Section: General Surgery

Original Research Article

COMPARISON OF CENTCHROMAN, TAMOXIFEN AND EVENING PRIME ROSE OIL IN REGRESSION OF MASTALGIA, IN CORRELATION WITH ER, PR STATUS

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Received : 09/11/2023
Received in revised form : 30/12/2023
Accepted : 16/01/2024

Keywords:
Mastalgia, centchroman, Tamoxifen, Evening prime Rose oil, Breast pain.

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DOI: 10.47009/jamp.2024.6.1.141

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 715-720

Abstract

Background: Mastalgia (breast pain) is most common symptoms among reproductive age group and annually about 2,00,000 patients reported with mastalgia. Mastalgia may be severe enough to disturb the routine daily activities for woman. Several drugs and treatment options has been tried with variable success rates. We planned to conduct this study to compare the regression of pain in three groups of patients with mastalgia using each drug (Centchroman, Tamoxifen and Evening prime rose oil) separately and to compare the effect of three drugs on regression of nodularity of benign breast disease, adverse effects and cost effectiveness of the drugs. **Materials and Methods:** Patient presenting with mastalgia who satisfy the inclusion criteria were taken for the study. Detailed history and clinical examination were done and the Pain scores were assessed at first visit. Imaging and core needle biopsy were done for diagnosis and receptor status. Patient were randomly divided in to three groups A, B,C and the following drugs were given to them: Group A – centchroman (30 mg OD) ,Group B – Tamoxifen (10 mg OD),Group C – Evening prime rose oil(1gm TDS) were given for 12 weeks. Pain scores and regression of nodularity were assessed during the follow up visits at 1,4,8,12 and 24 weeks. **Result:** ?. **Conclusion:** Centchroman, tamoxifen and evening prime rose oil had effect on reduction of pain as well as nodularity among mastalgia patients. Centchroman remains the better drug in pain alleviation and regression of nodules in our study.

INTRODUCTION

Breast pain or mastalgia is one of the common clinical conditions for which women visit the surgical outpatient department. Around 60 to 70 % of women experience some degree of breast pain during their reproductive period and in 10 to 20 % of cases, it is estimated as severe pain.[1] Mastalgia may be unilateral or bilateral and commonly affects the women of 30-50 years of age. Apart from hormonal factors, the pathophysiology of mastalgia is complex associated with a number of illnesses, including high levels of stress and anxiety, depression, chronic myalgia, irritable bowel syndrome, chronic pelvic pain, and other psychiatric diseases.[2] Increased estrogen, decreased progesterone levels, or alterations in the estrogen/progesterone ratio and increased prolactin are some hormonal factors responsible for breast pain. Mastalgia is classified as cyclical mastalgia, noncyclical mastalgia and non-specific extra-mammary pain.[3] Cyclic mastalgia is characteristically related to the menstrual cycle whereas non-cyclic pain is not related to the menstrual cycle which is unilateral and most commonly seen in women of 40-50 years of age. The fear of breast cancer and the presence of severe pain are the major concerns of patients presenting with mastalgia.

Breast pain is not a key symptom in breast cancer and the prevalence of breast cancer in patients presenting with breast pain is reported to be 0-3.2%.[4] But when pain is severe and persistent, it interferes with the women's everyday activities and may significantly impair their quality of life. Hence breast pain requires thorough assessment and proper investigation in the same manner as any other breast symptom.[5] Depending on the severity and chronicity, many therapy approaches have been tested for the efficient treatment of mastalgia. Reassurance and management with medical management are

ISSN (O): 2687-5365; ISSN (P): 2753-6556

considered as treatment of choice. There are several drugs used in the current practice for mastalgia. Some of the drugs used for mastalgia are Evening prime rose oil, oral contraceptives and hormone replacement therapy (HRT) on breast pain is common nowadays.[6] Many studies have been conducted to show the effectiveness of various drugs in reducing the breast pain. Hence this study aims to compare the effectiveness of three drugs tamoxifen, Centchroman and Evening prime rose oil on patients with mastalgia

Objectives

- To compare the regression of pain in three groups of patients with mastalgia using each drug (tamoxifen, Centchroman and Evening prime rose oil).
- To compare the effect of three drugs on regression of nodularity of benign breast disease
- To assess the adverse effects of the drugs

MATERIALS AND METHODS

This study was undertaken as a randomised controlled trial involving female patients attending out- patient department (OPD) in Department of Surgery with breast pain at SRM Medical college, Trichy for the duration of two years from June 2020 – November 2022. The patients with mastalgia presenting with pain scores (VAS > 3) for three months and above in the age group of 20 – 40 years was included in the study. The patients with the Suspicion of malignancy, history of breast cancer in the family, Acute inflammatory condition, PCOD, Pregnancy/planning to conceive, first 6 months of lactation, Fibroadenoma, Patient on oral contraceptive pill, pain scores visual Analogue Scale of < 3, Contraindication to centchroman, Tamoxifen and evening prime rose oil, Costochondritis, Liver disease and Patient on antipsychotic drugs were excluded from this study.

By convenient sampling method, a total of 75 patients were enrolled in this study. Patients were randomized into three groups, Group A (n=25) participants received centchroman 30 mg once a day for mastalgia for up to three months duration. Group B (n=25) participants received tamoxifen 10 mg once a day for mastalgia for three months duration. Group C (n=25) participants received evening prime rose oil 1 g TDS for mastalgia for three months duration. The randomization was done by simple randomization using lots method. The lots were taken by the participants and they were blinded to the group which they belonged to. The study was conducted by the investigator and the investigator was also blinded to the groups. After getting written consent from study participants, the questionnaire was distributed to collect the necessary data on socio demographic variables and detailed history of symptoms along with history of menstruation, marital history and obstetric history were collected. All the patients undergo thorough breast examination and pain scoring were assessed using VAS scoring scale. Ultrasound breast was done to all the patients. Core needle biopsy was explained to the patient and done among the patients who gave consent for biopsy. The drug treatment was given for a total of 12 weeks and patient will be followed at 1, 4,8,12 and 24 weeks.

After proper positioning of patient under strict aseptic precaution, 2ml of (2% plain lignocaine) local anaesthesia is injected into the area to be biopsied. A small incision was made and core biopsy was performed using a 14G automated biopsy gun. Pressure was applied locally for 5 min to stop bleeding. The biopsy was sent to pathology department for examination.

The data were entered using Microsoft Excel 2019 and analysed using SPSS (Statistical Package of Social Sciences) version 21. The variables were analysed using descriptive and inferential statistics. The link between the continuous variables' data and their normal distribution was examined using an unpaired T-test and ANOVA. The data were reported as "mean standard deviation (x s)". The percentage-based categorical variables were examined for relationships using the chi-squared test. Each statistic was evaluated using a two-sided test, with a p value of 0.05 or less being regarded as statistically significant and All confidence intervals (CI) were set at 95%. After getting verification clearance from the Research Committee (IRCHS) followed by ethical approval from Ethical Committee (IECHS), the study was initiated. All the ethical principles were adhered in the study. Participants were informed about the purpose of the study. Written informed consent was obtained from participants. The participants were assured that the information details obtained will be only for research purposes and would therefore be anonymous and kept strictly confidential. The researcher will discard the entire data gathered after the publication of this study.

RESULTS

This randomized controlled trial was conducted in the Department of Surgery among seventy-five patients randomized into three groups. This study was undertaken to determine the regression of pain, side effects/the regression of nodularity of centchroman, tamoxifen and evening prime rose oil and to compare the parameters observed among three groups of drugs.

There were 75 participants, and 25 were assigned to each group (group A, group B, and group C). Group A participants received centchroman 30 mg once a day for mastalgia for up to three months duration. Group B participants received tamoxifen 10 mg once a day for mastalgia for three months duration. Group C participants received evening prime rose oil 1 g TDS for mastalgia for three months duration.

The mean age of participants was 32.13±7.673 among the total participants in this study. The age group follows a normal distribution. The mean age in group A was 32.44±7.523 ranging from 22 – 46

ISSN (O): 2687-5365; ISSN (P): 2753-6556

years. The mean age in group B was 31.8±7.869 ranging from 21 – 45 years. The mean age in group C was 32.16±7.925 ranging from 23 – 47 years. The 84% of participants were married in group A, 64% in group B and 76% in Group C. 76%, 56% and 68% of participants were parous in Group A, Group B and Group C respectively. Cyclical mastalgia was present 88%in group A, 80% in group B and 72% in group C. The mean duration of pain was 7.08±4.32 months ranging from 1 – 16 months among Group A participants. The mean duration of pain was 6.04±3.553 months ranging from 1 – 15 months among Group B participants. The mean duration of pain was 5.96±3.553 months ranging from 1 – 15 months among Group C participants. 28% of participants in group A, 12% of participants in group B and 20% of participants in group C had vitamin E for the treatment of mastalgia before the study.

Bilateral mastalgia presented in 52% of participants in group A,56% in group B,48% in group C. Right side mastalgia presented in 32% of participants in group A,32% in group B,32% in group C. Left side mastalgia presented in 16% of participants in group A,12% in group B,20% in group C.

VAS scores

The mean VAS score before treatment was 4.52±1.122 in Group A ranging from 3 – 7. The mean VAS score before treatment was 4.16±0.943 in Group B ranging from 3 – 6. The mean VAS score before treatment was 4.64±1.469 in Group C ranging from 3 – 7.

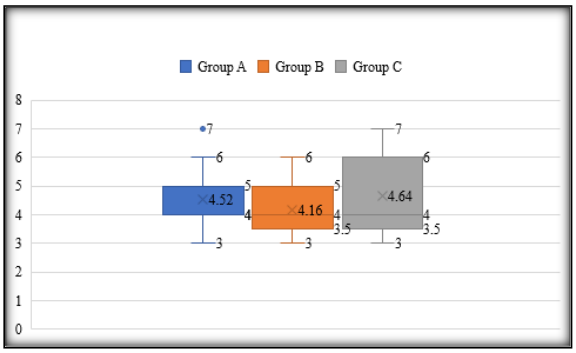

Figure 1: VAS scores before treatment

The VAS scores were lower among Group A (centchroman) participants compared with Group B and C participants in one, four-, eight-, twelve- and twenty-four-week follow-up period.

Regression of Nodularity: The Lucknow-Cardiff scale was applied to determine breast nodularity. The increasing order of nodularity is depicted schematically in the upper outer quadrants of a paired breast on this 5-point ordinal scale. Grade 0 denotes a breast with a smooth texture and the maximum amount of normalcy, while grade 4 denotes nodules to the fullest extent. 16%, 72% and 12% of participants had grade 0, grade 1 and grade 2 nodularity in Group A. 16%, 68% and 16% of participants had grade 0, grade 1 and grade 2 nodularity in Group B. 8%, 76% and 16% of participants had grade 0, grade 1 and grade 2 nodularity in Group C.

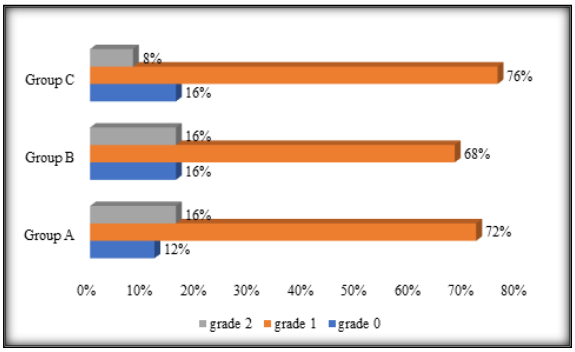

Figure 2: Distribution of nodularity

Group A (centchroman) participants had a higher grade of 0 (no nodules) than Group B and C participants during eight weeks and twelve weeks follow up period.

Adverse Events

2 patients (8%) reported delayed in menstruation in group A and others reported nil events. They were counselled and the treatment was continued.

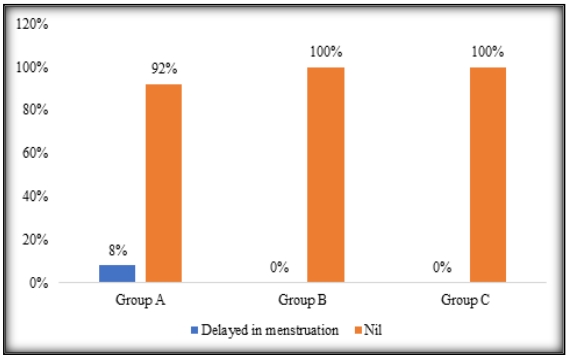

Figure 3: Adverse events

Table 1: Descriptive data of participants (n = 75)

S No	Variables		Group A	Group B	Group C
1	Mean age		32.44±7.523	31.8±7.869	32.16±7.925
2	Marital status	Married	21 (84%)	16 (64%)	19 (76%)
		Unmarried	4 (16%)	9 (36%)	6 (24%)
3	Parity	Parous	19 (76%)	14 (56%)	17 (68%)
		Nulliparous	6 (24%)	11 (44%)	8 (32%)
4	Type of mastalgia	Cyclical	22 (88%)	20 (80%)	18 (72%)
		Non-cyclical	3 (12%)	5 (20%)	7 (28%)
5	Site of mastalgia	Bilateral	13 (52%)	14 (56%)	12 (48%)
		Right	8 (32%)	8 (32%)	8 (32%)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

		Left	4 (16%)	3 (12%)	5 (20%)

Table 2: Comparison of VAS scores among groups

VAS scores	Group A	Group B	Group C	p-value
One week	2.6±0.577	3.24±0.970	4.36±1.15	0.001
Four weeks	1.8±0.408	2.48±0.918	3.04±0.841	0.001
Eight weeks	1.72±0.458	2.0±0.645	2.2±0.408	0.006
12 weeks	0.08±0.277	1.0±0.646	1.68±0.69	0.001
24 weeks	1.4±0.5	2.0±0.546	2.92±0.759	0.001

Table 3: Nodularity scores among participants

S No	weeks	Nodularity	Group A	Group B	Group C	p-value
1	Four weeks	Grade 0	12 (48%)	6 (24%)	4 (16%)	0.078
		Grade 1	13 (52%)	17 (68%)	18 (72%)	
		Grade 2	0%	2 (8%)	3 (12%)	
2	Eight weeks	Grade 0	17 (68%)	10 (40%)	6 (24%)	0.028
		Grade 1	8 (32%)	13 (52%)	17 (68%)	
		Grade 2	0%	2 (8%)	2 (8%)	
3	12 weeks	Grade 0	23 (92%)	14 (56%)	10 (40%)	0.001
		Grade 1	2 (8%)	11 (44%)	15 (60%)	
		Grade 2	0%	0%	0%	
4	24 weeks	Grade 0	12 (48%)	6 (24%)	4 (16%)	0.078
		Grade 1	13 (52%)	17 (68%)	18 (72%)	
		Grade 2	0%	2 (8%)	3 (12%)	

DISCUSSION

This randomized trial was conducted among patients with mastalgia to compare the efficacy of centchroman (Group A), tamoxifen (Group B) and evening prime rose oil (Group C) in the regression of pain and nodularity.

Ahluwalia AS et al,[7] in a study among 80 patients found that 35% of them had cyclical mastalgia and 65% of them had non-cyclical mastalgia. Sharma et al,[8] study among 130 patients found that 80.7% of patients had non-cyclical pain and 19.3% of them had cyclical pain. Jain et al,[9] found that the patients included in a randomised trial receiving centchroman and tamoxifen had no significant difference based on age, marital status, partity, type of mastalgia and duration of symptoms. Our study is similar to their studies, with no significant difference between age group, type of mastalgia, parity and marital status.

Regression of pain

Significant pain relief is considered when VAS score is less than 3. VAS scores of less than three in one week of follow-up period is 44% in Group A, 20% in Group B and 100% in Group C participants. VAS scores of less than three in one month of the follow up period is 100% in Group A, 56% in Group B, 32% in Group C participants. VAS score of less than three in eight weeks of follow-up period is 100% in Group A, 80% in Group B, 80 % C participants.

VAS scores of less than three in 12 weeks of follow-up period is 100% in Group A, 100% in Group B and 88% in Group C.VAS scores of less than three in 24 weeks of follow-up period is 100% in Group A, 80% in Group B and 32% in Group C participants. After the cessation of treatment in three months the pain scores were relapsed among the three groups. The VAS scores were lower among Group A (centchroman) participants compared with Group B (Tamoxifen) and Group C (Evening Prime Rose) participants after one, four-, eight-, twelve- and twenty-four-week follow-up period.

A Study by Jain B. K. et al,[9] showed that patients in both groups (centchroman 30 mg daily and tamoxifen 10 mg daily) gradually improved their mastalgia over the course of up to 12 weeks. After the discontinuation of medication at twelve weeks, a minor recurrence of pain was reported at 24 weeks. No significant difference in mean VAS score and percentage of women reporting pain alleviation at 4, 8, 12, and 24 weeks was noted in the Group A and Group B patients. In Jain et al study Effect of Tamoxifen and centchroman in pain alleviation was same. In our study the centchroman has better pain alleviation than Tamoxifen and Evening Prime Rose oil.

According to Ahluwalia AS et al,[7] Centchroman (30 mg alternate day for three months), provides early and greater pain relief in 3 months than evening primrose oil (3 gram daily for three months) in mastalgia patient. Thirteen publications were included in a systematic evaluation by Ghassab N et al,[10] and 12 of those papers demonstrated a substantial reduction in breast discomfort after three months as a result of centchroman use Dhar A. et al,[11] showed that centchroman (30 mg on alternate days for a period of three months) had a favourable effect on mastalgia patients by showing a drop in VAS scores from 10 to 3 in 90% of patients in the first week, and virtually complete pain relief at the end of one month. Rathi et al,[12] in a single arm trial among hundred patients of mastalgia found Mastalgia is considerably reduced with centchroman (30mg/day for twelve weeks), and Over subsequent visits, the median pain score was significantly lowered (1, 4, 12, and 24 weeks). Ahluwalia AS et al,[7] Ghassab N et al,[10] Dhar A. et al,[11] and Rathi et al,[12] studies were demonstrated that centchroman was an effective drug in pain alleviation of mastalgia.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In our study also the centchroman has better pain alleviation.

Neogi P et al,[13] compared three drugs Tamoxifen, centchroman and danazol and found that tamoxifen and centchroman was effective in pain alleviation and had lower mean score.Centchroman had better pain relief and lower mean scores in our study also.

According to Sharma et al,[8] there was a good response to centchroman (30 mg daily for three months) in the mastalgia group, with a drop in VAS scores from 10 to 3 in 69 (78.40%) of the patients in the first week and nearly complete pain relief by the end of the first month. Brahmachari et al,[14] and Sharma et al,[8] studies showed that mastalgia patients had lower mean VAS scores by the use of centchroman. In a systematic analysis, Adhi N. et al,[15] comprised 13 trials with 1752 randomly assigned participants, which demonstrated that evening prime rose oil has no different efficacy in reducing breast pain compared to topical NSAIDS, danazol, or vitamin E among mastalgia patients. Adhi N. et al15 demonstrated that evening prime rose oil had no superior efficacy in reducing the pain among patients with mastalgia.

Regression of nodularity

There was no significant association between nodularity between Group A, B and C in one week, four week and 24-week follow-up period.

There was a significant regression in nodularity between Group A, B and C in the eight-week and 24-week follow-up period. Group A (centchroman) participants shows no nodules than Group B and C participants. Dhar A et al,[11] showed that the mastalgia patients had a good response to centchroman, with nearly all of them experiencing total elimination of the nodules at the end of one month.

There was a significant regression in nodularity between Group A, B and C in the eight-week and 24-week follow-up period. Group A (centchroman) participants shows no nodules than Group B and C participants. Dhar A et al,[11] showed that the mastalgia patients had a good response to centchroman, with nearly all of them experiencing total elimination of the nodules at the end of one month.

Sharma et al8 discovered that the mastalgia group responded well to centchroman (30 mg daily for three months). Nearly all of the patients indicated that their nodularity had completely disappeared by the end of the first month. Dhar A et al,[11] and Sharma et al,[8] studies were single arm studies demonstrated that nodules regression with the use of centchroman. Our study demonstrated that the nodule was regressed among patients with mastalgia with the use of centchroman and tamoxifen. At the end of treatment (after three months) centchroman remains the better drug in regression of nodules.

Adverse effects

Our study found that 8% of the participants had delayed in menstruation centchroman group and other drugs reported nil events. Jain B. K. et al,[9] found that among Group A (centchroman), 15 individuals experienced side effects including ovarian cyst growth, menstrual abnormalities, and dizziness whereas in group B (tamoxifen), there were no negative effects reported. According to Ahluwalia AS et al,[7] Centchroman, results in delayed menstruation among 10% of participants whereas evening prime rose oil had no adverse events which was similar to our study results. Sharma et al,[8] discovered that the mastalgia group experienced amenorrhea or scanty menses after taking centchroman (30 mg for three months). Centchroman has some adverse events like menstrual irregularities which can be considered as minor side effects. Centchroman, tamoxifen and evening prime rose oil had effect on reduction of pain among mastalgia patients, and centchroman remains the superior drug in pain alleviation and regression of nodules. Since the receptor study results were of poor outcome, we couldn't correlate the receptor status and disease and drug.

CONCLUSION

Mastalgia is a typical condition that stresses out women and puts a burden on health care institutions. Although the exact cause is uncertain, mastalgia can be broadly divided into cyclic and noncyclic variants. In many instances, a thorough examination for mastalgia is important to rule out cause and reassure the patient is sufficient to alleviate pain. In some patients, however, mastalgia is severe enough to require further evaluation and treatment. In an effort to find a better treatment for mastalgia, we tried centchroman, tamoxifen and evening primrose oil were given orally for 3 months in 25 patients each. All these drugs are effective in relieving mastalgia, both cyclical and noncyclical mastalgia. However, patients taking centchroman experienced early and better relief of mastalgia. It maintains normal ovulatory cycles. Mean pain (VAS) score in centchroman group was lower as compared to tamoxifen and evening primrose oil group at all visits. However, further evaluation is needed for patient compliance and comfort regarding use of these drugs in future studies

Limitations

The present study with small sample size and conducted at a single center might have shown altered rate in effects of these drugs.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556