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Original research

Centchroman vs tamoxifen for regression of mastalgia: A randomized controlled trial

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HIGHLIGHTS

- Several pharmacological agents have been used in the management of mastalgia.
- Tamoxifen is currently considered the drug of choice for mastalgia.
- A prospective randomized controlled trial was conducted to compare Tamoxifen with Centchroman (Ormeloxifene) in the management of mastalgia.
- Both centchroman and tamoxifen were found to be of similar effectiveness in providing pain relief in mastalgia.
- High frequency of side effects, particularly development of ovarian cyst, in patients receiving centchroman was observed.

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ABSTRACT

Introduction: Several agents have been tried in the management of mastalgia. Centchroman (Ormeloxifene), a novel non-steroidal selective estrogen receptor modulator (SERM), has also been recently used in the management of mastalgia.

Methods: Eligible patients, who had mastalgia for more than 3 months, were randomized into two groups – Group A received centchroman 30 mg daily and Group B received tamoxifen 10 mg daily. Treatment was continued for a total of 12 weeks; thereafter, patients were followed for another 12 weeks without medication to assess the continuum of relief. Pain severity was measured with VAS score. Patients were considered to have complete pain relief if their VAS score decreased to 3 or less.

Results: Patients, in both the groups, showed gradual improvement in mastalgia with passage of time up to 12 weeks. Following cessation of treatment at 12 weeks, partial relapse of pain was observed at 24 weeks. There was no significant difference between Group A and Group B in terms of mean VAS Score and proportion of women reporting pain relief at 4, 8, 12, and 24 weeks. Fifteen patients in Group A had side effects namely dizziness, menstrual irregularities and development of ovarian cysts. There was no side effect noted in group B.

Conclusion: Centchroman and tamoxifen were found to be of similar effectiveness in providing pain relief in mastalgia. High frequency of side effects, particularly development of ovarian cyst, in patients receiving centchroman is a matter of concern.

1. Introduction

Mastalgia is one of the common breast related complaint for which a woman seeks medical consultation. Non-medical therapy for mastalgia includes reassurance and good external breast support- "sports brassier". There are a number of drugs which have been tried in the treatment of mastalgia namely danazol, bromocriptine, tamoxifen, evening primrose oil, topical nonsteroidal anti-inflammatory drugs, and more recently centchroman (Ormeloxifene). In a recent meta-analysis of randomized trials comparing bromocriptine, danazol, evening primrose oil, and tamoxifen, with placebo, it was concluded that tamoxifen should be the drug of

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choice considering significant relief from mastalgia (RR = 1.92, 95% CI 1.42–2.58) and least side effects [1]. Centchroman is a novel non-steroidal selective estrogen receptor modulator (SERM) [2]. It is primarily used as an oral contraceptive pill and is being distributed in India free of cost under National Family Welfare Programme. It is a unique need-oriented contraceptive, being effective when taken immediately after coitus or routinely as a weekly pill, and has the advantage of less frequent administration. Its contraceptive action is quickly reversible. Dhar et al., in a pilot study of centchroman in mastalgia, showed 100% response in pain relief after 12 weeks of treatment while nodularity and tenderness disappeared in all patients after 4 weeks [2]. In a randomized controlled trial comparing centchroman with danazol, Tejwani et al. showed that centchroman was more effective in reducing pain on Visual Analogue Scale (VAS) (0.019) [3]. Menstrual irregularities were reported as the most common side effect of centchroman in both these studies [2,3]. Centchroman is considered safe for chronic administration [4,5]. Considering encouraging results of centchroman in mastalgia, this randomized trial was designed to compare centchroman with tamoxifen in the treatment of mastalgia.

2. Methods

2.1. Study design and settings

The study was a two-arm randomized controlled trial of Centchroman vs Tamoxifen in mastalgia. The study was conducted in the Out Patient Department of Surgery Unit 1 of a tertiary teaching hospital in North India. The study was approved by the Institutional Ethical Committee – Human Research and the Drug Controller General of India. The study was registered prospectively on Clinical Trials Registry – India (CTRI number CTRI/2012/05/002658, http://www.ctri.nic.in).

2.2. Sample size

Sample size of 52 (26 in each group with allocation ratio 1.0) was calculated using PASS software (Power and Sample Size), to achieve 81% power to detect a non-inferiority margin difference between the group proportions of −0.15. Pain relief proportion was taken as 0.95 for Tamoxifen. Pain relief proportion by centchroman was assumed to be 0.80 under the null hypothesis of inferiority. The power was computed for the case when the actual pain relief proportion by Centchroman was 0.95. The test statistic used was the one-sided Z test. Significance level of the test was targeted at 0.05. Considering 10% follow up loss, sample size was calculated to be 58.

2.3. Patient eligibility and selection

All the consecutive patients, aged >18 years, reporting with history suggestive of benign breast disease were screened. Patients, who complained of mastalgia with or without breast nodularity for more than 3 months duration and who were having pain severity of >3/10 on visual analog scale, were assessed for inclusion in the study. A detailed history was taken from all the patients followed by thorough physical examination. Patients aged <40 years were subjected to bilateral breast ultrasonography while bilateral mammography was done in patients >40 years of age. A gynecological evaluation and ultrasonography pelvis was performed in all patients. Patients were excluded if they met any of following criteria: clinical or radiological suspicion of malignancy, past history of breast carcinoma or family history of breast carcinoma, presence of acute inflammatory breast conditions or discrete breast lumps, presence of polycystic ovarian diseases or cervical hyperplasia, patient was pregnant or was planning to conceive, and patients during first six months of lactation period. Eligible patients were reassured against the possibility of breast cancer and were advised well fitting brassier for external support. All the patients, who continued to have mastalgia of severity >3 on VAS after one month period of further observation, were encouraged to participate in the study. The study was explained to the patients, and those who agreed for inclusion were enrolled into the study.

2.4. Randomization and allocation concealment

A randomization table, with a block size of six, was generated through computer to assign 60 patients to two groups: Group A and B. A nursing sister, who was not involved into the study, assigned the enrolled patients to Group A or B through a sealed envelope technique.

2.5. Trial flow

Patients in group A were treated with centchroman, 30 mg daily, and patients in Group B were treated with tamoxifen, 10 mg daily. Medicines were dispensed free of cost to the patients. The response assessor was made blind to the treatment prescribed to a particular patient. Patients were evaluated at one week to check for tolerance to the drug. Subsequently, they were followed up at 4, 8, 12 and 24 weeks. After the clinical evaluation, pain severity was measured with VAS score to assess the response to therapy. Patients were considered to have complete relief of pain if VAS score fell below 3/10. Treatment was continued for a total of 12 weeks and then, patients were followed up for another 12 weeks without medication to assess the continuum of relief. All the patients were sonographically examined at 12 and 24 weeks of study to look for ovarian cysts.

2.6. Outcome measures

Primary outcome measure of the trial was pain relief defined as VAS score ≤3. Secondary outcome measure was side effects of therapy.

2.7. Data management and statistical analysis

Data was analyzed by using SPSS version 16. Two arms were assessed for homogeneity of variances at baseline using t-test for quantitative data and Chi-square test for qualitative variables. Effectiveness of treatment arms was assessed by proportions of patients having relief from mastalgia at 4, 8, 12 and 24 weeks. The relative risk (95% confidence interval) for significant pain relief (VAS < 3) with Centchroman as exposed and Tamoxifen as reference category was calculated at 4, 8, 12 and 24 weeks. Significant differences were considered when p-value was less than 0.05.

3. Results

In the present study, 65 women presenting with mastalgia to the Surgery Out-Patient Department of Surgery Unit 1, at Guru Teg Bahadur Hospital, Delhi, were enrolled. Five women were excluded from the study group as they met the exclusion criteria: four women did not consent for inclusion in the study, and one was breast feeding her baby. The sixty women were randomized into two groups: Group A (Centchroman) – 30 women and Group B (Tamoxifen) – 30 women. Fig. 1 shows the trial flow.

There was no statistically significant difference between the two groups with respect to age, marital status, parity, type of mastalgia, duration of symptoms, and pretreatment severity of mastalgia.