

A Prospective Clinical Study to Evaluate the Role of Centchroman in the Treatment of Mastalgia and ANDI (Aberrations of Normal Development and Involution) of the Breast Surgery

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Abstract: Background: Benign breast disorders has been classified by the ANDI system (aberrations of normal development and involution of breast) and includes mastalgia, fibroadenoma among other disorders. Drugs used for these disorders are expensive with side effects and do not show any improvement. Ormeloxifene (Centchroman) is a selective estrogen modulator synthesized by the Central Drug Research Institute, Lucknow. It has been previously used in patients with mastalgia and fibroadenoma and has shown promising results. This study is being undertaken to understand the role of centchroman as an effective treatment for mastalgia and ANDI. Materials and Method: The present randomized control trial was conducted in the Department of Surgery, Rama Medical College Hospital & Research Centre, Mandhana, Kanpur, U. P which was conducted from January 2021 to September 2022. The study was conducted in two groups with mastalgia and fibroadenoma. The trial was with 170 women of age 20 - 40 years with complaints of mastalgia (with or without nodularity) or with those with fibroadenoma <4cm. The collected data was analyzed by using SPSS (Statistical Package for Social Sciences) Version 15.0 Results: The trial of 170 women showed that married, multiparous women between ages 36 - 40 were affected the most by mastalgia and fibroadenoma. The mean VAS score for mastalgia at 3 months after the use of Centchroman suggest that centchroman is effective in reducing the pain of mastalgia. The size of lump before and after the use of Centchroman at 3 months in Fibroadenoma was reduced suggesting centchroman is effective in reducing size of lump. Conclusion: Centchroman is an effective drug for treatment of mastalgia and fibroadenoma

Keywords: ANDI, Centchroman, Mastalgia, Fibroadenoma, Benign, Breast

1. Introduction

Breast diseases are the leading cause of worry in women. Benign disorders of breast are now known collectively as "Aberrations in the normal development and involution of the breast". This is based on the rationality that most breast complaints are minor aberrations of the normal processes of development, cyclical change and involution. The term ANDI has been introduced to allow benign breast diseases to be placed within an overall framework of pathogenesis, for detailed individual assessment with respect to normality and disease¹.

Mastalgia is classified as cyclical, non - cyclical and extramammary. Fibroadenoma is the commonest benign solid lump in women aged between 15 - 30 years, with diagnosis being confirmed by triple assessment².

Mastalgia could be unilateral or bilateral, is often extremely tender to touch and the pain may be associated with swelling and nodularity³⁻⁴

Classification of mastalgia is given by Cardiff Mastalgia Clinic⁵ classifying mastalgia into cyclical, non cyclical and

chest wall pain. Cyclical mastalgia is associated with menstrual cycle. Non cyclical mastalgia is pain which is not associated with menstrual cycle and chest wall pain is due to underlying pathology of chest wall disease⁶.

Research criteria for the diagnosis of severe cyclic mastalgia includes pain severity greater than 4 measured with a 10 VAS (visual analogue Scale) with pain duration of minimum 7 days every month. For the evaluation of mastalgia, a thorough history and a careful physical examination of the patient should be done with a special attention to the type of pain, its location and its relation to the menstrual cycle⁷.

Fibroadenoma is the most common breast lump in young girls and is a constituent of ANDI. Approximately 10-15 % of lesions regress spontaneously⁸. Fibroadenoma is hyperplasia of the lobules from terminal ductal lobular units which are benign and do not increase rapidly in size. They are labelled as giant fibroadenoma when the size is more than 5cm.

Mild symptoms of mastalgia are treated symptomatically with mechanical breast support, topical or oral non steroidal anti inflammatory drugs⁹. These drugs are expensive and have numerous side effects. The most

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commonly used drug is danazol with other drugs being used are bromocriptine, tamoxifene, evening primrose oil¹⁰.

A new agent called Ormeloxifene (Centchroman) is a weak estrogen receptor (ER) agonist, a strong ER antagonist (SERA) and therefore a selective ER modulator (SERM). This drug was developed at the Central Drug Research Institute, Lucknow and is a non steroidal, selective anti estrogen, once - a - week oral contraceptive. It was sold in India in 1992 as SAHELI and CHOICE - 7 (Hindustan Latex Ltd., Thiruvananthapuram) and CENTRON (Torrent Pharmaceuticals India Ltd., Ahmedabad), and was included in the National Family Welfare Program in 1995 for contraception. It has been introduced as a once - a - week short - term contraceptive pill/oral contraceptive. Contraception action of this drug is reversible. As opposed to danazol and anti prolactins which is contraindicated in pregnancy and lactating women, centchroman can be safely used in pregnancy and lactation¹¹⁻¹².

Centchroman, because of its selective antiestrogen action, has been used for treatment of mastalgia and fibroadenoma¹³. Even though the role of this drug is lesser known in mastalgia and ANDI, as opposed to the other treatment options such as Anti prolactins (Bromocriptine and Cabergoline) and Danazol, it was found to be the safer alternative⁴. There is a need to know more about the effects of this drug as it is made and marketed in India. Centchroman sold under the brand name "Saheli" is a cost - effective treatment and easily available.

Ormeloxifenewas used in 42 women with mastalgia at a dose of 30 mg taken on alternate days who reported an improvement of 90% and complete disappearance of fibroadenoma in 40% women after 3 months of treatment¹³. In a randomized trial done on 81 women, it was found to be superior to danazol for the treatment of mastalgia¹⁵. This study was being undertaken to understand the role of centchroman as an effective treatment for mastalgia and ANDI in our Department of Surgery at Rama Medical College Hospital and Research Center, Kanpur.

2. Materials and Method

The present Randomized Control Trial was conducted in Department of surgery, Rama Medical College and Hospital Mandhana Kanpur from January 2021 to September 2022

Benign breast disease patients, up to 40 years of age, attending surgery outpatient department of the hospital (January 2021 to September 2022) and fulfilling the inclusion criterion were included in this study. Subsequently, clinical examination and investigations was done and Centchroman, 30mg once a day, for 4 weeks following which 30mg alternate day dosing for 8 weeks was administered. Patients were evaluated after one week for tolerance. Follow up was taken every 1 month. Any side effect of the drug was noted and symptomatic relief or lack of desired effect was noted. The patients were provided with a detailed printed information sheet (inboth Hindi and English) to explain about benign nature of breast pain and breast lump after excluding the other diagnosis. The current available therapy, its possible side effects, the potential

benefits of Centchroman and its common use by Government of India as a contraceptive pill were also explained. We also informed patients about the possibility of scanty or delayed menstruation by Centchroman. Patients signed a consent form in Hindi or English after understanding this information. We conducted the study in two groups. Mastalgia group and Fibroadenoma group as representative of aberration was included in ANDI. We calculated the sample size for mastalgia as 140 and for fibroadenoma as 30 with the total sample size of 170. All the patients of mastalgia attending the OPD Surgery, were invited to participate in the study. Around 170 female patients fulfilling the inclusion criteria and giving their consent for their inclusion in the study were enrolled as study subjects. We separated these patients in two groups - experimental group and control group. Patients with mastalgia, satisfying inclusion criteria as given below were separated in two groups randomly by computer. In trial, the experimental group was given Centchroman 30 mg once daily for 4 weeks following which alternate day dosing of 30mg for 8 weeks and control group was given placebo for the same duration.

Inclusion criteria: (i) 20 - 40 year old women presenting with complaints of mastalgia with or without nodularity not on any treatment at the time, (ii) Fibroadenomas more than 4cm

3. Methodology

All women in reproductive age group having mastalgia, with or without nodularity and fibroadenoma, presented to surgery OPD during January 2021 to September 2022 and fulfilling the inclusion and exclusion criteria after giving consent were recruited in the study. A total of 170 patients were included in the study. In this 70 patients who were presented with mastalgia were randomized to first group (group A) and were treated with Centchroman. The other 70 included in control group (group B) which were treated with placebo. Also 30 patients presented as fibroadenoma were treated with centchroman. A baseline haematological and biochemical workup was conducted in all. After an initial clinical assessment and breast imaging with ultrasound (and mammogram for cases above age 35 years) to exclude any lump or mammary ductal disease, patients were asked to keep a record of their breast pain in a "pain diary". In this diary patient filled the occurrence of pain on a day to day basis. The time of menses was also marked on pain diary. The severity of mastalgia was assessed by visual analogue scale score ranging from 0-10. Zero (0) indicating no pain and 10 indicating very severe pain. • Ultrasound scan of pelvis and gynecological evaluation was performed to exclude the patients with polycystic ovarian disease and cervical hyperplasia, as Centchroman is known to worsen these conditions. • Patients were randomized to get Centchroman 30 mg daily or placebo, daily for 4 weeks and then on alternate days for next 8 weeks. The patients were evaluated after one week to assess tolerance to the drug. Subsequently patients were followed at an interval of every month for 3 months and response to therapy was assessed by VAS score along with ultrasounds in patients diagnosed with fibroadenoma. The drug treatment was continued for a total of 12 weeks. At each visit pain charts were assessed. Any

side - effects experienced by the patients were recorded at each visit. The outcomes were based on global assessment of patient's condition and side effect.

Statistical Analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

4. Result

The present study was conducted in the Department of Surgery, Rama Medical College and Hospital Kanpur to evaluate the effectiveness of Centchroman in control of mastalgia measured by visual analogue scale and fibroadenoma measured with pre and post intervention ultrasounds. A total of 170 participants were included in this study. The study participants were divided into 3 groups:

- 1) Mastalgia intervention group - 70 participants
- 2) Mastalgia Control Group - 70 participants
- 3) Fibroadenoma intervention group - 30 participants

Table 1: Distribution of Age among study participants

Age (years)	Group			Total	Chi square value	p - Value
	Mastalgia intervention	Mastalgia Control	Fibroadenoma intervention			
20 - 25	10	4	5	19	6.420	0.378
26 - 30	18	17	5	40		
31 - 35	19	17	10	46		
36 - 40	23	32	10	65		
Total	70	70	30	170		

P<=0.005 significant

Table 1 shows the distribution of age of study participants. In group 1, 14.2% (10) participants were in the age group 1, 25.7% (18) participants in the age group2, 27.1% (18) participants in the age group 3 and 13.5% (23) in the age group 4. In group 2, 5.71% (4) participant were from the age group 1, 24.2% (17) participants each from the age group 2

and 3, while 45.7% (32) participants from age group 4. In group 3, 7.1% (5) participants each were in the age group 1 and 2, while 14.2% (10) participants each were in the age group 3 and 4. The age distribution of study participants among different groups did not show any statistically significant difference

Table 2: Distribution of Marital Status among study participants

Parity	Group			Total	Chi square value	p - Value
	Mastalgia intervention	Mastalgia Control	Fibroadenoma intervention			
Unmarried	9	5	2	16	1.662	0.436
Married	61	65	28	154		
Total	70	70	30	170		

P<=0.005 significant

Table 2 shows distribution marital status of participants in the study. The number of married participants were 9, 5 and 2 in group 1, 2 and 3 respectively. The number of unmarried participants were 61, 65 and 28 in group 1, 2 and 3

respectively. The distribution of marital status parity among study participants in different groups did not show any statistically significant difference.

Table 3: Distribution of Parity among study participants

Parity	Group			Total	Chi square value	p - Value
	Mastalgia intervention	Mastalgia Control	Fibroadenoma intervention			
Nulliparous	9	5	2	16	1.662	0.436
Multiparous	61	65	28	154		
Total	70	70	30	170		

P<=0.005 significant

Table 3 shows distribution parity of participants in the study. The number of nulliparous participants were 9, 5 and 2 in group 1, 2 and 3 respectively. The number of multiporous participants were 61, 65 and 28 in group 1, 2 and 3 respectively. The distribution of parity among study participants in different groups did not show any statistically significant difference.

Table 4: Comparison of VAS scores before and after the use of Centchroman in Group1 (mastalgia) at 3 months

	N	Mean	Standard Deviation	Median	p Value
Baseline VAS Score	30	6.4714	0.65323	6.00	<0.001
At 3 month VAS Score	30	5.1571	0.47045	5.00	

	N	Mean	Std. Deviation	Percentiles			Z - value	p - Value
				25 th	50 th (Median)	75 th		
Baseline VAS Score	70	6.4714	0.65323	6.0000	6.0000	7.0000	-7.636	<0.001
At 3 month VAS Score	70	5.1571	0.47045	5.0000	5.0000	5.0000		

P<=0.005 significant

Table 4 shows the mean VAS scores before and after the use of Centchroman at 3 months in Mastalgia patients in Group 1. Wilcoxon signed rank test was done to compare mean VAS scores before and after the use of Centchroman. The mean VAS score at baseline was 6.47±0.65, which reduced to 5.15±0.47 at 3 months after the use of Centchroman which suggest that centchroman is effective in reducing the pain of mastalgia. There was a statistically significant difference in the mean. VAS score before and after the use of Centchroman at 3 months; (p<0.001)

Table 5: Comparison of baseline and after 3 months VAS scores in the control mastalgia group.

	N	Mean	Std. Deviation	Median	P Value
Baseline VAS score	70	4.4857	0.5034	4	<0.001
At 3 months VAS score	70	3.5143	0.53141	3.5	

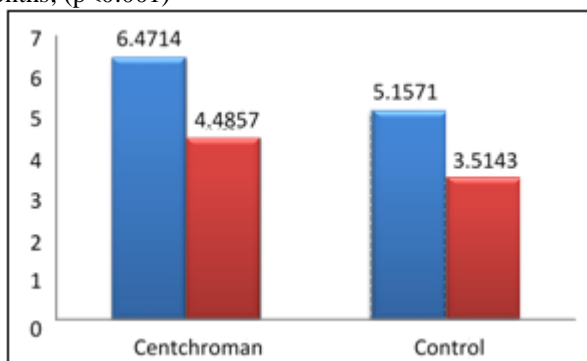
P<=0.005 significant

Table - 5 shows the baseline mean VAS scores and at 3 months mean VAS scores of mastalgia patients in the control group. Wilcoxon signed rank test was done to compare mean VAS scores. The mean VAS score at baseline was 4.48±0.50, which reduced to 3.51±0.53 at 3months. There was a statistically significant difference in the mean VAS score at 3 months (p<0.001)

	N	Mean	Std. Deviation	Percentiles			Z - value	p - Value
				25 th	50 th (Median)	75 th		
Lump size in cm before	30	2.573	0.7891	2.075	2.7	3.025	-4.345	<0.001
Lump size in cm after	30	2.49	0.7787	2	2.65	3		

P<=0.005 significant

Table 7 shows the size of lump before and after the use of Centchroman at 3 months in Fibroadenoma patients in Group 3. Wilcoxon signed rank test was done to compare the size of lump before and after the use of Centchroman. The mean size of lump at baseline was 2.57±0.78, which reduced to 2.49±0.77 at 3months after the use of Centchroman. There was a statistically significant difference in the lump size before and after the use of Centchroman at 3 months; (p<0.001)



Graph 1: Change in VAS score in Centchroman and control group after 3 months

Table 6: Comparison of VAS scores at 3 months between Centchroman group (mastalgia) and Control group

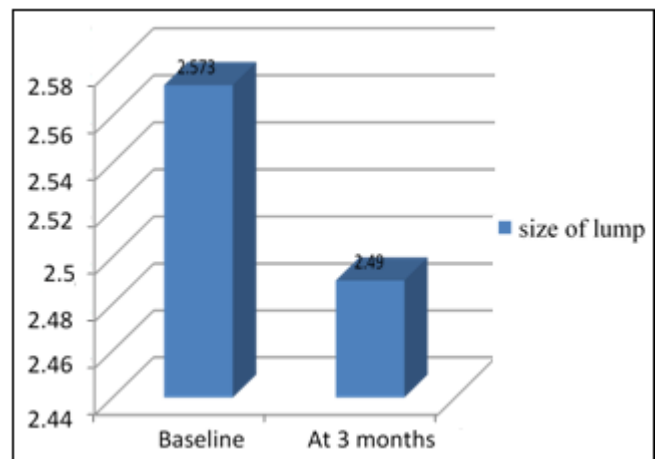
Group	N	Mean Rank	Sum of Ranks	Mann Whiney value	p Value
Centchroman	70	80.86	5660.00	1725	<0.001
Control	70	60.14	4210.00		

P<=0.005 significant

Table 6 shows the comparison of change in mean VAS scores of mastalgia between the Centchroman and Control groups at 3 months of the trial. Mann - Whitney U test was done to compare mean VAS scores between the Centchroman group and Control group. The mean rank of control group (60.14) is less than that of Centchroman group (80.86). There was a statistically significant difference between mean ranks of VAS score of both the groups; (p<0.001), indicating greater change in VAS scores were demonstrated in Centchroman group.

Table 7: Comparison of size of fibroadenoma before and after the use of Centchroman in Group 3 at 3 months

	N	Mean	Standard Deviation	Median	P Value
Lump size - Baseline	30	2.573	0.7891	2.7	<0.001
Lump size - at 3 months	30	2.49	0.7787	2.65	



Graph 2: Change in size of lump after the use of Centchroman at 3 months

5. Discussion

Centchroman is also used as a contraceptive pill, post coital pill, as treatment for abnormal uterine bleeding anti - osteoporotic and in advanced breast cancer along with other

palliative measures. It was first formulated by Central Drug Research Institute, Lucknow, India and was included in the National Family Welfare Program in 1995 (Trade name SAHELI by Hindustan Latex Ltd. usual price Rs 2 per 30 mg tablet per day). Centchroman is free from side effects like nausea, vomiting, weight gain and dizziness. It does not delay return of fertility after stoppage and has only one side effect of delayed menses in less than 10% of cases. It has mild adverse effects on endocrine, haematologic, liver, cardiovascular, central nervous and lipid functions. On review of literature only a very few studies are found on the usage of Centchroman for Mastalgia and fibroadenosis and fibroadenoma. These studies have recommended that centchroman is similar to or better than other medications because of its minimal side effects and cost effectiveness.

In our study, a total of 170 patients were enrolled divide into three groups

- 1) Mastalgia intervention group - 70 participants
- 2) Mastalgia Control Group - 70 participants
- 3) Fibroadenoma intervention group - 30 participants

On comparison of VAS scores before and after the use of Centchroman for mastalgia at 3 months showed statistical significant difference in the centchroman group which was statistically higher than the control group stating that centchroman is useful in resolution of mastalgia after treatment of 30mg everyday for at least 3 months

There was a statistically significant difference in the lump size before and after the use of Centchroman at 3 months stating that there is reduction in size of lump of fibroadenoma after intake of Centchroman 30mg everyday for at least 3 months.

In a study conducted by Bhupendrasharma, it was observed that the VAS scores in mastalgia patients were reduced to less than or equal to 3¹⁶. There results are in unison with our study. Ormeloxifene is a novel non - steroidal, selective antiestrogen (SERM) which has been used for the treatment of mastalgia and multiple small fibroadenomas. It is relatively free from adverse effects such as vomiting, nausea, dizziness, and weight gain. It does not interfere with ovulation, and hence, there is no delay in return of fertility after stopping the drug. The only adverse effect observed is delayed menses in <10% of cycles¹⁵.

Our results of centchroman on fibroadenoma and mastalgia showing complete dissolution in 34% partial response in 46 % and no response in 17% This is consistent with that of Dharet *al*, Tejwani et al and Gupta et al who studied the effect of Ormeloxifene in the management of mastalgia and fibroadenoma^{13, 15, 17}.

6. Conclusion

From this study, we infer that centchroman is a safe and cost effective drug with significant efficacy on regression of mastalgia and fibroadenoma in the women of reproductive age group with minimal side effects.

Our results are in consistent with seven other studies available in the medical literature. One of the previous seven

studies had high frequency of side effects, particularly development of ovarian cyst with Centchroman.

Though small in number, available studies greatly favour this drug as a treatment of choice in mastalgia and fibroadenoma. However, multicentric randomised double blind controlled studies with larger sample size in comparison with other drugs are needed for global acceptance.

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