

## Comparison of effectiveness among Centchroman, Danazol & Evening primrose oil for the management of mastalgia in benign breast diseases

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**Introduction:** Most women who present at the breast clinics have benign breast conditions which range from nonspecific breast pain to discrete lumps such as fibroadenoma. The term "benign breast diseases" encompasses a heterogeneous group of lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations and neoplasm. Quantifying breast pain may be difficult because of its variability.

**Aims and objectives** To estimate and compare the proportion of patient relieved from mastalgia in three groups using each drug separately. To compare the effect of three medicines in reducing the size of nodularity of benign breast diseases. To find out the extent of compliance and pattern of adverse events among three group of patients. To ascertain the cost effectiveness of therapy between the above mentioned therapeutic options.

**Materials and method** Quasi experimental Randomized clinical trial undertaken on 120 patients who were clinically suspected of having mastalgia with or without nodularity and were randomized into 3 groups: Group 1 Centchroman {30 mg twice weekly for 3 months}, Group 2 Danazol {50 mg bid for 3 months} Group 3 Evening Primrose Oil {100mg bid for 3 months} in single surgical unit in the Department of General Surgery, BSMCH, Bankura between February, 2017 to July, 2018

**Conclusion** Centchroman, is a better option compared to Danazol and Evening Primrose Oil for the management of mastalgia in terms of relief of clinical manifestations, side effects and cost-effectivity.

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### I. Introduction

Most women who present at the breast clinics have benign breast conditions which range from nonspecific breast pain to discrete lumps such as fibroadenomas. The term "benign breast diseases" encompasses a heterogeneous group of lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations and neoplasms. That may present a wide range of symptoms generally undetected or may be detected incidentally during screening mammography or in the microscopic findings of surgical specimens for cancer. Breast pain which is termed as mastalgia or mastodynia in literature is one of the most common symptom of which the aetiology and treatment have not been fully clarified BREAST PAIN ASSESSMENT Quantifying breast pain may be difficult because of its variability[6,7]. Before starting any therapy for breast pain, patients should be asked to document the frequency and severity of their pain on daily basis for at least one menstrual cycle using a visual analog scale.

### II. Aims & Objectives Aim Of The Present Study

□ Mastalgia, with or without nodularity, is a common disorder affecting women and is usually corrected by reassurance and dietary & lifestyle changes. Occasionally mastalgia becomes an incapacitating problem and necessitates analgesics and other pharmacological agents. The present study will be an attempt to evaluate the effectiveness of oral Centchroman in relief of mastalgia. The results will be compared with the oral administration of Danazol & Evening Primrose Oil by quasi experimental randomized clinical trial. The cost effectiveness between the three mentioned therapies will also be compared. The study will be undertaken to formulate a standard protocol for a common but bizarrely managed problem among women of reproductive age group

### **SPECIFIC OBJECTIVES**

1. To estimate and compare the proportion of patient relieved from mastalgia in three groups using each drug separately.
2. To compare the effect of three medicines in reducing the size of nodularity of benign breast diseases.
3. To find out the extent of compliance and pattern of adverse events among three group of patients.
4. To ascertain the cost effectiveness of therapy between the above mentioned therapeutic options.

### **III. Materials & Methods**

This was a randomized clinical trial undertaken on 120 patients who were clinically suspected of having benign breast diseases and were randomized into 3 groups: Group 1 Centchroman {30 mg twice weekly for 3 months}, Group 2 Danazol {50 mg bid for 3 months} Group 3 Evening Primrose Oil {1000mg bid for 3 months} in single surgical unit in the Department of General Surgery, BSMCH, Bankura in collaboration with Department of Radiology between February, 2017 to July, 2018 among premenopausal patients attending surgery outdoor with persistent mastalgia (with or without lump even after 3 months of initial reassurance and dietary modification starting from their first visit, and fulfilling the inclusion criteria. we conducted a Randomized clinical trial of Single blind Type: Quasi experimental Superiority / Equivalence trial taking a sample size of 120 patients, 3 groups - in each 40 patients. Sample size for the randomized control trial has been calculated by using RCT formulae of sample size  $N$  (for each arm) =  $(Z\alpha + Z\beta)^2 \times (P1Q1 + P2Q2) / d^2$ , where  $N$  = sample size for each group,  $Z\alpha = 1.65$  at 5% precision (one tail),  $Z\beta = 0.84$  at 80% power,  $P2$  = prevalence of relief of mastalgia after treatment with other drugs, Danazol &  $P1$  = prevalence of relief of mastalgia after treatment with centchroman,  $d$  = effect size for getting optimum clinical benefit = 20. Value of  $P1 = 69.44$ ,  $P2 = 89.7$ , taken from the journal Tejwani et al. [4] Putting all the values in this equation, the sample size for the proposed study =  $N = 41$ . Now, assuming 10% drop out this value will be  $n = 40$  for each of the study arms. Data collection was done once in a week for ten months i.e. 43 weeks. So total attendance during the period of data collection 860 out of which 120 was selected randomly. Study subjects were included per week  $120/43 = 03$  (approx). These three study subjects were selected from 20 weekly attendances. 3 patients were selected out of 20 anticipated attendances following a systemic random sampling. So, sampling interval is  $20/3 = 7$  (approx.), i.e., every 7th patient were selected. Study was done unbiased by the help of simple random sampling on the starting day of data collection. A random number was  $\leq 7$ th and already attended patients were numbered serially. Then out of them the 1st subject was chosen as per random number via simple random sampling. This way 3 patients were selected on each day of data collection on an interval of every 7th selection till 120 patients were selected.

### **INCLUSION CRITERIA**

1. Premenopausal women in the age group of 15 – 45 years, willing to participate in the study.
2. Chief complaint of mastalgia (cyclical or non cyclical) of benign breast diseases.
3. All those patients who do not have any malignant breast disease, dysplastic lesion of breast, simple breast cyst, infective breast changes (mastitis, breast abscess), fibroadenoma (>5 cm), PCOD, cervical hyperplasia etc. after confirming clinically, radiologically and histopathologically.
4. Patient complaining of breast pain with or without nodularity for more than 3 months duration.
5. Pain severity >3 on VAS.

### **EXCLUSION CRITERIA**

1. Patients unwilling to enroll herself in the study,
2. Patients who are responding with initial reassurance and dietary modification.
3. All patients with malignant diseases of breast (breast carcinoma)
4. Dysplastic lesions which mandate compulsory surgical intervention,
5. Simple breast cyst and infective breast changes (e.g.: breast abscess, mastitis)
6. Fibroadenoma of more than 5 cm size,
7. Patient desirous of removing the lump (if lump is present with mastalgia)
8. Contraindications to oral centchroman, danazol and evening primrose oil.
9. Polycystic ovarian disease and cervical hyperplasia
10. Lactation and pregnancy
11. Patient on OCP for last 3 months
12. Patient receiving HRT.
13. Pain severity < 3 on VAS.

14. Patient complaining of breast pain with or without nodularity for less than 3 months duration.

**STUDY VARIABLES:**

1. Measurement of pain perception (Visual Analogue Scale). 2. Measurement of lump (if present)- Clinically (Lucknow-Cardiff Scale) and by USG. 3. Occurrence of various side effects. 4. Assessment of cost of therapy per month.

**IV. Data Collection And Interpretation:**

Allocation of patient in the study arms:

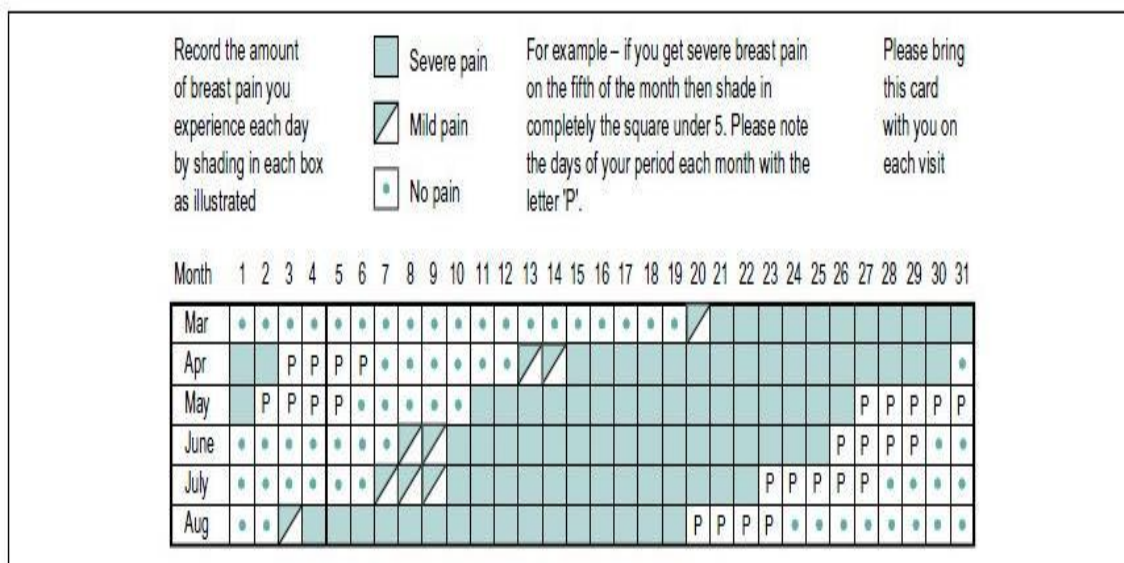
Types of mastalgia either cyclical or non cyclical were randomly distributed in all the three groups.

Group I – Those receiving Centchroman 30 mg biweekly for 3 months.

Group II – Those receiving Danazol 50 mg bid for 3 months.

Group III – Those receiving Evening Primrose Oil (EPO) 1000 bid for 3 months.

For this study, we assumed Group II is the control group and Group I and Group III as group so that we can compare between these three treatment modalities individually with respect to each other. For the first 12 week patient were under drug treatment and for the next 12 week without medication to assess response and recurrence to mastalgia and breast nodularity. All results were evaluated at the end of 4 week, 8 week, 12 week and 24 week for which VAS and lump size (if present) are to be recorded. The patients were provided with a printed sheet with detailed information in Bengali, Hindi or English according to their vernacular. The information sheet explained about the benign nature of the breast pain and nodularity and the currently available therapies with their possible side effects and potential benefits of all the three agents under trial in this study. An informed consent was obtained from each patient after explanation of the various aspects of the trial in mother tongue of patient (Bengali or Hindi or English). All patients were evaluated by ultrasound if clinically warranted to exclude breast lump, malignancy, polycystic ovarian disease and cervical hyperplasia. Polycystic ovarian disease and cervical hyperplasia are excluded as it gets aggravated by centchroman. Pain score was recorded on a visual analogue scale (VAS) from 0 to 10 (0 indicating minimum pain perception and 10 maximum pain perception). After an initial clinical assessment and breast ultrasound & FNAC (in presence of a lump), patients were asked to keep a record of their breast pain in the provided “breast pain chart” on a day to day basis. The menstrual periods were also recorded on pain chart. Breast nodularity was also measured in Lucknow-Cardiff Scale. Initially all the patients were treated with reassurance, dietary modification and breast support and if the symptoms still persisted 3 months, then patients were put on trial.



Pain chart of a patient with cyclical pronounced mastalgia showing 2–3 weeks of severe premenstrual mastalgia per cycle over 6 months.

Diagram showing Breast pain chart with cyclical pain The main outcome of interest in those groups was relief of breast pain which were measured by the VAS of 0–10 at 1 week to assess the drug tolerance, and followed at the end of 4 week, 8 week, 12 week and 24 week. The outcome in patients with lump was assessed by measuring regression in size of the lump by Lucknow-Cardiff Scale and with the help of serial ultrasound at the beginning, at the end of 4 week, 8 week, 12 week and 24 week.

## V. Discussion

Benign breast disease encompasses a spectrum of conditions that range from normal to disorder to disease. ANDI classification includes this spectrum and classifies it according to age their presentations. Mastalgia with or without nodularity is one of the commonest presentation of ANDI in OPD. This study was conducted on a total of 120 patients whose age ranged from 20 to 50 years among which the largest number of patients 72(60%) belong to 20-30 years of age. Earlier study of Dhar et al.[13] in 2007 shows that 40 % patients having these symptoms were between 21-30 years of age. Hence benign breast disease is more common in younger age group. Out of our 120 patients, 88 (73.33%) patients were married with 2 or more than 2 issues, 76 (63.33%) patients had menarche at the age of 13-14 years. Breast pain was the presenting symptom in each 120 patients among which cyclical mastalgia was observed in 30 (25%) patients and non cyclical pain in 90 (75%) patients where as fibroadenoma was observed in 30 (25%) patients and nodularity was observed in 80 (66.66%) patients. Three hormonal theories emerged regarding the aetiology of painful nodular breasts: (1) Increased estrogen secretion from the ovary (2) Deficient progesterone production – “Relative hyperestrogenism” (Sitruk-Ware R et al. 1979) [9](3)Hyperprolactinemia. One further study of daily sampling of prolactin in fixed time throughout the menstrual cycle conducted by Cole et al.[10] in 1977 which revealed a small but statistically significant difference between women with cyclical pain and controls. In 1981, Pashby et al. [6] conducted a study of 73 patients with painful breast investigated in randomized double blind cross over study in which Evening Primrose Oil was given orally over three months and pre trial LAS (Linear Analogue Scale) for pain rating in EPO group LAS was 50 in cyclical pain group and 54 in non cyclical pain group. In placebo group, LAS was 45 in cyclical pain group and 56 in non cyclical pain group. After 3 month of treatment in EPO group LAS was 32 in cyclical mastalgia and 40 in non cyclical mastalgia. In placebo LAS after 3 months was 42 in cyclical mastalgia group and 60 in non cyclical mastalgia group. This study concluded EPO reduces pain in non cyclical group ( $p < 0.05$ ) and less marked in cyclical group. In our study, baseline mean VAS was  $4.95 \pm 0.893$  in Centchroman,  $5.13 \pm 0.842$  in Danazol and  $5.23 \pm 0.851$  in EPO group. In Evening Primrose Oil group after starting the treatment mean VAS was  $4.00 \pm 1.432$  at 1 month,  $2.5 \pm 1.732$  at 3 months and  $4.9 \pm 1.640$  at 6 months (after stopping Evening Primrose Oil for 3 months). From study it is evident that significant reduction of pain (VAS) present after starting of Evening Primrose Oil in between 0 and at 1, 3 months indicating good response of drugs in decreasing breast pain. But there was significant recurrence in pain (VAS) during follow up period of 3 months after stopping of drug, which indicate that Evening Primrose Oil has no long term efficacy for treatment of mastalgia. In our study there was significant reduction of pain (VAS) present after starting of Danazol in between 0 and at 1,3 months ( $p < 0.05$ ) indicating good response of Danazol in treatment of mastalgia. But there was significant increase in VAS ( $2.35 \pm 1.726$ ) at 6 months, during follow up period of 3 months after stopping of Danazol ( $p < 0.05$ ). Danazol has no long term efficacy in treatment of mastalgia. Recently published meta-analysis of randomized placebo controlled clinical trial by Srivastava A et al. [21] in 2007 on drug treatment of mastalgia included 4 common agents viz, Bromocriptine, Tamoxifen, Evening Primrose Oil (EPO) and Danazol. Weighted mean difference in pain score in favour of Bromocriptine was -16.31 (95% CI-26.35 to -6.27), Danazol had benefit mean pain score difference 20.23 (95% CI-28.12 to -12.34), EPO didn't show any advantage with mean pain score -2.78(95%CI-7.97 to -2.40) and Tamoxifen achieved a relative risk (RR) of pain relief of 1.92 (95% CI-1.42 to -2.58) with least side effects and was recommended to be the drug of first choice for treating mastalgia by the authors. In our study there is significant reduction in mean VAS after starting of Centchroman in between 0 and 1, 3 months indicating good response of Centchroman. On stopping treatment at 3 month, these patients followed up for 3 months. There was no significant increase in pain (VAS) during follow up period of 3 months after stopping of Centchroman which indicates long term efficacy of Centchroman after discontinuation of drug and patients remain pain free. At 3 months of treatment 92.5% patients had no pain, at 6 months 87.5% patients remained pain free In our study, at 12 weeks Centchroman achieved 92.5% response rate (reduction of pain to less than or equal to 3 on VAS), Danazol achieved 77.5% response rate and EPO achieved 55% response rate. At 24 weeks, Centchroman achieved 87.5% response rate, Danazol achieved 55% response rate and EPO achieved 27.5% response rate. In our study, both Centchroman and Danazol are efficacious at 1 month and 3 months of treatment, On stopping treatment at 3 month, these patients were followed up for 3 months, at 6 months there was no recurrence in Centchroman group while 30% patients had recurrence of nodularity, thereby indicating that the Danazol does not have long term efficacy while Centchroman is effective in treatment of breast nodularity. In comparison of Centchroman with Evening Primrose Oil, significant difference in decrease of nodularity at 1 month, at 3 and 6

months from starting of treatment indicating better response of Centchroman in treatment of nodularity than Evening Primrose Oil. There was significant reduction in nodularity in Danazol in comparison to Evening Primrose Oil at 3 months indicating better response of Danazol in patients with breast nodularity. During follow up period of 3 months after stopping treatment 3months there was no significant difference in both group indicating no long term efficacy of Danazol. Centchroman is economical and easily available drug for therapy of mastalgia and nodularity. Usual price Rs. 3/- per 30 mg tablet (Trade name- Saheli, Torrent pharma) as compared to Danazol costing Rs. 11/- or more per 50 mg tablet and Evening Primrose Oil costing Rs. 12.50/- per 1000 mg tablet.

## VI. Conclusion

From the above mentioned study the following important information can be concluded-

1. Mastalgia is a condition affecting females mostly in their reproductive age group .
2. Centchroman is more efficacious than Danazol and Evening Primrose Oil in providing pain relief in Mastalgia .
3. Danazol and Evening Primrose Oil provide some pain relief in both cyclical and non cyclical mastalgia .
4. The efficacy of Danazol is more in mastalgia than Evening Primrose Oil in term of pain relief.
5. For reduction of size of fibroadenoma neither Centchroman nor Danazol nor Evening Primrose Oil is more beneficial than each other.
6. Centchroman is more efficacious for regression of nodularity and prevention of recurrence than Danazol and Evening Primrose Oil as because the later two have good efficacy in regression of nodularity but also have very poor efficacy to prevent recurrence after stopping of treatment.
7. Centchroman is minimally associated with some acceptable side effects, whether Danazol is associated with frequent adverse effects and Evening Primrose Oil is also associated with few adverse effects.
8. Very high cost of Danazol and Evening Primrose Oil can render these regimens as less preferable over Centchroman which has a much wider safety profile and minimum contraindications making it suitable for use in a larger population of patients with mastalgia. Thus it can be concluded that Centchroman is economical, effective with minimal side effect for treatment of mastalgia and nodularity mainly with fibroadenoma to some extent in benign breast disease. Although a longer follow up period is necessary to prove its long term efficacy.

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