Original Article

Eur J Breast Health 2022; 18(3): 248-251
DOI: 10.4274/ejbh.galenos.2022.2022-2-6

Open-Label Three Arm Trial Comparing Ormeloxifene, Gamma Linolenic Acid With Methylcobalamine + Vitamin C and Placebo in Mastalgia

Amrendra Verma, Deepti Bala Sharma, Sanjay Kumar Yadav, Dhananjaya Sharma

Department of Surgery, Netaji Subhash Chandra Bose Medical College, Jabalpur, India

ABSTRACT

Objective: We evaluated the beneficial effect of Ormeloxifene (Centchroman) versus a combination of Gamma Linolenic acid (GLA), methylcobalamine and vitamin C on mastalgia in a three-arm, open-label, placebo-controlled trial.

Materials and Methods: Patients aged above 18 years with mastalgia were recruited between January 2019 and July 2021. Patients were divided in three arms: Ormeloxifene arm, GLA arm and Placebo arm. Response was evaluated using visual analogue scale (VAS) and score below 3/10 was defined as complete relief.

Results: A total of 113 consecutive women with mastalgia were randomized to the GLA group (Group 1, n = 39 women), Ormeloxifene (Group 2, n = 36) and Placebo (Group 3, n = 38). Complete response was observed in 94% patient in Group 1, 96% in Group 2 and 87% in Group 3 at the end of 12 weeks and it was not significant (p = 0.49). Adverse events were reported by eleven patients taking Ormeloxifene, compared to none in the other two groups.

Conclusion: In this study Ormeloxifene and GLA were not superior to placebo for pain relief in mastalgia. Furthermore, there were concerning side effects associated with Ormeloxifene therapy. The role of Ormeloxifene in mastalgia needs further evaluation before recommending it as preferred therapy.

Keywords: Benign, breast disease, mastalgia

Cite this article as: Verma A, Sharma DB, Yadav SK, Sharma D. Open-Label Three Arm Trial Comparing Ormeloxifene, Gamma Linolenic Acid With Methylcobalamine + Vitamin C and Placebo in Mastalgia. Eur J Breast Health 2022; 18(3): 248-251

Key Points

- Centchroman, also known as Ormeloxifene, is a relatively new drug under the class of non-steroidal selective estrogen receptor modulators which is being used to treat mastalgia.
- We evaluated the beneficial effect of Ormeloxifene (Centchroman) versus a combination of Gamma Linolenic acid (GLA), methylcobalamine and vitamin C on mastalgia in a three-arm, open-label, placebo-controlled trial.
- In this study Ormeloxifene was not superior to GLA or placebo and was also associated with concerning side effects.

Introduction

Mastalgia or breast pain is one of the commonest breast disorders in women that affects quality of life, with a reported incidence of 70% during a woman's lifetime (1, 2). Concern regarding cancer is one of the major reasons for this, impacting psychosocial well-being, prompting evaluation and treatment and hence exclusion of malignancy is the first step in treating women with mastalgia, which often relieves these symptoms leading to improved psychosocial well-being (2). Other non-pharmacological interventions, such as use reassurance with relaxation therapy and breast support, dietary supplements, and pain relief with a non-steroidal anti-inflammatory drug, gamma linolenic acid (GLA)with methylcobalamine and vitamin C have been reported to improve the quality of life in the majority of patients (3-6).

However, pharmacological interventions in the form of low dose oral contraceptives (OCP), tamoxifen, danazol and bromocriptine are required in severe and chronic mastalgia (7). Centchroman or Ormeloxifene is a relatively new drug under the class of non-steroidal selective estrogen receptor

Corresponding Author:
Sanjay Kumar Yadav; sky1508@gmail.com

Received: 17.02.2022
Accepted: 18.03.2022
Available Online Date: 01.07.2022

modulators, which is being used to treat mastalgia and fibroadenoma (8, 9). We evaluated the beneficial effect of Centchroman and GLA on mastalgia in a three-arm, open-label placebo-controlled trial.

Materials and Methods

Study Design

This was a prospective, open label, interventional study conducted between January 2019 to May 2021 on patients attending the outpatient department of General Surgery at Netaji Subhash Chandra Bose Medical College, Jabalpur, after approval from institutional ethics committee. The study was a three-arm randomized trial of Centchroman *versus* GLA *versus* Placebo in mastalgia.

Patient Eligibility and Selection

All female patients with complaint of breast pain reporting to our department were identified. All patients were evaluated as per protocol and underwent triple assessment, consisting of complete clinical examination, ultrasonography (USG) and/or X-ray mammography of both breasts and fine needle aspiration cytology (FNAC) or core needle biopsy, if indicated. Exclusion criteria were: women unwilling to participate; patients with malignant pathology; fibroadenoma >5 cm; patients taking oral contraceptive pill (OCP); pregnancy; known polycystic ovarian disease; cervical hyperplasia; recent jaundice; and females planning to conceive within 6 months.

Sample Size, Randomization, Treatment Plan and Response Evaluation

Based on a power of 80%, the aim was to recruit 36 participants in each arm to detect an intervention effect size w = 0.30. A randomization table was generated *in silico* to assign patients to three groups: Groups 1, 2 and 3. A resident, who was not involved in the study, assigned the enrolled patients to groups. Patients in Group 1 received GLA (100 mg) in combination with methyl-cobalamin (100 mg) and vitamin C (100 mg) one capsule/day for three months. In Group 2 patients received Ormeloxifene 30 mg on alternate days and Group 3 received placebo. All patients were reassured on every follow up, while dietary modification and external breast support was advised to all.

Patients were followed up at 4^{th}, 8^{th} and 12^{th} weeks. Pain severity was measured with visual analogue scale (VAS) score to assess the response to therapy (10). Patients were considered to have complete relief of pain if the VAS score fell below 3/10. Treatment was continued for a total of 12 weeks and then patients were followed up for another 12 weeks without medication to assess the continuum of relief. All drugs were stopped after three months and the last follow up was done at three months interval from stopping treatment.

Outcome Measure

Primary outcome measure for the mastalgia group was pain relief defined as

VAS score <3. If a woman also had fibroadenoma, its size was assessed by ultrasonography at baseline. No response was defined as no change in size of nodule or increase in size, partial regression was defined as decrease in size of more than 30 percent and complete regression was defined as complete disappearance of nodule. Secondary outcome measure was the occurrence of side effects of therapy.

Statistical Analysis

Demography, clinical, radiological, pathological and treatment data was collected in a pre-designated proforma. Statistical analysis was done using SPSS, version 16 (IBM Inc., Chicago, IL, USA). All analyses are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) following intention-to-treat (ITT) procedures. Normality of data was assessed using Q-Q plot and it was normally distributed. For all statistical analyses, the significance level was set at $p<0.05$. Effectiveness of treatment arms was assessed by proportions of patients having relief from mastalgia or decrease in the size of fibroadenoma at 4^{th}, 8^{th} and 12^{th} weeks. Categorical data was analyzed by Freeman-Halton extension of Fisher's exact test or chi-square test, as required.

Results

A total of 113 consecutive women with mastalgia were enrolled. Cyclical pain was observed in 56% patients and noncyclical breast pain in 44% patients. The mean age at presentation was 40.32±11.5 (range 18–53 years) and all were pre-menopausal. The GLA group (Group 1) included 39 (34.5%) women, Ormeloxifene group (Group 2) included 36 (31.9%) and the Placebo group (Group 3) included 38 (33.6%) women. There was no significant difference with regards to age, baseline pain scores or cyclical and non-cyclical mastalgia between the three groups. On USG examination five patients had fibroadenomas and eight had diffuse fibrocystic breast disease. The majority of patients reported pain relief in both Ormeloxifene and GLA arm as compared to placebo at the end of 4 weeks of therapy (100% *versus* 94% *versus* 80%). At the end of 12 weeks of therapy, complete relief (reduction of pain to <3 on VAS and pain duration to ≤7 days/month) was observed in 92% patients in Group 1, 96% in Group 2 and 87% in Group 3, which was not significant ($p = 0.49$). At the end of follow up (three months after stopping drugs) 94% patients in Group 2 were pain free as compared to 87% in Group 1 and 82% in Group 3 (Table 1), which again was not significantly different ($p = 0.24$). Subgroup analysis for patients with cyclical and non-cyclical mastalgia was performed. For the cyclical mastalgia group (n = 63), complete response rates were 90%, 90% and 81% for Groups 1, 2 and 3 respectively ($p = 0.9$). As patients with underlying breast pathologies were very few, subgroup analysis was not done.

In terms of adverse events, there were no adverse effects observed with Group 1 (GLA arm) or the placebo arm (Group 3). However, 11% (n = 4) of patients complained of dizziness and 11% (n = 4) patients suffered from abnormal menstrual cycles and per vaginal discharge due to cervical inflammation taking Ormeloxifene (Group 2). Three patients developed cystic adnexal pathology (Table 2). Overall, eight patients were forced to discontinue Ormeloxifene before completing three months of treatment as compared to none in the GLA and placebo arms.

Discussion and Conclusion

In the present study, Ormeloxifene, 30 mg on alternate days for 12 weeks, was not superior to placebo or GLA in relieving moderate and severe mastalgia. We also found that GLA was as effective as Ormeloxifene in providing early relief (within 4 weeks) from mastalgia.

Table 1. Comparison of response at 12 weeks between three groups on mastalgia

Group	Complete response	Partial response	No response	Follow up (proportion pain free three months after stopping treatment)
Group 1 (n = 39)	36 (92.4%)	2	1	34 (87%)
Group 2 (n = 36)	34 (94.4%)	1	1	34 (94.4%)
Group 3 (n = 38)	33 (86.8%)	2	3	31 (82%)
p-value (chi-square test)	0.49	0.76	0.70	0.24

n: number

Table 2. Comparison of side effects between three groups

Group	Dizziness	Ovarian cyst	Menstrual irregularity
Group 1 (n = 39)	0	0	0
Group 2 (n = 36)	11% (4)	8% (3)	11% (4)
Group 3 (n = 38)	0	0	0

n: number

The rapid response to and early efficacy of Ormeloxifene in mastalgia was reported by Dhar and Srivastava (8) in 2007, which generated a huge interest in the drug, leading to multiple studies. They reported a response rate of 71% at the end of one week and almost all the patients were pain-free at the end of one month of Ormeloxifene therapy in this single arm study. Another study by Rathi et al. (10) reported that Ormeloxifene had a response rate of 88% at the end of 12 weeks and 85% at the end of 24 weeks in relieving mastalgia. However, neither study contained a control arm. We too observed a good response rate with Ormeloxifene (96% at the end of 12 weeks) but this was not superior to the responses reported by either the GLA arm or even the placebo arm in our study.

Kumar et al. (11) conducted a randomized, double-blind, placebo-controlled trial and reported that the mean pain level significantly reduced in the active group compared to that in the placebo group ($F = 18.66$, $p<0.0001$). The significant clinical difference in this study could be due to the use of a mean pain score instead of proportion of patients cured. Tejwani et al. (12) compared Ormeloxifene with danazol and reported significant reduction in mastalgia with Ormeloxifene as compared to danazol (89% *versus* 69%, $p = 0.001$). However, these studies did not report if other measures, such as reassurance, dietary modification and external breast support, were used along with Ormeloxifene. This information is crucial, as various studies have reported that reassurance and dietary modifications are effective in 50%–90% of mastalgia patients (13-15). A similar outcome was observed with the placebo and GLA arms in our study compared to the Ormeloxifene arm, but it should be noted that all patients were advised to modify diet and seek breast support while all patients received reassurance at all visits.

Eleven patients in the Ormeloxifene group reported side effects during the study. Dizziness was reported by 11%, menstrual irregularity by 11% and ovarian cyst by three patients. Tejwani et al. (9), reported that 75% patients receiving Ormeloxifene experienced scanty menstruation and 19% had ovarian cyst on follow up USG. Again, daily Ormeloxifene used by the authors rather than the alternate day regimen used in our study could be the cause for higher adverse events reported by Tejwani et al. (12) Gupta (16) and Rathi et al. (10) also used an alternate day regimen and reported 14% and 8% menstrual irregularity respectively, similar to that seen in our study. However, both did not have follow up USG protocol and did not report ovarian cysts. Overall, there are some concerning side effects with Ormeloxifene which needs further evaluation.

One of the limitations of the current study is that it was open label. Further studies with larger sample size with blinding are required to verify the findings of the present study.

In our study, no significant difference was found in symptom relief obtained in patients receiving Ormeloxifene, GLA or placebo in terms of proportion of women reporting pain relief. GLA was as effective as Ormeloxifene in providing early relief from mastalgia and we suggest can be given in place of Ormeloxifene. The development of ovarian cyst and menstrual irregularity in patients receiving Ormeloxifene is a matter of concern, and it needs further evaluation in larger number of cases.

In conclusion, in this study Ormeloxifene and GLA were not superior to placebo for pain relief in mastalgia. Furthermore, there were concerning side effects associated with Ormeloxifene therapy. The role of Ormeloxifene in mastalgia needs further evaluation before recommending it as preferred therapy.

Ethics Committee Approval: Ethics clearance was obtained from Institute Ethics Committee of NSCB Medical College, Jabalpur, India approval number – MS PG Thesis- Surg/1/2018.

Informed Consent: Written informed consent was taken from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.V., D.B.S.; Design: A.V., D.B.S.; Data Collection and/or Processing: A.V., D.B.S.; Analysis and/or Interpretation: S.K.Y.; Literature Search: A.V., D.B.S., S.K.Y.; Writing: S.K.Y., D.S.; Revision and editing: D.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Santen RJ, Mansel R. Benign breast disorders. N Engl J Med 2005; 353: 275-285. (PMID: 16034013) [Crossref]
2. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. Mayo Clin Proc 2004; 79: 353-372. (PMID: 15008609) [Crossref]
3. Hafiz SP, Barnes NLP, Kirwan CC. Clinical management of idiopathic mastalgia: a systematic review. J Prim Health Care 2018; 10: 312-323. (PMID: 31039960) [Crossref]
4. Horrobin DF. The effects of gamma-linolenic acid on breast pain and diabetic neuropathy: possible non-eicosanoid mechanisms. Prostaglandins Leukot Essent Fatty Acids 1993; 48: 101-104. (PMID: 8380930) [Crossref]
5. Pasta V, Dinicola S, Giuliani A, Harrath AH, Alwasel SH, Tartaglia F, et al. A Randomized Pilot Study of Inositol in Association with Betaine and Boswellia in the Management of Mastalgia and Benign Breast Lump in Premenopausal Women. Breast Cancer (Auckl) 2016; 10: 37-43. (PMID: 27127407) [Crossref]
6. Jaiswal G, Thakur GS. An alternative yogic approach for cyclical mastalgia-A narrative review. J Family Med Prim Care 2021; 10: 601-608. (PMID: 34041048) [Crossref]
7. Faiz O, Fentiman IS. Management of breast pain. Int J Clin Pract. 2000; 54: 228-232. (PMID: 10912311) [Crossref]
8. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg 2007; 31: 1178-1184. (PMID: 17431715) [Crossref]
9. Tejwani PL, Nerkar H, Dhar A, Kataria K, Hari S, Thulkar S, et al. Regression of Fibroadenomas with Centchroman: a Randomized Controlled Trial. Indian J Surg 2015; 77: 484-489. (PMID: 26730050) [Crossref]
10. Rathi J, Chawla I, Singh K, Chawla A. Centchroman as First-line Treatment for Mastalgia: Results of an Open-label, Single-arm Trial. Breast J 2016 ; 22: 407-412. (PMID: 27059808) [Crossref]
11. Kumar S, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V. A randomized, double-blind, placebo-controlled trial of ormeloxifene in breast pain and nodularity. Natl Med J India 2013; 26: 69-74. (PMID: 24093978) [Crossref]
12. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, Thulkar S, et al. Centchroman regresses mastalgia: a randomized comparison with danazol. Indian J Surg 2011; 73: 199-205. (PMID: 22654331) [Crossref]
13. Barros AC, Mottola J, Ruiz CA, Borges MN, Pinotti JA. Reassurance in the Treatment of Mastalgia. Breast J 1999; 5: 162-165. (PMID: 11348279) [Crossref]
14. Ngô C, Seror J, Chabbert-Buffet N. Syndrome douloureux mammaire: recommandations Breast pain: Recommendations. J Gynecol Obstet Biol Reprod (Paris) 2015; 44: 938-946. [Crossref]
15. Hadi MS. Sports Brassiere: Is It a Solution for Mastalgia? Breast J 2000; 6: 407-409. (PMID: 11348400) [Crossref]
16. Gupta N. A Prospective Study to study the Efficacy and Side Effects of Ormeloxifene in Regression of Mastalgia and Fibroadenoma: Is It the Ideal Drug?. J South Asian Feder Obs Gynae 2016; 8: 48-56. [Crossref]