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COMPARATIVE STUDY OF THE EFFICACY OF ORMELOXIFENE, DANAZOL AND EVENING PRIMROSE OIL ON TREATMENT OF BREAST NODULARITY

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ABSTRACT **Introduction:**Mastalgia is a common problem and 60-70% women encounter it at least once in their lifetime. Manydrugs have been used and are been used with varying response, like Tamoxifen, Danazol, primrose oil, topicalanalgesics and recently Centchroman. This study was undertaken to compare the clinical efficacy of ormeloxifene, danazol and evening primrose oil and treatment response on breast nodularity with help of Lucknow- Cardiff scale. **Materials and Methods:**The present study was carried out on approximately 100 women attending out-patient and in-patient service of department of Obstetrics and Gynecology at Swaroop Rani Nehru Hospital, Allahabad and Kamla Nehru Memorial Hospital, Allahabad, of Moti Lal Nehru Medical College, Allahabad over a period from August 2014 to July2015.Written informed consent was obtained from these women after explaining in detail about the study.The distribution of patient characteristics was expressed as frequencies and percentage. All statistical analysis was done using Microsoft excel. **Results:**Maximum numbers of cases (71.8%) were of age group of 21 to 30 years. The mean age of cases of ormeloxifene group was 26.96±5.257 years, mean age of danazol group was 26.81±5.497 years and mean age of evening primrose oil group was 27±5.345 years.In all the three groups, one half of patients had grade-4, grade-5 of breast nodularity, in ormeloxifene group 50%, in danazol group 50% and in evening primrose oil group 46.14% cases had grade-4 and grade-5 nodularity. **Conclusion:**Ormeloxifene was found to be superior to danazol in treating mastalgia and danazol was found to be superior to evening primrose oil for management of mastalgia.

KEYWORDS : Breast nodularity, ormeloxifene, danazol, evening primrose oil

Introduction:

Commonly seen benign lesions of the breast are summarized as developmental, inflammatory lesions, fibrocystic changes, stromal lesions, and neoplasm. The term "benign breast diseases" encompasses a heterogeneous group of lesions that may present a wide range of symptoms or may be detected as incidental microscopic findings. The incidence of benign breast lesions begins to rise during the second decade of life and peaks in the fourth and fifth decades.(1) Breast pain or mastalgia is one of the most common benign conditions of the breast.(2)It was first described in the medical literature in 1829 but was known to medical practitioners much earlier. During luteal phase of menstruation, cell proliferation of duct lobular tissue and increase in interstitial fluid, result in up to 15% increase in breast size and volume. This increase in breast tissue volume results in pressure on pain sensitive nerve endings and causes premenstrual pain. Just prior to menstruation the oestrogen and progesterone levels fall with reducing cellular proliferation in the early follicular phase and consequent relief of pain and breast engorgement.(3)Rarely mastalgia is only symptom of breast cancer. Although an association between mastalgia and the subsequent development of breast cancer may exist, the nature of the relationship is not clear. Based on current evidence, clinical examination of the breasts and assessment of the patient's individual risk for breast cancer should be the main determinants of the need for imaging or other investigation.Benign breast disorders that present as pain, inflammation, nipple areola problems, discrete lump and nodularity are common. Pain and nodularity in the breast is the single most common reason for which women seek medical advice about their breasts.(4) This was the presenting symptom in 45–85% of women with breast problems.(5) The problem of benign breast diseases has so far received scant attention in India but it is expected to increase due to lifestyle changes, dietary modifications, early menarche, delayed first child birth and exogenous hormone administration. An apparent increase is occurring on account ofincreasing awareness. Estimates regarding breast pain as the presenting feature and the underlying causes of breast pain in the Indian population remain speculative because of lack of population-based studies and lack of uniformity in terminology.(6,7) Breast nodularity with or without pain of the breast is a symptom that deserves full attention and careful evaluation. This condition has been described in literature for the past 2 decades as ANDI or Aberration of Normal Development and Involution.(8)Objective of this study is to compare clinical efficacy of ormeloxifene, danazoland evening primrose oil and assessment of treatment response on breast nodularity with help of Lucknow- Cardiff scale.

Material and methods:

The present study was carried out on approximately 100 women attending out-patient and in-patient service of department of Obstetrics and Gynecology at Swaroop Rani Nehru Hospital, Allahabad and Kamla Nehru Memorial Hospital, Allahabad, of Moti Lal Nehru Medical College, Allahabad over a period of one year (August 2014 - July2015).

Inclusion criteria:

- All women with mastalgia and breast lump attending OPD were eligible for inclusion in the study except the cases as specified in exclusion criteria.

Exclusion criteria:

- Clinical or radiological suspicion of malignancy
- Patient deemed as a candidate for surgical treatment by treating physician
- Patients with renal or hepatic dysfunction
- Lactating and pregnant women
- Patients with mal absorption syndrome
- Patient taking analgesics on regular basis for some unrelated cause like rheumatoid arthritis, surgery, migraine etc

Study procedure:

A thorough history of patient's illness was taken at the time of recruitment. The history was specially focused on the presenting symptoms, it's duration, progression and its impact on patient's personal and social life. History of any significant co-morbidity was also documented. Patients were also enquired about any medical or other modality of treatment which patient had tried for her illness.

On follow up at one month and three month the same was repeated with special note on the objective and subjective change in patient's symptom. As pain is most important and most troublesome symptom, special attention was paid on this symptom.

Breast examination was done at the time of first visit then after one and three months.

A special note was made on size, site, number, consistency and presence or absence of tenderness in breast lump/ mass. Objective assessment of treatment response on breast nodularity / lumpy breast was done with help of Lucknow- Cardiff scale of breast nodularity.(9)This scale is a 5-point ordinal scale depicting increasing order of nodularity shown schematically in the upper outer quadrants of a paired breast. Grade 0 indicates a smooth textured breast with extreme extent of normalcy and grade 4 the maximum nodularity. There were five figures that provided a cue for the examining physician

to chart nodularity in the index breast. The examining physician made 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 at each visit. For the purpose of data analysis, the grades were renumbered as 1 to 5, and labelled as normal, mild, moderate, severe and very severe, respectively. To take advantage of ordinal outcomes and summarize the association over all grades, it was informative to do the analysis using the cumulative frequencies of the nodularity grades in the groups. A note was made on Lucknow- Cardiff scale of breast nodularity at the time of presentation, one month and three months follow up.

Patient's compliance to the treatment was assessed by interrogation at each follow-up visit. At the end of treatment patient were specifically asked for their own view regarding the efficacy of treatment and impact of treatment on their personal and social life. Treatment response on breast pain was assessed using Cardiff breast pain score. This is a four-point ordinal scale using score of 1 to 4 for different response.

Table-1: Assessment of treatment response on breast nodularity

Score	RESPONSE
Grage-1	Excellent response with no residual pain
Grage-1	Substantial response but with some residual pain, considered by patient to be bearable
Grage-1	Poor response with substantial residual pain
Grage-1	No response at all

After initial evaluation, only those patients were recruited in the study in whom medical management was decided as treatment of choice by treating physician. Study protocol was explained to patients and they were randomized in three groups. A very simple method of randomization was used. We serially prescribed ormeloxifene, danazol and evening primrose oil to the patients recruited in the study. We have recruited 108 patients in study but 14 patients were lost during follow up. Remaining 96 patients completed the treatment and only these patients were included in final analysis.

Ethical issues:
Permission from ethical committee of the institute was taken, and all beneficiaries were explained about the purpose of study. Written informed consent was obtained from these women after explaining in detail about the study.

Data collection and statistical analysis:
Details of patients and disease characteristics including symptoms, clinical findings and imaging studies were recorded in specified proforma. The distribution of patient characteristics was expressed as frequencies and percentage. All statistical analysis was done using Microsoft excel.

Result:
The present study was carried out on women attending the outpatient department whose age ranged from 17 to 40 years with mastalgia, with or without breast nodularity and cases of fibroadenoma of less than 5 cm size.

Table-2: Distribution of Cases

Groups	Drug used	No. of cases	Percentage
1.	Ormeloxifene	31	32.29%
2.	Danazol	33	34.37%
3.	Evening Primrose Oil	32	33.33%
Total		96	100%

First group included 31cases who were given oral ormeloxifene 30 mg on alternate day. Second group included 33 cases, who were given oral danazol 100 mg daily and third group included 32 cases, who were given oral evening primrose oil 1000 mg daily. Subsequently patient was evaluated at 4 weeks and 12 weeks(Table-2).

Table-3: Age Distribution in different groups

Age group (years)	Group- 1		Group- 2		Group- 3		Total
	No.	%	No.	%	No.	%	
<20	2	6.45%	3	9.09%	3	9.37%	8
21-25	11	35.48%	12	36.36%	11	34.37%	34
26-30	12	38.70%	11	33.33%	12	37.5%	35
31-35	4	12.90%	4	12.12%	4	12.50%	12
36-40	2	6.45%	3	9.09%	3	9.37%	8
Total	31		33		32		96
Mean	26.96±5.257		26.81±5.497		27±5.345		

Among all the three groups maximum number of patient belonged to age of 21-30 years(group 2 & 3). In the age group 31-15 years (group-4), there were 12 women, 4 in ormeloxifene group, 4 in danazol group, 4 in EPO group. In the age group 36-40 years, there were 8 women, 2 in ormeloxifene group, 3 in danazol group, 3 in EPO group.Overall mean age of ormeloxifene group was 26.96±5.257 years of danazol group 26.81±5.497 years and of EPO group was 27±5.345 years. (table-3)

Table-4: Effect of Ormeloxifeneon Breast Nodularity

Grades of nodularity	Pretreatment		After 4 weeks		After 12 weeks	
	No.	%	No.	%	No.	%
Grade 1	2	16.66%	4	33.33%	0	0
Grade 2	2	16.66%	4	33.33%	3	25%
Grade 3	2	16.66%	3	25%	1	8.33%
Grade 4	3	25%	1	8.33%	1	8.335
Grade 5	3	25%	0	0	0	0
Total no. of cases	12		12		5	

In ormeloxifene group, at start of study out of 12 cases had nodularity of grade 1 to 5. After four weeks 4(33.33%) cases had grade 1 nodularity, 4(33.33%) cases had grade 2 nodularity, 3(25%) cases had grade 3 nodularity and 1(8.33%) case had grade 4 nodularity. After 12 weeks 7(58.33%) cases were relieved of nodularity, 3(25%) cases had grade 2 nodularity, 1(8.33%) cases had grade 3 nodularity, and 1 (8.33%) case had grade 4 nodularity. (Table-4)

Table-5: Effect of Danazol on Breast Nodularity

Grades of nodularity	Pretreatment		After 4 weeks		After 12 weeks	
	No.	%	No.	%	No.	%
Grade 1	3	25%	3	25%	4	33.33%
Grade 2	1	8.33%	3	25%	2	16.66%
Grade 3	2	16.66%	3	25%	1	8.33%
Grade 4	3	25%	2	16.66%	2	16.66%
Grade 5	3	25%	1	8.33%	0	0
Total no. of cases	12		12		9	

In danazol group, at start of study out of 12 cases, After four weeks 3(25%) cases had grade 1 nodularity, 3(25%) cases had grade 2 nodularity, 3(25%) cases had grade 3 nodularity and 2(16.66%) cases had grade 4 nodularity , 1(8.33%) case had grade 5 nodularity. After 12 weeks 3(25%) cases were relieved of nodularity, 4(33.33%) cases had grade 1 nodularity, 2(16.66%) cases had grade 2 nodularity, 1(8.33%) cases had grade 3 nodularity and 2(16.66%) cases had grade 4 nodularity .(Table-5)

Table-6: Effect of Evening Primrose Oil on Breast Nodularity

Grades of nodularity	Pretreatment		After 4 weeks		After 12 weeks	
	No.	%	No.	%	No.	%
Grade 1	3	23.07%	4	30.76%	1	7.69%
Grade 2	2	15.38%	2	15.38%	3	23.07%
Grade 3	2	15.38%	2	15.38%	4	30.76%
Grade 4	3	23.07%	3	23.07%	2	15.38%
Grade 5	3	23.07%	2	15.38%	1	7.69%
Total no. of cases	13		13		11	

In EPO group, at start of study out of 13 cases, After four weeks of treatment 4cases (30.76%) had grade 1 nodularity, 2(15.38%) cases had grade 2 nodularity, 2(15.38%) cases had grade 3 nodularity and 3(23%) cases had grade 4 nodularity , 2(15.38%) case had grade 5 nodularity. After 12 weeks 2 cases were relieved of nodularity, 1 case had grade 1 nodularity, 3 cases had grade 2 nodularity, 4 cases had grade 3 nodularity, 2 cases had grade 4 nodularity and 1 case had grade 5 nodularity. (Table-6)

Table – 7: Treatment Response in Mastalgiaat Four Weeks (According To Cardiff Breast Pain Score)

Grade	Response	At 4 weeks		
		Group-1	Group-2	Group-3
1	EXCELLENT	12(46%)	11(40.74%)	9(34.61%)
2	SUBSTANTIAL	11(42.30%)	10(37.03%)	6(23.07%)

3	POOR	2(7.69%)	4(14.81%)	6(23.07%)
4	NONE	1(3.84%)	2(7.40%)	5(19.23%)

At four weeks, grade 1 (excellent) response was observed in 12(46%) cases in ormeloxifene group, 11(40.74%) cases in danazol group and 9(34.61%) cases in evening primrose oil group. Grade 2(substantial) response was observed in 11(42.30%) cases in ormeloxifene group, 10(37.03%) cases in danazol group and 6(23.07%) cases in evening primrose oil group. Grade 3(poor) response was observed in 2(7.69%) cases in ormeloxifene group, 4(14.81%) cases in danazol group and 6(23.07%) cases in evening primrose oil group. Grade 4(none) response was observed in 1(3.84%) cases in ormeloxifene group, 2(7.40%) cases in danazol group and 5(19.23%) cases in evening primrose oil group.(Table-7)

Table – 8: Treatment Response inMastalgiaat Twelve Weeks (According To Cardiff Breast Pain Score)

Grade	Response	At 12 weeks		
		Group-1	Group-2	Group-3
1	EXCELLENT	21(80.79%)	20(74.07%)	18(69.23%)
2	SUBSTANTIAL	4(15.38%)	4(14.81%)	3(11.53%)
3	POOR	1(3.84%)	3(11.11%)	3(11.53%)
4	NONE	0	0	2(7.69%)

At twelve weeks, grade 1 (excellent) response was observed in 21(80.79%) cases in ormeloxifene group, 20(74.07%) cases in danazol group and 18(69.23%) cases in evening primrose oil group. Grade 2(substantial) response was observed in 4(15.38%) cases in ormeloxifene group, 4(14.81%) cases in danazol group and 3(11.53%) cases in evening primrose oil group. Grade 3(poor) response was observed in 1(3.84%) cases in ormeloxifene group, 3(11.11%) cases in danazol group and 3(11.53%) cases in evening primrose oil group. Grade 4(none) response was observed in 2 (7.69%)cases in evening primrose oil group. (Table-8)

DISCUSSION:

Many drugs have been used with varying response, like Tamoxifen, Danazol, oil of evening primrose, topical analgesics and much recently, at least in India, a very commonly used, cheap oral contraceptive pill, Centchroman. Pharmacologically, Centchroman is Ormeloxifene, a nonsteroidal selective oestrogen receptor modulator (SERM) used primarily as an oral contraceptive. (10) In present study, age distribution is comparable to previous studies on benign breast disease and consistent with the fact that benign breast disease commonly affects young women. Another study showed 70% belonged to the age group 15-25 years, 20% to 26-35 years. (11) Mean age of patients studied by Dhar et al. (12) was 26 years. In present study, ormeloxifene group, at the start of study out of 12 cases had nodularity of grade 1 to 5.After four weeks of treatment 33.33% cases had grade 1 and 2 nodularity. After 12 weeks of treatment nodularity was completely resolved in 58.33% of cases. In danazol group, After four weeks of treatment, 3(25%) cases had grade 1 and 2 nodularity, only 1(8.33%) case had grade 5 nodularity. After 12 weeks of treatment, 3(25%) cases were relieved of nodularity.In EPO group, After four weeks of treatment 30.76%had grade 1 nodularity, only15.38% case had grade 5 nodularity. The result of present study was comparable with that of Kumar et al (13) in which significant improvement in breast nodularity was noted after treatment with Ormeloxifene. After four weeks 4(33.33% vs 37.3%) cases had grade 1nodularity, After 12 weeks 7(58.33% vs 62.7%) cases were relieved of nodularity. They summed up that oral ormeloxifene showed significant efficacy for treating breast pain and nodularity. Similar results were achieved by Dhar et al (12). Nodularity was present in 35 cases. At the end of first week of Ormeloxifene therapy, nodularity disappeared in 14% and regressed partially in 46% but no change was seen in40% of cases. At the end of 12 weeks, there was complete resolution in all cases.In present study, at four weeks, grade 1 (excellent) response was observed in 46% cases in ormeloxifene group, 40.74% cases in danazol group and 34.61% cases in evening primrose oil group. Grade 2(substantial) response was observed in 42.30% cases in ormeloxifene group, 37.03% cases in danazol group and 23.07% cases in evening primrose oil group. At twelve weeks, grade 1 (excellent) response was observed in 80.79% cases in ormeloxifene group, 74.07% cases in danazol group and 69.23% cases in evening primrose oil group. Sughra et al (2007) reported that amongst those patients who used Danazol, Grade-I response was observed in 44% patients at 4 weeks and 76% patients at 12 weeks in comparison to OEP patients with 36% at four and 68% at 12 weeks.(11)In a study by Dhar et al, for Centchroman in mastalgia, they found a 100% relief after 12 weeks of treatment with this drug.(12)On the other hand, in a meta-analysis done by Srivastava et al, it was found that Tamoxifen is the most effective form of treatment of mastalgia when compared withbromocriptine, Danazoland oil of evening primrose. Centchroman was not included in this study.(14)Rathi et al, reported 88% pain relief after 12 weeks of initiation of therapy with Centchroman. (15)Tejwani et al, found Centchroman to be better than Tamoxifen in reducing breast pain in a randomized trial.(16)

CONCLUSION:

According Cardiff breast pain score, at the end of 12 weeks excellent response was found to have in 80.79% of cases after ormeloxifene treatment, 74.07% of cases after danazol, 69.23% of cases after EPO treatment.Thus it was concluded from present study that all the three drugs are effective in treating mastalgia and nodularity. Ormeloxifene was found to be superior to danazol in treating mastalgia and danazol was found to be superior to evening primrose oil for management of mastalgia.

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