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Role of Centchroman in Regression of Benign Breast lumps

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ABSTRACT:
Background: The breast is a very dynamic structure that undergoes a lot of physio-clinical changes across the menstrual cycle in young women. Mastalgia and fibroadenoma are the most common type of benign breast disorders found in the women younger than 30 years with a peak incidence around 20 years of age. Centchroman also known as Ormeloxifene is a non-steroidal class of drug with antiestrogen activity. Many different classes of drugs have been used for the treatment of breast lumps like Bromocriptine, Danazol, LH-RH analogue and Tamoxifen but still no unanimity for any drug has been reached. Centchroman because of its selective antiestrogen activity has become a drug of choice. The aim of the current study is to evaluate the efficacy of centchroman in the treatment of benign breast lumps.
Patients and Methods: The study was conducted on eligible patients attending the surgical outpatient department of Government Medical College, Jammu, over the time period of 1 year from 1st November 2018 to 31st October 2019. The study included 50 females in the age group of 15-55years with benign breast lumps of size up to 3 centimeters in diameter. The Centchroman (Saheli) was administered to the patients with a dose of 30 milligrams twice in a week for 3 months. The effectiveness of drug Centchroman was noted on the regression of lump size. The patients were subjected to triple assessment and the lump size was noted both clinically and by radiological assessment.
Results: At the end of 6 months 58.93% showed complete regression in size; 33.93% showed >75% regression in size; 5.36% showed up to 75% regression in size and 1.79% showed increase in size. Fewer side effects were observed such as scanty menstruation cycle in 16% women and delayed periods in 4% patients.
Conclusions: The study demonstrates that Centchroman is safe, user friendly and cost-effective non-surgical treatment modality for small benign breast lumps.

Keywords: Benign breast lumps, Centchroman, Fibroadenoma, Saheli, SERM

I. INTRODUCTION:

Benign breast diseases (BBD) are most common in young women between the age group of 20-30 years with incidence peaking in second and third decades (Singla et al., 2021). Different hypothesis for the occurrence of these lumps in the breasts have been given such as increase in the level of estrogen secretion from ovary, increase in prolactin secretion, decline in progesterone production etc (Alipour et al., 2021). Almost all the benign breast disorders come under the umbrella of 'Aberration of normal development and Involution' (ANDI), under which most of the breast complaints have been characterized as Benign Breast Lumps including fibroadenomas, breast cysts and fibroadenosis. Of all the above Fibroadenoma is the most frequent cause of breast lump (Meera et al., 2016). The World Health Organization (WHO) has described fibroadenoma as "a discrete benign tumor showing evidence of connective tissue and epithelial proliferation". Breast lumps presents as smooth, non-tender, firm, painless, well localized glob which moves unhindered within the breast tissue. These lumps are mostly found in the upper outer quadrant of the breasts. The diagnosis of the breast lumps involves a triple test, which is a combination of clinical examination, radio imaging and non-surgical tissue biopsy. The development of breast lumps in females has most widely been attributed to differential secretion of estrogens and progesterone (Brisken et al., 2020; Santen et al., 2015).

The surgeon often face the dilemma whether to remove the mass or monitor it by means of periodic follow up examinations. Most of the fibroadenomas are left in-situ and monitored. Many treatment choices are available like observation, hormonal therapy, surgical excision and few other less invasive therapies (Khoja et al., 2021). A growth rate of less than 16% per month in women under the age of 50 year and less than 13% per month in women above 50 years age have been

considered a safe growth rates for continuing non operative treatment or clinical observation. Certain disadvantages of surgical procedures include that it is an invasive procedure, expensive as compared to conservative and medical management and it involve unnecessary excision of benign lesions leaving a bad scar after the procedure.

The Centchroman is a novel and safe non-steroidal Selective Estrogen Receptor Modulator (SERM) synthesized by Central Drug Research Institute, Luckhnow, India in the 1980s. It was introduced as an oral contraceptive in the National Family Welfare Program India in 1995. It has been marketed in India under the trade name 'Saheli' at a cost of Rs. 2 per 30mg tablet. The use of this drug has been permitted by the Drug Controller of India for the treatment of benign breast lumps (Andolf et al., 1987).

Centchroman arouses a weak estrogen agonist and potent antagonistic activities but is deficit of progesterone, androgenic, and anti-androgenic activities. After the treatment has been stopped, there is an early return of fertility therefore, it is safe for unmarried women and those who want to conceive after treatment (Girish and Faraz, 2020). The role of Centchroman in mastalgia and Fibroadenoma is an evolving issue of interest in order to find an effective and definitive non-surgical modality for Fibroadenoma. The current study attempts on evaluation of efficacy of the drug in our setting.

II. PATIENTS AND METHODS:

The current study conducted in the tertiary care hospital, Government Medical College, Jammu from 1st November 2018 to 31st October 2019 included patients on accrual basis. Keeping in view the short duration of study and the long period of follow up of 6months, 50 patients meeting the following criteria were included in this study.

Inclusion criteria: Women within the age group between 15 to 55 years were selected. The patients with benign breast lumps including fibroadenoma ≤3 cm in diameter, benign breast nodularity and fibroadenosis were included in the present study.

Exclusion criteria: Women who were pregnant, lactating or who were planning to have pregnancy in near future were excluded from the study. The patients with history of breast carcinoma or family history of breast carcinoma, patients with Fibroadenoma >3cm in size, patients with deranged hepatic function or renal impairment, patients with polycystic ovarian diseases and cervical hyperplasia, patients diagnosed to have associated chest wall disorder and dermatological lesions, women with undiagnosed or abnormal uterine bleeding, allergy to the drug and denial to give written informed consent were excluded from the present study.

All patients with clinical feature of lump in the breast with or without other symptoms meeting the above criteria were subjected to triple assessment including clinical examination, ultrasound examination of the lump in the breast and FNAC of the lump. Initial assessments were done at the beginning of the active treatment and then follow up at was done at 1, 2, 3 and 6 months.

III. RESULTS:

50 diagnosed cases of benign breast disorders attending the surgical outpatient department of Government Medical College, Jammu were included in the study and the following observations were made.

Age Distribution

In the present study, it was seen that most of the patients were in the age group of 25-29years (34%). Mean age of the study group was 27.9 years and median was of 27 years. The youngest patient in the study was of 18 years old and the oldest patient in the study was 45 years old.

Duration of Lump

The duration of symptom of lump in the breast varied from 7 days to 2190 days with a median of 90 days, mean of 273.24 days and a standard deviation of 529.02 days. Most of the patients had symptom of lump for 30 to 90 days (54%).

Association with Pain

It was observed that 35 (70%) patients presented with pain in association with breast lump whereas 15 (30%) patients didn't have any associated pain. The mean and median time of presentation of patients with lump associated with pain was 148.34 and 30 days respectively whereas the mean and median time of presentation of patients without pain was 564.67 and150 days respectively.

History of Oral Contraceptive Pill intake and response to therapy

It was observed that out of 50 patients, 9 (18%) patients had a history of oral contraceptive pills (OCP) intake while 41 (82%) patients had no history of OCP intake. All the patients who had a history of OCP intake showed >75% response at 3 and 6 months.

History of previous surgery for benign breast lumps

Out of 50 patients, 6 patients (12%) had a history of previous surgery for benign breast lump and 44 patients (88%) didn't have any previous

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history of surgery. This signifies that benign breast lumps like Fibroadenomas do reoccur following surgical excision and surgery is not the definitive treatment for benign breast lumps.

Number of lumps and response to therapy

Out of 50 patients, 4 patients had 2 lumps one in each side of the breast, 1patient had 3 lumps one in right breast and 2 in left breast while rest 45patients had unilateral single lump in the breast. All the patients with more than 1 lump showed response >75% at 3 months and 6 months. All the lumps were included in the study (i.e., 50 patients with 56 lumps).

Change in distribution of size of lump with therapy

It is evident from the present study that over a time span of 3 months of therapy, the percentage of lump size less than 1 cm increased from 12.50% initially to 82.14% at 3rd and 6th month of follow up suggesting a significant reduction in size of the initial lump. However 10.72% lumps showed an increase in the size over 6 months of follow up (Table 1).

Table 1

Size (in cm)	Initially		1 month		2 month		3month		6month	
	%	N*	%	N*	%	N*	%	N*	%	N*
<1	12.50	7	37.50	21	71.43	40	82.14	46	82.14	46
1-2	39.29	22	44.64	25	17.86	10	12.50	7	3.57	2
2-3	48.21	27	14.29	8	8.93	5	3.57	2	3.57	2
>3	0.00	0	3.57	2	1.79	1	1.79	1	10.72	6

*

N represents number of patients

Change in distribution of volume of lump with therapy

The volume of lump was calculated using the following formula,

Volume of lump = 0.52 x a x b x c

Where a is length,

b is breadth

c is 0.5 (a + b)

It is evident from the present study that over 3 months of therapy, the percent of lump volume (<1cm³) increased from 30.36% initially to 92.86% at 3rdand 6th month of follow up suggesting a significant reduction in the volume of the initial lump (Table 2).

Table 2

Volume (in cm^3)	Initally		1 month		2month		3 month		6 month	
	%	n	%	N	%	N	%	N	%	N
<1	30.36	17	71.43	40	76.79	43	92.86	52	92.86	52
1-5	41.07	23	17.86	10	19.64	11	3.57	2	3.57	2
5-10	19.64	11	7.14	4	0	0	0	0	0	0
>10	8.93	5	3.57	2	3.57	2	3.57	2	3.57	2

Overall response to therapy

The response of centchroman therapy at 3rd month i.e., after completion of therapy and 6th month i.e., 3 months after the completion of therapy was calculated as percent of volume reduction as compared to initial volume using the following formula.

$$Volumereduction\ (in\ \%) = \frac{(\text{Initial volume of lump} - \text{Volume of lump at x month})}{\text{Initial volume of lump}} \times 100$$

Here, x = 3 months for volume reduction at 3rd month and 6th month for volume reduction at 6 months.

Poor response: Response to the therapy was considered poor if the reduction in volume of lump was <75% of the initial volume.

Good response: Response to the therapy was considered good if the reduction in volume of lump was between 75% - 99.99%.

Complete response: Response to the therapy was considered complete if the reduction in the volume of lump was 100%.

Negative responders: This group of patient showed increase in volume of lump as compared to initial volume of the lump.

The data has been given in table 3.

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Table 3

Time	Poor Response	Good Response	Complete Response	Negative Response	Total
3 months	2 (3.57%)	32(5.14%)	21(37.50%)	1(1.79%)	56(100%)
6 months	3(5.36%)	19(33.93%)	33(58.93%)	1(1.79%)	56(100%)

Side effects observed

Out of 50 patients included in the study, 8 (16%) had scanty menses, 2 (4%) had delayed menses and 40 (80%) didn't have any menstrual irregularities or any other side effect. All the patients had regular menstrual history and were scanned for any abnormality before starting the treatment. All the patients had their normal menstrual cycles after stopping the centchroman therapy within 1 month (Table 4). Similar results were obtained by Dhar and Srivastava, 2007. They found minimum side effects.

Table 4

Side effects	Frequency	Percentage
Scanty menses	8	16
Delayed menses	2	4
No side effects	40	80
Total	50	100

Statistical Analysis:

Using, two dependent sample T-test for the lump volume, it was found that the data is statistically significant. Comparing the data at the end of therapy i.e., 3 months to the initial data the t-value was found to be -7.123084 and p value was<0.00001. Thus the result was found to be statistically significant at p <0.05. Comparing the data at 6th month of observation to the initial data the t-value was -7.14956 and p value was recorded to be <0.00001. Thus the overall result was noted to be statistically significant at p <0.05.

IV. DISCUSSION:

Benign breast diseases (BBDs) are the most common occurrence in the breasts of the reproductive age group women. Most of the BBDs are found to be mild subside spontaneously but the other severe grade BBDs require treatment at certain point (Shashikala et al., 2016). Literature suggests that hormonal imbalance such as increase in estrogen secretion, decrease in progesterone levels and increase in Prolactin level is primarily responsible for painful and nodular breasts (Sangama et al., 2013).

Centchroman is a non-steroidal selective oestrogen receptor modulator that has a high anti-estrogen and mild anti-progestin effect (Ravibabu et al., 2013). On specific regions of the body, such as the bones, it also exerts some modest estrogenic effects. It was formulated at the Chandigarh Drug and Research Institute in India and was previously used as a substitute for steroidal oral contraceptives. In 1995, it was included in the National Family Welfare Program. It is widely utilised due to its specific anti-estrogen effect and the benefit of less frequent administration (Balganesh et al., 2014).

The present study concludes that Centchroman is a safe and cost effective non-steroidal, non-hormonal drug for regression of Benign Breast Lumps ≤ 3cm in size. Similar results were reported by Bansal et al., 2015. They also found centchroman to be safe for the treatment of benign breast lumps. Twice a week protocol made it more patient friendly with a better compliance for the drug. Lal et al., 2001, found the same dose to be effective. The drug was given to 60 female volunteers and most effective group set was found to be following 30 mg twice a week regime. Ultrasound was found to be more reliable for follow up measurements since it has shown to be more reliable and accurate in measuring the dimensions of the lump (Table 5). Burgess and O'Neal, 2019 showed the utility of High-quality breast ultrasonography as the reliable mean for the diagnosis of breast lumps.

Table 5

SNo.	Authors	Study type	Sample size	Age distribution	Dose of Centchroman	Follow up period	Outcome/ Response

				(years)			
1	Dhar A et al (2007)	Non-randomized study	60	<35	30 mg on alternate days for 3 months.	6 months	At 6months 40% showed complete regression; 20% showed partial regression and rest 40% did not show any response.
2	Kumar S et al (2013)	Randomized Placebo control trial	151	33.7±7.45	30mg twice weekly for 3 months	6 months	Breast nodularity grade showed significant improvement
3	Bansal V et al (2015)	Randomized Control Trial	203	20-25	30mg twice weekly for 3 months	6 months	Breast nodularity grade showed significant improvement
4	Tejwani PL et al (2015)	Comparative study	80	≤30	30 mg daily for 3 months.	24 weeks	At 6months 31.88% showed complete regression; 19.23% showed partial regression
5	Meera SS et al (2016)	Non Randomized Prospective study	100	15-55	60mg twice weekly for 3 months	12 weeks	At 3months 60% showed complete regression; 30% showed upto 75% regression in size and 10% showed 25-30% regression in size
6	Sharma B et al (2016)	Non Randomized prospective study	130	16-40	30mg daily for 3 months	24 weeks	At 6months 35% showed complete regression; 48.30% showed partial regression and rest 16.70% did not show any response.
7	Rajswaroop U et al (2016)	Non Randomized prospective study	51	26-35 (70.6% patients)	30mg on alternate days for 3 months	6 months	At 6months 74.50% showed complete Regression
8	DharDebasis et al(2018)	Randomized prospective	84	15-39	--	3 months	At 3months 26.67% showed complete Regression

9	Present study	Prospective study	50	18-45	30mg twice weekly for 3 months	6 months	At 6months 58.93% showed complete regression; 33.93% showed > 75% regression in size; 5.36% showed up to 75% regression in size and 1.79% showed increase in size

V. CONCLUSION:

The present study concludes that Centchroman is an effective drug for the treatment of benign breast disorders. Centchroman is safe with a fewer side effects. However, further metacentric randomized double blind controlled studies with a larger sample size and a longer duration of follow up are required in order to firmly establish Centchroman as preferred non-hormonal non-steroidal therapy for the treatment of benign breast lumps

REFERENCES:

[1]. Alipour, S., Abedi, M., Saberi, A., Maleki-Hajiagha, A., Faiz, F., Shahsavari, S., & Eslami, B. (2021). Metformin as a new option in the medical management of breast fibroadenoma; a randomized clinical trial. BMC Endocrine Disorders, 21(1), 1-10.

[2]. Andolf, E., Jörgensen, C., Svalenius, E., Sundén, B., & Andolf, E. (1987). Ultrasound measurement of the ovarian volume. Acta obstetricia et gynecologica Scandinavica, 66(5), 387-389.

[3]. Aslam HM, Saleem S, Shaikh HA, Shahid N, Mughal A, Umah R. Clinico-pathological profile of patients with breast diseases. DiagnPathol. 2013;8:77.

[4]. Balganesh, T., Kundu, T. K., Chakraborty, T. K., & Roy, S. (2014). Drug discovery research in India: current state and future prospects.

[5]. Bansal, V., Bansal, A., & Bansal, A. K. (2015). Efficacy of Sevista (Ormeloxifene) in treatment of mastalgia and fibrocystic breast disease. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 4(4), 1057-1061.

[6]. Burgess, M. D., & O'Neal, E. L. (2019). Breast ultrasound for the evaluation of benign breast disease. Current Radiology Reports, 7(3), 1-11.

[7]. Cant PJ, Madden MV, Coleman MG, Dent DM. Non-operative management of breast masses diagnosed as fibroadenoma. Br J Surg. 1995 Jun;82(6):792-4.

[8]. Dhar, A., & Srivastava, A. (2007). Role of centchroman in regression of mastalgia and fibroadenoma. World journal of surgery, 31(6), 1180-1186.

[9]. DharDebasis, P. Ghosh, S. K. Mukherjee, S. K. Paira, R. Mukherjee, S. Halder. "A Comparative Study of Centchroman VS Danazol VS Evening Primrose Oil in the management of mastalgia and fibroadenoma." IJSR 6 (2018); 7(3): 2277-8179.

[10]. Estevão RA, Nazário AC, Baracat EC. Effect of oral contraceptive with and without associated estriol on ultrasound measurements of breast fibroadenoma: randomized clinical trial. Sao Paulo Med J. 2007 Sep 6;125(5):275-80.

[11]. Girish, T. U., & Faraz, M. (2020). Role of ormeloxifene in regression of benign breast diseases. International Surgery Journal, 7(3), 743-750.

[12]. Khoja, H. R., Barala, B. R., Sharma, S., Om, P., & Saini, D. (2021). Role of centchroman versus danazol in treatment of benign breast disorders. International Surgery Journal, 8(2), 616-618.

[13]. Kumar N. and Janardan Prasad. "Epidemiology of benign breast lumps, is it changing: a prospective study." International Surgery Journal 6 (2019): 465.

[14]. Kumar S, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V. A randomized, double blind, placebo-controlled trial of ormeloxifene in breast pain and nodularity.

The National Medical Journal of India 2013; 26(2):69-74.

[15]. Lal, J., Nitynand, S., Asthana, O. P., Nagaraja, N. V., & Gupta, R. C. (2001). Optimization of contraceptive dosage regimen of Centchroman☆. Contraception, 63(1), 47-51.

[16]. Meera S S., N. Tamilselvan, P. Kumar and Dr.V. Rishigowtham. "A Prospective Study of Efficacy of Selective Estrogen Receptor Modulator (Serm) In Aberration of Normal Development and Involution of Breast (Andi)." IOSR Journal of Dental and Medical Sciences 15 (2016): 26-29.

[17]. MohakulSubrat Kumar, SujathaGuttala and PurnimaTiru. "Role of Ormeloxifene(Centchroman) in Benign Mastalgia of Diverse Origin." (2017); 3(1):56.

[18]. Rajswaroob U, Kannan R, Kannan NS, Tirouaroul T. Effectiveness of Centchroman on Regression of Fibroadenosis and Mastalgia. J ClinDiagn Res. 2016;10(10).

[19]. Sangma, M. B. M., Panda, K., & Dasiah, S. (2013). A clinico-pathological study on benign breast diseases. Journal of clinical and diagnostic research: JCDR, 7(3), 503.

[20]. Santen, R. J., Yue, W., & Wang, J. P. (2015). Estrogen metabolites and breast cancer. Steroids, 99, 61-66.

[21]. Sharma B., S. Narayan, N. Sharma and A. Parmar. "Centchroman Regress Mastalgia and Fibroadenoma: An Institutional Study." journal of medical science and clinical research (2016); 4(7):11334-39

[22]. Shashikala, V., Sonia, R. P., & Victor, A. J. (2016). Clinicopathological study of benign breast diseases. Int J Biomed Adv Res, 7(9), 424-7.

[23]. Singla, N. K., Bhatia, R., Verma, R., & Bhatia, S. K. (2021). A prospective study on the role of centchroman in regression of fibroadenoma. International Surgery Journal, 8(11), 3327-333.

[24]. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, Thulkar S, Chumber S, Kumar S. Centchroman regresses mastalgia: a randomized comparison with danazol. Indian J Surg. 2011;73(3):199-205.