes (26%).

CONCLUSION(S) : Raloxifene favourably affected the biochemical markers of the cardiovascular risk and has a good tolerability profile.

Key words : raloxifene, HRT, fibrinogen, high density lipoproteins, low density lipoproteins, total cholesterol, triglycerides, very low density lipoproteins

Introduction

Menopause signifies the end of the monthly reproductive cycle and is an outward manifestation of ovarian failure that leads to estrogen deficiency. Estrogens play important role not only in reproductive system but also in the normal functioning of cardiovascular, central nervous, immune, and skeletal systems. Hence, fall in the level of estrogens after menopause leads to detrimental effects on the above mentioned systems. After menopause, there occurs an increase in total cholesterol (TC), low density lipoproteins (LDL-c), triglycerides (TG), fibrinogen (FG) and factor VII, and reduction in high density lipoproteins (HDL-c); all these are important metabolic markers of cardiovascular diseases [1,2]. Long term effects of these physiological changes lead to accelerated atherosclerosis and an increase in the incidence of cardiovascular diseases in menopausal women. Hormone replacement therapy (HRT) in the form of estrogen alone or in combination with progesterone given after menopause can prevent bone changes and also reverse some of the adverse lipid changes. However, HRT is associated with increased risk of breast cancer, endometrial cancer, ovarian cancer, gall stones and venous thromboembolism [3]. During the last decade a novel class of agents called selective estrogen receptor modulators or (SERMs) have been identified. Raloxifene is a commonly used second generation SERM. Like estrogen, it has potential to reduce osteoporosis and various surrogate markers of cardiovascular risk in menopausal women but without deleterious effects like

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endometrial and breast stimulation [4,5]. The present study was undertaken to elicit the effects of raloxifene and HRT on cardiovascular endpoints like TC, LDL-c, TG, very low density lipoproteins (VLDL-c), HDL-c and FG levels, and to compare their safety in healthy postmenopausal women. Moreover, there is a paucity of data regarding the effects of raloxifene on the above mentioned parameters in Indian women.

Methods

This is a prospective, randomized, parallel designed study. It was conducted on randomly selected 89 postmenopausal healthy females, aged 45 to 77 years. Written informed consent was obtained from all subjects after explaining the nature and purpose of the study. They were subjected to detailed history taking, complete general, physical and systemic examinations, and vaginal and speculum examinations. Subjects with unexplained uterine bleeding, hot flashes, diabetes mellitus, other endocrinopathies, and those with a history of breast cancer, thromboembolic disorders or cardiovascular accidents, and impaired liver or kidney functions were excluded. Subjects receiving other medications likely to interfere with the drugs being studied, and with serum lipid profile and fibrinogen levels were also excluded. Subjects were randomized by using two digit table of random numbers to receive for 6 months either tablet raloxifene hydrochloride 60mg/day or tablet conjugated equine estrogen 0.625 mg/day with tablet medroxy progesterone acetate 2.5 mg/day. The list of allocation for randomization of patients was prepared by a colleague not clinically associated with the study. Raloxifene treated group consisted of 46 women and 43 women were included in HRT group. All of them were evaluated at day zero, 3 months and 6 months for TC, LDL–c, TG, VLDL-c, HDL-c and FG. All adverse events experienced during the trial were also recorded. Blood samples for lipid estimation were obtained after overnight fasting. The estimation of serum lipid levels was made by standard enzymatic method in a semi –automatic analyser (ERBA–chempro). Quantitative determination of fibrinogen in plasma was done by Clauss clotting technic. The results obtained were analyzed by applying unparied t test for evaluation of intergroup significance. The intragroup significance was assessed by paired t test.

Results

Baseline laboratory values of are given in Table 1. In the raloxifene group, 42 out of 46 women completed the study while in HRT group, 39 out of 43 completed it. Results obtained at day zero, 3 months, and 6 months with raloxifene and HRT are shown in Table 2.

Table 1. Baseline laboratory characteristics.

	HRT (n=39)	Roloxifene (n=42)
T C (mg/dL)	203.38+6.74	208.02+6.48
LDL-c (mg/dL)	125.65+6.01	132.95+5.48
T G (mg/dL)	139.25+4.89	142.80+7.45
VLDL-c(mg/dL)	27.85+0.97	28.55+1.49
HDL-c (mg/dL)	46.69+1.39	46.88+1.91
Fibrinogen (g/L)	2.95+0.049	2.87+0.048

Values are expressed as mean ± SEM. The differences were statistically not significant.

Total cholesterol (TC)

HRT lowered TC by 4.26mg /dL (2%) and 9.67mg /dL (4.74%) at the end of 3 months and 6 months of the study respectively (P<0.001) with peak at 6 months. Raloxifene decreased total cholesterol levels by 16.9 mg/dL (8.12%) and 12.6mg/dL (6%) at 3 and 6 months respectively (P<0.001) with peak at 3 months. Comparison of the two groups revealed that raloxifene resulted in greater decrease at 3 month(P<0.001).

Table 2. Effect on serum lipids

	Total cholesterol (g/L)	Triglycerides (mg/dL	HDL-c (mg/dL)	LDL-c (mg/dL)	VLDL-c (mg/dL)	Fibrinogen (g/L)
Raloxifene (n=42)						
Zero day	208.02 ± 5.68	142.8 ± 7.45	46.88 ± 1.91	132.10 ± 5.21	28.55 ± 1.49	2.87 ± 0.048
3 months	191.12 ± 5.66 [b]	139.30 ± 7.29	45.76 ± 1.8	117.41 ± 5.13 [a]	27.86 ± 1.49	2.72 ± 0.048 [b]
6 months	195.35 ± 5.37 [b]	140.21 ± 7.30	45.38 ± 1.79	122.07 ± 4.9 [a]	28.04 ± 1.46	2.49 ± 0.043 [b]
HRT (n=39)						
Zero day	203.38 ± 6.74	139.25 ± 4.89	46.69 ± 1.93	125.65 ± 6.01	27.85 ± 0.97	2.95 ± 0.049
3 months	199.12 ± 6.87 [b]	146.28 ± 5.02 [a]	53.56 ± 1.39 [b]	116.65 ± 6.35	29.25 ± 1.00 [b]	2.94 ± 0.049
6 months	193.7 ± 6.63 [b]	154.64 ± 4.78 [b]	56.07 ± 1.41 [b]	107.03 ± 6.06 [b]	30.92 ± 0.95 [b]	2.91 ± 0.051

Values are expressed as mean ± SEM [a] P< 0.01 when compared with day zero values [b] P<0.01 when compared with day zero value

Low density lipoproteins (LDL-c)

Low density lipoproteins were reduced by 9 mg/dL (7.16%) in HRT group at 3 months (nonsignificant) and 18.6mg/dL (14.81%) at 6 months (P<0.001).While raloxifene decreased low density lipoprotein levels by 14.6 mg/dL (11.62%) and 10 mg/dL (8.18%) at 3 months (P<0.01) and 6 months (non significant) respectively. HRT caused more significant decrease at 6 months compared to raloxifene (P<0.01).

Triglycerides (TG)

HRT raised TG by 7.03 mg/dL (5.04%, P<0.01) and 15.4 mg/dL (11.05%, P<0.001) after 3 and 6 months respectively. Whereas raloxifene decreased it nonsignificantly.

Very low density lipoproteins (VLDL-c)

Raloxifene insignificantly decreased VLDL-c while HRT raised it by 1.4 mg/dL (4.56%) and 3.07 mg/dL (11.02%) at 3 and 6 months respectively (P<0.001).

High density lipoproteins(HDL-c)

HDL-c levels were raised by HRT by 6.8 mg/dL (14.71%) and 9.3 mg/dL (24.37%) at 3 and 6 months respectively (P<0.001), while raloxifene insignificantly decreased it.

Fibrinogen (FG)

Fibrinogen levels were not affected by HRT during 6 months of the study. Raloxifene caused reduction in fibrinogen levels by 0.15 g/L (5.2%) and 0.38 g/L (13.2%) at 3 months and 6 months respectively (P<0.001).

Figures 1 and 2 depict serum lipid changes with HRT and raloxifene over 3 months and 6 months respectively.

Adverse effects

Raloxifene was well tolerated. Incidence of hot flashes in raloxifene group was 26%, while none in the HRT group experienced hot flashes (p <0.001). HRT had higher incidence of mastalgia (33%), nausea (2%), vaginal bleeding (48%), abdominal pain (2%) and lucorrhea (7%). (Table 3).

Table 3. Adverse effects.

	HRT (n=39)	Raloxifene (n=42)	P value
Hot flashes	None	11 (26%)	< 0.001
Leg cramps	2 (5.12%)	3 (7.14%)	NS
Mastalgia	13 (33.33%)	2 (4.76%)	< 0.001
Nausea	1 (2.5%)	Nil	NS
Vaginal bleeding	19 (48.71%)	Nil	< 0.001
Abdominal pain	1 (2.5%)	Nil	NS
Lucorrhoea	3 (7.6%)	1 (2.3%)	NS

NS – Nonsignificant

Discussion

Raloxifene is a nonsteroidal benzothiophene derivative and has been classified as a SERM. SERMs bind to estrogen receptors and produce estrogen agonistic action on some tissues and estrogen antagonistic action on others [6]. Several studies have demonstrated that raised levels of TC, LDL-c, TG, and VLDL-c have a linear positive relationship with the

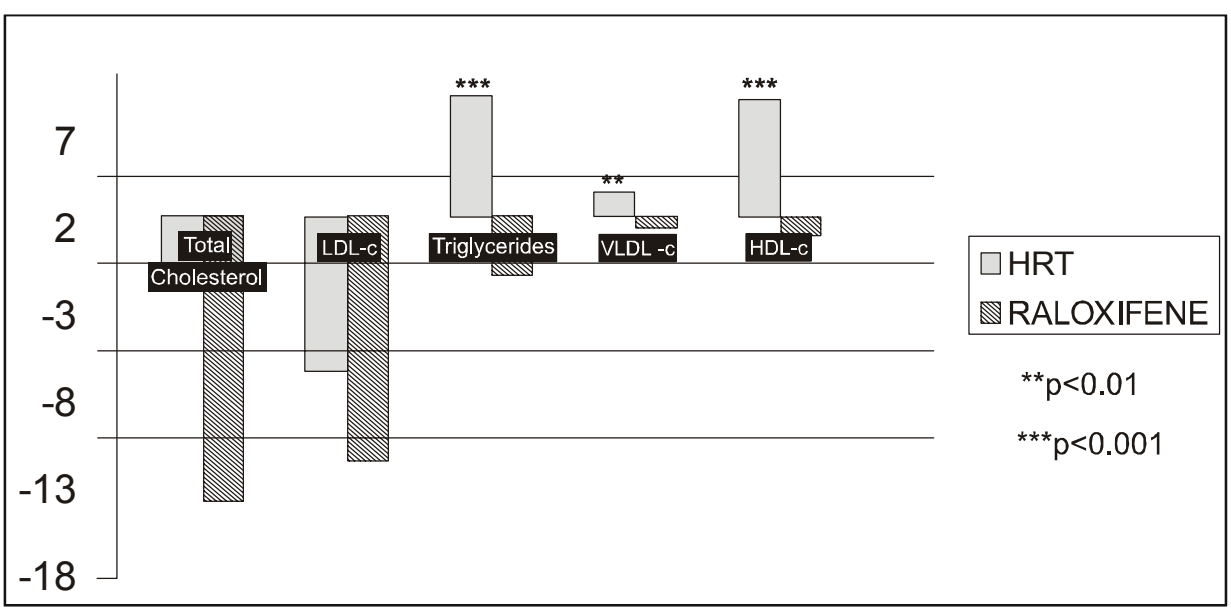

Figure 1. Mean changes in serum lipids with HRT and raloxifene over 3 months

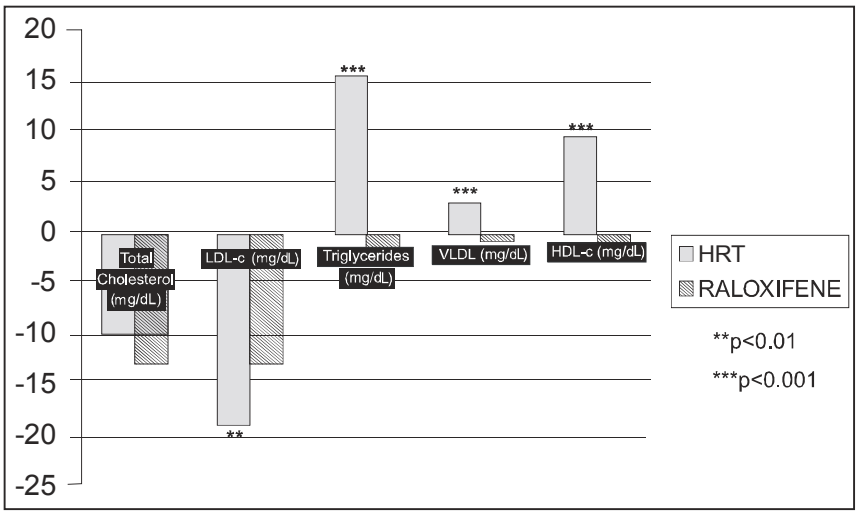

Figure 2. Mean changes in serum lipids with HRT and raloxifene over 6 months

risk of coronanry artery disease (CAD), while HDL-c levels have an inverse relationship [7]. In the present study, both raloxifene and HRT decreased total cholesterol and LDL-c levels, showing an overall beneficial effect on these markers by the two therapies. HRT significantly raised TG and VLDL-c concentrations while these two parameters were not significantly altered by raloxifene, suggesting a more favorable response with raloxifene. HRT raised HDL-c levels, raloxifene however failed to affect this parameter.

FG has been found to be an independent risk factor, for heart diseases. A reduction in 0.5% in incidence of cardio-vascular diseases for every 0.1 g/L decrease in fibrinogen level has been reported [8]. In the present study, raloxifene significantly decreased serum fibrinogen levels. HRT however failed to affect it. This decrease by raloxifene could translate into reduction of CAD risk.

Walsh et al [9] evaluated the effects of raloxifene and HRT (conjugated equine estrogen + medroxy progesterone acetate) on 390 healthy postmenopausal women. They found that both therapies lowered TC, LDL- c and lipoprotein-a. Raloxifene had less effect on lipoprotein-a and no effect on HDL-c. Serum TG and plasminogen activator inhibitor–I levels were not affected by raloxifene, but were elevated by HRT. Raloxifene therapy markedly reduced serum FG concentration. Our results are comparable with this study.

A matter of concern for HRT and SERMs is the incidence of adverse effects. In the present study, HRT caused higher incidence of vaginal bleeding, mastalgia, nausea, abdominal pain and lucorrhea than raloxifene, which had higher incidence of hot flashes. Our findings are comparable with those reported by Davies et al [10].

Our study shows that although there are similarities between the effects of raloxifene and HRT on some of these parameters, there are differences as well. Favorable effect of raloxifene on serum lipids and FG, and its good tolerability profile make it a good alternative to HRT in postmenopausal women. However, aggravation of hot flashes limits its use in women with intolerable menopausal symptoms. Though our results with raloxifene on cardiovascular risk markers like plasma lipids and FG are encouraging, it allows only for cautious optimism as there may be more fundamental factors involved in the pathogenesis of cardiovascular diseases. Moreover, the present study does suffer from limitations of being a short term study. A long term study is needed.

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