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COMPARATIVE RETROSPECTIVE STUDY OF EFFICACY OF ORMELOXIFENE AND EVENING PRIMROSE OIL IN SYMPTOMATIC RELIEF OF FIBROCYSTIC DISEASE OF THE BREAST

Breast Surgery

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ABSTRACT

INTRODUCTION - Fibrocystic disease of the breast is a prevalent, benign condition affecting a significant proportion, approximately 60-70% women of reproductive age at some point of time in their lives. It presents as mastalgia and a breast lump. Mastalgia is breast pain of benign origin, classified as cyclic or non-cyclic, depending on the pain intensity increasing with the menstrual cycle or not respectively. Many theories have been implicated in the cause of mastalgia like oestrogen excess, progesterone deficiency, changes in oestrogen progesterone ratio, difference in receptor sensitivity, secretion of FSH and LH, raised prolactin levels and low androgen levels. A variety of medications have been used to treat the Mastalgia pain in the past like Oral contraceptive pills, Evening Primrose Oil (EPO), Vitamin E, Bromocriptine, Tamoxifen etc. Here, we compare Ormeloxifene to Evening Primrose Oil to find out the most efficient treatment for Mastalgia and size of the breast lump in fibrocystic disease of the breast. **METHODS-** A retrospective observational study of 56 patients with clinically and radiologically diagnosed fibrocystic disease of the breast, divided into two groups, receiving either Ormeloxifene or EPO. Pain levels (assessed using the Visual Analogue Scale) and breast lump size (evaluated via ultrasound) were recorded at 2, 4, 6, 8 and 12 weeks. The two treatment groups were then compared to determine statistical significance. **RESULT-** Ormeloxifene, an estrogen receptor blocker, has demonstrated greater efficacy in symptomatic treatment of breast pain and reduction of breast lump as compared to evening primrose oil over a period of 3 months **CONCLUSION -** In this study, we see that Ormeloxifene is more efficacious than EPO in treatment of Fibrocystic disease of the breast, it decreases the pain and size of the breast lump earlier than EPO and is sustained for a longer period as compared to EPO.

KEYWORDS

Ormeloxifene, Mastalgia, Fibrocystic disease of the breast, breast pain

INTRODUCTION-

Fibrocystic disease of the breast, also known as fibrocystic breast changes or fibrocystic breast disease, is a common benign (non-cancerous) condition that affects the breast tissue. This condition is characterized by the formation of fibrous tissue and cysts within the breast, which can cause breast tenderness, lumpiness, and changes in breast appearance.

A study by Park and Hong showed that Fibrocystic disease of the breast is one of the most prevalent benign conditions affecting the breast tissue, occurring in up to 50% of women of reproductive age [1]. This condition is characterized by the formation of fibrous tissue and cysts within the breast, which can lead to symptoms such as breast tenderness, lumpiness, and changes in breast appearance [2].

PATHOPHYSIOLOGY- Fibrocystic breast changes, also known as fibrocystic breast disease, is a benign condition characterized by changes in the breast tissue, leading to a variety of symptoms. While the exact cause remains elusive, the pathophysiology is thought to involve a complex interplay of hormonal fluctuations, growth factors, and structural changes within the breast tissue.

HORMONAL INFLUENCES AND IMBALANCES-

ESTROGEN AND PROGESTERONE IMBALANCE: Fluctuations in estrogen and progesterone levels, particularly during the menstrual cycle, are strongly implicated in FBD. An excess of estrogen relative to progesterone is considered a key driver. This imbalance can arise from increased estrogen production, decreased progesterone production and altered estrogen metabolism [3]

ESTROGEN'S EFFECTS: Estrogen stimulates the growth and proliferation of breast ductal epithelial cells and stromal tissue. Excess estrogen can lead to ductal epithelial cell hyperplasia, increased stromal fibrosis and Fluid accumulation, forming cysts. [4]

PROGESTERONE'S ROLE: Progesterone counteracts some of estrogen's effects, promoting differentiation and maturation of breast tissue. Progesterone deficiency can contribute to ductal dilation and stromal edema. [4]

OTHER CONTRIBUTING FACTORS

Growth Factors: Imbalances in growth factors, such as epidermal growth factor and transforming growth factor-beta, may also play a role in FBD development.

LIFESTYLE FACTORS: While not fully established, some studies suggest that factors like caffeine intake, smoking, and high-fat diets might contribute to FBD symptoms.

STRUCTURAL CHANGES IN BREAST TISSUE

The hormonal imbalances and other contributing factors lead to characteristic structural changes in the breast tissue such as Cysts development within the breast tissue, often contributing to breast lumpiness and tenderness, increased fibrous tissue formation can make the breasts feel dense and lumpy and Ductal Changes causing the Breast ducts to become dilated or enlarged, further contributing to lumpiness. These structural changes and hormonal imbalances contribute to the common symptoms of FBD, that is

- **BREAST PAIN:** Often described as a dull, aching pain or tenderness, mastalgia can be cyclical (worsening before menstruation) or non-cyclical.
- **BREAST LUMPS:** Lumps associated with FBD are typically round, movable, and may feel tender to the touch.
- **BREAST SWELLING:** Breasts may feel swollen or full, particularly before menstruation.

At present drugs being used for treatment of mastalgia are evening primrose oil, bromocriptine, gamolenic acid, danazol, tamoxifen, luteinizing hormone releasing hormone (LHRH) analogue gosereline, oral contraceptive pills (centchroman), diuretics and topical non-steroidal anti-inflammatory drug (NSAID) gels [5]. In this study, we compare Ormeloxifene to EPO to find out the more efficacious treatment modality for the symptomatic treatment of fibrocystic disease of the breast.

ORMELOXIFENE AND ITS PHARMACOLOGY-

Ormeloxifene functions as a competitive antagonist at estrogen receptors, primarily ERα, which are highly expressed in breast tissue.

Structurally similar to estrogen, ormeloxifene binds to these receptors, effectively blocking estrogen from binding and eliciting its downstream effects. This competitive inhibition forms the foundation of ormeloxifene's therapeutic action in FBD. [7]

Upon binding to ERs, estrogen typically triggers a cascade of intracellular signaling events, ultimately leading to gene transcription and protein synthesis involved in cell growth and proliferation. Ormeloxifene, acting as an antagonist, disrupts this signaling cascade thereby causing-

- **REDUCED EPITHELIAL HYPERPLASIA:** By inhibiting estrogen-driven cell proliferation, ormeloxifene helps normalize the growth of breast ductal epithelial cells, reducing ductal dilation and hyperplasia often observed in FBD.
- **DECREASED STROMAL PROLIFERATION AND FIBROSIS:** Ormeloxifene's antagonistic action also extends to stromal cells, mitigating the excessive deposition of collagen and extracellular matrix components that contribute to breast density and lumpiness.
- **REDUCED FLUID RETENTION:** By counteracting estrogen's influence on vascular permeability and fluid balance within the breast, ormeloxifene can minimize fluid accumulation and cyst formation, further reducing breast pain and tenderness.

A key advantage of ormeloxifene lies in its tissue-specific action. While it acts as an estrogen antagonist in breast tissue, it exhibits estrogenic or neutral effects in other tissues like bone and the uterus. This selectivity profile minimizes the risk of adverse effects associated with systemic estrogen deprivation, such as bone loss or menopausal symptoms. [8]

AIM- To compare Ormeloxifene to EPO to find out the more efficacious treatment modality for the treatment of fibrocystic disease of the breast.

OBJECTIVES-
1. To assess pain reduction in women with mastalgia using VAS with follow up at 2, 4, 8 and 12 weeks, after treatment with Ormeloxifene compared to EPO.
2. To assess reduction in size of breast lump using serial USG with follow up at 2, 4, 8 and 12 weeks, after treatment with Ormeloxifene compared to EPO.

METHODS-
TYPE OF STUDY: Retrospective, observational study.

PLACE OF STUDY: MGM Medical College and Hospital, Navi Mumbai, Kamothe

PERIOD OF STUDY: January 2023 to January 2024
Institute Ethics Committee approvals and consent were obtained prior to the start of the study

SAMPLE SIZE: 56

STATISTICAL ANALYSIS: Plan and data were collected by using the standard tool and stored in MS excel. Basic descriptive statistics like frequency, percentage, mean, mode, median, standard deviation, and graphs were prepared using MS excel.
To test the significance, the level of significance <0.05 was used for parametric tests.
To test the test of significance, statistical package SPSS24 was used.

PLAN OF STUDY- In this retrospective study, 56 patients who were treated with Ormeloxifene or EPO in the time period of 12 months from January 2023 to January 2024 were selected. Out of the 56 patients, 30 patients received Tablet Ormeloxifene 30 mg three days a week (Group A) and 26 received EPO 1000mg od (Group B). All patients regularly attended the OPD for a period 3 months. Patients presenting to the OPD with mastalgia and breast lump, diagnosed with Fibrocystic disease of the breast were included in the study. Pain was assessed using the Visual Analogue Scale (VAS) and breast lump was evaluated using USG Breast. Observations of symptomatic pain relief and reduction in breast lump size were noted at an interval of 2, 4, 6, 8 and 12 weeks in both the groups, and compared to each other. The data was collected from the hospital records. Statistical significance was calculated

INCLUSION CRITERIA-
All symptomatic, female patients with radiologically diagnosed fibrocystic disease of the breast treated with EPO and Ormeloxifene at MGM Surgery OPD between January 2023 and January 2024.

EXCLUSION CRITERIA-
1. All pregnant and lactating females, and patients planning pregnancy.
2. Patients with clinical/ radiological suspicion/ diagnosis of malignancy
3. Patients on analgesics for other unrelated causes.

RESULTS-
Out of 56 patients with mastitis, 36 patients (64%) presented with a sonographically detectable breast lump.

Table 1- Patients with radiological diagnosis of breast lump

	GROUP A (30)	GROUP B (26)	PERCENTAGE
BREAST LUMP	21	15	64%
NO BREAST LUMP	9	11	36%

The mean age of group A was 23 years, and 33.5 years in group B.

Table 2- Age distribution of patients

AGE DISTRIBUTION		
	GROUP A (30)	GROUP B (26)
18-25	12	12
25-35	15	13
35-50	3	1
Avg Age	27.6	26.4

The mean VAS of Group A was 5.2 (On arrival), 2.8 (week 2), 1.7 (week 4), 1.4 (week 6), 1.2 (week 8) and 1.1 (week 12), whereas in Group B it was 4.8 (On arrival), 4.7 (week 2), 2.8 (week 4), 2.3 (week 6), 1.5 (week 8) and 1.1 (week 12). As shown above, Group A had a faster and more significant reduction in symptomatic mastalgia pain than Group B.

Table 3- Mean pain score of patients using VAS

MEAN VAS OF PATIENTS		
	Group A	Group B
Week 0	5.2	4.8
Week 2	2.8	4.7
Week 4	1.7	2.8
Week 6	1.4	2.3
Week 8	1.2	1.5
Week 12	1.1	1.1

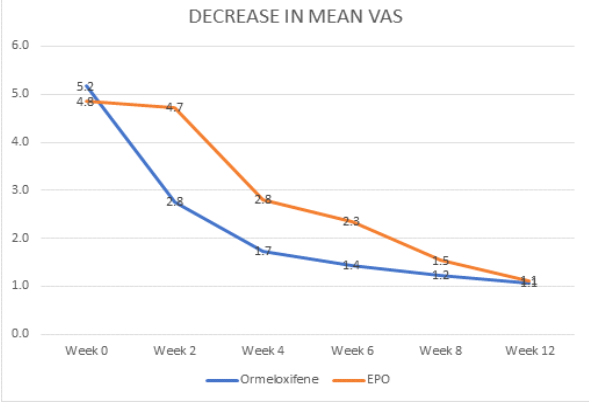

Figure 1- Table 3- Decrease in mean pain score of patients using VAS

Similarly, the average breast lump size (cm2) in Group A was 6.2 (On arrival), 3.9 (week 2), 3.3 (week 4), 2.5 (week 6), 2.5 (week 8) and 2.0 (week 12), whereas in Group B it was 7 (On arrival), 6.5 (week 2), 4 (week 4), 2.8 (week 6), 2.7 (week 8) and 2.4 (week 12). Group A had a faster decrease in size of the breast lump compared to group B.

Table 4- MEAN BREAST LUMP SIZE (cm2)

MEAN BREAST LUMP SIZE (cm2)		
	Group A	Group B
Week 0	6.2	7
Week 2	3.9	6.5
Week 4	3.3	4
Week 6	2.5	2.8
Week 8	2.5	2.7
Week 12	2.0	2.4

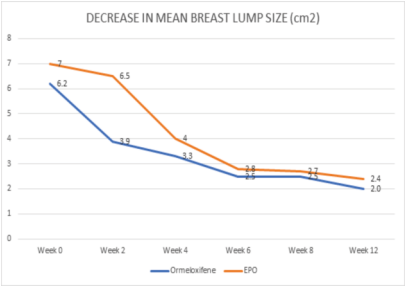

Figure 2 - DECREASE IN MEAN BREAST LUMP SIZE (cm2)

DISCUSSION-

In this study we have done a comparative study of Ormeloxifene versus EPO in treatment of mastalgia. In present study patients in Ormeloxifene group as well as in EPO group show gradual improvement in symptoms, in terms of decrease in mean pain (VAS) score at 3 months period of treatment. The mean pain score was lower in Ormeloxifene group patients at all visits. In our study, in group A (Ormeloxifene), out of 30 patients with a mean VAS of 5.2 on arrival, at the end of 12 weeks, the mean VAS was 1.1 (2 patients had a VAS of 2, 28 patients had a VAS of 1), an 84.61% decrease in pain ($p<0.005$). Similarly, the mean size of breast lump (cm2) on arrival was 6.2, at the end of 12 weeks it was 2, a 67.74% decrease in size ($p<0.005$). In group B (Evening Primrose Oil), out of 26 patients with a mean VAS of 4.8 on arrival, at the end of 12 weeks, the mean VAS was 1.1 (3 patients had a VAS of 2, 23 patients had a VAS of 1), an 77.08% decrease in pain. Similarly, the mean size of breast lump (cm2) on arrival was 7, at the end of 12 weeks it was 2.4, a 65.71% decrease in size, which was statistically significant ($p<0.005$)

CONCLUSION-

In this study, we see that Ormeloxifene is more efficacious than EPO in treatment of Fibrocystic disease of the breast, it decreases the pain and size of the breast lump earlier than EPO and is sustained for a longer period as compared to EPO. This study proved the objectives of comparing Ormeloxifene to EPO, even though both are effective in reducing the pain and the size of the breast lump, Ormeloxifene is a more effective treatment choice.

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