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ROLE OF ORMELOXIFENE IN MASTALGIAS AND FIBROADENOMAS

Breast Surgery

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ABSTRACT

Background: Published Literature has shown a role of Ormeloxifene in the management of mastalgia and fibroadenoma. However, the therapy has its own concerns around the safety profile. Therefore, we conducted this study to further our understanding about the role played by Ormeloxifene in mastalgia and fibroadenoma management at our centre alongwith its safety profile assessment. The purpose of this study is to assess the effectiveness of ORMELOXIFENE, a novel non-steroidal non-hormonal anti-estrogen (Selective estrogen receptor modulator or SERM) drug, on mastalgia and fibroadenomas. **Methodology :** The study was performed at the Department of Surgery of Jaipur Golden Hospital, Rohini, Delhi on 50 patients who presented with either mastalgia or fibroadenoma in the OPD. Ormeloxifene was prescribed to these patients for 3 months and the patients were followed up for 6 months. The pain associated with mastalgia was assessed in terms of VAS scores. Fibroadenoma size (volume in cc) was assessed using the sonographically measured dimensions of the lesion. **Results:** For the patients with mastalgia, who were initiated on Ormeloxifene, the average VAS scores were seen to decrease significantly across the follow up period. The proportion of patients with lower VAS scores increased gradually during the follow up period. The trend was statistically significant with p value of <0.0001. Only one of these patients had a side effect in the study, translating into a complication rate of 5%. For patients with fibroadenoma, the fibroadenoma size in terms of volume (in cc) was seen to decrease significantly in the follow up period. At 24 weeks, all the patients in the study had a fibroadenoma volume <1cc with 90% of fibroadenoma lesions seen to have a volume < 1cc by 12th week. Only 2 of these patients had side effects in the study, making a complication rate of 6.66%. **Conclusion:** The study was able to conclude that Ormeloxifene is an effective and safe option for management of mastalgia and fibroadenoma in young females. There was a statistically significant reduction seen in the pain score for mastalgia and the volume of fibroadenoma. The complication rate was very low (5-6%). The findings of the study were in line with the major published literature in this domain both nationally and internationally.

KEYWORDS

Ormeloxifene, Mastalgia, Fibroadenoma

INTRODUCTION

Fibroadenomas are frequent benign breast lesions that manifest as a painless breast lump in younger women of reproductive age group. They are thought to be abnormalities in normal breast development or the result of hyperplastic processes rather than actual neoplasms. Fibroadenomas are common in the population as a whole, being responsible for 15% of palpable breast lumps. Fibroadenoma is considered to arise from hyper-responsiveness of lobular tissue to estrogen. Presence of estrogen receptors on tissue obtained from fibroadenoma has been described. **[1]**

Mastalgia (Greek masto-breast and algia-pain) signifies breast pain. Mastalgia is the most prevalent complaint seen in breast clinic patients and a cause of significant anxiety and fear of breast cancer. Approximately 60 to 70% of women suffer some degree of breast pain at some point in their life, with severe pain occurring in 10 to 20% of instances.**[2]** Mastalgia can be of two types: (1) Cyclic mastalgia is associated with menstrual cycles due to increased susceptibility of breast tissue to hormonal variations and is usually bilateral. Such pain usually increases just before and during menstruation and frequently subsides after pregnancy or menopause, supporting the etiologic significance of hormonal changes. (2) Non-cyclic mastalgia is pain unrelated to the menstrual cycle. This type is not common and is difficult to diagnose. Non-cyclic breast pain is caused by anatomical changes like breast cyst, prior breast trauma or surgery, trauma to the chest wall, muscle, or joint, intercostal neuralgia, Tietze syndrome, as well as other spinal and paraspinal disorders that can cause referred breast pain. Certain drugs, like OCPs (oral contraceptive pills), estrogen and progesterone hormonal therapy, and certain antidepressants like SSRI (selective serotonin reuptake inhibitors) and antihistaminics, have also been linked to breast pain**. [3]**

Ormeloxifene has been a centre of recent interest because of its beneficial effect in mastalgia and fibroadenoma regression as reported by multiple studies. Ormeloxifene can be used to suppress the proliferation of ductolobular tissue of fibroadenoma. It has a weak agonist action on endometrium and bones, and strong antagonist action on breast ductolobular epithelium, and hence, it has been put to recent use for the treatment of mastalgia and fibroadenoma**[4]**.

Most of the drugs used for fibroadenoma and mastalgia are expensive and have side effects. This study was conducted to find out efficacy of Ormeloxifene, a selective estrogen receptor modulator (SERM) on regression of fibroadenoma and mastalgia as an alternative to presently available steroid-based drugs with significant side effects.

AIMS & OBJECTIVES

The purpose of this study is to assess the effectiveness of ORMELOXIFENE, a novel nonsteroidal non-hormonal anti-estrogen (Selective estrogen receptor modulator or SERM) drug, on mastalgia and fibroadenomas.

MATERIALS AND METHODS

Study Setting: Outpatient Department of Jaipur Golden Hospital, Rohini, Delhi, India

Study Time: August 2022 – January 2024

Study Duration – 1.5 years

Study Population – Patients who attended the outpatient department of Jaipur Golden Hospital, Rohini, Delhi, India.

Study Design: Prospective interventional study

Sample Size: 50 Patients attending the OPD with complaints of breast lump or breast pain and between 15 to 35 yrs of age were included in the study.

Reference Study - A Comparative Study on Effect of Ormeloxifene On Mastalgia and Fibroadenomas: A Dissertation Submitted to The Tamil Nadu Dr.M.G.R Medical University Chennai. (Senthil M. A Comparative study on Effect of Ormeloxifene on Mastalgia and Fibroadenomas (Doctoral dissertation, Madurai Medical College, Madurai)**[1]**

Based on the observations from the reference article, Minimum Sample Size(N)= 40 (minimum) patients. Based on the footfall, **50** patients were included in the study.

Inclusion Criteria :

- Females of age 15-35 years having mastalgia without any obvious breast lesion or identifiable cause.
- Patients with fibroadenomas of size ≤ 3 cm, single or multiple, in

one or both breasts.
- Patients who consented for inclusion in the study according to designated proforma.
- Patient not willing for surgical excision (fear of scar)
- Patients willing for follow-up for at least 6 months.

Exclusion Criteria :
- Patients <15 or >35 years of age.
- Patients who were pregnant or lactating or planning for pregnancy in near future.
- Patients with any other co-existing oestrogen dependent condition like polycystic ovarian syndrome, endometrial hyperplasia, endometriosis, adenomyosis, fibroids etc.
- Patients having associated chest wall disorders or dermatological lesions.
- Fibroadenoma >3 cm in size.
- Complex fibroadenoma.
- Patients with breast abscess or any active infective condition.
- Patients diagnosed with fibroadenosis or any ductal pathology like duct ectasia, intraductal papilloma, mammary duct fistula etc.
- Patients who had a history of breast trauma.

Methods And Study Flow –

1. Patients who attended the OPD with complaints of breast lump or breast pain and between 15 to 35 yrs of age were taken for detailed clinical history, clinical examination, ultrasonagram (USG) of both breast and fine needle aspiration (FNAC)/core needle biopsy of the breast lesion.
2. An ultrasound of abdomen and pelvic organs was also done to exclude any associated hyper-estrogenic condition like polycystic ovarian disorder (PCOD), endometrial hyperplasia, ovarian cysts and fibroids.
3. Patients who fulfilled the inclusion criteria and were willing to participate in the study were included in this study after getting written informed consent with sign.
4. Participating patients got Ormeloxifene 30mg orally on alternative days for 3 months.
5. USG was done at 0 days, 4, 8, 12 and 24 weeks to assess regression of fibroadenoma.
6. Mastalgia patients were assessed by visual analog scale (VAS) for breast pain at 0 days, 4, 8, 12, and 24 weeks.

RESULTS

VAS Score trends in MASTALGIA patients:

The average VAS scores were seen to decrease significantly across the follow up period for the patients with mastalgia who were initiated on Ormeloxifene. The P value was <0.0001 suggestive of statistical significance. The minimum VAS score was seen to reduce from 4 observed at baseline, to 0 at 24 weeks. The maximum VAS score was 8 at baseline which came down to 1, at 24 week follow up.

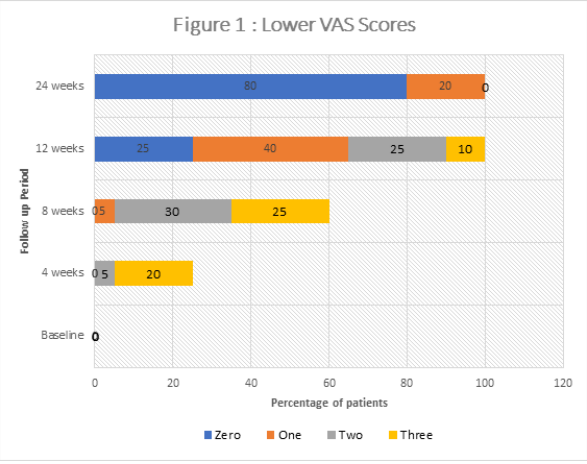


Table 1: VAS Score Trends

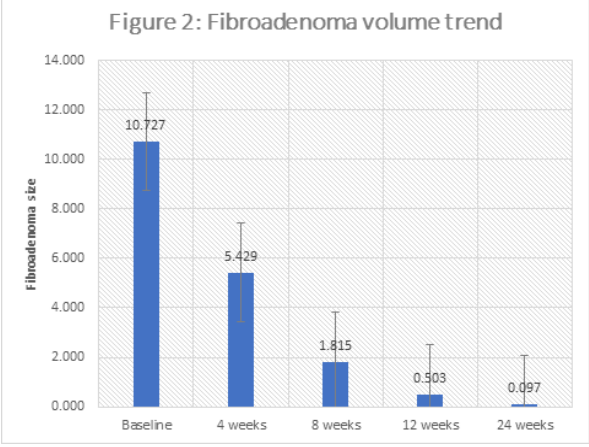
VAS score	Baseline	4 weeks	8 weeks	12 weeks	24 weeks
0	0	0	0	5 (25%)	16 (80%)
1	0	0	1 (5%)	8 (40%)	4 (20%)
2	0	1 (5%)	6 (30%)	5 (25%)	0
3	0	4 (20%)	5 (25%)	2 (10%)	0
4	5 (25%)	13 (65%)	7 (35%)	0	0
5	8 (40%)	1 (5%)	1 (5%)	0	0
6	3 (15%)	1 (5%)	0	0	0
7	0	0	0	0	0
8	4 (20%)	0	0	0	0
9	0	0	0	0	0
10	0	0	0	0	0
Total	20	20	20	20	20

It was seen that at baseline most of the patients had a VAS score of 4-8 with a progressive decline in the proportion of patients with higher VAS scores. The proportion of patients with lower VAS scores increased gradually during the follow up period. By the 12th week follow up it was seen that 25% of the patients had no pain suggested by a VAS score of 0. This proportion increased to 80% by the end of 24 weeks. The trend was significant statistically with P value of <0.0001.

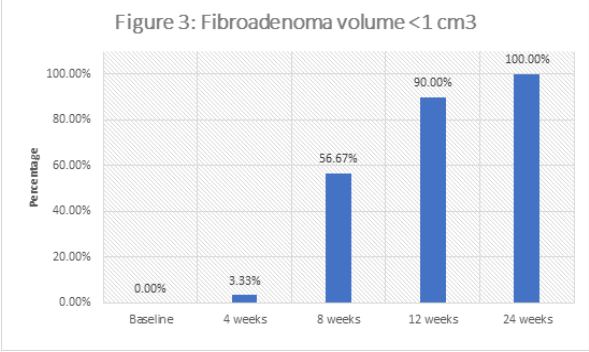
Side Effect Profile- Only one patient was seen to have a side effect in the study. The patient had menstrual irregularity.

FIBROADENOMA Volume Trend :

The fibroadenoma size in terms of volume (in cc) was seen to decrease significantly in the follow up period. The mean volume was 10.73±3.95 cc at baseline which decreased to 0.10±0.20 cc at 24 week follow up. The minimum volume was seen to reduce from 4.18 cc to 0 in the follow up period. The maximum volume was seen to go down from 14.09 cc to 0.52 cc. The trend was significant across the follow up period with a p value of <0.0001.



An assessment of the number of patients with fibroadenoma volume <1 cm3 was done. It was seen that at the baseline, none of the fibroadenoma lesions in the study had a volume of <1 cc. However, as the follow up period progressed, the proportion of patients with lesion volume <1 cc increased progressively. At 24 weeks, all the patients in the study had a fibroadenoma volume of <1 cc with 90% of the fibroadenoma lesions seen to have a volume less than 1 cc by 12th week.



Side Effect Profile- Only two patients were seen to have side effects in the study. There was one case of menstrual irregularity and another of gastritis.

DISCUSSION

The study was performed at the Department of Surgery of Jaipur Golden Hospital, Rohini, Delhi on 50 patients who presented with either mastalgia or fibroadenoma in the OPD. Ormeloxifene was prescribed to these patients and they were followed up for 24 weeks. The pain associated with mastalgia was assessed in terms of VAS scores. Fibroadenoma size (volume in cc) was assessed using the

sonographically measured dimensions of the lesion. It was seen that 30 (60%) patients had fibroadenoma in the study while 20 (40%) presented with mastalgia.

Mastalgia: In our study, the average age of patients with mastalgia was 22.40±6.15 years with a range of 15-35 years. Most of these patients were between 15-25 years of age(12, 60%). 8 patients were above 25 years of age. Most of the patients had a left sided mastalgia (10, 50%) followed by right sided mastalgia (8, 40%). Only 2 patients had bilateral mastalgia (2,10%). Only one patient was seen to have a side effect of menstrual irregularity in the study. This translated into a complication rate of 5%.

Fibroadenoma: The average age of patients with fibroadenoma in our study was 26.30±5.89 years with a range of 15-35 years. 16 patients belonged to the age group of 25+ years (53.33%) while 14 patients (46.67%) were between 15-25 years of age. Most of the patients had a right sided fibroadenoma (46.67%) followed by left sided fibroadenoma (40%). 4 patients (13.33%) had bilateral fibroadenomas. Most of the patients had a single fibroadenoma (26, 86.67%), 3 patients had 2 lumps (10%) and 1 patient had 3 lumps (3.33%).Only two patients were seen to have side effects in the study- one had menstrual irregularity and another had gastritis. The complication rate was 6.66%.

Brahmchari et al 2021**[5]** showed that Ormeloxifene proved to be safe drug for the treatment of mastalgia and fibroadenoma. Its results were great in mastalgia group. At the end of 6 months, the number of surgeries (if needed) decreased and there was considerable improvement in patient satisfaction rate. Overall final response was noted in terms of complete dissolution and change in size was noted in 34%, partial response in 46 %, no changes in 17 % and increase in size of fibroadenoma was noted in only one case.

Dhar A et al 2007 **[6]** showed good response with Ormeloxifene in mastalgia, with 90% of patients decreasing their VAS score from 10 to 3 in the first week. Almost all of those surveyed were pain-free at the end of one month, with complete disappearance of nodularity. There was mixed response in the fibroadenoma group, with total elimination in 40%, partial regression in 20%, and no response in 40%. There were extremely few negative side effects.

In a recent review by Abdollahi et al 2019**[7]** 12 out of 13 included studies showed a significant effect of Ormeloxifene in reducing breast pain at 3 months. Most of the papers showed similar favourable safety profile as seen in this study.

Nidhi Gupta et al 2016**[4]** showed that the major side effects were allergic rash development (2%) and delayed menstruation of 7-10 days (14%) during therapy.

Rajswaroob et al 2016**[3]** showed that three patients (5.9%) reported epigastric pain and ten patients (19.6%) reported menstrual delay.

CONCLUSION

The study was able to conclude that Ormeloxifene is an effective and safe option for management of mastalgia and fibroadenoma in young females. There was a statistically significant reduction seen in the pain score for mastalgia and in the volume of fibroadenoma. The complication rate was very low (5-6%). The findings of the study were in line with major published literature in this domain both nationally and internationally. Thus, Ormeloxifene can be considered an attractive option for enhancing management in such patients. However, the findings of the study have to be validated by larger studies in this domain to further strengthen relevance for clinical application.

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