ABSTRACT

Background. Breast pain and non-discrete breast nodularity are common in women.

Methods. We did a randomized, double-blind, placebo-controlled trial of oral ormeloxifene 30 mg, a selective oestrogen receptor modulator (SERM) or placebo twice a week for 3 months in 20–50-year-old women with breast pain with or without lumpiness. Women with a discrete benign lump or cancer were excluded from the study. Serial assessments of pain on a visual analogue scale and nodularity grade on a 5-point ordinal Lucknow–Cardiff scale were done.

A total of 151 patients were randomly allocated to two interventions using a block size of 4.

Results. Of the 151 patients, 121 (active 57, placebo 64) were available for efficacy analysis. The mean pain level showed a systematic downward trend over five visits ($F = 105.23, p < 0.0001$) that significantly reduced in the active group compared to that in the placebo group ($F = 18.66, p < 0.0001$). The patterns of variation in pain over time for the individual groups differ from the overall mean pattern for the two groups and thus from one another ($F = 44.43, p < 0.0001$). Cumulative frequencies of breast nodularity grades during successive visits showed significant improvement ($p = 0.001$) compared to placebo at the end of the third month. The effect of the active drug persisted till the completion (6 months) of treatment ($p < 0.001$). At the last visit, 93.3% of women in the active group had grade 2 or lower nodularity as compared to 71.1% in the placebo group. Oligomenorrhoea alone was reported by 12 patients.

Conclusion. Ormeloxifene showed significant efficacy for treating breast pain and nodularity.

INTRODUCTION

Screening for breast cancer and reassurance of the absence of cancer may relieve anxiety in women with a breast lump and mastalgia. However, it does not alleviate symptoms and a large number of women continue to suffer from mastalgia.1–4 Cyclic mastalgia without treatment may last several years.5 A recently published meta-analysis of drugs for the treatment of mastalgia included bromocriptine, tamoxifen, evening primrose oil (EPO) and danazol.6 The weighted mean difference in pain score for bromocriptine was $-16.31$ (95% CI $-26.35$ to $-6.27$), for danazol $-20.23$ (95% CI $-28.12$ to $-12.34$) and for EPO $-2.78$ (95% CI $-7.97$ to $2.40$). Tamoxifen achieved a relative risk (RR) of pain relief of 1.92 (95% CI 1.42–2.58) with least side-effects. The authors recommended tamoxifen as the drug of first choice for treating mastalgia. Besides these, gonadotropin-releasing hormone (GnRH) analogues7 have been found to be equally effective but with considerable side-effects.

In the past, several agents such as vitamins B6 and E, diuretics, gamolenic acid, non-steroidal anti-inflammatory drugs and caffeine withdrawal have been tried but were found to be ineffective in randomized studies. Similarly, progesterone creams, tablets and injectables were discarded after randomized studies. Oral contraceptive pills generally contain low doses of ethinyl oestradiol and an oral progestogen and have shown beneficial effects. However, these have not been tested in a randomized controlled trial. Other alternative therapies such as dietary manipulations, relaxation therapy, reflexology and kinesiology have also not been tested in a randomized manner.8–10

A relatively new agent called ormeloxifene (Centchroman) is a weak oestrogen receptor (ER) agonist, a strong ER antagonist (SERA) and therefore a selective ER modulator (SERM).11 It is used as a non-steroidal, anti-oestrogenic oral contraceptive pill and was developed by the Central Drug and Research Institute (CDRI), Lucknow, Uttar Pradesh, India in the 1980s. Its only side-effect is prolongation of the menstrual cycle. It was introduced in July 1991, and was marketed in India in 1992 as Saheli, Choice-7 (Hindustan Latex Ltd.) and Centron (Torrent Pharmaceuticals India Ltd.). It was included in the National Family Welfare Programme in 1995. It was used in breast cancer.12 Ormeloxifene has previously been used in 42 women with mastalgia who reported 90% improvement at a dose of 30 mg taken on alternate days.13 It was also reported to lead to complete disappearance of
fibroadenoma in 40% women after 3 months of treatment. In a randomized trial including 81 women, it was found to be superior to danazol for the treatment of mastalgia.

We studied the efficacy of ormeloxifene in women with pain and nodularity in the breast, assessing benign breast nodularity on a pre-validated Lucknow–Cardiff scale.

**METHODS**

This randomized, double-blind, placebo-controlled clinical trial was done during 2008–2010 at the Department of Surgery, King George's (Chhatrapati Shahuji Maharaj) Medical University, Lucknow, Uttar Pradesh, India.

**Inclusion criteria**

Women in the age group of 20–50 years with cyclical breast pain and nodularity were considered for inclusion in the study. If the patient was >35 years of age, a thorough clinical examination of the breast was done followed by bi-planer mammography. Firm reassurance against cancer was given to all the patients. After 1 month, if breast pain and nodularity persisted and the patients desired medical treatment, we offered them the opportunity to participate in this trial. Demographic variables, clinical history, general examination and breast examination were carefully recorded on a pre-designed proforma. All patients were given a simple daily breast pain self-recording chart and those with severe cyclical breast pain that continued for more than 10 days in a month were included in the study. Informed written consent was obtained from all patients.

**Exclusion criteria**

Patients with a discrete lump, which was suspicious of cancer after clinical, imaging and cytological examination were excluded from the study. Patients taking alternative treatment, lactating women, those planning a pregnancy or taking other oral contraceptive pills were also excluded. Women suffering from polycystic ovarian disease, other hormonal abnormalities requiring additional investigations, and liver and kidney problems were also excluded from the study.

**Intervention**

Oral ormeloxifene 30 mg or a placebo was given twice a week for 3 months. The active drug was supplied by Hindustan Latex Limited and the placebo tablets by the CDRI, Lucknow.

**Sample size**

The sample size was calculated assuming a 20% difference (superiority) in morbidity as clinically significant with a 5% level of significance and 80% power. The number of patients required in each group was 48; and accounting for a 20% drop-out rate, we decided to enrol 70 patients in each group.

**Randomization and allocation concealment**

A statistician, not associated with clinical care, generated the randomization scheme; with block size of 4 for 160 patients and allocation was done using the sealed envelope technique. The bottles with drug/placebo were dispensed free of charge from the trial office. The participants, physicians doing serial clinical assessments and the dispensing office were all blinded to the randomization.

**Outcomes**

Breast pain and nodularity was assessed serially on initial and all subsequent visits by the same person (RR). For pain, a visual linear analogue (VLA) scale, with a 10 cm line with markings 1 cm apart was used. The extreme left end marked as 0 denoted no pain and the extreme right end marked as 10 denoted extreme pain. Each patient was carefully explained to tick on the line at a point corresponding to her level of pain on each visit. The earlier charts were available to the patient when documenting pain at a subsequent visit.

For nodularity, the Lucknow–Cardiff scale was used. This scale is a 5-point ordinal scale depicting increasing order of nodularity shown schematically in the upper outer quadrants of a paired breast. Grade 0 indicates a smooth textured breast with extreme extent of normalcy and grade 4 the maximum nodularity. There were five figures that provided a cue for the examining physician to chart nodularity in the index breast. The examining physician made a holistic interpretation of breast nodularity as a sum of areas or quadrants involved and the coarseness of nodularity. Breast nodularity was assessed longitudinally, by the same clinician on an ordinal scale of 0–4 in the breast clinic at each visit. For the purpose of data analysis, the grades were renumbered as 1 to 5, and labelled as normal, mild, moderate, severe and very severe, respectively. To take advantage of ordinal outcomes and summarize the association over all grades, it was informative to do the analysis using the cumulative frequencies of the nodularity grades in the two groups.

A proportional odds model for cumulative logit was applied to compare the active and placebo group which gave us the odds ratio, confidence interval and value of significance at each successive visit. At 3 months, both the active treatment and placebo were stopped. However, the blinded assessment and follow-up continued up to 6 months. This provided with a wash-out period of 3 months without any treatment or placebo. Adverse drug reaction forms were filled for all patients and sent to the review board.

**Follow-up**

Breast pain and nodularity were assessed at the start of the active treatment or placebo and on follow-up at 1, 2, 3 and 6 months. At each visit, photocopies of the pain and nodularity charts were available. The tablet count and self-reporting were taken as compliance. Any side-effects experienced by the patients were recorded at each visit.

**Secondary efficacy variable and assessment**

The secondary outcomes were the clinicians’ global assessment of each patient’s condition and side-effects.

**Statistical methods**

Breast pain was recorded repeatedly on a continuous analogue scale. The hierarchical (nested) linear model was used for analysing longitudinal data. For testing various hypotheses about time factor in repeated measure analysis of variance, we used the Gesisser and Greenhouse method, and Huynh and Feldt method of obtaining F-statistics with appropriate degrees of freedom. Breast nodularity was recorded serially on a 5-point ordinal scale. The ‘proportional odds regression model’ has been used to take full advantage of the ordinal outcomes.

This model is linear and additive on the logit scale and uses maximum likelihood methods to estimate a summary odds ratio. The estimated odds ratio is not based on a particular dichotomization of the outcome variable, but summarizes the association of interest over all levels of outcome.

Informed written consent was taken from all patients and they were at liberty to withdraw from the study at any time. The study
was approved by the Drug Controller General of India and the Institutional Ethics Committee. This trial was registered with Clinical Trials Registry-India (www.ctri.in, registration no. CTRI/2008/091/000279.)

RESULTS

We included 151 patients in the study; 75 in the drug ormeloxifene group and 76 in the placebo group (Fig. 1). The mean (SD) age of those enrolled in the ormeloxifene group was 33.7 (7.45) years and in the placebo group was 32.8 (8.36) years. Thirty (19.6%) patients—18 in the drug group and 12 in the placebo group—did not complete the mandatory visit at 6 months and were considered lost to follow-up.

Amelioration of pain

At the initial visit, there was not much difference in the mean pain score between the drug and the placebo groups. However, the mean pain score in the subsequent visit decreased considerably in the drug compared with the placebo group. At the end of 3 months when both the drug and placebo were stopped, there was an ongoing decrease in pain in the drug group whereas pain recurred in the placebo group (Table I, Fig. 2).

The variations in pain in the two groups and group by time interaction when analysed showed significant differences between visits ($F=105.23$, Geisser and Greenhouse $p<0.0001$). Comparing the drug and placebo groups at any given point of time, the two groups were statistically different ($F=18.66$, $p<0.0001$). The patterns of mean pain level over successive visits for the individual group differs from the overall mean pain level for the two groups ($F=44.43$, Geisser and Greenhouse $p<0.0001$).

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the start of the study</td>
<td>5.71</td>
</tr>
<tr>
<td>At the end of first month</td>
<td>4.06</td>
</tr>
<tr>
<td>At the end of second month</td>
<td>2.62</td>
</tr>
<tr>
<td>At the end of third month</td>
<td>1.39</td>
</tr>
<tr>
<td>At the end of 6 months</td>
<td>0.98</td>
</tr>
</tbody>
</table>

In the drug group, grades 1 and 2 nodularity were seen in 25 (33.3%) patients whereas grades 3, 4 and 5 were seen in 50 (66.7%). At the end of the third month of treatment, 65 (86.7%) patients had grades 1 and 2 nodularity compared with 10 (13.3%) patients with grades 3, 4 and 5 nodularity. After 2 months without any drug, 70 (93.3%) patients had grades 1 and 2 nodularity and only 5 (6.7%) had high grades 3, 4 and 5 nodularity (Table II).

In the placebo group, grades 1 and 2 nodularity were seen in 37 (48.7%) patients whereas grades 3, 4 and 5 were seen in 39 (51.3%). At the end of the third month of treatment, 52 (68.4%) patients had grades 1 and 2 nodularity as compared to grades 3, 4 and 5 nodularity in 24 (31.6%). After 3 months without any drug, 54 (71.1%) patients had grades 1 and 2 nodularity and 22 (28.9%) had grades 3, 4 and 5 nodularity (Table II). Overall, in both the groups there was an improvement in the grade of nodularity. There was significantly greater improvement in the grade of nodularity in the drug group in the third and sixth months as compared to the placebo group.

Table I. Mean pain assessment at successive visits for the drug and placebo groups

![Fig 1. Consort flow diagram]

![Fig 2. Mean pain assessment by visual analogue scale for the two groups]
At the time of recruitment, the patients in the drug group were more likely to have high grade of nodularity as compared to the placebo group (Fig. 3). During successive visits, the drug group showed improvement and had lower grades of nodularity. At the fourth and last visits, the drug group was more likely to have nodularity of a low grade (Fig. 3).

In the first or initial pre-treatment visit somewhat higher grades of nodularity were present in the drug group than in the placebo group. However, there was no significant difference (p<0.001, p=0.585 and p=0.202) in the initial and subsequent two follow-up visits in both the groups. Significant difference (p=0.001) was noticed at the end of the third month while on drug treatment. Assessment of nodularity at 6 months in the two groups showed that the effect of the active drug still persisted and was significant (p<0.001; Table III).

**Table II. Frequency (probability) of benign breast nodularity grades in patients receiving drug and placebo at initial (before treatment) and subsequent visits**

<table>
<thead>
<tr>
<th>Treatment visit</th>
<th>Grade of breast nodularity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug group</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>7 (0.093) 18 (0.240) 26 (0.347) 16 (0.210) 8 (0.107)</td>
</tr>
<tr>
<td>At 1 month</td>
<td>28 (0.373) 14 (0.187) 24 (0.320) 5 (0.067) 4 (0.053)</td>
</tr>
<tr>
<td>At 2 months</td>
<td>37 (0.493) 15 (0.200) 18 (0.240) 3 (0.040) 2 (0.027)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>47 (0.627) 18 (0.240) 8 (0.107) 2 (0.027) 0</td>
</tr>
<tr>
<td>At 6 months</td>
<td>55 (0.733) 15 (0.200) 3 (0.040) 2 (0.027) 0</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>10 (0.132) 27 (0.355) 29 (0.382) 8 (0.105) 2 (0.026)</td>
</tr>
<tr>
<td>At 1 month</td>
<td>17 (0.224) 30 (0.395) 23 (0.303) 6 (0.079) 0</td>
</tr>
<tr>
<td>At 2 months</td>
<td>21 (0.276) 29 (0.382) 22 (0.289) 3 (0.039) 1 (0.013)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>24 (0.316) 28 (0.368) 20 (0.263) 3 (0.039) 1 (0.013)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>26 (0.342) 28 (0.368) 19 (0.250) 2 (0.026) 1 (0.013)</td>
</tr>
</tbody>
</table>

**Side-effects**

No major side-effect was reported by the patients except for oligomenorrhea by 12 patients.

**Table III. Odds ratio, confidence interval and significance of nodularity at each successive visit**

<table>
<thead>
<tr>
<th>Visits</th>
<th>Odds ratio (OR)</th>
<th>Confidence interval (CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Beginning)</td>
<td>2.180</td>
<td>1.21, 3.94</td>
<td>0.009</td>
</tr>
<tr>
<td>2 (End of 1st month on treatment)</td>
<td>1.190</td>
<td>0.64, 2.79</td>
<td>0.585</td>
</tr>
<tr>
<td>3 (End of 2nd month on treatment)</td>
<td>0.670</td>
<td>0.36, 1.24</td>
<td>0.202</td>
</tr>
<tr>
<td>4 (End of 3rd month on treatment)</td>
<td>0.316</td>
<td>0.16, 0.62</td>
<td>0.001</td>
</tr>
<tr>
<td>6 (End of 3 months without any treatment)</td>
<td>0.164</td>
<td>0.08, 0.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Fig 3.** Cumulative percentage of breast nodularity grading in drug versus placebo for five visits

![Graph showing cumulative percentage of breast nodularity grading in drug versus placebo for five visits](image-url)
DISCUSSION

Mastalgia is a common symptom. Patients with mild mastalgia when reassured that this is a normal or slight variation from normal phenomenon—aberrations in the normal development and involution of the breast (ANDI)—may not require any further treatment. Nevertheless, a subset of women (15%) who have severe mastalgia which interferes with their quality of life would require drug treatment.4,5,19 The need to find a drug for mastalgia which is effective and safe is suggested from a review of the literature.18 Several agents have been tried for mastalgia. The two broad categories of drugs used are hormonal and non-hormonal. Hormonal manipulation has been done by using danazol, tamoxifen, bromocriptine, progesterone, oral contraceptive pill and more recently luteinizing hormone-releasing hormone (LHRH) analogue or goserelin. The non-hormonal agents used include analgesics (oral/topical), plant extracts such as fructus-agri-casti, EPO and and gamma linolenic acid (GLA).

Our study is the first randomized clinical trial of ormeloxifene in breast pain and nodularity. This drug was developed by the CDRI in 1970 and licensed for marketing in 1990.11 The drug has not been licensed so far in the European countries, UK and North America.20–22 It is a weak ER agonist and SERA. The contraceptive effects of ormeloxifene are related to the slight acceleration of embryo transport through the fallopian tubes, accelerated blastocyst formation along with suppression of uterine proliferation and decidualization as well as alteration of biochemical parameters of implantation. These create an asynchrony between the embryo and uterine development, a critical requisite for nidation. It does not affect the hypothalamic–pituitary–ovarian axis. Administration of ormeloxifene does not inhibit ovulation either. Its oestrogenic activity is mediated through its ER interaction. No progestational, androgenic, anti-androgenic effects were seen at the recommended contraceptive doses. There is also no effect on the thyroid or adrenal secretary functions. Extensive studies on animals and human volunteers have shown that it is relatively free from side-effects. Safety has been established by haematological, biochemical tests as well as by laparoscopic and ultrasonographic examination of the ovaries and uterus. Even with long-term use, ormeloxifene does not have chronic toxicity, teratogenic, mutagenic or carcinogenic properties. A return to fertility has been reported within 6 months.21 Babies born to user failures present normal milestones. This drug was reported to be useful in the treatment of advanced breast cancer in a single, open-label clinical case series.21 The l-isomer of ormeloxifene or levormeloxifene is more oestrogenic at the genital tract with much higher activity against ERs. It may be a useful drug for post-menopausal osteoporosis. However, it was not marketed because of the higher anticipated side-effects on the genital tract. A critical requisite for nidation. It does not affect the hypothalamic-pituitary-ovarian axis. Administration of ormeloxifene does not inhibit ovulation either. Its oestrogenic activity is mediated through its ER interaction. No progestational, androgenic, anti-androgenic effects were seen at the recommended contraceptive doses. There is also no effect on the thyroid or adrenal secretary functions. Safety has been established by haematological, biochemical tests as well as by laparoscopic and ultrasonographic examination of the ovaries and uterus. Even with long-term use, ormeloxifene does not have chronic toxicity, teratogenic, mutagenic or carcinogenic properties. A return to fertility has been reported within 6 months.21 Babies born to user failures present normal milestones. This drug was reported to be useful in the treatment of advanced breast cancer in a single, open-label clinical case series.21 The l-isomer of ormeloxifene or levormeloxifene is more oestrogenic at the genital tract with much higher activity against ERs. It may be a useful drug for post-menopausal osteoporosis. However, it was not marketed because of the higher anticipated side-effects on the genital tract. No such side-effects have been reported for ormeloxifene even after its long-term use.23–25

A meta-analysis to evaluate drugs commonly used for the treatment of mastalgia was published recently.6 Several randomized, placebo-controlled trials were included in this meta-analysis. Seven trials on bromocriptine were analysed and the weighted mean difference in pain score in favour of bromocriptine was –16.31 (95% CI –26.35 to –6.27) indicating a significant relief from mastalgia. Four trials of danazol showed a mean pain score difference of –20.23 (95% CI –28.12 to –12.34) showing its effectiveness in relieving breast pain. However, the use of EPO in three trials did not show any advantage over a placebo with a mean pain score of –2.78 (95% CI –7.97 to 2.40). Tamoxifen achieved an RR of pain relief of 1.92 (95% CI 1.42–2.58) with least side-effects and was recommended as the drug of choice for treating mastalgia. Tamoxifen thus is a useful and effective drug for the treatment of mastalgia and it is inexpensive too. However, it is also used as an anticancer agent too and hence patients are often concerned when asked to take tamoxifen.

In addition, the above-mentioned drugs have several side-effects. For example, bromocriptine (2.5 mg twice daily) causes headache, nausea, vomiting and dizziness. This led to a 20% drop-out rate in some trials.8,21 Danazol (100–400 mg) results in weight gain, acne, greasy hair and skin, headache, nausea, hirsutism, decrease in the size of the breast and voice change (due to an androgenic effect). These side-effects occur in about one-quarter of patients. The incidence of amenorrhoea or irregular menstruation (due to gonadal suppression) increases at higher dosages of 400 to 800 mg.8,26 The acceptance of EPO is higher and it has mild nausea as the only side-effect with an incidence of <2%. However, it has not been shown to be very efficacious.6,27 The major side-effects of tamoxifen are hot flushes and peri-menopausal-like symptoms. The long-term safety of tamoxifen has been a cause of concern, particularly its possible association with endometrial cancer. It is contraindicated in pregnancy and appropriate contraception is therefore mandatory. As goserelin has unwanted side-effects including menopausal symptoms and bone mass reduction, it is reserved for short-term use in patients with severe mastalgia refractory to other forms of therapy. The gonadotropin-releasing hormone agonists, although proven to be extremely effective, have a risk of ‘menopausal’ osteoporosis and cardiovascular disease for their long-term use to be acceptable.7

We used a validated scale for breast nodularity and assessed the results of treatment longitudinally. Ordinal outcomes are often analysed by altering the attributes of the scale—collapsing the scale to a dichotomous one, treating it as nominal or considering it to be continuous. Important information is lost when the ordinality of ranked data is not fully exploited. In addition, because they ignore the ordinality of data, chi-square tests have less than optimal power, potentially leading to incorrect inferences. We used a statistically powerful method, referred to as the proportional odds regression model, designed to take full advantage of ordinal outcomes. This model is linear and additive on the logit scale and uses maximum likelihood methods to estimate a summary odds ratio. The estimated odds ratio is not based on a particular dichotomization of the outcome variable, but summarizes the association of interest over all levels of outcome. For pain, the recordings were taken on a 10 cm continuous linear analogue scale. Trials with repeated measurements need an overall pre-specified strategy for statistical analysis. First, for each patient, the mean value of pain scores over five different occasions was taken as the summary measure of response. The hierarchical (nested) linear model was used for analysing longitudinal data. For testing various hypotheses about the time factor in repeated measure analysis of variance, we used the Geisser and Greenhouse method, and Huynh and Feldt method of finding F-statistics with appropriate degrees of freedom.18

In a published trial from the All India Institute of Medical Sciences, New Delhi, India, which included 42 patients, ormeloxifene was given to patients with mastalgia in a dose of 30 mg on alternate days for 3 months. At the end of 3 months, 90% patients were pain-free with complete disappearance of nodularity (35/35).13

In India, ormeloxifene is used by doctors as a contraceptive, and for treatment of menorrhagia, dysfunctional uterine bleeding and breast diseases. The only reported side-effect of ormeloxifene is a prolonged menstrual cycle in <10% of women. The significant
improvement in cyclical breast pain or mastalgia and breast nodularity in our patients indicates that ormeloxifene is an effective agent for these conditions.

ACKNOWLEDGEMENTS
This study was supported by an ad hoc research scheme funded by the Indian Council of Medical Research (ICMR), New Delhi, India, Ref No: 5/13/90/06/NCD–III. RR and VD received salary as research officers from the ICMR. The drug was supplied by Hindustan Latex Limited and the placebo was supplied by the CDRI, Lucknow, India.

Conflict of interest. None declared.

Contributions. SK, RR and SK conducted the breast clinic, collected the initial and follow-up clinical data. VD managed the trial office, randomization, adverse drug reaction forms, follow-up and manuscript. GG did the statistical analysis. VD facilitated capacity building.

REFERENCES