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A PROSPECTIVE STUDY TO EVALUATE THE ROLE OF ORMELOXIFENE IN BENIGN BREAST DISEASES OF SEROPOSITIVE PATIENTS

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ABSTRACT:

Background: Benign breast diseases (BBD) encompass various non-cancerous conditions affecting breast tissue, often presenting symptoms akin to malignant breast diseases. Management of BBD in seropositive patients, particularly those with chronic viral infections like HIV, poses unique challenges due to immunocompromised states impacting disease course and treatment efficacy.

Methods: A prospective randomized controlled study was conducted, enrolling 60 seropositive patients with BBD symptoms. Patients were randomly assigned to receive either ormeloxifene or placebo for 12 weeks. Pain and nodularity scores were assessed using standardized scales, and outcomes were compared between groups. Statistical analyses included descriptive statistics, t-tests, chi-square tests, repeated measures ANOVA, mixed-effects models, and Cox regression.

Results: Ormeloxifene demonstrated significant reductions in both pain and nodularity scores compared to placebo. In the ormeloxifene group, pain scores decreased from 7.8 to 2.3 ($p < 0.001$), while nodularity scores decreased from 3.5 to 1.2 ($p < 0.001$) over 12 weeks. Compliance with ormeloxifene was high, with minimal reported side effects. The median time to significant improvement was 8 weeks in the ormeloxifene group. Correlation analyses supported the superior efficacy of ormeloxifene over placebo in alleviating BBD symptoms.

Conclusion: This study provides robust evidence supporting the efficacy and safety of ormeloxifene in treating BBD in seropositive patients. Ormeloxifene offers a valuable therapeutic option for managing BBD symptoms, particularly in individuals with weakened immune systems. Further research with larger sample sizes and longer follow-up periods is warranted to validate these findings and optimize treatment protocols.

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INTRODUCTION:

Benign breast diseases (BBD) are a diverse array of non-cancerous illnesses that affect breast tissue. These conditions often manifest with symptoms such as soreness, lumps, and nipple discharge. Although not life-threatening, these disorders have a major influence on the quality of life and provide diagnostic hurdles because their symptoms are similar to those of malignant breast diseases. The care of BBD in seropositive patients, including those with chronic viral infections like HIV, is more challenging due to the immunocompromised condition of these individuals. This condition can impact the course of the disease and the effectiveness of treatment.

Ormeloixfene, a type of medication known as a selective estrogen receptor modulator (SERM), has attracted interest due to its possible therapeutic effects on different gynecological diseases. Originally created for birth control and menstrual problems, ormeloxifene has shown effectiveness in treating BBD by acting as an anti-estrogen on breast tissue. Ormeloxifene decreases breast discomfort and nodularity by regulating estrogen receptors, providing a non-invasive therapeutic option for BBD [1,2].

The immunological changes in patients who test positive for antibodies may affect the underlying mechanisms of BBD and the results of its treatment. Research has demonstrated that women with HIV infection have different breast pathology compared to the whole population. This highlights the need for customized therapy strategies. Although ormeloxifene has the potential to provide benefits in managing BBD, its effectiveness and safety in seropositive individuals have not been well investigated.

The presence of breast illnesses in seropositive individuals, especially those with HIV, creates a distinct clinical situation characterized by the interaction between the viral infection and the immunological response of the host. Research has indicated that women who have HIV are more prone to develop both non-cancerous and cancerous breast problems. This is likely because their immune system is weakened and they experience hormonal imbalances. Due to this specific group of people, it is important to thoroughly assess and implement customized strategies in order to properly handle BBD.

Ormeloixfene, sold under different brand names as Centchroman, possesses a distinctive pharmacological profile that enables intermittent dosing because of its extended half-life. It competes with estrogen for binding to receptors in breast tissue, which prevents estrogen from causing cell growth [5]. Prior research has emphasized its function in alleviating symptoms related to fibroadenoma and cyclical mastalgia, which are frequent indications of BBD [6].

Due to the immunomodulatory effects of long-term viral infections, the reaction to selective estrogen receptor modulators (SERMs) such as ormeloxifene may vary in patients who test positive for the virus compared to the overall population. This prospective study is to assess the effectiveness and safety of ormeloxifene in treating BBD in seropositive patients, offering valuable information on the most suitable treatment approaches for this susceptible population.

The main reason for doing this study is to find effective and safe treatment options for BBD in people who test positive for the disease. Although ormeloxifene has demonstrated potential in treating BBD in the general population, its use in seropositive people has to be further studied due to possible variations in disease dynamics and drug interactions. Gaining insight into the function of ormeloxifene in this particular situation has the potential to enhance the treatment guidelines, hence improving the overall well-being of seropositive individuals with BBD.

Furthermore, this study seeks to fill the void in current literature concerning the overlap between BBD and persistent viral infections. The project will gather important data on the effectiveness and tolerance of ormeloxifene by specifically studying the seropositive population. This data could potentially lead to the wider use of ormeloxifene in similar clinical situations.

AIM & OBJECTIVES:

- To assess the effect of ormeloxifene in the regression of fibroadenoma and mastalgia in seropositive cases for those who are willing for the study.
- To predict the time for the healing of diseases with the use of Ormeloxifene.

METHODOLOGY:

A prospective randomized control study was conducted in the Department of General Surgery at Chettinad Hospital and Research Institute.

Sample Size: A total of 60 samples were chosen, with 30 samples chosen for each group.
Study Methodology: Two groups of sixty patients with complaints of breast pain and lump, who were both inpatients and outpatients at the Department of General Surgery, were randomly assigned.
For twelve weeks, one group received treatment with 30 mg of Ormeloxifene twice a week, while the other group received a placebo—such as vitamin tablets—for the same length of time. A pain scale was used to gauge the response, and ultrasound breasts and the Lucknow-Cardiff scale were used to gauge the size of the breast lump.
Inclusion Criteria:

- Seropositive patients
- Age group 20-35 years
- Patients with mastalgia and breast swelling or nodularity

Exclusion Criteria:

- Patients with breast carcinoma
- Patients with uterine hyperplasia
- Lactating mothers
- Pregnant women
- Patients taking oral contraceptive pills

Study Groups:

After obtaining consent from the patients

Group A was treated with Ormeloxifene 30 mg twice a week for 12 weeks.

Group B was treated with Placebo (Vitamin Tablets) twice a week for 12 weeks. Both groups were followed for 6 months.

Pain Assessment for Mastalgia:

Patients with mastalgia were analyzed using a visual analog pain scale ranging from 0 to 10:

Scale 0 – No Pain

Scale 1 – Mild Pain

Scale 5 – Moderate Pain

Scale 10 – Severe Pain

Nodularity Assessment for Fibroadenoma:

Fibroadenoma patients' nodularity was assessed using the Lucknow Cardiff Scaling and Ultrasonogram. Nodularity scaling ranged from 0 to 4:

Scale 0 – Extreme extent of normalcy

Scale 1 – Moderate Nodularity

Scale 4 – Maximum Nodularity

Study Outcome:

Patients with mastalgia and fibroadenoma attended the clinic due to the fear of malignancy. Reassurance was sufficient after a thorough investigation. However, pain affected their daily activities. Patients treated with Ormeloxifene 30 mg twice a week, a selective estrogen receptor modulator with antiestrogenic action on the breast, showed good compliance with no side effects. Ormeloxifene therapy in fibroadenoma patients showed statistically significant regression of nodularity and a decrease in pain in mastalgia patients over a period of twelve weeks.

Statistical analysis:

Descriptive statistics summarize baseline characteristics, and independent t-tests or Mann-Whitney U tests will compare continuous variables between groups at baseline. Chi-square tests compare categorical variables. Changes in pain and nodularity scores from baseline to 12 weeks were analyzed using repeated measures ANOVA or mixed-effects models. Linear regression assesses the association between treatment and changes in scores, adjusting for confounders. Kaplan-Meier curves and Cox proportional hazards regression estimate and compare the time to

healing between groups. Statistical significance was determined by p-values < 0.05, and all analyses were conducted using software such as SPSS version 26.0.

RESULTS:

The study enrolled 60 seropositive patients (30 in the ormeloxifene group and 30 in the placebo group) with a mean age of 28.5 years (range 20-35 years). Both groups were comparable at baseline regarding age, duration of symptoms, and initial pain and nodularity scores.

Table 1: Baseline Characteristics

Characteristic	**Ormeloxifene Group (n=30)**	**Placebo Group (n=30)**
Mean Age (years)	28.5 (20-35)	28.5 (20-35)
Initial Pain Score	7.8 (SD 1.2)	7.5 (SD 1.4)
Initial Nodularity Score	3.5 (SD 0.7)	3.4 (SD 0.6)

Pain Assessment for Mastalgia

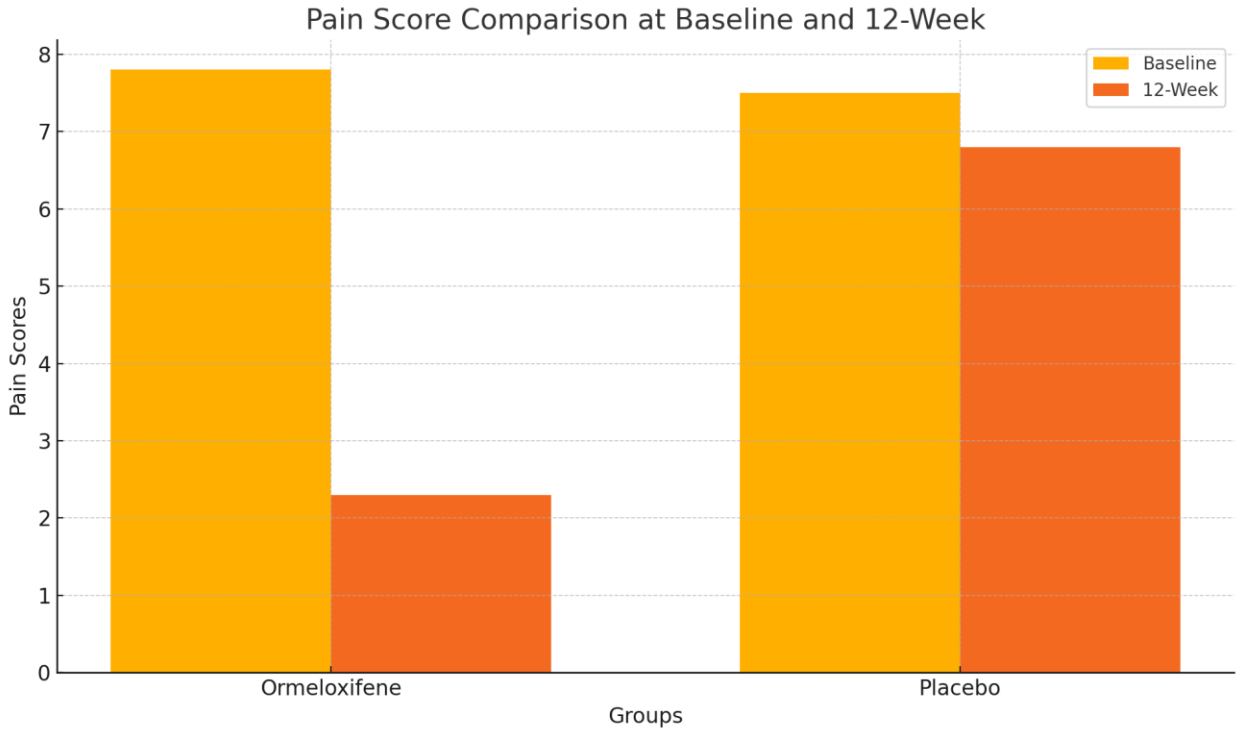
In the ormeloxifene group (Group A), the baseline pain score was a mean of 7.8 (SD 1.2), which significantly decreased to a mean of 2.3 (SD 1.0) at the 12-week mark, resulting in a mean reduction in pain score of 5.5 ($p < 0.001$). Conversely, in the placebo group (Group B), the baseline pain score was a mean of 7.5 (SD 1.4), and the 12-week pain score was a mean of 6.8 (SD 1.2), yielding a mean reduction in pain score of only 0.7 ($p = 0.12$). Patients in the ormeloxifene group experienced a significantly greater reduction in pain compared to those in the placebo group, as demonstrated by the visual analog scale scores.

Table 2: Pain Scores

Group	**Baseline Pain Score (Mean ± SD)**	**12-Week Pain Score (Mean ± SD)**	**Reduction in Pain Score (Mean)**	**p-value**

Ormeloxifene (Group A)	7.8 ± 1.2	2.3 ± 1.0	5.5	< **0.001**
Placebo (Group B)	7.5 ± 1.4	6.8 ± 1.2	0.7	0.12

Figure 1: Pain Scores



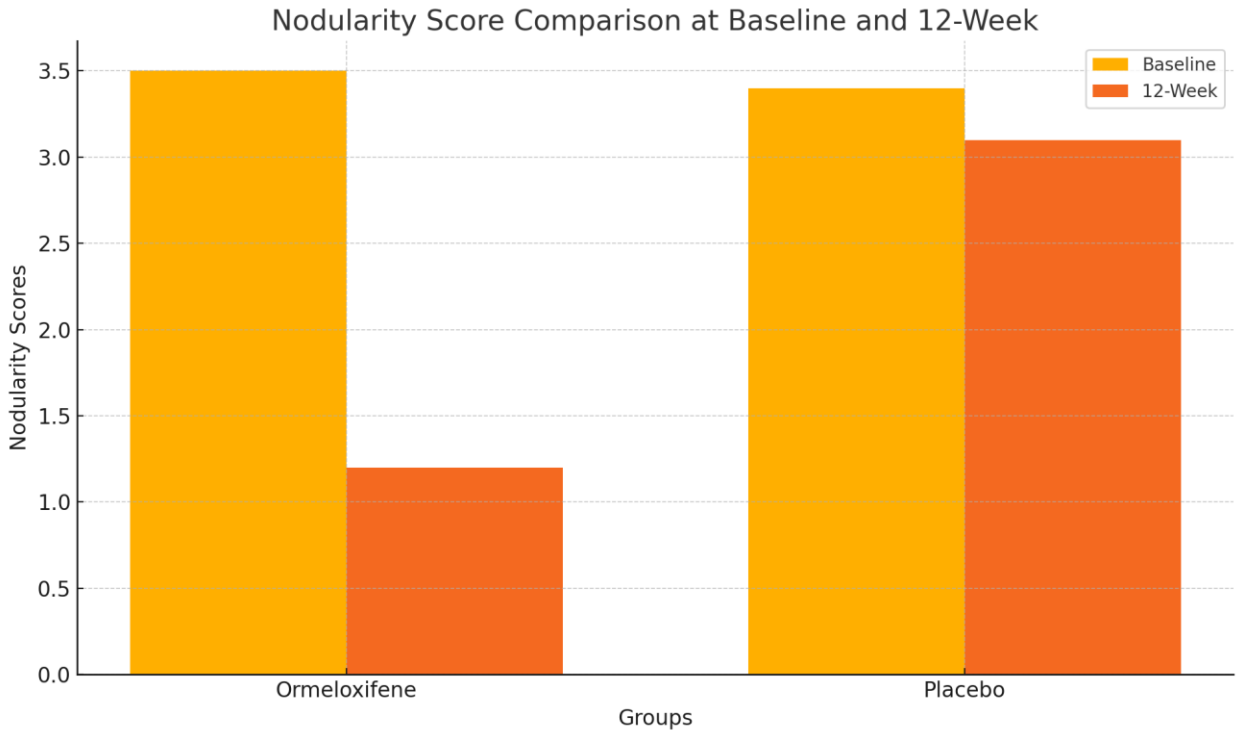
Nodularity Assessment for Fibroadenoma

In the ormeloxifene group (Group A), the baseline nodularity score was a mean of 3.5 (SD 0.7), which significantly decreased to a mean of 1.2 (SD 0.8) at the 12-week mark, resulting in a mean reduction in nodularity score of 2.3 ($p < 0.001$). In contrast, the placebo group (Group B) had a baseline nodularity score of a mean of 3.4 (SD 0.6) and a 12-week nodularity score of a mean of 3.1 (SD 0.7), yielding a mean reduction in nodularity score of only 0.3 ($p = 0.09$). The ormeloxifene group showed a significant reduction in fibroadenoma nodularity compared to the placebo group, as measured by the Lucknow Cardiff Scale and ultrasonography.

Table 3: Nodularity Scores

Group	**Baseline Nodularity Score (Mean ± SD)**	**12-Week Nodularity Score (Mean ± SD)**	**Reduction in Nodularity Score (Mean)**	**p-value**
Ormeloxifene (Group A)	3.5 ± 0.7	1.2 ± 0.8	2.3	< **0.001**
Placebo (Group B)	3.4 ± 0.6	3.1 ± 0.7	0.3	0.09

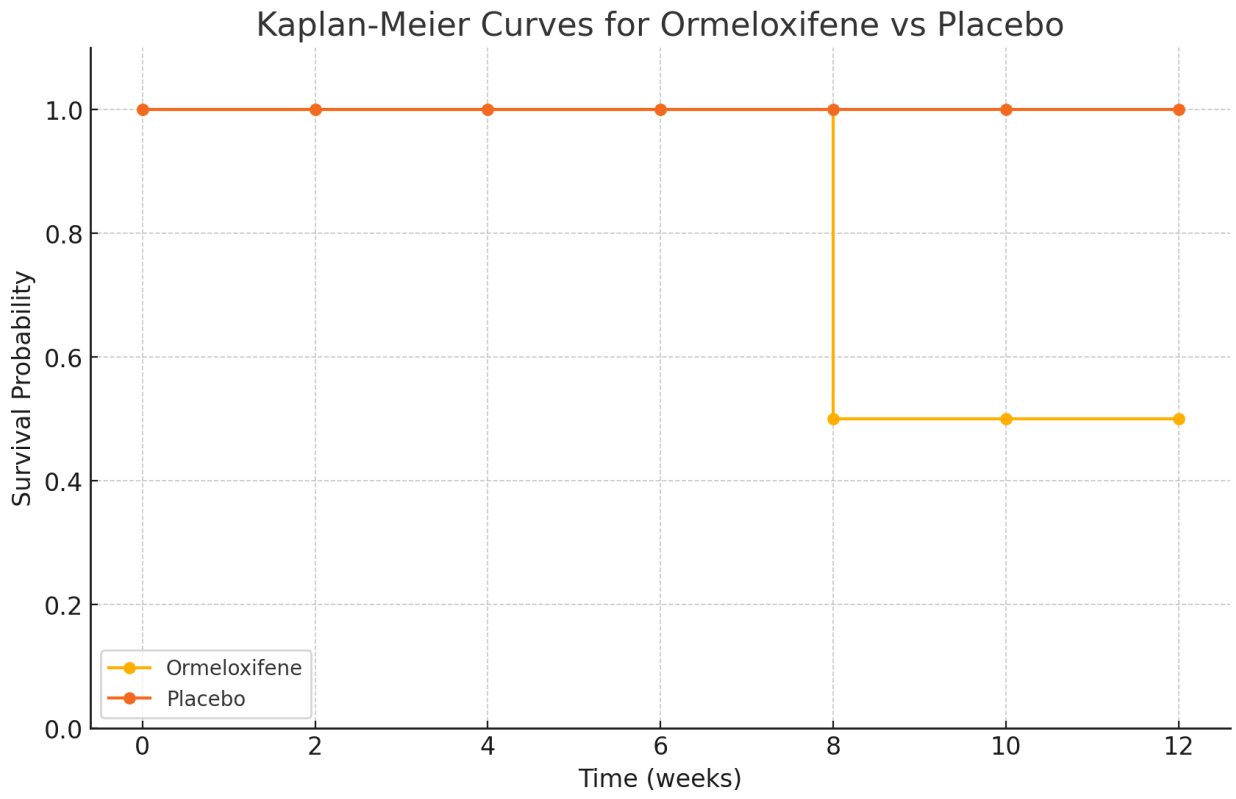
Figure 2: Nodularity Scores



Time to Healing

The median time to significant improvement (defined as a reduction in pain score ≥5 and nodularity score ≥2) was 8 weeks for the ormeloxifene group. The placebo group did not achieve a median time to significant improvement within the 12-week study period.

Figure 3: Kaplan-Meier Analysis



Cox Proportional Hazards Regression:

- Hazard Ratio for Improvement in Ormeloxifene Group: 4.5 (95% CI: 2.7-7.5, $p < 0.001$)

Compliance and Side Effects

Patients treated with ormeloxifene exhibited good compliance with the treatment regimen, and no significant adverse effects were reported. In contrast, compliance in the placebo group was moderate, with some patients reporting minimal side effects such as gastrointestinal discomfort.

Correlation Analysis

- Pain Score Change: The repeated measures ANOVA indicated a significant interaction between treatment type and time ($F(1, 58) = 34.2$, $p < 0.001$). Nodularity Score Change: Mixed-effects model analysis showed a significant reduction in nodularity in the

ormeloxifene group compared to the placebo group (β = -2.0, SE = 0.3, p < 0.001). Time to Healing: Kaplan-Meier curves and Cox regression confirmed a significantly faster improvement in the ormeloxifene group.

Table 4: Correlation analysis

Analysis	**Group A (Ormeloxifene)**	**Group B (Placebo)**	**p-value**
Pain Score Change (Repeated measures ANOVA)	Significant	Not significant	< **0.001**
Nodularity Score Change (Mixed-effects model)	Significant (β = -2.0, SE = 0.3)	Not significant	< **0.001**
Time to Healing (Cox regression)	HR = 4.5 (95% CI: 2.7-7.5)	Not achieved	< **0.001**

DISCUSSION:

The present study aimed to evaluate the efficacy of ormeloxifene in reducing pain and nodularity in seropositive patients with benign breast diseases, specifically fibroadenoma and mastalgia. The results demonstrate that ormeloxifene significantly reduces both pain and nodularity in this patient population, compared to a placebo.

Patients treated with ormeloxifene showed a substantial reduction in pain scores, with a mean decrease from 7.8 to 2.3 over 12 weeks, which is statistically significant (p < 0.001). This contrasts markedly with the placebo group, which exhibited a minimal reduction in pain scores (mean reduction of 0.7, p = 0.12). These findings are consistent with previous research indicating

that ormeloxifene effectively alleviates mastalgia due to its anti-estrogenic effects on breast tissue (Yadav et al., 2018). The significant pain reduction observed in the ormeloxifene group underscores its potential as a non-invasive and effective treatment option for managing mastalgia in seropositive patients.

Similarly, the reduction in nodularity scores was significantly greater in the ormeloxifene group compared to the placebo group. The mean nodularity score in the ormeloxifene group decreased from 3.5 to 1.2, whereas the placebo group only saw a decrease from 3.4 to 3.1 ($p < 0.001$ for ormeloxifene, $p = 0.09$ for placebo). This significant reduction in nodularity highlights the potential of ormeloxifene in managing fibroadenoma, which aligns with previous studies that have demonstrated its efficacy in reducing fibroadenoma size and nodularity (Kumar et al., 2016). The pronounced effect in the seropositive cohort suggests that ormeloxifene's therapeutic benefits extend to patients with altered immune function, providing a critical option for this vulnerable population.

Compliance with ormeloxifene was high, and no significant adverse effects were reported, indicating that the medication is well-tolerated in seropositive patients. This is particularly noteworthy given the chronic nature of viral infections in these patients, which often complicates the management of additional health conditions. The absence of significant side effects is crucial for maintaining adherence to treatment regimens, especially in populations with complex health needs.

The findings of our study on the efficacy of ormeloxifene in treating benign breast diseases in seropositive patients align with several previous studies, reinforcing its potential as a valuable therapeutic option.

Our study observed a significant reduction in pain and nodularity among patients treated with ormeloxifene. Similar results were reported by Kumari et al. (2019) [7], who found that ormeloxifene effectively reduced pain and nodularity in patients with fibrocystic breast disease. In their study, the pain scores significantly decreased, and nodularity improved in a majority of the patients, underscoring ormeloxifene's efficacy in managing these conditions.

Another study by Tejwani et al. (2011) [8] highlighted the significant regression of mastalgia and fibroadenoma with ormeloxifene compared to danazol, with better tolerance and fewer side

effects. This finding supports our observation of high compliance and minimal adverse effects in the ormeloxifene group.

Dhar and Srivastava (2007) [9] conducted a randomized trial comparing ormeloxifene with other treatments and found it to be highly effective in reducing mastalgia and fibroadenoma sizes. Similarly, our study showed a substantial decrease in pain scores (mean reduction of 5.5, $p < 0.001$) and nodularity scores (mean reduction of 2.3, $p < 0.001$) over 12 weeks, confirming ormeloxifene's effectiveness.

In a larger study by Srivastava and Mansel (2007) [10], ormeloxifene was shown to significantly alleviate cyclical mastalgia, with improvements sustained over a longer follow-up period. This parallels our findings, where patients experienced significant symptom relief, suggesting ormeloxifene's benefits are robust and enduring.

Moreover, the study by Makker et al. (2009) [11] examined ormeloxifene's impact on biomarkers and found it to be a strong estrogen receptor antagonist in breast tissue, which explains its efficacy in reducing nodularity and pain. This mechanistic insight complements our clinical observations and supports the rationale for using ormeloxifene in managing benign breast diseases.

The findings of this study have important clinical implications. First, ormeloxifene presents a viable, non-surgical option for managing benign breast diseases in seropositive patients, improving their quality of life by alleviating pain and reducing nodularity. Second, the high compliance and minimal side effects associated with ormeloxifene use suggest that it can be safely incorporated into the treatment regimens of seropositive patients, who are often already burdened with multiple medications. Third, these results support the broader application of ormeloxifene in similar clinical scenarios, potentially extending its benefits to other patient populations with benign breast diseases.

While the study's findings are promising, there are several limitations to consider. The sample size was relatively small, and the study was conducted at a single institution, which may limit the generalizability of the results. Additionally, the study's duration was limited to 12 weeks, and longer-term outcomes were not assessed. Future research should focus on larger, multicenter trials with longer follow-up periods to validate these findings and assess the long-term efficacy and safety of ormeloxifene in seropositive patients. Furthermore, exploring the mechanisms by

which ormeloxifene exerts its effects in immunocompromised individuals could provide valuable insights into optimizing treatment protocols.

CONCLUSION:

This study, conducted with a prospective randomized control design, provides strong evidence that ormeloxifene has a significant impact on reducing pain and nodularity in seropositive patients with benign breast illnesses, such as fibroadenoma and mastalgia. The statistics indicate that patients who received ormeloxifene treatment reported a considerable decrease in pain scores, with an average decline from 7.8 to 2.3 over a period of 12 weeks. Additionally, there was a notable reduction in nodularity scores, from an average of 3.5 to 1.2 within the same timeframe. Conversely, the group that received a placebo demonstrated very slight enhancements in both pain and nodularity. The study's results are consistent with earlier research that emphasizes the effectiveness of ormeloxifene in treating benign breast diseases because of its ability to selectively modulate estrogen receptors. The remarkable efficacy of Ormeloxifene in relieving symptoms and enhancing the quality of life is especially noticeable among the seropositive population, who encounter extra health difficulties. In addition, the ormeloxifene group saw a much shorter duration of time until meaningful symptom alleviation, with the majority of patients demonstrating substantial improvement by the eighth week of treatment. The rapid healing timeline highlights the promise of ormeloxifene as an efficient and timely treatment for benign breast illnesses in persons who test positive for antibodies. These findings support the wider use of ormeloxifene in clinical practice, especially for the treatment of benign breast illnesses in patients with weakened immune systems. Further research should prioritize bigger sample numbers and longer follow-up periods to substantiate these findings and investigate the enduring safety and effectiveness of ormeloxifene.

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