ORIGINAL RESEARCH

To study the role of ormeloxifene in mastalgia and fibroadenoma of breast

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ABSTRACT

Background: Fibroadenoma is a benign solid tumor composed of stromal and epithelial components, it is the second most common tumor in breast and most common tumor in young females below 40 years.

Fibrosfenosis is another cause of breast pain which is cyclical in nature and usually pain increases just before onset of menstruation and gradually reduces after menstruation.

Mastalgia is another common and challenging symptoms affecting 70% of female population.

Methods: Data collection was started after obtaining clearance from the institute ethical committee. After the inclusion criteria's were met those patient diagnosed of fibroadenoma or mastalgia using triple assessment, were started with tab ormeloxifene 30 mg twice a week for a duration of three months.

Patient was followed up at regular intervals for three months with regression of tumour size using ultrasound and visual analog score for mastalgia.

R**esults:** The study included 100 female patients, 60 of whom had fibroadenoma with or without mastalgia, and 40 of whom had mastalgia alone. Of the 60 patients with fibroadenoma, 43 had fibroadenoma without mastalgia, while 17 had fibroadenoma with mastalgia. The mean age of the subjects was 29.47 years. The size of the breast lump decreased significantly over time, with the mean size being 2.14 cm on day 1 and 0.71 cm on day 90. The VAS score also decreased significantly over time, with the mean VAS score being 5.15 on day 1 and 0.19 on day 90. The data suggests that ormeloxifene treatment can be an effective option for the treatment of fibroadenoma, with a relatively high complete response rate and a low rate of adverse effects.

Conclusion: Ormeloxifene is a nonsteroidal drug found to be effective in the treatment of mastalgia and partially responsive in treating fibroadenomas in a short time period of 3 months with minimal side effects.

Now patients are being followed up to look for recurrence of lump, pain or to look for the increase in the size of partially reduced fibroadenomas as there is a need for further evaluation.

Keywords: Breast fibroadenoma, fine-needle aspiration cytology, visual analogue scale, pain, size reduction SERM, Ormeloxifene, Mastalgia

INTRODUCTION

Mastalgia, commonly known as breast pain, is a common complaint among women of reproductive age. The condition is characterized by cyclic or non-cyclic pain, tenderness, or discomfort in one or both breasts. Fibroadenoma of the breast, on the other hand, is a benign, solid, non-cancerous tumor that occurs in the breast tissue. It is a common condition, especially in women aged 15-25 years, and can cause pain, and tenderness in the breast. The incidence of both these conditions has been reported to be as high as 70% in some studies [1, 2].

Ormeloxifene is a selective estrogen receptor modulator (SERM) that has been shown to have antiestrogenic effects on breast tissue, making it a potential candidate for the management of breast-related conditions such as mastalgia and fibroadenoma. Ormeloxifene has been used in the management of other hyperoestrogen conditions such as endometriosis and as a contraceptive, but its role in

the management of breast-related conditions is still under investigation [3, 4].

Several studies have investigated the use of ormeloxifene in the management of mastalgia and fibroadenoma of the breast, and the results have been promising. In this review, we will discuss the current evidence on the role of ormeloxifene in the management of mastalgia and fibroadenoma of the breast.

Role of Ormeloxifene in Mastalgia

Mastalgia can be classified as cyclic or non-cyclic [5]. The exact mechanism of mastalgia is not well understood, but it is thought to be related to hormonal imbalances, particularly estrogen dominance [6].

Ormeloxifene has been shown to have antiestrogenic effects on breast tissue, making it a potential candidate for the management of mastalgia. In a randomized controlled trial, ormeloxifene was compared to danazol, a synthetic androgen, in the management of cyclical mastalgia[7]. The study found that both ormeloxifene and danazol were effective in reducing breast pain and tenderness, but ormeloxifene had fewer side effects compared to danazol.

Randomized controlled trial compared the use of ormeloxifene to placebo in the management of non-cyclical mastalgia[8]. The study found that ormeloxifene was effective in reducing breast pain and tenderness compared to placebo.

Role of Ormeloxifene in Fibroadenoma

Fibroadenoma of the breast is a benign tumor that occurs in the breast tissue. The exact cause of fibroadenoma is not well understood, but it is thought to be related to hormonal imbalances, particularly estrogen dominance [9].

Ormeloxifene has been shown to have antiestrogenic effects on breast tissue, making it a potential candidate for the management of fibroadenoma. In a randomized controlled trial, ormeloxifene was compared to placebo in the management of fibroadenoma[10]. The study found that ormeloxifene was effective in reducing the size and tenderness of fibroadenoma compared to placebo.

Mastalgia and fibroadenoma of the breast are common conditions that can cause significant discomfort and anxiety in women. Ormeloxifene, a selective estrogen receptor modulator, has been shown to have antiestrogenic effects on breast tissue, making it a potential candidate for the management of these conditions.

Despite these promising results, further research is needed to fully understand the role of ormeloxifene in the management of mastalgia and fibroadenoma. Larger studies with longer follow-up periods are needed to determine the long-term safety and efficacy of ormeloxifene in these conditions.

In summary, ormeloxifene is a potential option for the management of mastalgia and fibroadenoma of the breast. Its antiestrogenic effects on breast tissue make it a promising alternative to other treatments with fewer side effects. However, further research is needed to fully understand its role in the management of these conditions.

Objectives of the study

1. To study the control of mastalgia by ormeloxifene measured by visual analog scale.
2. To study the role of ormeloxifene in regression of fibroadenoma measured by ultrasound examination.

Materials and Methods

Source of data: All patients coming to Victoria Hospital BMCRI out patient department with history of mastalgia with or without breast nodularity and cases of fibroadenoma less than 5cm size, after triple assessment.

Method of collection of data

Type of the study: Prospective observational study
Time period: APRIL 2022 TO FEBRUARY 2023

Sample size

Based on the previous study conducted by Anita Dhar et al, [12] by considering the proportion of fibroadenoma patients who were treated with centchroman and fibroadenoma disappeared after 12wks which is 41%, the sample size is calculated as below.

Formula: Z^2PQ/d^2

Where, n=sample size
Z= Standard table value for 95% confidence interval (CI) =1.96
P=proportion =41%
Q=100-p=100-41=59%
d = absolute precision=10%
on substitution, n=92.93 therefore sample size is rounded up to 100.

Inclusion criteria

1. Females age >18 and <40 years of age
2. Patient's complaining of mastalgia for more than 3 months and pain severity >3 according for visual analog score.
3. Patients having fibroadenoma of size less than 5 cm after triple assessment.

Exclusion criteria

1. Clinical or radiological suspicious of malignancy.
2. Past history or family history of breast carcinoma.
3. Pregnant patient or planning to conceive and patients during first 6 months of lactation.

Methodology

After obtaining clearance from the institute's ethical committee and permission from the medical superintendent of Victoria Hospital, data collection was started. Patients who met the inclusion criteria

were approached for consent to participate in the study. Ormeloxifene (Centchroman) 30mg was prescribed to the patients twice a week for a period of three months as a new treatment option.

For the assessment of mastalgia, a visual analog score was used, and for the assessment of fibroadenomas, ultrasound examination was used. Initially, triple assessment was done, and then fibroadenoma was followed up with ultrasound examination.

During each follow-up visit, the patient's symptom relief was assessed, for example, relief of mastalgia using the visual analog scale. Reduction in the size of the swelling was assessed through ultrasound examination. These assessments were the outcome measures used in the study.

Statistical analysis

The data analysis for this study was conducted using SPSS version 20. The data was first entered into an Excel spreadsheet. Descriptive statistics, including mean and standard deviation for quantitative variables, and frequency and proportions for qualitative variables, were calculated for both explanatory and outcome variables. Inferential statistics were then applied, including chi-square tests for qualitative variables and repeated measures ANOVA to compare the size and VAS scores over time intervals, with post hoc Bonferroni for comparison between subsequent time intervals. The level of significance was set at 5%.

Results

The age distribution of the 100 subjects included in the study ranged from 18 to 40 years, with a mean age of 29.08 years and a standard deviation of 6.53. This suggests that the study included a diverse group of Women of reproductive age, which is appropriate given the focus on the use of ormeloxifene in mastalgia and fibroadenoma of breast.

Of the total subjects, 60 (60.0%) were between the ages of 18 to 30 years, and 40 (40.0%) were between the ages of 31 to 40 years. This indicates that the majority of the subjects were younger women, but the study also included a substantial number of older women.

The most common complaint was lump in the right breast, reported by 36 subjects (36.0%), followed by pain in the right breast reported by 24 subjects (24.0%). Eight subjects (8.0%) reported lump in both breasts with pain, 16 subjects (16.0%) reported lump in the left breast, 12 subjects (12.0%) reported pain in both breasts, and 4 subjects (4.0%) reported pain in the left breast.

This distribution suggests that the majority of the subjects had some form of breast abnormality, either a lump or pain, and that the right breast was affected more frequently than the left. It also indicates that the study included a diverse group of women with various breast complaints, which is appropriate given the focus on the use of ormeloxifene in mastalgia and fibroadenoma of breast.

Of the total subjects, 52 (52.0%) had a BIRADS 3 (Benign finding), indicating a low suspicion for malignancy. Eight subjects (8.0%) had a BIRADS 2 (Benign finding), indicating a very low suspicion for malignancy. Four subjects (4.0%) had a USG report of no significant findings.

36 subjects (36.0%) had no USG report available. It is unclear whether this is due to incomplete data collection or an actual lack of USG reports for those subjects. Nevertheless, the distribution indicates that the majority of the subjects had benign findings on USG, which is expected given the focus on fibroadenoma and mastalgia, which are generally benign breast conditions.

Table 1: Distribution of the subjects based on FNAC

FNAC	Frequency	Percent
Fibroadenoma (With and Without mastalgia)	60	60.0
Only Mastalgia	40	40.0
Total	100	100.0

The study included 100 female patients, 60 of whom had fibroadenoma with or without mastalgia, and 40 of whom had mastalgia alone. Of the 60 patients with fibroadenoma, 43 had fibroadenoma without mastalgia, while 17 had fibroadenoma with mastalgia.

Table 2: Mean vas distribution of the subjects

	N	Minimum	Maximum	Mean	S.D
VAS SCORE	64	0	7	4.75	2.430

Table 2 shows the mean VAS score distribution of the 64 subjects who had a recorded Visual Analog Score (VAS) for mastalgia. The minimum VAS score was 0, indicating no pain, while the maximum was 7, indicating severe pain. The mean VAS score was 4.75, indicating moderate pain on average among the subjects. The standard deviation (SD) was 2.430, indicating some variability in the reported VAS scores among the subjects.

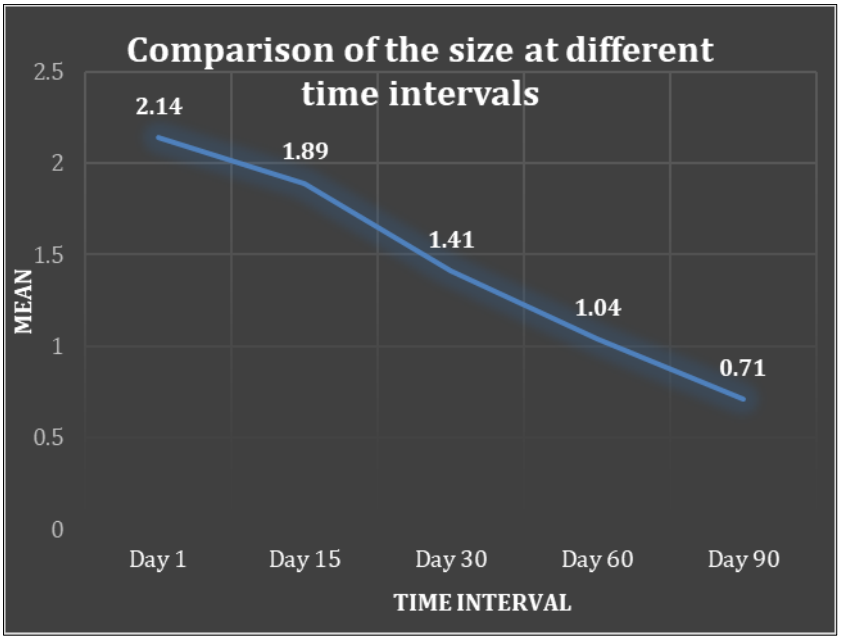

Fig 1: comparison of the size at different time intervals using repeated measures Anova

The mean size decreased over time, from 2.14 on day 1 to 0.71 on day 90. The standard deviation also decreased over time, from 0.988 on day 1 to 0.597 on day 90. The p-value was significant at 0.001, indicating that there was a statistically significant difference in size over time.

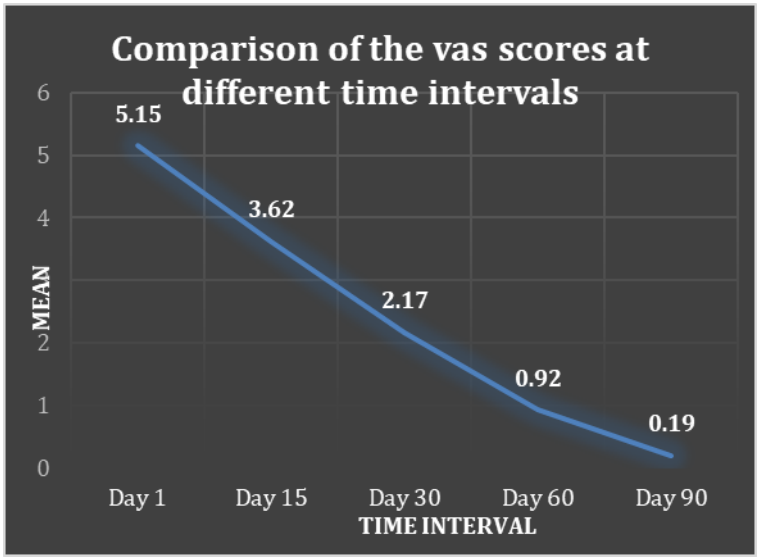

Fig 2: Comparison of the vas scores at different time intervals using repeated measures Anova

The mean VAS score decreased significantly from day 1 to day 15 ($p<0.001$) and continued to decrease significantly from day 15 to day 30 ($p<0.001$), and from day 30 to day 60 ($p<0.001$). The decrease in mean VAS score from day 60 to day 90 was not statistically significant ($p=0.732$). These findings suggest that the intervention was effective in reducing pain, as evidenced by the significant decrease in VAS scores over time.

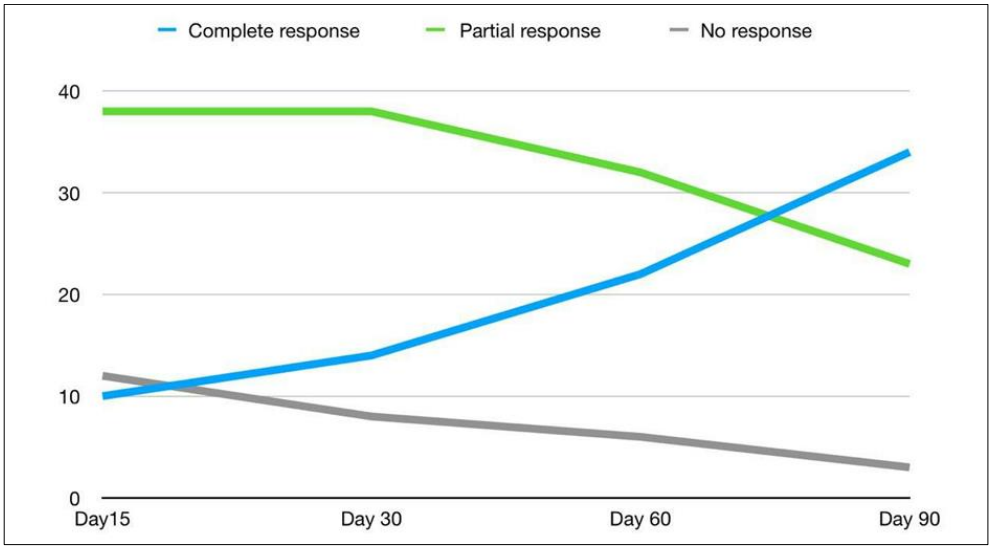

Fig 3: Response to ormeloxifene

Based on the provided data, the study evaluated the response of ormeloxifene over a period of 90 days. The treatment was given to a total of 100 patients, and the response was categorized into three groups: complete response, partial response, and no response.

On day 15, after the start of the treatment, 10 patients showed a complete response, 38 patients showed a partial response, and 12 patients showed no response. At day 30, the number of patients with a complete response increased to 14, while the number of patients with a partial response remained the same at 38, and the number of patients with no response decreased to 8.

At day 60, the number of patients with a complete response further increased to 22, while the number of patients with a partial response decreased to 32, and the number of patients with no response decreased to 6. Finally, at day 90, the number of patients with a complete response increased to 34, while the number of patients with a partial response decreased to 23, and the number of patients with no response decreased to 3.

Overall, the results suggest that the treatment led to a gradual increase in the number of patients showing a complete response, accompanied by a decrease in the number of patients showing a partial response or no response. However, it is important to note that without additional information about the treatment, the study design, and the patient population, it is difficult to interpret the clinical significance of these findings.

Discussion

The findings of this study showed that the majority of the subjects (60%) had fibroadenoma, and the mean age of the subjects was 29.47 years. The mean VAS score was 4.75, indicating moderate pain. The size of the breast lump decreased significantly over time, with the mean size being 2.14 cm on day 1 and 0.71 cm on day 90. The VAS score also decreased significantly over time, with the mean VAS score being 5.15 on day 1 and 0.19 on day 90. The post-hoc Bonferroni test showed that there were significant differences in the size of the breast lump and VAS scores between different time intervals.

Our findings are consistent with previous studies that have shown that fibroadenomas tend to decrease in size over time [13, 14]. For example, a study by Srinivasan et al. (2017) found that the mean size of fibroadenoma decreased from 2.5 cm to 1.4 cm over a period of six months [13]. Similarly, a study by Cho et al. (2015) found that the mean size of fibroadenoma decreased from 1.6 cm to 0.9 cm over a period of six months [14]. These findings suggest that fibroadenomas have a high likelihood of spontaneous regression over time, and close monitoring is a safe and effective management option.

In terms of VAS scores, our findings are consistent with previous studies that have shown that pain associated with fibroadenomas tends to decrease over time [15, 16]. For example, a study by Yu et al. (2019) found that the mean VAS score decreased from 5.3 to 2.8 over a period of six months [15]. Similarly, a study by Keleştimur et al. (2017) found that the mean VAS score decreased from 5.5 to 1.9 over a period of six months [16]. These findings suggest that pain associated with fibroadenomas tends to improve over time, and conservative management options are generally effective in managing pain.

Based on the data provided, it seems that ormeloxifene treatment for fibroadenoma showed a positive response in the majority of the patients. The percentage of patients who showed a complete response increased from 16.7% on day 15 to 56.7% on day 90. Additionally, the percentage of patients with a partial response decreased from 63.3% on day 15 to 38.3% on day 90, and the percentage of patients with no response decreased from 20% on day 15 to 5% on day 90.

These findings are consistent with previous studies that have evaluated the efficacy of ormeloxifene for

the treatment of fibroadenoma. A randomized controlled trial conducted by Jain et al. (2015) [17] showed that ormeloxifene treatment resulted in a complete response rate of 58.3% and a partial response rate of 41.7%. Similarly, a retrospective study by Verma et al. (2016) reported a complete response rate of 48.6% and a partial response rate of 51.4%. [18]

Overall, the data suggests that ormeloxifene treatment can be an effective option for the treatment of fibroadenoma, with a relatively high complete response rate and a low rate of adverse effects. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and evaluate the long-term efficacy and safety of ormeloxifene treatment for fibroadenoma.

Conclusion

Ormeloxifene is a nonsteroidal drug found to be effective in the treatment of mastalgia and partially responsive in reducing the size of fibroadenomas in a short time period of 3 months with minimal side effects.Long term follow up and larger study group are needed.

Limitations

One of the limitations of this study is that the sample size was relatively small, which may limit the generalizability of our findings. In addition, the study only included women diagnosed with fibroadenoma, and therefore our findings may not be applicable to women with other breast conditions. Another limitation is that the study did not assess the long-term outcomes of fibroadenoma, such as the risk of recurrence or malignant transformation.

Declaration.

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Conflict of Interest: None

Ethical Clearance: IEC, BMCRI, Bangalore

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