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Centchroman Regress Mastalgia and Fibroadenoma: An Institutional Study

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Abstract
Objectives: *Centchroman (also known as Ormeloxifene) is one of the selective estrogen receptor modulators, or SERMs, a class of medication which acts selectively on the estrogen receptor. Because of its selective antiestrogen action, centchroman has been used for treatment of mastalgia and fibroadenoma.*
Materials And Methods: *Benign breast disease patients up to 35 years of age attending surgery outpatient department from August 2012 to September 2014 and fulfilling inclusion criterion were included in the study. The patients were started on centchroman 30 mg on daily for a period of 12 weeks and were followed at weeks 4, 8, 12, and 24 to assess response to therapy. The Results were recorded as per clinical examination, ultrasonography for breast lump size and visual analog scale (VAS) for pain.*
Results: *A total of 130 patients were included in the study, 88 (67.70%) of whom had mastalgia with or without nodularity, and 42 (32.30%) had fibroadenoma. Noncyclical pain was in 71 patients (80.70%), and cyclical pain was recorded in only 17 (19.30%) patients. A VAS score of 10 was recorded by 62 (70.50%) patients (severe pain), and the remaining 26 patients (29.50%) had VAS score from 7 to 10. Fibroadenoma size ranged from 1.5 to 5 cm, single or multiple in one or both breast. There was a good response in the mastalgia group, with a decrease in the VAS scoring from 10 to 3 in 69 (78.40%) of the patients in the first week. Almost all of the patients were painless at the end of first month, with complete disappearance of the nodularity. In the fibroadenoma group there was a mixed response, with complete disappearance in 21 (35%), partial regression (decrease in volume of fibroadenoma) in 29 (48.30%) and no response at all in the remaining 10 (16.70%) a period of 6 months. There were few side effects with scanty menses or amenorrhea as the only side effect.*
Conclusions: *Centchroman is a safe drug for the treatment of mastalgia and fibroadenoma. It has shown good results in mastalgia and fibroadenoma, is an effective, safe and inexpensive.*
Key Words: *Fibroadenoma, Centchroman, Saheli.*

Introduction

Mastalgia is one of the most common benign conditions of the breast. Mastalgia may be cyclic or non-cyclic, intermittent or constant, localized or diffuse. The pattern and severity of pain can be assessed by breast pain chart.[1] Cyclical mastalgia is defined as breast pain with either only premenstrual exacerbation or pain throughout the month with premenstrual exacerbation. Non-cyclical mastalgia is defined as intermittent or continuous breast pain without premenstrual exacerbation and no obvious source of

musculoskeletal disease means it can be true i.e arising from breast tissue or it can arise from chest wall e.g Tietze's syndrome and lateral chest wall pain. During luteal phase of menstruation, cell proliferation of ductolobular tissue and interstitial fluid increase result in up to 15% increase in breast size and volume. Increase in breast tissue volume results in pressure on pain nerve endings causing premenstrual pain. Just prior to menstruation the estrogen and progesterone levels fall with reducing cellular proliferation in the early follicular phase and consequent relief of pain and engorgement.[2]

Other different hypotheses for mastalgia suggest that it may be caused by either increased estrogen secretion from ovary or deficient progesterone production or increased Prolactin secretion.[3] Different pharmacological agents have been tried in the therapy of mastalgia. The drug therapy includes agents that induce hormonal manipulation such as Danazol, Bromocriptine, Tamoxifen, and LH-RH analogue. Some of the effective non-hormonal agents in mastalgia are Non- steroidal anti-inflammatory gels, reassurance and breast support with sport's bra.

There is considerable debate about drug of choice for management of mastalgia. We present our results of antiestrogen drug "Centchroman". It is best known as a non-hormonal, non-steroidal oral contraceptive which is taken once per week. In India, ormeloxifene has been available as birth control since the early 1990s, and it is currently marketed there under the trade name Saheli. The objective of the study was to evaluate the effectiveness of Centchroman in control of mastalgia measured by visual analogue scale (VAS), and ultrasonography for breast lump.

Patients and Methods

The patients were provided with a detailed printed information sheet (in Hindi or English depending on the language understood by her) to explain about benign nature of breast pain, the currently available therapy with side effects, the potential benefits of Centchroman and its common use by Government of India as a contraceptive pill. 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.

Benign breast disease 130 patients up to 35 years of age attending surgery outpatient department from August 2012 to September 2014 and fulfilling inclusion criterion were included in the study. The patients were started on centchroman 30 mg on daily for a period of 12 weeks and were followed Sat weeks 4, 8, 12, and 24 to assess response to therapy. The results were recorded as per clinical examination, ultrasonography for breast lump size and visual analog scale (VAS) for pain.

Results

A total of 130 patients were included in the study, 88 (67.70%) of whom had mastalgia with or without nodularity, and 42 (32.30%) had fibroadenoma. Noncyclical pain was in 71 patients (80.70%), and cyclical pain was recorded in only 17 (19.30%) patients. A VAS score of 10 was recorded by 62 (70.50%) patients (severe pain), and the remaining 26 patients (29.50%) had VAS scores from 7 to 10 (Table 1). Fibroadenoma size ranged from 1.5 to 5 cm, single or multiple in one or both breasts. Patients with fibroadenoma equal to or larger than 5 cm and with polycystic ovarian disease were excluded There was a good response in the mastalgia group, with a decrease in the VAS scoring from 10 to 3 in 69 (78.40%) of the patients in the first week. Almost all of the patients were painless at the end of one month, with complete disappearance of the nodularity (Fig.1). In the fibroadenoma group there was a mixed response, with complete disappearance in 21 (35%), partial regression (decrease in volume of fibroadenoma) in 29 (48.30%) and no response at all in the remaining 10 (16.70%) a period of 6 months (Fig. 2). There was amenorrhea or scanty menses as the only side effect.

Table1. Demographic characteristics of the breast cancer

Characteristic		Total patients
		N=130 (%)
Age (years)		
Median (16-40)	**≤20**	13 (10.00%)
	21-30	87 (67.00%)
31-35		30 (23.00%)
Disease profile		
Mastalgia with or without nodularity		88 (67.70%)
Fibroadenoma		42 (32.30%)
Symptoms (Pain)		
Unilateral		76 (.70%)
Bilateral		12 (.70%)
Cyclical pain		
Yes		71 (80.70%)
No		17 (19.30%)

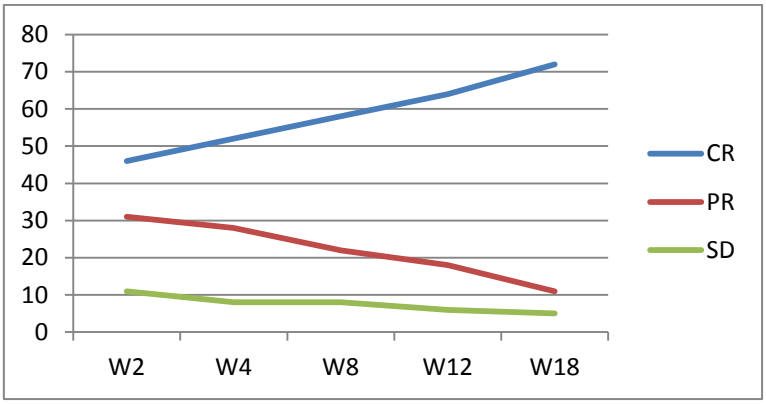

Fig 1: Response of Mastalgia to Centchroman

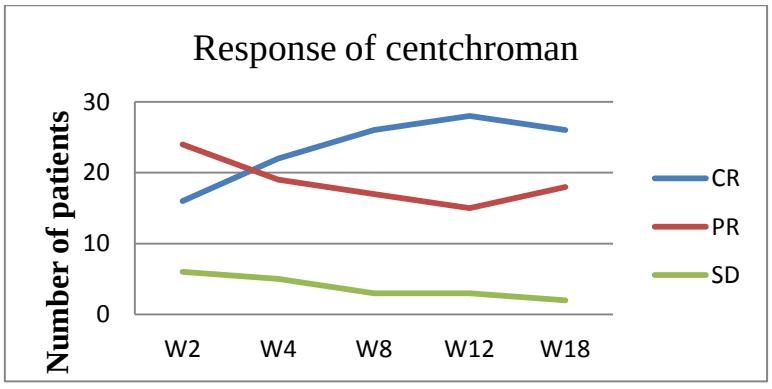

Fig 2: Response of fibroadenoma to Centchroman

Discussion

Severe breast pain/ Mastalgia interfere with the daily routine life of women and raises fear of breast cancer. In most patients with mild pain, reassurance means that the symptoms are not due to cancer is required. A Brazilian study verified success rate of around 70.2% with reassurance in a study of 85 patients with mastalgia. [4] The other non medical means are dietary measures i.e. fat restriction and avoidance of methylxanthines.[5] A randomized trial of 200 patients has revealed that the breast support with sport's brassier relieved the pain in 89% of patients.[6] The relief of pain with support garments provided by reducing the

tension on overstretched Cooper's ligament especially in women endowed with large mammary glands.

The drugs available for the treatment of mastalgia are Danazol, Bromocriptine, Tamoxifen, Evening Primrose Oil, LHRH analogue Goserline, oral contraceptive pills, diuretics and topical NSAIDs gels with varying efficacy and side effects. [7]

A meta-analysis on mastalgia found that Tamoxifen, Danazol, and Bromocriptine to be significantly effective in treatment of mastalgia compared with placebo.[8] However the response to Evening Primrose oil was no better than placebo. This meta-analysis suggested that antiestrogen, Tamoxifen may be the drug of choice. Bromocriptine and Danazol are best avoided because of their side effects and high cost. Also there is no evidence of benefit with Vitamin E preparations.

Greenblat and co-workers suggested that Danazol might have a role in mastalgia. Danazol is unique in its action on the pituitary ovarian axis. In monkeys Danazol was shown to act as anti-gonadotrophin, as it suppressed serum levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) and prevented ovulation. The action of Danazol is not so clearly defined in humans because it only interferes with FSH and LH levels at higher doses. The usual dose of Danazol for treatment of mastalgia is 100–400 mg per day. Danazol is a very effective agent for severe breast pain and nodularity, with an overall response rate of 70% and is superior to bromocriptine in treatment of cyclical mastalgia.[9, 10] In this study Danazol 100 mg once a day was effective in 69% cases at 12 weeks. After stopping the medication, the response rate was sustained only in 42% of cases at the end of 24 weeks. Meta-analysis of 4 randomized trials found highly significant relief of mastalgia using Danazol, as compared to placebo.[8] The adverse effect of Danazol are mainly amenorrhea, the incidence of which increases with dose up to 100% at 600–800 mg per day. It causes weight gain, acne, amenorrhea and hirsutism. Most of side effects of Danazol are dose dependent. Now a day Danazol is not commonly used in most breast clinics because of side effects and is reserved as a second line drug for mastalgia.

Tamoxifen is now considered drug of choice in most breast clinics in the West for treatment of mastalgia (under supervision for 3 months, as drug is not licenced for this use). Tamoxifen is a steroidal antiestrogen and has been found to be effective in relief of mastalgia in various randomized trials.[11–13] It has been used in dosage ranging from 5 mg–20 mg/ day for a period of 12 weeks. In a meta-analysis the overall relief of pain achieved with Tamoxifen compared to placebo had a relative risk (RR) of 1.92 (95% CI; 1.42–2.58) which was highly significant with $p < 0.0001$.[8] Tamoxifen is a very well tolerated drug at low dosage of 10 mg daily for 3 months, with minimal side effects. However use of Tamoxifen may be associated with hot flashes, vaginal dryness, low libido, mood swings, nausea and rarely fluid retention. Centchroman is a novel non-steroidal, selective estrogen receptor modulator, 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".

Centchroman has a weak estrogen agonistic activity in some tissues like bones, and potent anti-estrogenic action in uterus and breast. It is devoid of progesterone, androgenic and anti-androgenic activities.[14] Centchroman is free from adverse effects like nausea, vomiting, weight gain and dizziness. Centchroman does not disturb ovulation as it does not delay return of fertility (after stopping). It has only one adverse effect, delayed menses in less than 10% of cycles. It maintains normal ovulatory cycles. Centchroman has no apparent adverse effects on endocrine, hematologic, liver and lipid function and, to date, has not been associated with any serious complications viz. heart attack, stroke or thrombosis.[15–18]

Centchroman is well absorbed when given orally and single 30 mg dose results in maximum serum concentration of 30 to 78 ng/mL in 3 to 8 hours. In nursing mothers, the drug is well absorbed with maximum serum concentration of 50 to 79 ng/ ml achieved in 6 hours. The drug is widely distributed throughout the body due to high lipid solubility. The mean residence time of Centchroman was found to be 128 days. It binds strongly with serum albumin. The drug does not compete with cortisol, oestradiol, progesterone, diethylstilbosterol, testosterone and tamoxifen. In target tissues such as endometrium and breast, it competes with estradiol for binding to estrogen receptors and shows an anti-estrogenic activity. The drug is demethylated and about 26% is excreted unchanged in faeces. [18]

Centchroman is an easily available and economic drug therapy of mastalgia (Trade name SAHELI by Hindustan Latex Ltd. usual price Rs 2 per 30 mg tablet per day as compared to Danazol costing Rs 15 or more for 100 mg per day). In the initial enrolled patients Centchroman was given as 30 mg on alternate days to 59 patients with significant pain relief. The frequency of dosage was later increased to once daily; as there were no major side effects seen and some women missed doses with alternate day therapy. Hence to improve compliance and effect, in latter part of study it was given as 30 mg once a day to 71 patients. The initial response was more pronounced when Centchroman was administered on daily basis as compared to alternate day regimen.

In randomized trial combining both alternate and daily dosage, Centchroman was found to have response rate of 89.7 % (reduction of pain to less than or equal to 3 on VAS). At the end of 12 weeks, Danazol achieved 69.44% response rate at 12 weeks. A higher proportion of women in Centchroman group continue to pain free life even after stopping the drug, suggesting a longer carry-over effect. Thus the probability of remaining pain free at 6 months was 71% with Centchroman and 42% with Danazol. The response of pain relief was 29% better with Centchroman at 24 weeks (71%-42% = 29%). The trial has demonstrated that this drug is not inferior to Danazol. However, we cannot claim the superiority of Centchroman. There is a need to launch a larger trial in many centres to control commonest breast symptom, based on a Superiority hypothesis.

In various study, Centchroman scores over Tamoxifen in being non-steroidal molecule hence devoid of steroid like side effects in the long term therapy. It is also cheaper than Tamoxifen and Danazol. Moreover, there are no reports of endometrial carcinoma or thromboembolic side-effects with long term use of Centchroman as compared to Tamoxifen.

Bromocriptine and evening primrose oil have been shown to be effective therapies for mastalgia in European studies.[27] Favorable responses as high as 92% for cyclic and 64% for noncyclic mastalgia have been reported but sequential therapies may be required. Only danazol is Food and Drug Administration-approved (FDA-approved) for the treatment of mastalgia till date. The initial dose is 100 mg orally twice per day continued until the patient has symptomatic relief, and then the dose usually can be decreased and remain effective. Unfortunately, many women using danazol experience bothersome side-effects (such as hot flushes, acne, amenorrhea, weight gain, hirsutism, and masculine voice) and discontinue therapy. A breast pain chart for daily monitoring of the occurrence and intensity of the mastalgia before, during, and after treatment is useful in documenting the results of therapy.[19]

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