



## A COMPARATIVE STUDY OF CENTCHROMAN VS TAMOXIFEN IN THE MANAGEMENT OF MASTALGIA AND FIBROADENOMA

### General Surgery

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### ABSTRACT

We conducted an interventional, experimental, randomized, prospective study to compare the efficacy of a newer therapeutic agent Centchroman with established therapeutic agents Tamoxifen in the treatment of mastalgia and fibroadenoma. Total 84 patients have been participated in the study (only mastalgia-36, mastalgia with fibroadenoma-48). In mastalgia group 19 and 17 patients were treated with Centchroman and Tamoxifen respectively. In fibroadenoma group 26 and 22 patients received Centchroman and Tamoxifen respectively. Centchroman was found to be the most effective drug with the post intervention pain scores  $\leq 2$  in 30 (66.67%) patients and 17 (43.59%) with Tamoxifen. In fibroadenoma group complete response rate was highest in Centchroman arm 12(26.67%) in comparison to 2(5.13%). Side effects are maximum with Tamoxifen and Centchroman is the cheapest.

### KEYWORDS

Centchroman, Tamoxifen, Mastalgia, Fibroadenoma

**Introduction:** Mastalgia and fibroadenoma are the two major causes of morbidity amongst Indian women presenting with benign breast diseases. Incidence of these are sparsely documented in literature and probably quiet underestimated. Conventional conservative treatment of these diseases are less rewarding and sometime with lots of untoward effects. So cost and side effects are the limiting factors for the conventional conservative therapies in our country. Finding a efficacious drug with low cost and less side effects is a challenge in Indian subcontinent.

**Method:** We have conducted an interventional, single blind randomized prospective study on 84 patients attending the outpatient department of a tertiary care teaching hospital in eastern India over a period of one and half year. The aim of the study is to compare the efficacy of the newer therapeutic agent Centchroman with Tamoxifen in the treatment of mastalgia and fibroadenoma. All premenopausal women with mastalgia with or without nodularity and fibroadenoma, after performing triple assessment, were included in the study. The exclusion criteria were 1. All malignant breast diseases 2. Dysplastic lesion which mandate compulsory surgical intervention 3. Simple breast cysts 4. Fibroadenoma of more than 5 cm size 5. Patients on oral contraceptive pills 6. Patients desirous to remove the lump 7. Patients unwilling to enrol herself in the study 8. Contraindications of Centchroman : i. Pregnancy ii. Polycystic ovarian diseases ( PCOD ) iii. Cervical hyperplasia iv. Recent history or clinical evidence of jaundice or liver diseases v. Conditions like severe allergic states, chronic illness such as tuberculosis, renal diseases etc. vi. Patients willing to conceive within six months 9. Contraindications of Tamoxifen. An ethical committee clearance has been taken before initiation of the study and prior informed consent was obtained in all the cases. Ultrasound guided fine needle aspiration cytology was done in fibroadenoma and dominant nodule in patients with nodularity of the breast. All sexually active women were sent for a detailed gynaecological examination, as well as ultrasound of the pelvis to rule out polycystic ovarian disease. Cases of mild mastalgia were treated with supportive care only and not included in the study. All the patients received the same supportive care that included reassurance, breast support and stopping of methyl xanthenes in diet ( abstinence from coffee, tea etc ). Two groups ( only mastalgia and mastalgia with

fibroadenoma ) of the patients were divided into two arms, the first arm treated with Centchroman and second arm with Tamoxifen. All the cases were recorded in a predesigned and pretested schedule. Patients with mastalgia were asked to maintain breast pain chart. After 3 months all patients were evaluated by 0-10 visual analogue score (VAS) and by ultrasound (USG). All results were evaluated by an independent reviewer. Evaluation of response of fibroadenoma by ultrasound are categorised in 3 groups, namely no response (no change in size or increase in size), partial response (some decrease in size but not to zero) and complete response (lump vanished). Results of the study analysed statistically.

### Results :

Among total 84 patients, 45 patients were treated with Centchroman and 39 patients were treated with Tamoxifen.

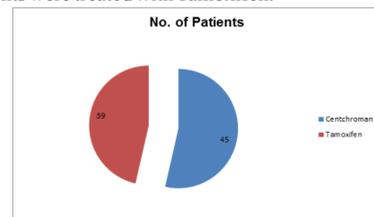


Figure 1: No. of patients in each group

Table 1: No. of patients in each group

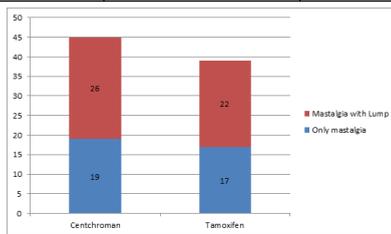
Drugs	No. of Patients
Centchroman	45
Tamoxifen	39

In the Centchroman group out of 45 patients 19 patients was suffering from only mastalgia and 26 patients were suffering from mastalgia with lump.

In the Tamoxifen group out of 39 patients 17 patients was suffering from only mastalgia and 22 patients were suffering from mastalgia with lump.

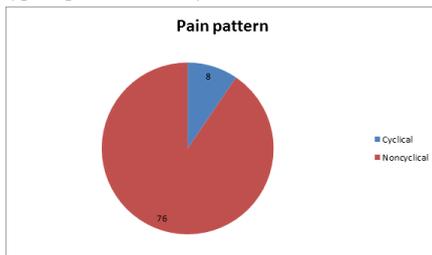
**Table 2: Patient distribution in both group**

Drugs	Only mastalgia	Mastalgia with lump
Centchroman	19	26
Tamoxifen	17	22



**Figure 2: Patient distribution in both group**

Out of the 84 patients with mastalgia, only 8(9.52%) patients were suffering from cyclical pain and 76 (90.48%) patients from non-cyclical pain thus concluding non-cyclical mastalgia as the most common type of pain in this study.



**Figure 3: Pain pattern**

**Table 3: Pain pattern**

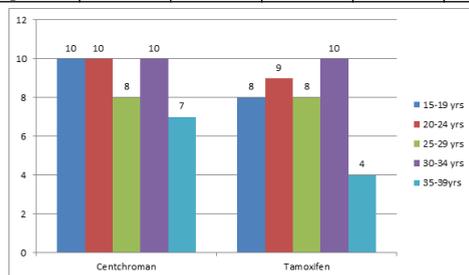
Cyclical pain	Noncyclical pain
8	76

**Table 4: Age distribution in Centchroman group**

Age group	15-19	20-24	25-29	30-34	35-39
No. of patients	10	10	8	10	7

**Table 5: Age distribution in Tamoxifen group**

Age group	15-19	20-24	25-29	30-34	35-39
No. of patients	8	9	8	10	4



**Figure 4: Age distribution**

In our study, most of the patients with mastalgia with or without lump presented in their third decade of life.

Difference in mean age in both the groups was not statistically significant (p=0.86) thus avoiding a bias in the result due to age as a confounding factor.

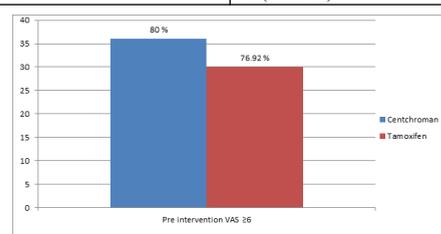
**Table 6: Difference in mean age in both the groups**

Drugs	Mean	SD	t	df	p-value
Centchroman	26.58	7.095	0.177	82	0.860
Tamoxifen	26.31	6.802			

Before starting medications the VAS was  $\geq 6$  in about 66% patients. In patients treated with Centchroman the pre intervention VAS score of  $\geq 6$  in 80% (36/45) of the patients, and in patients treated with Tamoxifen the pre-intervention VAS score of  $\geq 6$  in 76.92% (30/39) of the patients.

**Table 7: Pre-intervention VAS  $\geq 6$**

Drugs	Pre intervention VAS $\geq 6$ (%)
Centchroman	36 (80%)
Tamoxifen	30 (76.92%)

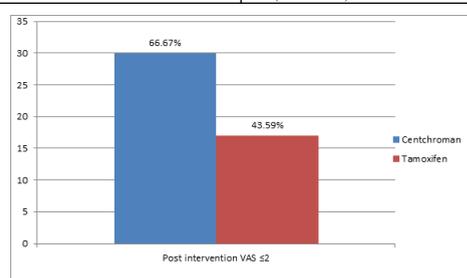


**Figure 5: Pre intervention VAS  $\geq 6$**

At the end of 3 months the analysis was done as per the interventions done in the both groups. Centchroman was found to be the more effective drug with the post intervention pain scores  $\leq 2$  in more than 66.67% patients, but in tamoxifen group post intervention VAS score  $\leq 2$  in 43.59% patients.

**Table 8: Pre-intervention VAS  $\leq 2$**

Drugs	Post intervention VAS $\leq 2$ (%)
Centchroman	30 (66.67%)
Tamoxifen	17 (43.59%)



**Figure 6: Post intervention VAS  $\leq 2$**

Comparison between two groups for decrease in the VAS at the end of three months was found to be statistically significant, suggesting that both the drugs are effective for pain relief and can be used interchangeably in each group. As the sample size (n) is small, it was not possible to show the temporal decrease of pain relief (of statistical significance) in each group. So, further studies need to be done for accurate measurement of individual drug and their efficacy for pain relief by recruitment of larger number of patients in each study arm.

Difference in average initial VAS in both the groups was not statistically significant (p = 0.897) suggesting absence of selection bias in each group.

**Table 9: Average initial VAS score**

Drugs	Mean	SD	t	Df	p-value
Centchroman	6.53	1.65	1.30	82	0.897
Tamoxifen	6.49	1.59			

Difference in average final VAS in both the groups was statistically significant (p = 0.001)

**Table 10: Average Final VAS score**

Drugs	Mean	SD	t	Df	p-value
Centchroman	1.82	1.435	-3.310	82	0.001
Tamoxifen	2.95	1.685			

Difference in average initial lump size in both the groups was not statistically significant (p=0.360) suggesting absence of selection bias in each group.

**Table 11: Average initial lump size**

Drugs	Mean	SD	t	Df	p-value
Centchroman	19.73	7.723	-0.925	46	0.360
Tamoxifen	21.82	7.872			

Difference in average final lump size in both the groups was

statistically significant (p=0.000)

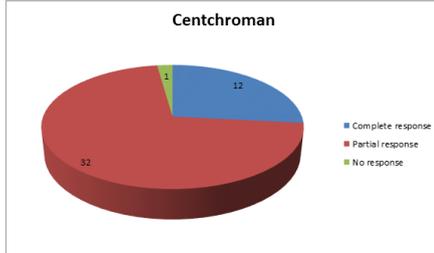
**Table 12: Average final lump size after 3 months of therapy**

Drugs	Mean	SD	t	Df	p-value
Centchroman	3.58	4.244	-4.505	46	0.000
Tamoxifen	13.00	9.631			

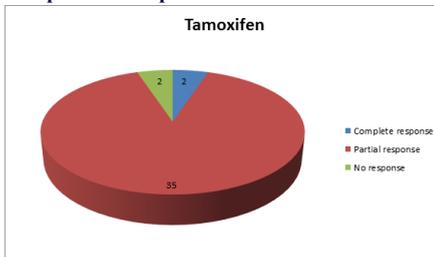
At the end of three months the changes in the size of lump (in whom present) were graded in three groups namely complete response, partial response and no response. Results showed maximal resolution and disappearance was in 26.67% of patients receiving Centchroman as compared to 2.22% in Tamoxifen group.

**Table 13: Response of drug on lump in different group**

Drugs	Complete response(%)	Partial response(%)	No response(%)
Centchroman	12(26.67%)	32(71.11%)	1(2.22%)
Tamoxifen	2(5.13%)	35(89.74%)	2(5.13%)



**Figure 7: Response of lump to Centchroman**

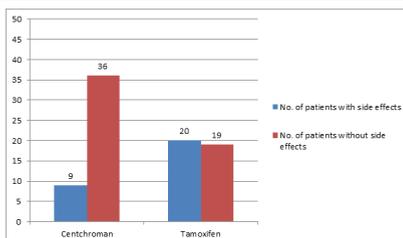


**Figure 8: Response of lump to Tamoxifen**

The side effects were recorded in about 51.28% patients in Tamoxifen group and 20% in Centchroman group. Centchroman usage was associated with adverse effects such as oligomenorrhea, in about 13.33% of patients. The side effects was observed with Tamoxifen was mainly nausea & vomiting in about 20% of the patients, about 18% of the patients have irregular menses with heavy bleeding(persisting more than 5 days).

**Table 14: side effects**

Drugs	No of pts with side effects (%)	No of pts without side effects (%)
Centchroman	9(20%)	36(80%)
Tamoxifen	20(51.28%)	19(48.72%)

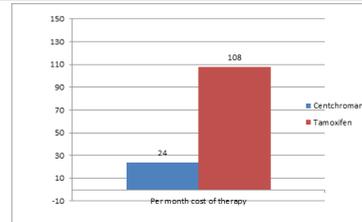


**Figure 9: Side effects**

Both drugs are not expensive. Centchroman was the cheapest with monthly cost of therapy of Rs 24.00. Tamoxifen costs Rs 108.00 per month.

**Table 15: Cost of therapy per month (Rs)**

Drugs	Cost per month (Rs)
Centchroman	24.00
Tamoxifen	108.00



**Figure 10: Cost of therapy per month (Rs)**

**Discussion**

Mastalgia with or without lump or nonmalignant painless breast lump is frequent complaint in premenopausal female patients. Painful nodularity of more than one week of the cycle is a useful definition for differentiation from normal discomfort. Severity of the pain can be quantified with a VAS chart. It is broadly categorized into cyclical and non-cyclical mastalgia. The most common type of discomfort is related to the menstrual cycle, and particularly to ovulation. 2 or 3 days of premenstrual breast tenderness or heaviness every month should be regarded as temporary/normal. Duration of symptoms of more than 1 week per cycle is taken as significant and can be termed "pronounced." Again, severity is documented using the VAS chart. The commonly used drugs for treatment include EPO, Danazol, Bromocriptine and Tamoxifen. In an effort to treat mastalgia, Centchroman is compared with Tamoxifen in this study.

Among the 84 patients of mastalgia in our study, 36 were suffering from mastalgia and 48 had mastalgia associated with lump. In our study, we found that mastalgia with or without lump was the most common type of benign breast conditions. This observation is comparable with the observations of Nichols S, Waters WE & Wheeler MJ and Roberts MM, Elton RA, Robinson SE et al. The mean age of patients in both the Centchroman and Tamoxifen groups was 26.45years. This however is in contrast to the median age of patients of Cardiff series where it was 30 years.

Regarding the nature of the breast pain most of the patients in our study presented with non-cyclical mastalgia (90.48%). This finding similar to the Indian study conducted at AIIMS, where noncyclical pain was also recorded in 90% patients and cyclical pain was recorded in only 10% of patients though cyclical mastalgia was more common in most of the other studies. This calls for an investigation into the etiology of non cyclical mastalgia .

66.67% (30/45) of our patients showed excellent pain response to Centchroman as measured by VAS of  $\leq 2$ , while Tamoxifen showed 43.59% (17/39) response. In a double-blind study, Tamoxifen, 10 mg daily, significantly improved mastalgia with response rates of 98% for cyclical and 56% for non-cyclical pain. Study with Centchroman in Mastalgia conducted by Dhar and Srivastava in AIIMS, who reported near complete response to mastalgia with a decrease in VAS score from 10 to 3 in 90% of the patients.

Comparison between average final VAS of each two groups of patients receiving Centchroman and Tamoxifen, revealed statistically significant difference of pain relief in favor of use of Centchroman (p=0.001).

We had total 48 patients of mastalgia with lump of which 26 in Centchroman group, 22 in Tamoxifen group. The mean lump size in the Centchroman group was 19.73 mm and in Tamoxifen group was 21.82 mm before treatment. After 3 month of treatment 26.67% of patients in Centchroman group showed complete response, that is complete disappearance of the lump, while only 5.13% in Tamoxifen group. 89.74% of lump showed partial response in Tamoxifen, while 71.11% in Centchroman group.

No response (remained same or size increased) showed in 5.13% patients in the Tamoxifen group, while 2.22% in Centchroman group. The AIIMS study also reported a mixed response in the mastalgia with lump group with Centchroman, 40% showing complete disappearance, 20% lump showing partial regression and no response in 40% cases of lump.

Comparison between two groups of patients on Tamoxifen or Centchroman in final size of fibroadenoma revealed statistically significant difference in lump size in favour of use of Centchroman

( $p=0.000$ ). Centchroman is better option than Tamoxifen in reducing lump size associated with mastalgia.

Centchroman usage was associated with adverse effects such as oligomenorrhea (6 out of 45, that is, in about 13.33% of patients and this is high in comparison to AIIMS study where 3 patients (5%) out of 60 suffered from oligomenorrhea.

The maximal side effects observed with Tamoxifen was mainly nausea & vomiting (20.51%). The side effects were recorded in about 51.28% patients in this group. In Fentiman's study the commonest side-effects were hot flushes (27%) and vaginal discharge (17%).

Both drugs are quite cheap with a monthly cost of Rs 24.00 for Centchroman whereas Tamoxifen is costing Rs 108.00 per month.

Thus in conclusion a clear benefit of Centchroman over Tamoxifen in treatment of Mastalgia (with or without lump) is evident by better pain relief, more decrease in lump size and less side effects in Centchroman group.

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