

## An Analytical Study to Evaluate Role of Ormeloxifene in Cases of Benign Breast Diseases

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Conflict of interest: Nil

**Abstract:**

**Background:** Benign disorders of the breast are usually seen in the reproductive period of life, thought to be largely hormone induced. The most common symptoms are pain (47%) and a lump (37%). Benign breast disease is 4-5 times more common than breast cancer. There is a dramatic fall in the incidence after menopause due to cessation of ovarian stimulation.

**Objective:** To study the role of Ormeloxifene in the management of Benign Breast diseases with a follow up at 1, 3 and 6 month intervals. Reducing the symptoms of Mastalgia and Nodularity in patients with Benign Breast Disease.

**Method:** The materials for the clinical study of Role of Tablet Ormeloxifene in Benign Breast Diseases were collected from Civil Hospital Ahmedabad, 100 cases of patients having Benign Breast Diseases have been studied. They will be subjected to undergo only relevant investigations. Tablet Ormeloxifene will be started at a dose of 30 mg twice a week for 1 month and follow up at 1, 3 and 6 months intervals. At each follow up visit, the patient is evaluated to look for changes in clinical features, decrease in nodularity as per Lucknow Cardiff Scale or decrease of pain as per Visual Analogue Scale.

**Conclusion:** Ormeloxifene is useful and safe nonsteroidal drug in the management of Benign Breast Diseases. It can be easily managed with a twice weekly dose and majority of the patients show relief of their symptoms

**Keywords:** VAS(Visual Analogue Scale),LCS(Lucknow cardiff scale).

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**Introduction**

Benign conditions account for 90% of the clinical presentations related to the breast. About 30% of all women suffer from breast disorders requiring treatment at sometimes in their life time. Benign disorders of the breast are usually seen in the reproductive period of life, thought to be largely hormone induced. There is a dramatic fall in the incidence after menopause due to cessation of ovarian stimulation. The most common symptoms are pain (47%) and a lump (37%). Benign breast disease is 4-5 times more common than breast cancer. The concept of ANDI-Aberrations of Normal Development and Involution is gaining acceptance. Most benign breast diseases are relatively minor aberrations of normal process of development, cyclical hormonal response, pregnancy and lactation related and involution that interact throughout a woman's life.

The disease consists essentially of four features that may vary in extent and degree in any one breast.

Cyst formation: variable in size.

Fibrosis: fat and elastic tissue disappears and replaced with white dense fibrous trabeculae. The

interstitial tissue is infiltrated with chronic inflammatory cells.

Hyperplasia of epithelial lining of ducts and acini may occur with or without atypia.

**Papillomatosis:** with extensive hyperplasia papillomatous overgrowth occurs within ducts.

The breast is a dynamic structure which undergoes changes throughout woman's reproductive life and cyclical changes during menstrual cycles. The symptoms of ANDI are many but often include an area of lump (seldom discrete) and/or breast pain (mastalgia). A benign discrete lump in the breast is commonly a cyst or a fibroadenoma. True lipomas occur rarely. Lump may be bilateral, commonly in the upper outer quadrant or less commonly confined to one quadrant of one breast. The changes may be cyclical, with an increase in both lump size and often tenderness before a menstrual period.

**Selective Estrogen Receptor Modifiers (SERMs):**

Selective estrogen receptor modulators (SERMs) are now being used as a treatment for breast cancer, osteoporosis and postmenopausal symptoms, as these drugs have features that can act as an estrogen

agonist and an antagonist, depending on the target tissue. After tamoxifen, raloxifene, lasofoxifene and bazedoxifene SERMs have been developed and used for treatment.[8] The clinically decisive difference among these drugs (i.e., the key difference) is their endometrial safety. The mechanism of action of SERM class of compounds relies on their tissue-selective estrogen receptor agonist or antagonist activity in their interaction with the estrogen receptor, and these properties encompass a certain level of molecular and functional complexity. The estrogen receptor has two subunits ( $\alpha$  and  $\beta$  chains), and SERMs interact with either of these subunits, and from this interaction, there is a certain level of target-site specificity and tissue-specificity for SERM action. This differential behaviour of SERMs depends on eliciting varying signalling properties from the estrogen receptor that is tissue specific, and such effects have profound physiological effects and are not dictated at the DNA level. With regards to bone loss and osteoporosis, the action of SERMs on the estrogen receptor affects bone homeostasis by downmodulating the activity of osteoclasts in a transforming growth factor- $\beta$ -dependent manner and reducing bone resorption. This affect allows in preventing and treating osteoporosis. Ormeloxifene is a novel nonsteroidal, selective estrogen receptor modulator, anticancer and anti-osteoporotic drug formulated by the Central Drug Research Institute Lucknow, India. Ormeloxifene has weak estrogen agonistic activity in some tissues like bones, and potent antiestrogenic action in uterus and breast. It is devoid of progesterone, androgenic and anti-androgenic activities. Ormeloxifene is free from side effects like nausea, vomiting, weight gain and dizziness. Ormeloxifene does not delay return of fertility (after stopping) as it does not disturb ovulation. It has only one adverse effect, delayed menses in less than 10% of cycle. Ormeloxifene is well absorbed when given orally. In target tissues such as endometrium and breast, it competes with estradiol for binding to estrogen receptors and shows an anti-estrogenic activity. The drug is demethylated and about 26% is excreted unchanged in feces. It is used as a weekly oral contraceptive.

Ormeloxifene has also been tested in experimental setting as a treatment for menorrhagia.

Use in treatment of mastalgia and fibroadenosis has also been described.

#### **Aims and Objectives of Study:**

To study the role of Ormeloxifene in

- The management of Benign Breast diseases with a follow up at 1-, 3- and 6-month intervals.
- Reducing the symptoms of Mastalgia and Nodularity in patients with Benign Breast Disease.

- The dose of Tablet Ormeloxifene that is to be given among these patients
- The time period in which maximum benefit is achieved.
- To identify the age group which is benefitted the most by the treatment.

#### **Inclusion Criteria**

- 1) Age more than 18 years
- 2) Patients having complaints of Mastalgia Bilateral /Unilateral Breast
- 3) Patients having complaints of Breast Lump Bilateral /Unilateral Breast
- 4) Patients having Benign Breast disease confirmed by Radiological Modalities such as Ultrasound or Cytological study such as FNAC
- 5) All those patients fulfilling the above and consenting to be part of the study

#### **Exclusion Criteria**

- 1) Patients with a discrete lump, which was suspicious of cancer after clinical, imaging and cytological examination were excluded from the study.
- 2) Patients taking alternative treatment, lactating women, those planning a pregnancy or taking other oral contraceptive pills.
- 3) Women suffering from polycystic ovarian disease, other hormonal abnormalities requiring additional investigations, and liver and kidney problems were also excluded from the study.
- 4) All infective conditions and congenital anomalies will be excluded.
- 5) Patients who had previous operative history for benign Breast condition.
- 6) Age less than 18 years

#### **Material and Methods**

The materials for the clinical study of Role of Tablet Ormeloxifene in Benign Breast Diseases were collected from Civil Hospital Ahmedabad, 100 cases of patients having Benign Breast Diseases have been studied. Patients belonged to age groups ranging from 18 years to 50 years. The patients included in the study will be subjected to a thorough history elicitation and physical examination. They will be subjected to undergo only relevant investigations.

Each patient will be evaluated for clinical features of benign Breast Disease at the first visit. Along with clinical correlation, Ultrasound of breast will be carried out and for females more than 35 years of age mammography will be carried out if any diagnostic dilemma present. Tablet Ormeloxifene will be started at a dose of 30 mg twice a week for 1 month and follow up at 1-, 3- and 6-months intervals.

At each follow up visit, the patient is evaluated to look for changes in clinical features, decrease in nodularity as per Lucknow Cardiff Scale or decrease of pain as per Visual Analogue Scale.<sup>12</sup> Each patient

will be followed up till a period of 6 months from the start of the study and responses recorded.

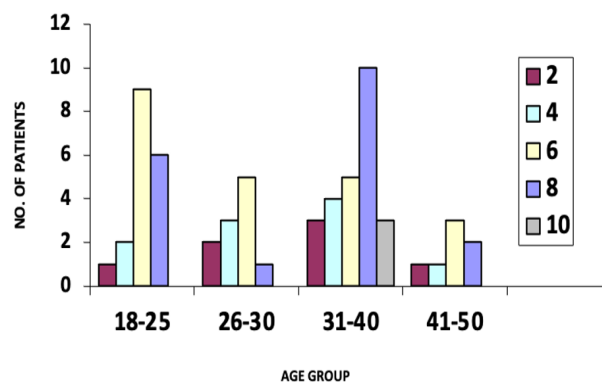
The complaint of mastalgia was assessed as per Visual Analogue Scale.<sup>12</sup>

VISUAL ANALOGUE SCALE										
0	1	2	3	4	5	6	7	8	9	10
NOPAIN		Annoying (mild)			Uncomfortable (moderate)			Horrible (severe)		W O R S T

For nodularity, the Lucknow–Cardiff scale was used. This scale is a 5-point ordinal scale depicting increasing order of nodularity shown schematically in the upper outer quadrants of a paired breast.<sup>12</sup> Grade 0 indicates a smooth textured breast with extreme extent of normalcy and grade 4 the maximum nodularity. There were five figures that provide a cue for the examining physician to chart nodularity in the index breast. The examining

physician makes a holistic interpretation of breast nodularity as a sum of areas or quadrants involved and the coarseness of nodularity. Breast nodularity was assessed longitudinally, by the same clinician on an ordinal scale of 0–4 in the breast clinic at each visit. Data collected from the case records will be entered in Microsoft excel worksheet and data will be analyzed.

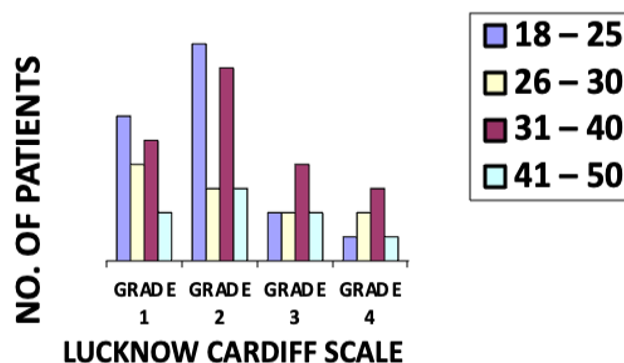
**Mastalgia (Visual Analogue Scale)[12]**



Among age group of 18-25 years Maximum VAS Scale was noted to be 6 in 9 patients. Among age group 26-30 years Maximum VAS Scale was noted to be 4 in 5 patients. Among age group 31-40 years

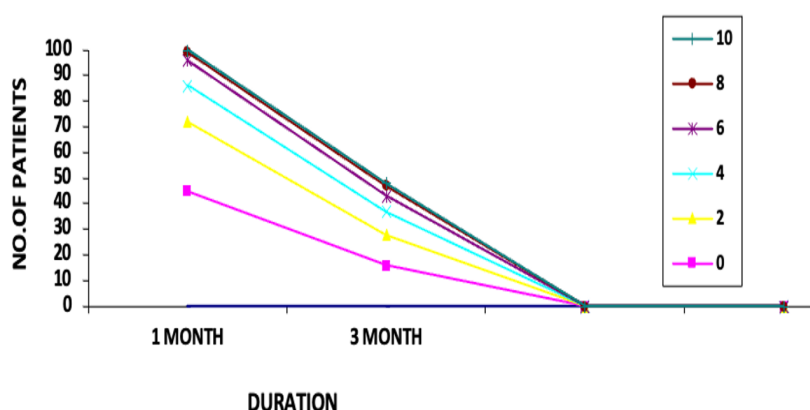
Maximum VAS Scale was noted to be 8 in 10 patients. Among age group 41-50 years Maximum VAS Scale was noted to be 6 in 3 patients.

**Nodularity (Lucknow Cardiff Scale)[12]**



Among age group 18-25 years 11 patients had nodularity of Grade 3. Among age group 26-30 years 14 patients had nodularity of Grade 2. Among age group 31-40 years 27 patients had nodularity of Grade 3. Among age group 41-50 years 5 patients had nodularity of Grade 1.

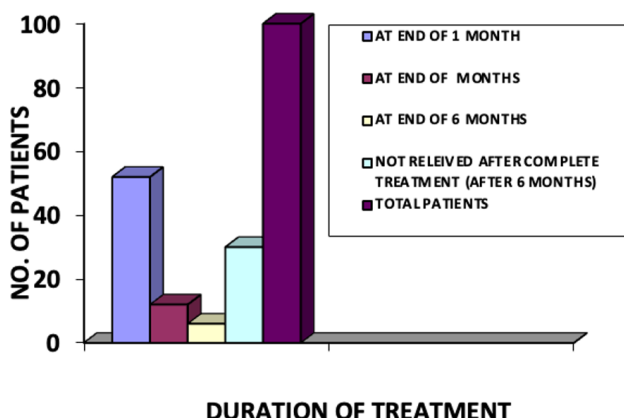
**Relief From Mastalgia (Visual Analogue Scale)[12]**



Visual Analogue Scale	My Study		Vinita Et Al	
	1 MONTH	3 MONTHS	1 MONTH	3 MONTHS
0	45	12	45	22
2	27	16	12	9
4	14	9	16	3
6	10	6	39	4
8	3	4	20	2
10	1	1	5	0

At end of 1 month 45 patients had VAS '0' and at end of 3 months 12 patients had VAS '0'. This symptomatic relief from Mastalgia can be comparable to study by Vinita et al with VAS Scale of '0' at end of 1 month in 45 patients and at end of 3 months in 22 patients.

**ROLE OF ORMELOXIFENE IN BENIGN BREAST DISEASES**



Relief Of Symptoms	Number Of Patients
At End Of 1 Month	52
At End Of 3 Months	12
At End Of 6 Months	6
Not Relieved After Complete Treatment (After 6 Months)	30
Total Patients	100

Amongst 100 patients included in the study, 52 patients were relieved with Tab Ormeloxifene 30mg twice a week within a month. Symptomatic relief from Pain and Nodularity by using Tablet Ormeloxifene 60 mg at end of 3 months is observed in 12 Patients. Symptomatic relief from Pain and

Nodularity by using Tablet Ormeloxifene 60 mg at end of 6 months is observed in 6 Patients. The rest 30 patients were not benefitted even with an increased dose at the end of 6 months.

**Conclusion**

Benign Breast Diseases are more common in Reproductive age group between 31 to 40 years. Mastalgia and Nodularity are common presentations in Benign Breast Disease. The most common age group with benign breast disease is between 31- 40 years among which most of them presented with Nodularity. Mastalgia was the common presenting complaint in the age group 10-20 years and 21-30 years. Clinical assessment of Breast along with Ultrasonography and FNAC is very useful in Diagnosis of Benign Breast Diseases. Out of 100 patients, 70 patients were relieved of their symptoms by Tablet Ormeloxifene(30mg,60mg) twice a week. Out of 70 patients, 52 patients were relieved by Tablet Ormeloxifene 30mg twice a week at the end of 1 month. Remaining 12 patients were benefited after 3 months with Tablet Ormeloxifene 60mg twice a week. Other 6 patients were relieved after 6 months with Tablet Ormeloxifene 60mg twice a week. The rest 30 patients were not relieved of their symptoms even after 6 months. Patients in age group of 31 to 40 years were most benefited by Tablet Ormeloxifene (30mg, 60mg) twice a week.

Ormeloxifene is useful and safe nonsteroidal drug in the management of Benign Breast Diseases. It can be easily managed with a twice weekly dose and majority of the patients show relief of their symptoms at a period of 1 month.

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