Effects of Different Hormone Therapies on Breast Pain in Recently Postmenopausal Women: Findings from the Mayo Clinic KEEPS Breast Pain Ancillary Study

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Abstract

Background: It is estimated that 70% of women in Western societies experience breast pain at least once during their lifetime. In the Women's Health Initiative (WHI), women treated with oral conjugated equine estrogen (0.625 mg) with or without continuous oral medroxyprogesterone acetate (2.5 mg) had a higher incidence of breast pain than those who received placebo. The effect of other hormone therapy regimens on breast pain is unknown. We compared breast pain among healthy, recently menopausal women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS) at Mayo Clinic.

Methods: Women were randomized to: 0.45 mg/day oral conjugated equine estrogen (o-CEE) plus 200 mg/day micronized progesterone (m-P) for the first 12 days of the month, 50 µg/day transdermal 17β estradiol (t-E2) plus m-P for 12 days, or placebo pills and patch. Participants completed the Mayo Clinic breast pain questionnaire at baseline and yearly for the duration of the study.

Results: Participants (116) averaged 53.0 years of age and 1.6 years past their last menses at baseline. At baseline, 12 women (10%) reported breast pain with an average worst pain score [from 0 (no pain) to 10 (worst pain)] of 0.39 ± 1.28 . With treatment, the number of women reporting pain did not increase, and with either intention-to-treat or per-protocol analyses, breast pain scores did not differ significantly ($p=0.39$) among groups: t-E2 (0.53 ± 1.21), o-CEE (0.32 ± 0.78), placebo (0.23 ± 0.87).

Conclusion: Four years of treatment with o-CEE at a lower dose than that studied in the WHI with cyclic m-P or transdermal E2 with cyclic m-P did not increase breast pain in healthy, recently menopausal women.

Introduction

IT IS ESTIMATED that up to 70% of women who live in Western societies will experience breast pain/mastalgia at least once during their lifetime.¹ Breast pain/mastalgia accounts for a large percentage of breast-related visits to health care providers and symptoms can range in severity from mild to severe. Severe breast pain may significantly affect activities related to quality of life including sexual, physical, social, and employment.²⁻⁴ Breast pain/mastalgia is classified as cyclic (pain associated with the menstrual cycle lasting ≥ 7 days) and noncyclic. Noncyclic mastalgia most commonly occurs in the fourth or fifth decade of life coincident with the cessation of menses and may be intermittent or of constant duration.⁵ Menopausal hormone therapy (MHT) prescribed

for the treatment of menopausal symptoms may cause or exacerbate noncyclic mastalgia as a result of the effects of the estrogen, progestogen, or both.⁶ Dose, method of administration, and the use of cyclic versus continuous progestogen may also affect the severity of mastalgia. For example, in the Women's Health Initiative (WHI), women randomized to treatment with oral conjugated equine estrogen (CEE) at 0.625 mg/day with or without continuous medroxyprogesterone acetate (MPA) 2.5 mg/day had a higher incidence of breast pain than those who received placebo. While breast pain occurred in both treatment groups, only those patients treated with CEE+MPA had an increase in mammographic breast density.⁶ In addition, women treated with CEE+MPA had an increased risk of breast cancer when compared to those who had received placebo. Risk of breast cancer was not

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significantly increased in women receiving CEE alone and the risk decreased at follow up after stopping the treatment.^{7,8} Subsequently, practice patterns changed and recommendations for the use of MHT for symptoms of menopause were revised.^{9,10} It is now recommended that the lowest effective dose of MHT be utilized for the shortest period of time for the control of menopausal symptoms.¹⁰

In addition to formulations of MHT, dosage and mode of hormone delivery (oral compared to transdermal, cyclic vs. continuous progestogen) may affect efficacy and risk profiles for the products.¹¹ For example, transdermal products carry a lower risk for thromboembolic disease than oral products, and micronized progesterone has fewer adverse effects on lipid metabolism, risk for thromboembolic disease, heart disease, and breast cancer than synthetic progestins.^{12–14}

To date, there has not been a systematic evaluation of the prevalence of breast pain in recently menopausal women who are using lower doses of CEE compared to transdermal 17 β -estradiol with intermittent progesterone. Therefore, the objective of this study was to evaluate and compare breast pain in healthy, recently menopausal women randomized to either low-dose oral CEE or transdermal 17 β -estradiol with cyclic oral, micronized progesterone or placebo as part of the Kronos Early Estrogen Prevention Study (KEEPS; NCT00154180).

Materials and Methods

Study design

The KEEPS was a multicenter, randomized, placebo-controlled prospective clinical trial; the design and recruitment of which has been previously reported in detail.^{15,16} The KEEPS Breast Pain analysis was an approved ancillary study of the KEEPS conducted on women enrolled in the trial at Mayo Clinic. The study was approved by the Mayo Clinic Institutional Review Board and informed written consent was obtained from all participants.

Participants

Women between the ages of 42 and 58 were enrolled within 6–36 months of their final menstrual period. Menopause was defined as a serum follicle stimulating hormone level ≥ 35 ng/mL and/or estradiol levels < 40 pg/mL. Exclusions included a history of myocardial infarction, angina, congestive heart failure, thromboembolic disease, or cancer; coronary artery calcium score of > 50 Agatston units; heavy smoking (> 10 cigarettes/day); morbid obesity (body mass index > 35 kg/m²); dyslipidemia (LDL cholesterol > 190 mg/dL); hypertriglyceridemia (triglycerides > 400 mg/dL); uncontrolled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 95 mm Hg); fasting glucose > 126 mg/dL; specific bone-active medication use; and lipid lowering medications. Women who met inclusion criteria were randomized to one of three treatments: (1) oral conjugated equine estrogen (o-CEE; 0.45 mg capsule/day) plus cyclic micronized progesterone in oil (m-P, 200 mg capsule daily for 12 days) and a placebo skin patch; (2) transdermal 17 β -estradiol (t-E2, 50 μ g/day) plus cyclic m-P (200 mg capsule daily for 12 days) and a placebo capsule; or (3) placebos (two placebo capsules and a placebo patch). Mammograms were obtained prior to randomization and yearly thereafter.

Procedures

This study utilized the Mayo Clinic Breast Pain Questionnaire, which is adapted and modified from the short form of the McGill Pain Questionnaire, a validated and widely used instrument to measure breast pain.¹⁷ This questionnaire was modified by Khan et al.¹⁸ to assess both cyclic and non-cyclic pain. This questionnaire includes identification of the location, quality, and severity of pain on a scale of 0 (no pain) to 10 (worst pain). For this analysis, the patients were asked to rate their worst and average pain over the preceding 2 months.¹⁹

The Mayo Clinic Breast Pain Questionnaire was administered at baseline and once a year for the duration of the study. Visits at years 1, 2, and 4 were during the estrogen-only phase of the treatment (days 12–30 of the month); year 3 was during the progesterone phase of the treatment (days 1–12 of the month).

Outcomes

The primary outcome of the study was the presence or absence of breast pain. A secondary outcome was severity of breast pain.

Statistical analysis

The mean ($\pm$ standard deviation) of the worst pain and the average pain, scores from 0 (no pain) to 10 (extreme pain) at baseline, years 1, 2, 3, and 4 for all three groups, were analyzed by one-way analysis of variance (ANOVA). The difference at each time point from baseline was also compared by one-way ANOVA. These analyses were performed using intent-to-treat and per-protocol approaches. In intent-to-treat analysis, a missing pain record was filled by its previous record for those participants who did not complete the entire 4 year. Both approaches were used to assess the data, since all 116 participants had at least one missing data point. Frequencies (percentages) of categorical data were compared among groups using the Pearson chi-square test; *p* values less than 0.05 were considered as statistically significant. All statistical analyses were conducted by SAS version 9.3 software (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of women enrolled in the KEEPS at Mayo Clinic have been reported elsewhere,¹⁵ and as expected, are representative of the entire KEEPS cohort.¹⁶ Of 118 women randomized to treatment, 2 declined to complete the breast pain form at baseline. Thus, the remaining 116 participants were included in the analysis. At baseline, 116 participants averaged 52 years of age (range 45–59) and were 1.6 years (range 0–3) beyond the final menstrual period. At baseline, 12% of women reported any breast pain: 14% of women assigned to o-CEE, 14% of women assigned to t-E2, and 10% of women assigned to placebo (*p*=0.78). Of these 116 participants with baseline assessments, 26 terminated treatment prior to year 4, with 8 lost to follow-up (Table 1). Over the 4 years of the study, no woman discontinued participation due to breast pain (Table 2).

Pain status from baseline to year 4 was similar for all three groups (*p*=0.18, Table 3). At baseline, neither “worst pain” scores nor “average pain” scores differed among groups

TABLE 1. PARTICIPANTS IN ANCILLARY BREAST PAIN STUDY

	<i>o</i> -CEE	<i>t</i> -E2	Placebo	Total
At baseline	37	36	43	116
Terminated treatment	6	5	5	
Lost to follow-up	0	0	1	
At year 1	31	31	37	99
Terminated treatment	0	1	0	
Lost to follow-up	0	0	2	
At year 2	31	30	35	96
Terminated treatment	0	1	0	
Lost to follow-up	2	1	0	
At year 3	29	28	35	92
Terminated treatment	0	0	0	
Lost to follow-up	1	0	1	
At year 4	28	28	34	90

Women in the active treatment groups also received oral micronized progesterone for the first 12 days of each month.

o-CEE, oral conjugated equine estrogen; *t*-E2, transdermal 17 β -estradiol.

(Tables 4, 5). The highest score of pain reported was 7, and this was not a recurrent score; the highest average pain score reported was a 6 and occurred in the *t*-E2 group (Table 5). Using intention-to-treat analysis, among women who remained in the study, "worst pain" and "average pain" scores also did not differ among groups or over time (Table 4, $p=0.54$). Similar results were obtained using per-protocol analysis.

Discussion

Following the WHI, clinical practice adopted lower doses of MHT, including those used in the KEEPSP trial. Results from this subset of participants in KEEPSP at Mayo Clinic indicate that neither the lower dose of *o*-CEE nor transdermal 17 β -estradiol, each with cyclic progesterone for 4 years, increased self-reported breast pain or its severity. In contrast, breast tenderness or pain is recognized in the literature as an adverse effect of MHT with frequency estimates ranging from 10% to 25%.²⁰ Our results indicate that prior to initiation of MHT, the frequency for breast pain was comparable in each group and did not increase with the MHT regimens used in this study or differ from placebo.

TABLE 2. REASONS FOR DISCONTINUATION OR LOST TO FOLLOW-UP

Reasons	Number discontinued medication but remained in the study	Number lost to follow-up
Patch reaction	2	
Breakthrough bleeding	3	
Mood swings	5	
Migraines	2	
Breast cancer	1	
Medical issues unrelated to study		2
Personal reasons or unspecified	5	6

TABLE 3. PAIN CHANGES

Intention-to-treat analysis or per protocol analysis	<i>o</i> -CEE (<i>n</i> =37) ^{a,b} No. (%)	<i>t</i> -E2 (<i>n</i> =36) ^b No. (%)	Placebo (<i>n</i> =43) No. (%)
(A) Any pain at baseline	5 (14%)	5 (14%)	4 (10%)
(B) Baseline: none; Later: none	20 (54%)	13 (36%)	24 (56%)
Baseline: none; Later: yes	12 (32%)	18 (50%)	15 (35%)
Baseline: yes; Later: none	3 (8%)	0 (0%)	2 (5%)
Baseline: yes; Later: yes	2 (5%)	5 (14%)	2 (5%)

Pain scores: None, 0; Yes, any pain score 1–10.

Part (A) Pearson chi-square test $p=0.78$, and Part (B) Pearson chi-square test $p=0.18$.

^aTwo participants dropped out prior to the study.

^bWomen in the active treatment groups also received oral micronized progesterone for the first 12 days of each month.

Side effects from MHT can lead to discontinuance of regimens that are prescribed to treat menopausal symptoms that are significant enough to the individual to warrant therapy. An ideal therapy would have few side effects and few long-term negative outcomes. Results of this study are reassuring in that none of the women discontinued treatment because of breast pain. Reasons for discontinuation were similar across all three treatment groups and included vaginal bleeding, increased migraine, altered mood, skin reaction to the patch, other medical issues not related to the study, and personal issues. One participant withdrew because of a diagnosis of breast cancer. The relationship between breast pain and breast cancer remains unclear. However, in the WHI, in which a higher dose of CEE with continuous administration of a synthetic progestin (MPA) or with CEE alone was used, the risk of breast cancer in women treated with CEE+MPA was statistically higher in women with new onset breast tenderness than in those without.⁸ In addition, the risk was double in women who received CEE+MPA and who reported breast tenderness at baseline.⁶ This association was not found in women who received CEE alone.⁸ In the present study, there were no differences in the number of women reporting pain at 36 months, but the average pain tended to be higher in the *t*-E2 group during the progesterone treatment. One woman in the *t*-E2 group withdrew from the study due to a breast cancer diagnosis. Mammographic breast density will be evaluated for all KEEPSP participants and it will be important in the future to evaluate the pain scores with mammographic density.

Limitations of this ancillary study include the evaluation of breast pain by participants from only one site of the KEEPSP trial. Furthermore, although it might appear that breast pain was worse in the *t*-E2 group compared with the *o*-CEE group, the small sample size dictates that this observation requires statistical validation in a larger study. It is not possible to know for certain from post-hoc analysis of the forms, but it is possible to speculate that women who did not provide information for a particular question most likely did not have pain to report, as women are likely to report a positive than a negative event. In spite of these limitations, this analysis is the first evaluation of breast pain in healthy, recently menopausal women who have not undergone a hysterectomy.

TABLE 4. INTENTION-TO-TREAT ANALYSIS

Variable	<i>o</i> -CEE (n=37) mean $\pm$ SD ^a	<i>t</i> -E2 (n=36) mean $\pm$ SD ^a	Placebo (n=43) mean $\pm$ SD	ANOVA p-value
Worst pain				
Baseline	0.32 $\pm$ 1.03	0.56 $\pm$ 1.61	0.30 $\pm$ 1.17	0.64
Time point 1	0.49 $\pm$ 1.07	0.44 $\pm$ 1.25	0.16 $\pm$ 0.57	0.28
Time point 2	0.43 $\pm$ 1.01	0.58 $\pm$ 1.65	0.23 $\pm$ 0.78	0.42
Time point 3	0.43 $\pm$ 0.99	0.78 $\pm$ 1.81	0.19 $\pm$ 0.59	0.10
Time point 4	0.32 $\pm$ 0.78	0.53 $\pm$ 1.21	0.23 $\pm$ 0.87	0.39
Average pain				
Baseline	0.19 $\pm$ 0.62	0.39 $\pm$ 1.18	0.12 $\pm$ 0.54	0.32
Time point 1	0.41 $\pm$ 0.96	0.22 $\pm$ 0.54	0.16 $\pm$ 0.57	0.30
Time point 2	0.30 $\pm$ 0.78	0.42 $\pm$ 1.13	0.23 $\pm$ 0.78	0.66
Time point 3	0.32 $\pm$ 0.85	0.61 $\pm$ 1.50	0.09 $\pm$ 0.29	0.07
Time point 4	0.30 $\pm$ 0.74	0.36 $\pm$ 0.93	0.16 $\pm$ 0.78	0.54

^aWomen in the active treatment groups also received oral micronized progesterone for the first 12 days of each month.
ANOVA, analysis of variance; SD, standard deviation.

TABLE 5. INDIVIDUAL RESPONSES TO AVERAGE PAIN SCORES ON THE PAIN QUESTIONNAIRE

Variable		<i>o</i> -CEE (n=39)	<i>t</i> -E2 (n=36)	Placebo (n=43)	p
Baseline	Average pain score (0–10)				0.72
	0	1	0	2	
	1	2	1	0	
	2	1	2	1	
	3	1	1	1	
	6	0	1	0	
	Lost to follow-up	2	0	1	
12 months	No information given	32	31	38	0.41
	Average pain score (0–10)				
	0	3	3	0	
	1	2	4	2	
	2	3	2	1	
	3	1	0	1	
	4	1	0	0	
24 months	Lost to follow-up	6	3	3	0.042
	No information given	23	24	36	
	Average pain score (0–10)				
	1	0	2	0	
	2	4	0	0	
	3	1	2	2	
	4	0	2	0	
36 months	Lost to follow-up	4	3	7	0.42
	No information given	30	27	34	
	Average pain score (0–10)				
	0	0	1	1	
	1	3	2	3	
	2	0	1	0	
	3	3	1	0	
48 months	4	0	1	0	0.33
	5	0	1	0	
	6	0	1	0	
	Lost to follow-up	5	1	5	
	No information given	28	27	34	
	Average pain score (0–10)				
	0	0	2	2	
48 months	1	1	2	1	0.33
	2	3	2	0	
	2.5	0	1	0	
	3	0	1	0	
	5	0	0	1	
	Lost to follow-up	8	2	5	
	No information given	27	26	34	

randomized to different hormone regimens as part of a clinical trial.

Conclusions

Results of this study demonstrate that administration of low-dose o-CEE or t-E2 with cyclic progesterone over a 4-year period did not increase breast pain in women. None of the participants withdrew from the study due to breast pain, and in those who continued, the presence and severity of breast pain remained low and did not differ between active treatment groups and placebo.

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Author Disclosure Statement

No competing financial interests exist.

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