**COMPARATIVE EVALUATION OF THE ROLE OF CENTCHROMAN IN BENIGN BREAST DISEASES**

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**ABSTRACT**

Background: Benign breast disease encompasses a heterogeneous group of lesions. The aim of the study is to evaluate the role of Centchroman in the treatment of benign breast disease in comparison to Danazol and Evening primrose oil. Materials and Methods: This was a prospective study undertaken on 120 patients having benign breast lesions. They were randomized into 3 groups: Group 1 (Centchroman 30 mg bi weekly for 3 months), Group 2 (Danazol 50 mg bid for 3 months) and Group 3 (Evening Primrose Oil 1000 mg bid for 3 months). The study was carried out in Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University between September 2011 to May 2013. Treatment was given for 3 months and patients were followed up for 6 months. Results were recorded as per clinical examination, visual analog scale, breast pain chart and ultrasonography for breast lump size. Results: Non cyclical mastalgia was the most common presentation (81.6%). 18.3% patients presented with one or more fibroadenomas while 38 patients (63.3%) had nodularity with or without mastalgia. All three subgroups showed at least 50% reduction in pain after 3 months of treatment but at 6 months follow up, VAS was > 4 in 13.33% patients in Centchroman group, 64.7% patients in Danazol group and 70.5% patients in EPO group. 80% patients had complete regression of nodularity at 3 months in Centchroman group. Danazol was effective in 71.43% while EPO group had no statistically significant effect. At 6 months follow up only Centchroman was found to be effective.

Only side effect noted in Centchroman group was prolongation of menstrual cycle in 30% of patients.

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**Introduction**

The term “benign breast diseases” encompasses a heterogeneous group of lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations and neoplasms. It may present as a wide range of symptoms. The incidence of benign breast lesions begins to rise during the second decade of life and peaks in the fourth and fifth decades, as opposed to malignant diseases, the incidence of which continues to increase after menopause, although at a less rapid pace (Donegan et al. 2002; Shaaban et al. 2002). The vast majority of the lesions that occur in the breast are benign and they are far more frequent than malignant ones (Caleffi et al, 2004; Kelsey et al, 1990). Mastalgia or breast pain is one of the most common conditions of breast. Prevalence of mastalgia is 41 to 69% (Roberts et al, 1987). Duration of painful nodularity of more than one week of the cycle is useful definition for differentiation from normal discomfort. It is broadly categorized into cyclical and non-cyclical mastalgia (Hughes et al, 2000). The most common type of discomfort is related to the menstrual cycle, and particularly to ovulation. Two or three days of premenstrual breast tenderness or heaviness every month should be regarded as temporary or normal. Research criteria for the diagnosis of cyclic mastalgia are (1) pain severity greater than 4.0 cm measured on a 10.0 cm visual analog scale and (2) pain duration of at least 7 days per month (Ader et al, 1997). Remission often occurs with hormonal events such as pregnancy or menopause. Only 14% of women with cyclic mastalgia experience spontaneous resolution; however, 42% experience resolution at menopause (Davies et al, 1999). Despite extensive studies done to identify causative histopathological, hormonal, nutritional, or psychiatric abnormalities, few consistent findings have been uncovered, and the etiology of cyclic mastalgia is unknown.
Noncyclic mastalgia involves constant or intermittent pain that is not associated with the menstrual cycle. Less common than cyclic mastalgia, it accounts for approximately 31% of women seen in mastalgia clinics (Davies et al, 1999). Most noncyclic breast pain arises for unknown reasons, yet is believed more likely to have an anatomical, rather than hormonal cause. Approximately 16% and 32% of women report breast pain as an adverse effect of estrogen and combined hormonal therapies, respectively (Davies et al, 1999).

Fibroadenomas are the most common breast masses in women younger than 30 years of age and the most common solid masses in breasts of woman of all ages, with a peak incidence at around 20 years of age (Lawrence et al, 1997). Fibroadenoma has a chance of spontaneous natural regression of about 30% over a period of years. Dent and Cant reported complete disappearance of fibroadenoma naturally in 31%, a decrease in size in 12%, remained static in 25%, and increased in 32% over a period of 24 months without treatment (Dent et al, 1989).

Different drugs have been used with varied responses. The most commonly prescribed drugs are evening primrose oil, danazol, bromocriptine, tamoxifen, and LHRH analog. Most of them are steroid based drugs with significant side effects.

Danazol, the only medication approved by the Food and Drug Administration for treatment of mastalgia, is a derivative of 17-alphaethyl testosterone that suppresses gonadotropin secretion, prevents luteinizing hormone surge and inhibits ovarian steroid formation. Bromocriptine blocks the release of prolactin by stimulation of dopaminergic receptors. But it's use is limited due to significant side effects like nausea, vomiting and dizziness. Tamoxifen, which is a selective estrogen receptor modulator, is being used in low doses in the treatment of mastalgia. It blocks the estrogen receptors and prevents the binding of estrogen to its receptors. Use of LHRH analog like Goserelin is usually reserved for patients whose pain is refractory to other treatment modalities.

Centchroman is a novel nonsteroidal, selective antiestrogen synthesized by the Central Drug Research Institute, Lucknow, India. It was included in the National Family Welfare Programme in 1995. It is an oral contraceptive and has the advantage of less frequent administration. In lactating women, it is excreted in milk in quantities considered unlikely to have any deleterious effect on suckling babies. It is free from side effects commonly associated with steroidal oral contraceptives like nausea, vomiting, weight gain, and dizziness. It does not delay return of fertility. It maintains normal ovulatory cycles because the low dose and two to three times a week administration schedule minimizes any effect on the hypothalamic – pituitary – ovarian axis. It has no side effects except that it may prolong the menstrual period duration in about 10% of the cycles and in a few cases of polycystic ovarian disease. Because of the advantages of this drug as a nonsteroidal antiestrogen with almost no side effects, it was used in the treatment of the benign breast diseases mastalgia and fibroadenoma.

**METHODS**

This is a prospective study carried out on 120 women who presented in Surgery OPD in Banaras Hindu University Hospital having signs and symptoms of benign breast disease (BBD) from August 2011 to July 2013. Women in the age group of 20 - 50 years with breast complaints suggestive of BBD such as - breast pain i.e. a fibroadenoma of more than 3 months of duration were included in the study. The exclusion criteria were women having a discrete mass suspicious of malignancy, pregnancy, patients on oral contraceptive pills (OCPs) for last 3 months, patients receiving hormone replacement therapy, inflammatory breast disease, those planning for pregnancy in near future.

Block randomization technique was used to allocate patients to the 3 different arms of the study. There were 3 arms of study having 40 patients each.

Group I – Those receiving Cenchroman 30 mg biweekly for 3 months

Group II – Those receiving Danazol 50 mg bd for 3 months

Group III – Those receiving Evening Primrose Oil (EPO) 1000 mg bd for 3 months

After a detailed history and clinically examination either an ultrasound of breasts or a mammography was done. Fine Needle Aspiration Biopsy (FNAC) was done in all cases of fibroadenoma to confirm the diagnosis and rule out malignancy. FNAC was also done of any dominant nodule in patients presenting with nodularity in breasts. Clinically, the size of the lump was recorded with the help of vernier calipers. Breast pain chart was provided to patients presenting predominantly with mastalgia. Those presenting with nipple discharge underwent cytology of the discharge. All sexually active women were sent for a detailed gynaecological examination and in suspected cases ultrasound (USG) of the pelvis was done to rule out polycystic ovarian disease.

The medical history and examination findings were recorded on a proforma. Pain score was recorded on a visual analog scale (VAS) from 0 to 10. 0 being minimum pain and 10 being maximum (intolerable) pain which hampers routine activity. In patients, in whom mastalgia was the only symptom, those having pain for at least 3 months duration or at least 7 days in every menstrual cycle were included in this study. Patients having polycystic ovarian disease, cervical hyperplasia or pregnancy were not included.

The clinical examination was done at the time of presentation, after 1, 3 and 6 months. Radiological examination was done at the time of presentation and after 3 months. The main outcome of interest in the mastalgia group was relief of breast pain as measured on the VAS of 0-10 and change in nodularity, which was recorded with palpation of the breast and coded as present or absent at 1, 3 and 6 months. The outcome in the fibroadenoma group was decrease in size of the lump measured clinically and with the help of ultrasound at the beginning, at the end of 3 months and again clinically at 6 months.

The various parameters studied were compared using Chi-square test for non continuous variables & ANOVA for continuous variables. The critical value of ‘p’ indicating the probability of significant difference was taken as <0.05 for comparison.

**Results**

This was a prospective study carried out in a single surgical unit’s outdoor patients from July 2011 to June 2013. The study group comprises of 120 female patients who presented with signs and symptoms suggestive of benign breast disease. Diagnosis were confirmed by triple assessment. By Block Randomization method, they were grouped into 3 study arms of 40 each. Age of patients ranged from 20-45 years, largest number being between 21 to 30 years of age (70 patients; 58%). Mastalgia was the most common presenting symptom (98 patients; 81.6%) of which 36 (36.5%)
had non-cyclical pain while 62 patients (63.5%) had cyclical mastalgia. 77.5% (76 patients) had mastalgia associated with nodularity while 22.4% (22 patients) had mastalgia without nodularity. (Table no. 1).

Mean size of fibroadenoma at the start of study was $3.00 \pm 0.43$ in EPO group, $4.03 \pm 0.90$ in Danazol group and $3.68 \text{ cm} \pm 1.13$ in Centchroman group. The baseline VAS score was 5.30, 5.20 and 4.90 in EPO, Danazol and Centchroman groups respectively.

At 1 month follow up, VAS >4 was present in 6 patients (20.7%), in 2 patients (7.1%) at 3 months and recurred in 1 patient. I.e. 3 patients (10.7%) had VAS >4 at 6 months in Centchroman group. On comparing it with patients in Danazol group 62.5% (20 patients) had VAS >4 at 6 months, implying that 12 patients had increase in the severity of mastalgia as it was initially present. Evening primrose oil was found to be least effective with 82.3% (28 patients) not responding at 1 month while 71.8% (23 patients) still had VAS >4 at 6 months. Though all groups show a reduction in VAS score by more than 50% after 3 months of treatment, only Centchroman group continued to have significant reduction of VAS score ($p=0.027$) at 6 months, suggestive of better efficacy of Centchroman.

Table 1 Comparison of baseline characteristics

<table>
<thead>
<tr>
<th>Age (years) (mean)</th>
<th>Centchroman (n=40)</th>
<th>Danazol (n=40)</th>
<th>EPO (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.30 (6.79)</td>
<td>38.10 (7.06)</td>
<td>31.15 (5.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS at baseline</td>
<td>4.90</td>
<td>5.20</td>
<td>5.30</td>
<td>0.85</td>
</tr>
<tr>
<td>Number of patients with mastalgia</td>
<td>30</td>
<td>34</td>
<td>34</td>
<td>0.41</td>
</tr>
<tr>
<td>Number of patients with cyclical mastalgia</td>
<td>10</td>
<td>14</td>
<td>12</td>
<td>0.62</td>
</tr>
<tr>
<td>Number of patients with cyclical mastalgia</td>
<td>20</td>
<td>22</td>
<td>22</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Table 2: Comparison of characteristics at different time intervals

<table>
<thead>
<tr>
<th>Mastalgia Size (cm)</th>
<th>Time interval (months)</th>
<th>Centchroman vs EPO</th>
<th>p-value</th>
<th>Danazol vs EPO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (0.07)</td>
<td>0.15</td>
<td></td>
<td>6 (0.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>2.7 (0.08)</td>
<td>0.21</td>
<td></td>
<td>2.7 (0.08)</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>3.1 (0.07)</td>
<td>0.25</td>
<td></td>
<td>3.1 (0.07)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

All the three drugs were not found to have any significant response on the size of the fibroadenoma at both 3 & 6 months follow up. The p-value was not significant in any group indicating no significant response of any drug in regression in size of fibroadenoma.

In nodularity group, at 3 months of treatment 81.9% and 72.5% showed complete regression of nodularity in Centchroman and Danazol group. At 6 months follow up, there were no recurrences in Centchroman indicating long term efficacy of the Centchroman, but there was recurrence in 43.9% patients of the cured group, which indicates that Danazol does not have long term efficacy.

In EPO, at 3 months of treatment, there was regression in nodularity in only 28.6% of patients. At 6 months follow up 61.3% showed recurrence of nodularity in cured group. In comparison of Centchroman with Evening Primrose Oil, significant difference at 1 month, at 3 and 6 months from starting of treatment indicating better response of Centchroman in treatment of nodularity. There was significant reduction nodularity in Danazol in comparison to evening primrose oil at 3 months indicating better response of Danazol. During follow up period of 3 months there was no significant difference in both groups indicating no long term efficacy of both drugs.

There was no significant side effect noticed except in 30% of patients in Centchroman group reported prolongation of menstrual cycle.
Discussion

Benign breast disease encompasses a spectrum of conditions that range from normal to disorder to disease. Aberrations of normal development and involution (ANDI) classification includes this spectrum and classifies it according to the age of their presentation. In our study, the majority of patients (70 patients) i.e. 58.3% were between 21 and 30 years of age. Another study from All India Institute of Medical Sciences (AIIMS) India (Dhar et al.,[9]) also reported 40% of their patients being in the age group of 21-30 years. Hence, benign breast disease seems to be more common in the younger age group.

In a study of 2400 women enrolled in a health maintenance organization in the United States for a 10 year period, the most common breast symptom was pain, prompting medical evaluation and accounting for 47% of breast related visits ([10] Barton MB). In most patients with mild pain, reassurance that lesion is not malignant, alleviates the symptoms to a large extent. A Brazilian study on 85 patients with mastalgia verified an overall success rate of 70.2% with reassurance [8] (Barros AC). Mastalgia was the most common presentation (98 patients 81.6%) in our study. Of which 62 patients (63.5%) had cyclical mastalgia and 36 patients (36.5%) had non cyclical mastalgia. Dhar et al. [9] have reported 70% incidence of mastalgia in their study of benign breast disease. Both pain and nodularity may occur simultaneously. Literature suggests three hormonal theories regarding the etiology of painful, nodular breasts: increased oestrogen secretion from the ovary, deficient progesterone production i.e. “relative hyperoestrogenism” [11] (Sitru R. - Ware R) and hyperprolactinemia. In our study, 77.5% (76 patients) had mastalgia associated with nodularity while 22.4% (22 patients) presented with mastalgia only.

There seems to be a definite role of estrogen receptor (ER) in the pathogenesis of benign breast diseases. ER positivity was found to be variable in various histological variants, being highest in fibroadenoma [13] (Khanna S). It was also found to diminish as age advances [13]. In a study to assess the responsiveness of drugs in relation to ER positivity, it was found that patients with ER positive breast disease responded better to danazol [12] (Khanna AK). Measurement of plasma fatty acids has confirmed abnormal profiles in patients with mastalgia. Saturated fatty acids were decreased and essential fatty acids were lower than normal. [14] (Gateley CA 1992). On assessing the lipid profile of patients with benign breast disease, only triglyceride and cholesterol levels were found to have statistically significant difference in the study and control group [13] (Khanna S).

The fatty acid deficiency hypothesis has led to the treatment of BBD by Essential Fatty Acids (EFA) in diet. The oil of evening primrose (EPO) which is unique in containing 7% linolenic acid and 72% linoleic acid, represents the richest natural source of EFAs known. In a randomized double blind cross over study on 73 patients by Pashby et al [15] EPO was given orally for 3 months. Pre-trial linear analog scale (LAS) for pain rating was 50 in cyclical pain group and 54 in non cyclical pain group. In placebo group, LAS was 45 in cyclical and 56 in non cyclical pain group. After 3 months of treatment, in EPO group LAS was 32 in cyclical mastalgia and 40 in non cyclical mastalgia group. In placebo group, it was 42 and 60 in cyclical and non cyclical group respectively. The study concluded that EPO reduces pain in non cyclical group (p<0.05) and lesser in cyclical group.

Danazol, the only medication approved by the FDA for treatment of mastalgia, suppresses gonadotropin secretion, prevents luteinizing hormone surge and inhibits ovarian steroid formation. Danazol appears to be the best agent for severe breast pain and nodularity, with an overall improvement rate of 70%. It is superior to bromocriptine in the treatment of cyclical breast pain [17] (Hinton CP 1986) but its efficacy is countered by the side effects like amenorrhea, weight gain, acne and hirsuitism with longterm use.

Centchroman is a novel nonsteroidal, selective antiestrogen. It was included in the National Family Welfare Programme in 1995. It is an oral contraceptive and has the advantage of less frequent administration. In lactating women, it is excreted in milk in quantities considered unlikely to have any deleterious effect on suckling babies. It does not delay return of fertility. It has side effects of prolongation the menstrual period. It was used in the treatment of the benign breast diseases mastalgia, nodularity and fibroadenoma.

Centchroman was found to have response rate of 89.7% (reduction of pain to less than or equal to 3 on VAS) at the end of 12 weeks. A greater proportion of women in Centchroman group continue to enjoy pain free life even after stopping the drug, suggesting a longer carry-over effect. Thus the probability of remaining pain free at 6 months was 71% with Centchroman [18] (Tejwani PL).

In our study, all the above 3 drugs were evaluated and comparative analysis done in terms of their efficacy to reduce pain, nodularity and size of fibroadenoma. At 1 month of treatment, there was no significant difference in the VAS score in all 3 groups, but all groups showed more than 50% reduction in VAS score at 3 months. But at 6 months follow up, only Centchroman was found to be efficacious both in comparison with danazol (p value 0.027) and EPO (p value <0.001). In a trial comparing Centchroman with Danazol in mastalgia, in Danazol group 69.44% women achieved reduction in pain score to ≤ 3 (p

REFERENCES


22 Mansel
