Regression of Fibroadenomas with Centchroman: a Randomized Controlled Trial

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Abstract Fibroadenoma is a common cause of breast lump in young girls. Nearly 10–15 % of lesions regress spontaneously over the period of 6 to 60 months. The aim of study was to investigate the role of Centchroman in regression of fibroadenoma in comparison to natural observation and to study the association of hormonal receptors with degree of regression. The study was carried out at the outpatient clinic of Department of Surgery, All India Institute of Medical Sciences, New Delhi, from November 2004 to November 2007. Patients aged ≤ 30 years with fibroadenoma were included. Patients with fibroadenoma equal to or larger than 5 cm and with polycystic ovarian disease were excluded. Patients were randomized in two groups. Patients in active therapy arm were prescribed Centchroman 30 mg daily for 12 weeks, and another group was observed without any intervention (control group). Patients were followed at weeks 4, 8, 12, and 24 to assess response to therapy. Twenty-two (31.88 %) fibroadenomas in Centchroman arm disappeared completely as compared to four (7.69 %) in control arm over a period of 6 months.

There was a decrease in the volume of fibroadenoma in ten (19.23 %) patients in control arm and 36 (52.17 %) patients in Centchroman arm. Centchroman therapy allowed 31 % fibroadenoma to regress completely with scanty menses or amenorrhea as the only side effect.

Keywords Fibroadenoma · Centchroman · Polycystic ovarian disease · Saheli · Hormone receptor · Antiestrogen

Introduction

Fibroadenoma is a common cause of discrete, firm, and mobile lump in the breast in young girls between ages 15 and 25 years. It is considered an “aberration in development and involution” of ductolobular tissue in the breast and not a true neoplasm [1]. Fibroadenoma begins as hyperplasia of the lobules from “terminal ductal lobular units” which progressively increases in size from 1 to 3. Most of them remain static, but some increase in size to more than 5 cm when they are named “giant fibroadenoma”. Multiple fibroadenomas can occur in the same breast or bilaterally. Nearly 10–15 % of lesions regress spontaneously over the period of 6 to 60 months [2].

Simple fibroadenoma is usually managed by natural observation, as they are benign and asymptomatic without any risk of future cancer [2]. Complex fibroadenoma is associated with moderate risk of cancer and those associated with atypia (relative risk of >2) or family history of breast cancer should be excised [1, 3, 4]. Some patients prefer to have the lump excised because of pain, discomfort, psychological reasons, or fear of cancer. Hormonal manipulation has been attempted to suppress the growth

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of fibroadenoma with antiestrogenic drug tamoxifen as fibroadenoma is considered to arise from hyperresponsiveness of lobular tissue to estrogen [5–7]. Presence of estrogen receptors on tissue obtained from fibroadenoma has been described [8]. Hence, we used an antiestrogen, Centchroman, in order to suppress the proliferation of ductolobular tissue of fibroadenoma. A pilot study at our center revealed the efficacy of Centchroman in regression of fibroadenoma [9].

Centchroman (ormeloxifene) is a nonsteroidal antiestrogen drug developed by the Central Drug Research Institute, Lucknow, India. It is a selective estrogen receptor modulator with weak agonist (on endometrium) and strong antagonist (on breast ductolobular epithelium) action [10].

An open-label, two-arm parallel design randomized controlled trial was started to assess the role of Centchroman versus natural observation in regression of fibroadenoma. The primary objective of the study was to investigate the role of Centchroman in regression of fibroadenoma as assessed by serial volume measurements on clinical examination and sonography up to 6 months of follow up. The secondary objective was to find an association of regression of lesion with estrogen and progesterone receptor status within tissue from fibroadenoma.

Patient and Methods

The study was carried out at the outpatient clinic of Department of Surgery, All India Institute of Medical Sciences, New Delhi, from November 2004 to November 2007. Patients aged ≤ 30 years with fibroadenoma diagnosed on triple assessment (clinical evaluation, ultrasound scan, and a large-core-needle biopsy under local anesthesia) were included. Permission was obtained from the Drug Controller of India for the use of Centchroman for mastalgia and fibroadenoma. The project was approved by the institute ethics committee. The patients with following features were excluded:

1. Patient above 30 years of age
2. Patients with fibroadenoma equal to or larger than 5 cm (giant fibroadenoma)
3. Past history of breast carcinoma or family history of breast carcinoma
4. Patients with polycystic ovarian diseases, cervical hyperplasia, and liver disease (these conditions may get worsened with Centchroman)
5. Lactation period for first 6 months
6. Pregnancy

Sample Size Consideration

We needed a sample of 48 patients and 48 controls to demonstrate a regression of fibroadenoma in 60 % of women receiving Centchroman and 30 % in control arm. This would have demonstrated a relative risk of regression of 2 with 95 % confidence and 80 % power at an allocation ratio of 1:1. The sample size calculation was performed for superiority hypothesis trial on Epi Info version 6.

The randomization codes were developed on the website www.randomization.com using permuted block randomization method. We used numbered sealed brown opaque envelopes for concealing treatment allocation. Patients in active therapy arm were prescribed with Centchroman 30 mg daily for 12 weeks, while the control arm women were observed without any intervention. Patients purchased tablet Centchroman 30 mg (trade name Saheli; Hindustan Latex Company, Ltd., a Government of India Undertaking) from the market for Rs 2 per tablet and knew about the medicine.

Patients Selection and Measurement of Fibroadenoma

All the consecutive patients coming to the surgical outpatient department with history suggestive of benign breast disease were screened after triple assessment. Patients presenting with fibroadenoma of less than 5 cm in size measured with a Vernier caliper (age of ≤ 30 years) were included in the study. Eligible patients were provided a printed information sheet in Hindi and English explaining the nature of fibroadenoma and possible benefit with Centchroman. They were recruited in the study after signing the consent form. A baseline breast ultrasound was performed using a 7.5-MHz linear probe on “Siemens Versa” ultrasound scanner. Sonographic morphology of the fibroadenoma was assessed, and dimensions were recorded. Large-core (Trucut) biopsy was performed to assess the histological features and to perform estrogen receptor and progesterone receptor (ER and PR) estimation. Patients were evaluated after 1 week to check the tolerance to the drug and later followed at weeks 4, 8, 12, and 24 to assess the response to therapy. The ultrasound examination of the breast served as an objective measurement of volume assessment at 12 and 24th weeks in both the groups (study plan and CONSORT flow chart in Fig. 1).

Statistical Analysis

The data were analyzed with SPSS version 15. Continuous variables were analyzed with *t* test (for normally distributed data) and Mann–Whitney *U* test for non-normally distributed data. The changes in fibroadenoma

Fig. 1 Showing the CONSORT flow chart

volume over time were analyzed by “repeated measure analysis of variance.” *P* value less than 0.05 was considered significant.

Volume of Fibroadenoma

The volume of fibroadenoma in cubic centimeter was calculated by using the following simplified formula for an ellipsoid [6, 7, 11]:

$$\text{volume of fibroadenoma} = a \times b \times c \times 0.52$$

where “*a*” is the largest dimension, “*b*” is the dimension at right angle to *a*, and “*c*”=average of *a* and *b*=(*a*+*b*)/2. The lesion was measured clinically with a Vernier caliper and with an ultrasound scanner.

Results

From November 2004 to November 2007, 80 patients with breast fibroadenoma were studied. Some patients had more than one fibroadenomata; hence, fibroadenoma was taken as a unit of study rather than the patient. In 80 cases, 102 fibroadenomas were detected by palpation, while on ultrasound, 121 fibroadenomas were detected. Of 80 patients, 40 cases were randomized to control arm, and 40 cases, to Centchroman arm. Forty cases in control arm had 52 fibroadenomas, and 40 cases in Centchroman arm had 69 fibroadenomas. Of 80 patients, 39 (49 %) patients had fibroadenoma in the right breast; 25 (31 %) patients, in the left breast; and 16 (20 %) patients had bilateral breast fibroadenomas. Table 1 describes the baseline characteristics and the median volume of fibroadenoma in the two

Table 1 The baseline characteristics

Variable	Centchroman group	Control group	<i>P</i> value between groups
Mean and range of age in years	22.43 (Range 16 to 30)	22.16 (Range 15 to 29)	0.69
Number of fibroadenoma	69	52	
Initial median volume (clinical)	6.82 cm ³ (Range 0.52–65 cm ³)	4.16 cm ³ (Range 0.52–46.8 cm ³)	0.35
Initial median volume (sonographic)	2.91 cm ³ (Range 0.5–37.44 cm ³)	1.95 cm ³ (Range 0.32–57.48 cm ³)	0.70

groups. Both the arms were comparable at baseline in terms of volume.

Effect of Centchroman on Volume of Fibroadenoma

Clinical Volume

The median volume of fibroadenoma (measured with a Vernier caliper) in Centchroman arm reduced from baseline 6.82 to 4.06 cm³ at 24 weeks. The median volume in the control arm increased from baseline 4.16 to 5.85 cm³ at 24 weeks (Table 2).

Sonographic Volume

The median volume in Centchroman arm reduced from 2.91 to 0.57 cm³ at 24 weeks. However, in the control group, the volume increased from 1.95 to 2.82 cm³. There was a statistically significant reduction in the volume of fibroadenoma in Centchroman arm (Table 3).

Twenty-two (31.88 %) fibroadenomas in Centchroman arm regressed completely as compared to four (7.69 %) in control arm over a period of 6 months. There was a decrease in the volume of fibroadenoma in ten (19.23 %) patients in control arm and 36 (52.17 %) patients in Centchroman arm. In 38 (73.07 %) patients, fibroadenoma increased in volume in control arm, and 11 (15.94 %) patients, in Centchroman arm.

Hormone Receptor Analysis

The estrogen and progesterone receptor analysis was done on 20 patients with 31 fibroadenomas. The receptor assay was performed by immunohistochemical staining of tissue section by monoclonal antibodies in dilution of 1:50 (Novocastra, UK) overnight at 4 °C. Staining of both stromal and epithelial components were recorded. The estrogen and progesterone receptors were mainly found in epithelial component of fibroadenoma. Brown staining of nucleus was

considered to be positive for ER and PR. For analysis, either estrogen or progesterone positivity was taken as receptor positive status. Receptor positivity was noted in 12 (38.7 %) , while 19 (61.3 %) out of 31 fibroadenomas were receptor negative.

The receptor-positive fibroadenomas were equal in Centchroman and control groups, with six fibroadenomas in each group. Among the receptor-positive lesions in Centchroman group, there was a decrease in the volume of fibroadenoma as compared to control arm, and it was statistically significant at follow-up of 24 weeks. There was 67 % response in receptor-positive fibroadenomas in Centchroman group (i.e., decrease in median volume from 3.62 to 1.20 cm³). Among receptor-negative fibroadenomas in Centchroman arm, there was a decrease in volume, but this was not statistically different from the control arm (Table 4).

Side Effects of Centchroman

None of the patients developed major side effect requiring withdrawal from the study. The only significant side effect was menstrual abnormality. Nine out of 40 patients in Centchroman group missed their menstrual periods after starting the drug compared to none in control group. This change of menstrual cycle in Centchroman arm was statistically significant. The duration of cycle was also prolonged in Centchroman group during therapy. The duration of menstrual cycles became normal after stopping medication. Menstrual periods resumed soon after stopping the Centchroman at the end of 12 weeks.

Discussion

Fibroadenomas are commonly seen in the surgical outpatient department among young women. The mean age of presentation is around 20 years [1]. It is emotionally disturbing for young girls because of the fear of cancer. Even after the reassurance that the lump is benign, many Indian

Table 2 Data on clinically measured volume in the two groups at baseline and during follow-up

Time in weeks	Clinical volume in control arm			Clinical volume in Centchroman arm			<i>P</i> value ^a
	Mean	Median	SD	Mean	Median	SD	
0	8.57	4.16	10.24	11.26	6.82	14.42	0.35
12	8.78	4.16	11.3	5.76	4.16	7.84	0.21
24	10.87	5.85	12.30	6.28	4.06	9.9	0.12
<i>P</i> value ^b	0.365			0.001			

All values are measured in cubic centimeter. Values were not distributed normally. Hence, nonparametric tests were applied

^a Two-sample Wilcoxon rank-sum (Mann–Whitney) test comparing volume between control and Centchroman groups

^b Greenhouse–Geisser test comparing volume “within group” with time

Table 3 Data on sonographic volume in the two groups at baseline and during follow-up

Time in weeks	Sonographic volume in control arm			Sonographic volume in Centchroman arm			<i>P</i> value ^a
	Mean	Median	SD	Mean	Median	SD	
0	6.38	1.95	11.31	5.66	2.91	8.28	0.70
12	6.88	2.67	11.86	3.25	0.65	7.89	0.001
24	7.44	2.82	12.55	2.75	0.57	7.78	0.001
<i>P</i> value ^b	0.536			0.001			

All values are measured in cubic centimeter. Values were not distributed normally. Hence, nonparametric tests were applied

^a Two-sample Wilcoxon rank-sum (Mann–Whitney) test is comparing volume between control and Centchroman groups

^b Greenhouse–Geisser test comparing volume within group with time

girls prefer to get it excised before the marriage. Till now, the only effective treatment available is excision, which leaves a scar on the breast and may damage mammary duct if present near the nipple areola complex. Khanna et al. [8] and Viviani et al. [6] described the drug therapy of fibroadenoma. Viviani et al. evaluated the effect of tamoxifen, an antiestrogenic drug on fibroadenoma showing regression in size by about 20 % in the treatment arm [6]. Khanna et al. evaluated estrogen receptor positivity and effect of danazol on fibroadenoma. They found that 62 % of fibroadenoma responded to danazol, and response to danazol was significantly greater in ER-positive fibroadenoma.

The mean age of the patients included in our study was 22.3 years. We excluded patients above 30 years of age from the study because many studies have suggested 30 as a safe limit of age up to which fibroadenoma can be observed with no malignant change occurring in any of them [12, 13].

There is a wide discrepancy in the natural history of fibroadenoma regarding the change in size over time. Many fibroadenoma, if left alone, will remain static or gradually increase in size until 1–3 cm in diameter in 1–5 years. Thereafter, it is likely to remain static for the rest of patient's life or gradually decrease in size [7]. Dent and Cant [12] followed 63 women with fibroadenoma for 2 years. They found that 31 % of 201 lumps disappeared, 12 % became smaller, 25 % remained static, and 32 % grew in size. Dobie et al. [14] studied 201 patients of fibroadenoma of age less

than 40 years, with conservative management for 5 years. During follow-up, 13 % were resolved, and 85 % remained unchanged, while 2 % increased in size. It appears that though fibroadenomas have a tendency to resolve naturally, the proportion of spontaneous regression is quite different in different studies. In the control arm of our study, only 7.69 % disappeared completely in 6 months follow-up, 19.23 % of them regressed partially, and 73 % increased in size. In control arm of our study, the fibroadenoma increased by 2–3 cm and then remained static. Our project was approved by the institute ethics committee for a follow-up of patients for 6 months only; hence, we have not recorded the data after 6 months of therapy.

Effect of Centchroman on Fibroadenoma

There was a gradual decline in volume with Centchroman till the end of treatment period, but the control group showed a progressive increase in the median volume. The volume measured by ultrasound at the end of treatment period also showed significant difference. Of 69 fibroadenomas followed with Centchroman therapy, 22 (31.88 %) disappeared completely as compared to only four (7.69 %) of 52 fibroadenomas in control group.

Sonography detected more lesions as many small fibroadenomas in breasts were missed on clinical examination but were picked up only on ultrasound. Khanna et al. [8] found

Table 4 Data on sonographic volume of fibroadenoma among receptor-positive and receptor-negative lesions

Weeks	Receptor-positive fibroadenoma					Receptor-negative fibroadenoma				
	Control (N=6)		Centchroman (N=6)		<i>P</i> value	Control (N=4)		Centchroman (N=15)		<i>P</i> value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
0	4.67	4.11	3.62	2.8	0.818	1.86	1.44	5.55	9.49	0.73
12	5.05	5.7	1.8	1.21	0.24	3.41	4.18	2.22	4.56	0.35
24	5.66	5.6	1.2	0.82	0.015	3.54	3.91	0.88	1.77	0.15

estrogen receptor positivity in 40 % of fibroadenoma in their study. In our study, also the receptor positivity was 40 %, but patients with receptor-negative status also responded to Centchroman. The response rate was equal at 12 weeks in receptor-positive and receptor-negative lesions. However, better response was seen at the end of study, i.e., at 24 weeks in receptor-positive fibroadenoma, which was statistically significant ($P<0.015$). This indicates some carry-over effect of Centchroman resulting in continued regression of fibroadenoma after stopping therapy at 12 weeks.

The regression of receptor-negative lesions with Centchroman is difficult to explain. The drug may be exerting its effect through some unknown pathway. Alternatively, our sample may be inadequately empowered to make a clear-cut statistical inference.

Limitation of study

The study presents data only up to 6 months. The long-term results of Centchroman on recurrence need to be studied in the future.

Conclusion

Centchroman, an antiestrogen drug, at a dosage of 30 mg daily for 3 months allowed complete regression of 31 % fibroadenoma, whereas only 7 % of lesions regressed completely with simple observation. The drug is inexpensive (Rs 2 a day) and is well tolerated with scanty periods or delayed menses as the only side effect. Long-term results beyond 6 months need further study.

Conflict of Interest None.

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