Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Determining the Efficacy of Centchroman in Treatment of Mastalgia

Md Najim[1], Biswajit Mukhopadhyay[2], Md Shabbirul Islam[3], Anand Kumar Singh[2], Antarik Sasmal[1]

[1]Senior Resident, Department of General Surgery, ESIC Hospital, Varanasi, Uttar Pradesh, India, [2]Consultant, Department of General Surgery, ESIC Hospital, Varanasi, Uttar Pradesh, India, [3]Senior Resident, Department of Paediatric Surgery, Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Background: Breast pain or mastalgia is a common complaint among the woman presenting in surgical as well as gynecological OPD. Several non-medical and medical management has been tried for the treatment of mastalgia since ages. In this study, we have studied role of centchroman in treatment of mastalgia and also tried to observe its side effects and compliance.

Materials and Methods: It was a prospective observational study. Seventy-eight eligible patients fulfilling the eligibility criteria were enrolled for study. Each patient was given separate patient information sheet and proper counseling was done about the study and consent was taken. Tablet centchroman was give 30 mg bi weekly for 3 months. Follow-up was done at 1, 2, and 3 months and final closure was done at 6 months. The results were observed on a daily breast pain chart improvised by author.

Results: A daily breast pain chart was used in the study for assessment of pain. The minimum value was zero depicting no pain while maximum value was 4 indicating breast pain at rest. At the start of study, mean pain score was 1.44 ± 1.273. After 1 month, mean pain score became 0.764 ± 0.599, which is decrease of about 47%. By the end of 2 months, it was 0.548 ± 0.601 (decrease of 62%). It rose slightly to 0.690 ± 0.478 (approximately 20% rise in mean pain score than 2 months) level indicating that few patients were having recurrences. By the end of 6 months, mean pain score was 0.810 ± 0.647 indicating 43% decrease in mean pain score with respect to pain at beginning of the study. The side effects encountered in this study were mostly menstrual related which were temporary and normal menses were resumed on stopping medication.

Conclusion: This study shows that centchroman is a very effective drug for treatment of mastalgia with minimal and less severe side effects. It also shows less recurrence and patient is more compliant due to easy dosage.

Key words: Mastalgia, Cyclical, Non-cyclical, SERM, Centchroman

INTRODUCTION

Mastalgia comes from Greek word mastobreast and algia-pain. It was described in the medical literature as early as 1829. Mastalgia is a common complaint among women presenting in gynecology and surgical OPD.[1] Since most of the causes of mastalgia are of benign etiology, it needs symptomatic relief only. Mastalgia affects a woman's personal and sexual life along with constant fear of cancer, and hence, it needs to be given utmost importance while dealing with patient of mastalgia.

Mastalgia can be cyclical or non-cyclical based on its relationship with menstrual cycle. It can be intermittent or constant, localized, or diffused. Cyclical mastalgia is the most common type of breast pain accounting for two-third of cases.[2]

Mastalgia commonly occurs due to hormonal imbalance – estrogen excess, progesterone deficiency, changes in progesterone/estrogen ratio, differences in receptor sensitivity, disparate secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), low androgen levels, and high prolactin levels.

Access this article online

www.ijss-sn.com

Month of Submission : 02-2023
Month of Peer Review : 03-2023
Month of Acceptance : 04-2023
Month of Publishing : 04-2023

Corresponding Author: Dr. Anand Kumar Singh, Department of General Surgery, ESIC Hospital, Varanasi, Uttar Pradesh, India.

Various drugs such as danazol, bromocriptine, tamoxifene, and LH-releasing hormone (LHRH) analogues have been used in the recent times for mastalgia, but most of them are known for their significant side effects.[3] In the search of a better remedy, there have been few attempts to try selective estrogen receptor (ER) modulator (SERM). Centchroman is one of such SERM synthesized by the Central Drug Research Institute, Lucknow, India. It was introduced as an oral contraceptive in the National Family Welfare Program India, in 1995. It antagonizes the effect of estrogen on uterine and breast tissue and agonizes its effects on vagina, bones, CVS, and CNS. It binds competitively to the ERs and antagonizes estrogen-induced gene expression.[4]

Centchroman had an advantage over the other steroidal oral contraceptives in not having side effects such as nausea, vomiting, weight gain, and dizziness. The other added benefit was its less frequent administration of twice weekly regimen. Due to its low dosage and less frequent administration, any effect over the hypothalamic-pituitary axis is minimal; hence, normal ovulatory cycles are resumed after withdrawal of the drug. It is safe in the treatment of unmarried women and those who wish to conceive after treatment. No teratogenic effect has been observed yet.

MATERIALS AND METHODS

This was a prospective observational study to compare the efficacy of centchroman in patients of mastalgia and also study its side effects and compliance. The study was conducted in Department of Surgery, ESIC Hospital, Varanasi, between December 2020 and July 2022. Patients in the age group of 16–40 years with cyclic or non-cyclic breast pain were included in the study. Patients were explained about the nature of study, drugs to be used, and its side effects. They were included in the study only after signing the consent from.

Exclusion Criteria

The following criteria were included in the study:

1. Age <16 years or more than 40 years
2. Benign breast lesions which require surgery for cosmesis
3. Women suspected or diagnosed with malignancy
4. Acute inflammatory breast lesions which are amenable to antibiotic or surgical drainage
5. Women who were planning pregnancy or pregnant women
6. Women with abnormal and undiagnosed uterine bleeding
7. Recent history of jaundice or hepatic impairment
8. Renal impairment
9. History of thrombosis.

Table 1: Comparison of age groups in various studies

Author	Types of study	Sample size	Age of patients	Outcome measures
Bansal *et al*.[5]	RCT	221	20–50	VAS
Dhar and Srivastava[6]	Clinical trial	60	17–35	VAS
Dhar *et al*.[7]	RCT	84	Reproductive age group	VAS
Karwasra *et al*.[8]	RCT	50	>18	VAS
Kumar and Hasan[9]	RCT	64	12–44	Breast pain chart
Mohakul *et al*.[10]	Prospective study	84	21–55	Pain scor e char
Shrivastava[11]	RCT	50	20–40	VAS
Tejwani *et al*.[12]	RCT	81	Reproductive age group	VAS+daily breast pain chart
Present study	Prospective study	78	16–40	Daily breast pain chart

Table 2: Comparison of types of mastalgia in various studies

Author	Total patient	Cyclical (%)	Non-cyclical (%)
Mohakul *et al*.[10]	84	37	63
Uma[13]	58	57	43
Present study	78	41	37

Detailed clinical history was taken to rule out acute conditions or history of malignancy in family. Routine baseline hematological and biochemical investigation was done in all patients. Initial clinical assessment and breast imaging was done with ultrasound (and mammography if age more than 35). FNAC of any lumps detected and cytological studies of the breast secretions if present were also done rule out malignancy.

Patients were provided with separate patient information sheet both in English and Hindi according to patient own language. The severity of Mastalgia was assessed using "The pain score" devised by author. It was different than standard visual analog scale (VAS) score commonly used.

The Pain Score

- Grade 4 – Breast pain at rest
- Grade 3 – Breast pain on movement
- Grade 2 – Pain on light palpation of breast
- Grade 1 – Pain on deep palpation of breast
- Grade 0 – No pain even on deep palpation of breast.

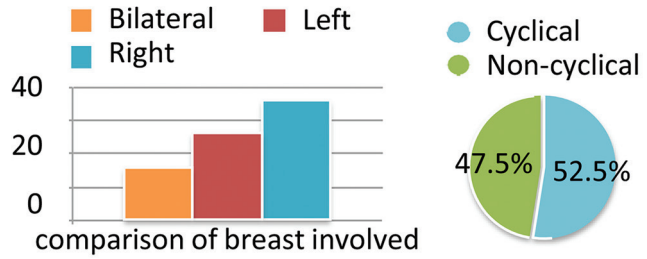
All the patients were taught and explained about grading of mastalgia. They were given a separate daily breast pain chart [Figure 1] and taught how to fill the chart and to bring it during each visit.

RESULTS AND ANALYSIS

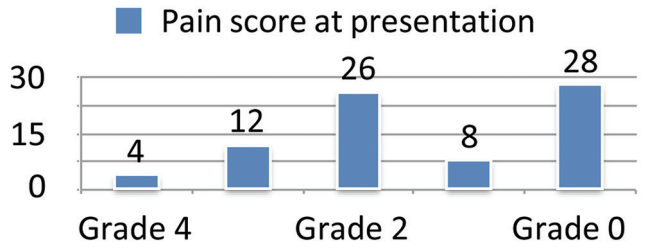
This prospective study was carried out in 78 cases of mastalgia who presented in surgery OPD of ESIC Hospital, Varanasi. The study was carried out between December 2020 and July 2022, and the data were collected in all these patients in terms of age, sex, clinical presentation, etiology, different severity score, ultrasound findings, side effects experienced, and compliance and follow-up was done after 1, 2, 3, and 6 months.

Age group	Number of patients	Percentage
≤20	24	30.8
21–25	24	30.8
26–30	14	17.9
31–35	6	7.7
36–40	10	12.8
Total	78	100

The study included 78 patients of mastalgia. Minimum age was 16 and maximum age was 40 with mean age of 24.97 ± 7.013 [Table 1]. Out of 78 patients, 62(79.5%) has disease in unilateral breast, whereas, 16(20.5%) has complaints in bilateral breast. Similarly out of 78 patients, 41(52.5%) had cyclical whereas, 37(47.5%) had non-cyclical mastalgia [Table 2].



Analysis of Pain Score [Table 3]



Comparison of Mean Pain Score

At presentation, 78 patients were enrolled. Mean pain score was 1.44 ± 1.273. After 1 month, mean pain score became 0.764 ± 0.599, which is decrease of about 47%. By the end of 2 months, mean score was 0.548 ± 0.601 (decrease of 62%). It rose slightly to 0.690 ± 0.478 (approximately 20% rise in mean pain score than 2 months) level indicating that few patients were having recurrences. By the end of 6 months, mean pain score was 0.810 ± 0.647 indicating 43% decrease in mean pain score with respect to pain at beginning of the study [Figure 2].

On detail follow-up, it was found that one patient loss to follow-up after 1 month and one patient after 3 months due to complete resolution of pain. One patient did not came for follow-up after 2 months due to some unknown reason.

Treatment of mastalgia

Various medical and non-medical methods have been adopted by doctors for treatment of mastalgia. In most patients with mild pain, reassurance is all that is required. A Brazilian study Barros *et al.*[14] verified overall success rate of 70.2% with reassurance in a study of 85 patients with mastalgia. The other non-medical means are dietary measures such as fat restriction and breast support with sport's brassier. The medical management includes use of drugs such as danazol, tamoxifen, bromocriptine, evening primrose oil, gamolenic acid (GLA), LHRH analogs, oral contraceptive pills (OCPs), and diuretics and topical NSAIDs gel. Centchroman is a non-steroidal, SERM drug formulated by the Central Drug Research Institute, Lucknow, India. In the present study, we studied effect of centchroman in mastalgia and we found out 43% decrease in mean pain score at the conclusion of study at 6 months.

In a study by Dhar and Srivastava using centchroman 30 mg on alternate day, drastic pain reduction was reported in 1 week period in 90% of the cases while almost all patients (n = 60) were painless at the end of 1 month.[6] Jain *et al.* reported a study of 60 cases where comparison was done between centchroman 30 mg daily versus tamoxifen 10 mg daily. More than 70% in both the group had complete pain relief by 3 months. There was no statistical difference in both groups.[15] In another randomized trial combining both alternate and daily dosage, Tejwani *et al.* reported centchroman to have response rate of 89.7% (reduction of pain to ≤3 on VAS) at the end of 12 weeks. Similar finding was found in study of Mohakul *et al.*[10] who reported 57% of patients to be pain free with the use of centchroman. Neogi *et al.*[16] concluded that pain relief was significantly better with centchroman after 24 weeks of treatment. Kumar and Hasan[9] reported similar reduction in symptom of mastalgia after 12 weeks of treatment. Karwasara *et al.*[8] concluded that patients showed gradual improvement in symptoms in terms of decrease in mean VAS during 3 months period of treatment (90%). This slightly higher percentage may be due dosage of centchroman. Centchroman was given on alternate day by Karwasara *et al.*, while, in our study, we gave 30 mg biweekly. The similar result was seen in study by Kumar *et al.* who gave centchroman twice a week.

Table 3: Analysis of pain score

	Mean pain score at presentation	Mean pain score at 1 month	Mean pain score at 2 month	Mean pain score at 3 month	Mean pain score at 6 month
Minimum	0	0.0	0.0	0.0	0.0
Maximum	4	2.1	2.2	1.6	2.6
Mean	1.44	0.764	0.548	0.690	0.810
SD	1.273	0.5999	0.6014	0.4784	0.6472
Media n	2.00	0.700	0.400	0.500	0.800
Standard error of mean	0.204	0.1200	0.1254	0.1044	0.1412
z		−4.288[a]	−4.016[a]	−4.018[a]	−3.900[a]
Asymp. Sig. (two-tailed.)		0.00	0.00	0.000	0.00

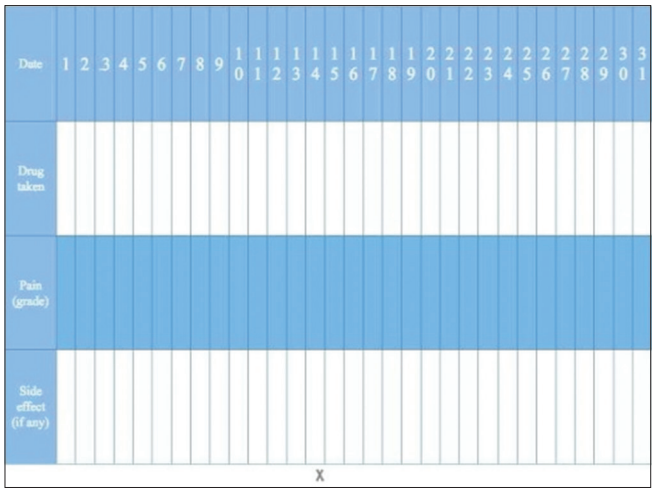


Figure 1: Daily breast pain self-recording chart

Analysis of Side Effects [Table 4]

On our first follow-up after 1 month, we found that out of 78 patients selected for study, one patient had loss to follow-up. Among the remaining 77, 71 (92.2%) had no side effects whereas 6 (7.8) experienced some kind of adverse effect. Two patients had oligomenorrhea, two had dizziness, and two patients had irregular cycle after taking the drugs. After 2 months, two patients (2.7%) had some kind of side effects while 75 (97.3%) had no effects. Of the two patients with side effects, one had complaints of oligomenorrhea, while other had delayed menses. Two patients loss to follow-up.

Similarly after 3 months, two patients had ovarian cyst on ultrasound scan. On last and final visit at 6 months (i.e., 3 months after discontinuation of drug), only one patient had ovarian cyst on ultrasound.

Analysis of Compliance

In this study, we tried to observe compliance of patient and found that the patient became more and more compliant due to efficacy, easy and less drug dosage, and less side effects.

Follow-up	After 1 month	After 2 months	After 3 months	After 6 months
Compliance (%)	89.5%	91.4%	97%	97%

DISCUSSION

Mastalgia was described in the medical literature as early as 1829 and it is derived from Greek word mastobreast and algia-pain. It is a common complaint amongst women of reproductive age group. Studies conducted on population-based and breast clinic-based[18] suggest that up to 70% of women under 55 years of age experience breast pain. Although 45% of them report minimal to mild symptoms, about 25% report moderate-to-severe mastalgia lasting for more than 5 days.

Classification

Mastalgia has been broadly classified into cyclical, non-cyclical, and extramammary musculoskeletal pain.[19]

A. Cyclical mastalgia: In cyclical mastalgia, discomfort commonly occurs around the menstrual cycle or ovulation, usually 2–3 days premenstrual. This is typically characterized by fine nodularity of breast before menstruation which subsides post-menstruation.
B. Non-cyclical mastalgia: Non-cyclical mastalgia lacks any relationship with the menstrual cycle. This falls

Table 4: Side effects of centchroman in different studies

Study	Oligomenorrhea	Delayedmenses	Irregular cycle	Dizziness	Urticaria	Ovarian cyst
Tejwani *et al*.[12]	31/41	6/41	2/4	0/41	0/41	0/41
Kumar *et al*.[17]	12/75	0/75	0/7	0/75	0/75	0/75
Kumar and Hasan[9]	24/64	2/64	1/6	0/64	0/64	0/64
Jain *et al*.[15]	2/30	2/30	0/3	8/30	0/30	5/30
Present study	3/78	3/78	2/7	2/78	0/39	1/78

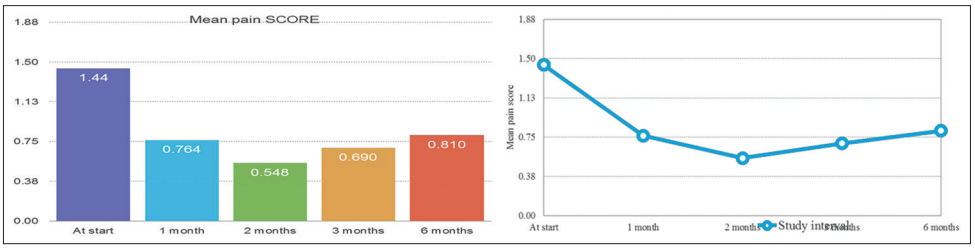


Figure 2: Variation of mean pain score

into two categories – true non-cyclical mastalgia and musculoskeletal pain. True non-cyclical mastalgia occurs in both premenopausal and postmenopausal women. This type of pain is well -localized to the breast especially in the sub-areolar and upper outer quadrants of the breast. Normally, the intensity and nodularity are less pronounced than that in the cyclical mastalgia.

C. Musculoskeletal pain is almost always unilateral (92%) and falls into two categories: Tietze's syndrome and lateral chest wall pain. In Tietze's syndrome, typically, the pain is felt within the medial quadrants of the breast and tenderness occurs on pressure over the affected costochondral junction.

Evaluation

The evaluation of mastalgia begins with a thorough history of pain, including the duration, site, severity, relationship with the menstrual cycle, and impact on everyday life. In non-cyclical mastalgia, the chest wall should be carefully palpated to exclude extramammary causes of the pain.

Etiology

Cyclical and non-cyclical mastalgia differ in the characteristics suggesting distinct etiology between these two forms.

Cyclical mastalgia is most severe before menstruation; therefore, a hormonal imbalance is suspected. Various theories were put to describe etiology of cyclical mastalgia. One of the earliest being edema due to water retention but Preece *et al*.[20] Later, the three hormonal theories were regarded as the etiology of mastalgia.

a. Increased estrogen secretion from the ovary
b. Deficient progesterone production (relative hyperestrogenism) and
c. Hyperprolactinemia.

The first two theories did not stand as earlier studies showed that there was no difference in the hormonal levels between the patients and the controls. A small but statistically significant difference in the prolactin levels between women with cyclical mastalgia and controls was recorded in a study, in which daily sampling of prolactin at a fixed time throughout the menstrual cycle was done. In a study by Peters *et al*., who examined, the stimulated prolactin response to thyrotropin-releasing hormone found that those with mastalgia had a significantly greater rise in prolactin compared to controls. However, the difference in the basal prolactin levels was not statistically significant between the groups, thus, strongly suggesting a disturbance of hypothalamic control in women with cyclical mastalgia.[21]

A definite role of ER in the pathogenesis of benign breast diseases is suspected based on a study done to estimate the value of ER. It was found that the patients with ER-positive breast disease responded better to danazol than patients with ER-negative breast disease.[22]

Possible causes of non-cyclical mastalgia include stretching of cooper's ligaments, pressure from brassiere, fat necrosis from trauma, focal/periductal mastitis, and Mondor's disease (sclerosing periphlebitis of breast veins).

Treatment of Mastalgia

Mastalgia affects both physical and mental health of patient. Apart from pain and discomfort, they are in constant fear of cancer. Therefore, the first step in treating women with mastalgia is to exclude malignancy and to counsel the patient.

Various methods have been tried for treatment of mastalgia which includes both medical and non-medical forms.

Non-medical Managements

1. Education and reassurance: The most successful treatment is the reassurance that a patient's symptom is not due to cancer. A Brazilian study verified on overall success rate of 70.2% with reassurance in a study of 85 patients with mastalgia. Reassurance was effective in 85.7% of the patient with mild form of mastalgia, in 70.8% with a moderate form, and in 52.3% with severe from
2. Well-fitting brassiere: Mastalgia may be due to active breast movement on the weak suspensory ligaments. Good external support by a sports bra can relieve most of the symptoms
3. Dietary measures: A number of dietary measures and therapies have been tried but on subsequent randomized trials have failed to demonstrate a clear advantage.

Medical Management

The drugs available for the treatment of mastalgia is topical NSAIDS, OCPs, diuretics, vitamin E, GLA, bromocriptine, tamoxifen, LHRH analogue, danazol, and the latest of them all being centchroman. All these agents have been tried with varying efficacy and side effects. There is no consensus about drug of choice for management of mastalgia.

- Topical NSAIDS: Topical application of NSAIDs was effective in mild type of mastalgia according to one study conducted in 2003, where diclofenac-diethyl-ammonium 2% gel was used.
- Oral contraceptives: OCP has been shown to have protective effect in benign breast diseases.
- Diuretics: There is no rational basis for the use of diuretics in the treatment of breast pain, which was demonstrated by the lack of correlation between retention of body water and symptoms.
- Vitamin E: Three RCTs had been conducted, all of which showed that vitamin E was no better than placebo in the treatment of benign breast disease.[23-25]
- GLA
- Evening primrose oil (EPO) had been introduced into the management of mastalgia based on the fatty acid deficiency hypothesis. It is rich in 7% linoleic and 72% linoleic acid which represent the richest natural source of essential fatty acids. Many trials have showed beneficial effects in mild and moderate mastalgia.[26] GLA is an essential polyunsaturated fatty acid (PUFA) present in large quantities in EPO. Low levels of the metabolites of GLA were found in women with cyclical mastalgia. As PUFA is denatured in the body by oxidation, adding antioxidants to PUFA were thought to enhance clinical response of PUFA. A Cardiff University study in 2005, on patients with mastalgia treated with GLA and placebo concluded that GLA efficacy did not differ from placebo, regardless of whether antioxidant vitamins were present.
- Bromocriptine: According to two different studies, significant reduction of cyclical mastalgia has been observed with bromocriptine 5 mg daily when compared to placebo.[27] It blocks the release of prolactin from the pituitary gland by dopaminergic receptor stimulation. In most women severe side effects have been noted, the commonest being nausea, vomiting, dizziness, headache, and postural hypotension. This could be overcome by increasing the drug doses gradually, and avoiding higher doses.
- Tamoxifen: A daily dosage of tamoxifen 10 mg has proven beneficial in both cyclical and non-cyclical mastalgia, with 98% and 56% response rates, respectively, according to a double blind study.[28] Side effects of short-term treatment characteristically include hot flashes, menstrual disturbances, weight gain, nausea, vaginal dryness, and bloating. A few rare yet serious side effects such as thromboembolic events, endometrial cancer, and cataracts have been reported in the literature; but their incidence in short-term, low-dose treatment regimens for mastalgia, is unknown.
- LHRH analog: In a randomized multicenter study on 147 premenstrual women with mastalgia treated with goserelin (LHRH analog) injection 3.6 mg/month for 6 months showed better outcome when compared to the placebo. Side effects include vaginal dryness, hot flushes, decreased libido, oily skin or hair, and a decrease in breast size which was more frequent than patients treated with placebo, thus making it the last resort in most of the refractory cases.[29]
- Danazol: Greenblat and co-workers introduced Danazol in 1971. Danazol is a synthetic testosterone which binds to progesterone and androgen receptors, but the precise mechanism of action in the treatment of mastalgia is unknown. It is a weak androgen, the isoxazole derivative of 17-a-ethinyl testosterone.

It acts at the hypothalamic level to prevent the rise in gonadotropins that would normally occur when estrogen and progesterone levels are low, without affecting basal gonadotropin concentrations. It interferes with FSH and luteinizing hormone at high doses. Thereby, it results in a low luteal progesterone level (suggesting anovulation) during treatment.[30] The usual dose of danazol in treatment of mastalgia is 100–400 mg per day. It has side effects such as amenorrhea and various androgenic effects such as weight gain, acne, and hirsutism. It is also a proven potential teratogen.

- Centchrom: Centchroman ($–C_{30}H_{35}NO_3$) is a novel non-steroidal, SERM, anticancer, and anti-osteoporotic drug, formulated by the Central Drug Research Institute, Lucknow, India. It was included in the National Family Welfare Program in 1995 as a "once a week pill." Since the early 1990s in India, centchroman has been available as birth control pill, and it is currently marketed there under the trade name Saheli. Centchroman binds competitively to the ERs and antagonises estrogen-induced gene expression. It shows weak estrogen agonistic and potent antagonistic activities but is devoid of progestational, androgenic, and antiandrogenic activities. Centchroman is free from side effects such as nausea, vomiting, weight gain, and dizziness. It does not delay return of fertility (after stopping) as it does not disturb ovulation and maintains normal ovulatory cycles. Centchroman has no apparent adverse effects on endocrine, hematologic, liver, and lipid function and has not been associated with any serious complications. After stopping this drug, there is an early return of fertility; therefore, it is safe in the treatment of unmarried women and those who wish to conceive after treatment. No teratogenic effect has been observed yet.

CONCLUSION

This study shows that both centchroman are very drug for treatment of mastalgia with minimal and less severe side effects. It also shows less recurrence and patient is more compliant due to easy dosage.

REFERENCES

1. Cooper A. Illustrations of the Diseases of the Breast. Part 1. London, England: Longman, Rees, Orme, Brown and Green; 1829.
2. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. Mayo Clin Proc 2004;79:353-72.
3. Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of Mastalgia: A meta-analysis of randomised trials. Breast 2007;16:503-12.
4. Daverey A, Saxena R, Tewari S, Goel SK, Dwivedi A. Expression of estrogen receptor co-regulators SRC-1, RIP140 and NCoR and their interaction with estrogen receptor in rat uterus, under the influence of ormeloxifene. J Steroid Biochem Mol Biol 2009;116:93-101.
5. Bansal V, Bansal A, Bansal AK. Efficacy of SEVISTA (ormeloxifene) in treatment of mastalgia and fibrocystic breast disease. Int J Reprod Contracept Obstet Gynecol 2015;4:1057-60.
6. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg 2007;31:1178-84.
7. Dhar D, Anand S, Sarkar D, Mukherjee SK, Paira SK, Mukherjee R. A comparative study of centchroman vs tamoxifen in the management of mastalgia and fibroadenoma. Int J Sci Res 2018;7:33-6.
8. Karwasra R, Batra R, Ranga HR. Centchroman vs danazol for regression of cyclical mastalgia: A randomized control trial. Int J Enhanc Res Med Dental Care 2016;3:18-22.
9. Kumar VK, Hasan A. Observation on role of centchroman versus danazol in treatment of benign breast disorder. Int J Sci Res 2017;6:683-5.
10. Mohakul SK, Guttala S, Tiru P. Role of ormeloxifene (centchroman) in benign mastalgia of diverse origin. Women's Health Gynecol 2017;3:1-8.
11. Shrivastava A. Efficacy and safety of ormeloxifene in regression of mastalgia associated with fibrocystic disease of breast. Int J Sci Res 2017; 6:1-2.
12. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, Thulkar S, *et al*. Centchroman regresses mastalgia: A randomized comparison with danazol. Indian J Surg 2011;73:199-205.
13. Uma K. Refractory mastalgia or inadequately treated mastalgia? Indian J Surg 2004;66:89-92.
14. Barros AC, Mottola J, Ruiz CA, Borges MN, Pinotti JA. Reassurance in the treatment of mastalgia. Breast J 1999;5:162-5.
15. Jain BK, Bansal A, Choudhary D, Garg PK, Mohanty D. Centchroman vs tamoxifen for regression of mastalgia: A randomized controlled trial. Int J Surg 2015;15:11-6.
16. Neogi P, Manwatkar S, Singh SK, Kola A, Imran Q, Katyayan I, *et al*. A comparative study of centchroman, tamoxifen and danazol in management of cyclical mastalgia. Int Surg J 2019;6:365-8.
17. 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. Natl Med J India 2013;26:69-74.
18. Makker A, Tandon I, Goel MM, Singh M, Singh MM. Effect of ormeloxifene, a selective estrogen receptor modulator, on biomarkers of endometrial receptivity and pinopode development and its relation to fertility and infertility in Indian subjects. Fertil Steril 2009;91:2298-307.
19. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr., Rados MS, *et al*. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med 1994;331:10-5.
20. Preece PE, Richards AR, Owen GM, Hughes LE. Mastalgia and total body water. BMJ 1975;4:498-500.
21. Peters F, Pickardt CR, Zimmerman G, Breckwoldt M. PRL, TSH and thyroid hormones in benign breast disease. Klin Wochenschr 1981;59:403-7.
22. Hughes LE, Mansel RE, Webster DJ, editors. Breast pain nodularity. In: Benign Disorders and Diseases of the Breast: Concepts and Clinical Management. 2nd ed. London: W. B. Saunders Company; 2000. p. 95-121.
23. London RS, Sundaram GS, Murphy L, Manimekalai S, Reynolds M, Goldstein PJ. The effect of Vitamin E on mammary dysplasia: A double-blind study. Obstet Gynecol 1985;65:104-6.
24. Ernster VL, Goodson WH 3rd, Hunt TK, Petrakis NL, Sickles EA, Miike R. Vitamin E and benign breast-disease: A double-blind, randomized clinical trial. Surgery 1985;97:490-4.
25. Meyer EC, Sommers DK, Reitz CJ, Mentis H. Vitamin E and benign breast disease. Surgery 1990;107:549-51.
26. Pashby NL, Mansel RE, Hughes LE. A clinical trial of evening primrose oil in mastalgia. Br J Surg 1981;68:801.
27. Nazli K, Syed S, Mahmood MR, Ansari F. Controlled trial of the prolactin inhibitor bromocriptine (Parlodel) in the treatment of severe cyclical mastalgia. Br J Clin Pract 1989;43:322-7.
28. Fentiman IS, Caleffi M, Brame K, Chaudary MA, Hayward JL. Double-blind controlled trial of tamoxifen therapy for mastalgia. Lancet 1986;1:287-288.
29. Mansal E, Goyal A, Preece P, Leinster S, Maddox PR, Gateley C, *et al*.

European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. Am J Obstet Gynecol 2004;191:1942-9.

30. Greenblatt RB, Dmowske WP, Mhesh VB, Scholer HF. Clinical studies with an antigonadotrophin-Danazol. Fertil Steril 1971;22:102-12.

How to cite this article: Najim M, Mukhopadhyay B, Islam MS, Singh AK, Sasmal A. Determining the Efficacy of Centchroman in Treatment of Mastalgia. Int J Sci Stud 2023;11(1):26-33.

Source of Support: Nil, **Conflicts of Interest:** None declared.