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Regression of Mastalgia with Ormeloxifene in comparison with Danazol- A randomized control trial

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Abstract

Background: The most common benign conditions of the breast is Breast pain or Mastalgia. Many drugs have been tried in the treatment of mastalgia. A randomized trial was conducted to evaluate the effectiveness of Ormeloxifene in the control of mastalgia and compared it with Danazol. There is considerable debate about drug of choice for management of mastalgia. We present our results of a trial of antiestrogen drug “Ormeloxifene”. The objective of this study was to determine whether pain relief achieved by Ormeloxifene is similar to or better than that achieved by Danazol.

Methodology: In a randomized controlled trial of Ormeloxifene vs. Danazol in mastalgia, 162 patients with mastalgia were selected for the study. Eighty one (81) patients were randomized to Danazol arm and 81 in Ormeloxifene arm. The treatment was given for 12 weeks, followed by observation for 12 weeks. The pain was measured by visual analogue scale (VAS) of 0–10. Progression of nodularity was measured using Lucknow cardiff scale (LCS).

Results: At 12 weeks 90.7% women achieved reduction in pain score to ≤3 in Ormeloxifene group. In Danazol group 71.1% women achieved reduction in pain score to ≤ 3 . Three months after stopping therapy, Ormeloxifene was found to be more effective in pain score reduction at 24 weeks as compared to Danazol.

Conclusion: Ormeloxifene is an effective, safe and inexpensive alternative to Danazol for treatment of mastalgia.

Keywords: Breast pain, Danazol, Mastalgia, Ormeloxifene, Randomized trial.

Introduction

Benign Breast disorders - ‘Universal phenomenon’ in all ages of women causing physical and psychological distress .The most common benign conditions of the breast is Breast pain or Mastalgia. Breast pain chart is helpful for assessing the pattern and severity of Breast pain.Mastalgia may be cyclic or non-cyclic, intermittent or constant, localized or diffuse. Non cyclicalmastalgia can be true i.e arising from breast tissue or it can arise from

chest wall e.gTietze's syndrome and lateral chest wall pain [1].

Cyclical mastalgia is defined as breast pain with either only premenstrual exacerbation or pain throughout the month with premenstrual exacerbation. Non-cyclical mastalgia is defined as intermittent or continuous breast pain without premenstrual exacerbation and no obvious source of musculoskeletal disease.

There is an increased cell proliferation of ductolobular tissue and interstitial fluid that result in up to 15% increase in breast size and volume during the Luteal phase of Mensturation. So the premenstrual mastalgia is due to this increase in breast tissue volumethat results in pressure on pain nerve endings. Just prior to menstruation the estrogen and progesterone levels fall with reducing cellular proliferation in the early follicular phase and consequent relief of pain and engorgement [2]. Different hypotheses for mastalgia have led to use of different medical and non medical therapies. The mastalgia may be caused by either[3]:

1. Increased estrogen secretion from ovary
2. Deficient progesterone production
3. Increased Prolactin secretion

The theories of hormonal influence in cyclical mastalgia areExcessive estrogen , Deficient progesterone , Changes in progesterone/estrogen ratio and Abnormalities in receptor sensitivity that includes abnormalities in follicle stimulatinghormone/luteinizing hormone levels, Low androgen levels andhigh prolactin levels.

Many drugs have been tried in the treatment of mastalgia. The pharmacological therapy includes agents inducing hormonal manipulation such as Danazol[4], Bromocriptine[5], Tamoxifen [6], and LH-RH [7] analogue like Goserelin. Some of the effective non-hormonal agents in mastalgia are Non- steroidal anti-inflammatory gels [8], reassurance [9] and breast support with sport's bra [10].

There is considerable debate about drug of choice for management of mastalgia. We present our results of a trial of antiestrogen drug "Ormeloxifene". The objective of the study was to evaluate the effectiveness of Ormeloxifene in Regresssion of mastalgia in comparison with Danazol severity of pain score which is assessed by VAS score and Progression of breast nodularity on pre-validated Lucknow–Cardiff scale.

Methodology

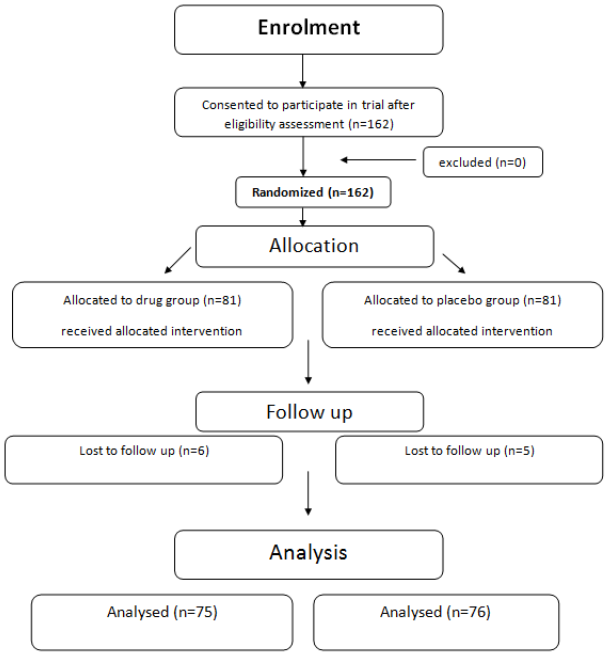
The study was approved by the Institute ethics committee of ESIC Medical College & PGIMSR, K.K.Nagar, Chennai. Women of age group 15 to 65 years presenting to General Surgery OP with complaints of mastalgia (both cyclical and non-cyclical)with VAS score ≥3 , nodularity, benign lumps Fibroadenoma less than 3 cms in diameter), nodularity were included after signing a consent form.If the patient was >35 years of age, a thorough clinical examination of the breast was done followed by bi-planer mammography. Demographic variables, clinical history, general examination and breast examination were carefully recorded on a pre-designed proforma. Patients were excluded from the study if they found suspicious of cancer after clinical, imaging and cytological examination. The Patients those who are taking alternative treatment, lactating women, those planning a pregnancy or taking other oral contraceptive pills, women suffering from polycystic ovarian disease, other hormonal abnormalities requiring additional investigations, and liver and kidney problems were excluded from the study.

Demographic variables, clinical history, general examination and breast examination were carefully recorded on a pre-designed proforma. The patients were provided with a detailed printed information sheet (in Tamil or English depending on the language understood by her) to explain about benign nature of breast pain, the currently available therapy with side effects, the potential

benefits of ormeloxifene and its common use by Government of India as a contraceptive pill. We also informed patients about the possibility of scanty or delayed menstruation by ormeloxifene. Informed written consent was obtained from all patients.

162 patients with mastalgia were selected for the study . Eighty one (81) patients were randomized to Danazol arm and 81 in Ormeloxifene arm (Figure 1).

Figure 1 : Randomization and follow up.



We used a single blind (investigator assessing the response was blinded) two arm parallel design randomized controlled trial. Block randomization with a block size of 4 was employed to generate a list of random number. The sealed numbered opaque brown envelopes were prepared with the label of case number e.g " case 1" . The envelopes were opened after ensuring inclusion criteria and signing the consent form. The envelope contained a folded slip of paper stating the assigned treatment, i.e Ormeloxifene or Danazol. The assigned treatment was given to the patient.

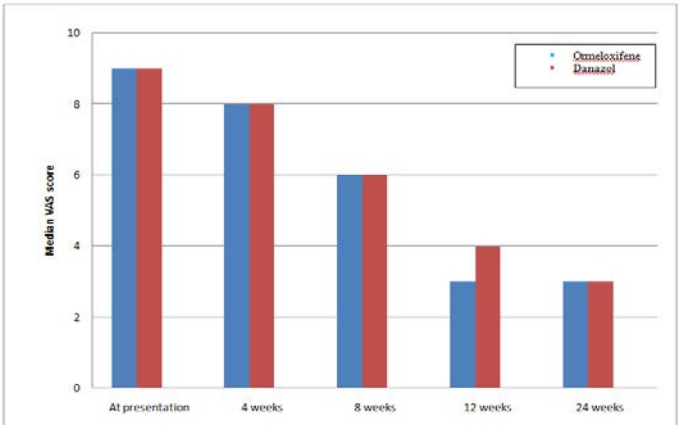
Patients were randomized to get Ormeloxifene 30 mg daily or Danazol 100 mg daily for 3 months. The patients were evaluated at one week to assess tolerance to the drug. Subsequently patients were followed at 4 weeks, 8 weeks,12 weeks and 24 weeks and response to therapy was assessed by VAS score. The drug treatment was continued for a total of 12 weeks and then the patient was followed for another 12 weeks without medication to assess sustained response or recurrence of mastalgia.

Pain at initial visit and at subsequent visits will be documented using New breast pain score (VAS)**.** Nodularity of the Breast will be documented on the Lucknow Cardiff scale in view of extent of breast involved with nodularity and extent of nodularity (consistency). This scale is a 5-point ordinal scale depicting increasing order of nodularity .Grade 0 indicates a smooth textured breast with extreme extent of normalcy and grade 4 the maximum nodularity. This scale will be documented by the same clinician for each patient at each visit to prevent observer bias and Ultrasonogram for size of the lump.

Results with Discussion

Seventy five patients were studied in Ormeloxifene arm and 76 in Danazol arm. The change in Median VAS pain score was followed up till 24 weeks (figure 2).

Fig 2: Change in Median VAS pain score till 24 weeks follow up



The median scores were similar for both Danazol and Ormeloxifene at baseline and also during 4 weeks and 8

weeks. There was significant relief of mastalgia in both arms.Patients in Ormeloxifene arm experienced early relief of mastalgia as compared to patients in Danazol arm as seen in Figure 2.

A higher proportion of patients showed regression of mastalgia after treatment with Ormeloxifene as compared Danazol arm. Moreover, three months after cessation of therapy, a higher proportion of patients showed continuation of pain relief with Ormeloxifene whereas only nearly 64% sustained pain relief in Danazol arm. The differences in proportions were found to be statistically signicant ($p<0.05$).by Chi-square test as shown in Table1.

Table 1: Proportion of patients showing regression of mastalgia with Danazol and Ormeloxifene

Weeks	Drug	Total	Regression of mastalgia		p value (chi-square)
			Number	%	
12 weeks	Ormeloxifene	75	68	90.7	0.003
	Danazol	76	54	71.1	
24 weeks	Ormeloxifene	75	73	97.3	0.00001
	Danazol	76	49	64.5	

The effect of the two drugs on mastalgia were analysed based on VAS score and LCS score using Mann Whitney U test (Table 2 and 3)

Table 2: Effect of Ormeloxifene and Danazol on mastalgia based on VAS score:

Weeks	Median VAS score (Range within brackets)		P value (Mann-Whitney U test)
	Danazol N=76	Ormeloxifene N=75	
At presentation	9 (8-10)	9 (8-10)	1
4	8 (7-9)	8 (7-9)	0.034
8	6 (5-7)	6 (5-7)	<0.05
12	4 (3-5)	3 (3-4)	<0.05
24	3 (3-4)	3 (2-3)	<0.05

Table 3: Effect of Ormeloxifene and Danazol on mastalgia based on LCS score:

Weeks	Median LCS score (Range within brackets)		P value (Mann-Whitney U test)
	Danazol N=76	Ormeloxifene N=75	
At presentation	4 (3-4)	4 (3-4)	1.000
4	4 (3-4)	4(3-4)	1.000
8	3 (3-4)	3(2-4)	0.003
12	2 (2-3)	2(2-3)	0.004
24	2 (2-3)	3(2-3)	0.001

VAS score was used to determine the regression of mastalgia after treatment in both the arms . The objective measurement of breast nodularity was done using the Luknow cardiff scale. The median VAS and LCS scores

were similar for both the drugs at presentation and 4 weeks of treatment. After 8 weeks of treatment the regression of mastalgia was more with ormeloxifene when compared to Danazol as measured by both VAS and LCS scores. The difference in the median scores for the two drugs was found to be statistically significant by Mann Whitney U test as shown in Table 2 &3.

Discussion

Severe breast pain interferes with the women day to day activities and this raises the fear of breast cancer. In most patients, reassurance (that the symptoms are not due to cancer) is all that is required if they experience mild breast pain symptoms. A Brazilian study [9] verified that reassurance alone for 85 patients with mastalgia had a overall success rate of 70.2%. Dietary measures like fat restriction and avoidance of methylxanthines [11] are the other non medical means of treatment. Breast support with sport's brassier [10] in a randomized trial of 200 patients relieved the pain in 89% of patients. The support garments reduces the tension on overstretched Cooper's ligament especially in women endowed with large mammary glands and thus provide relief from pain. Hence support garments should be advised in these patients. The drugs available for the treatment of mastalgia are Danazol, Tamoxifen, Bromocriptine, Evening Primrose Oil, Gamolenic acid [12], LHRH analogue Goserline, oral contraceptive pills, diuretics and topical NSAIDs gels with varying efficacy and side effects.

A meta-analysis of randomized trials was performed on mastalgia and found Tamoxifen, Danazol, and Bromocriptine to be significantly effective in treatment of mastalgia when compared to placebo [13]. However the response to Evening Primrose oil was no better than placebo. This meta-analysis suggested that antiestrogen, Tamoxifen may be the drug of choice. Because of the side effects and high cost Bromocriptine and Danazol are best avoided. As there is lack of benefit over placebo, Evening primrose oil can be avoided. Similarly there is no evidence of any benefit with Vitamin E preparations.

Danazol was introduced by Greenblat and co-workers in 1971. They suggested that it might have a role in mastalgia. Danazol is unique in its action on the pituitary ovarian axis. In monkeys it was shown to act as anti-gonadotrophin, as it prevented ovulation and depressed the serum levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH).As It interferes with FSH and LH levels only at higher doses [4], So the action of Danazol in humans is not so clearly defined. The usual dose of Danazol for treatment of mastalgia is 100–400 mg per day. Danazol is an efective drug for severe mastalgia and nodularity, with an overall success in improvement rate of 70%. Danazol is far superior to bromocriptine in treatment of cyclical mastalgia [14, 15]. In a meta-analysis of 4 randomized trials we found a highly significant relief of mastalgia using Danazol, as compared to placebo [13]. The side effects of Danazol are mainly amenorrhea, the incidence of which increases with dose up to 100% at 600–800 mg per day. It causes weight gain, acne, amenorrhea and hirsutism. All the side effects of Danazol are dose dependent. Presently because of several side effects Danazol is not commonly used in most breast clinics and is reserved as a second line drug for mastalgia.

Tamoxifen is now considered the drug of choice in most breast clinics in the West for treatment of mastalgia . Tamoxifen is a steroidal antiestrogen and has been found to be effective in relief of mastalgia in various randomized trials [16–18]. It has been used in dosage ranging from 5 mg–20 mg/ day for a period of 12 weeks. In a meta-analysis on 3 published randomized trials of tamoxifen, the overall relief of pain achieved with Tamoxifen compared to placebo had a relative risk (RR) of 1.92 (95% CI; 1.42–2.58) which was highly significant with $p<0.0001$ [13].

Tamoxifen is a very well tolerated drug at low dosage of 10 mg daily for 3 months, with minimal side effects. However its use may be associated with hot flashes, vaginal dryness, low libido, mood swings, nausea and rarely fluid retention.

Ormeloxifene (Centchroman–C30H35NO3) is a selective estrogen receptor modulator, anticancer, anti-osteoporotic and a novel nonsteroidal drug formulated by the Central Drug Research Institute, Lucknow, India. It was included in the National Family Welfare Program in 1995 as a "once a week pill". Ormeloxifene [19] has weak estrogen agonistic activity in some tissues like bones, and potent anti-estrogenic action in uterus and breast. It do not have 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. Only one adverse effect is delayed menses in less than 10% of cycles. It maintains normal ovulatory cycles. There are no apparent adverse effects on endocrine, hematologic, liver and lipid function and, to date, has not been associated with any serious complications viz. heart attack, stroke or thrombosis [20–22]. Ormeloxifene is orally well absorbed . Single 30 mg dose results in maximum concentration in serum of 30 to 78 ng/mL in 3 to 8 hours. The drug is well absorbed in nursing mothers with maximum serum concentration of 50 to 79 ng/ ml achieved in 6 hours. Due to high lipid solubility, the drug is widely distributed throughout the body. The mean residence time was found to be 128 days. It binds strongly with serum albumin. The drug does not compete with cortisol, oestradiol, progesterone, diethylstilbosterol, testosterone and tamoxifen. 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 [23]

Ormeloxifene is an economic and easily available drug for therapy of mastalgia. In our randomized trial combining both alternate and daily dosage, Ormeloxifene was found to have response rate of 90.7 % (reduction of pain to less than or equal to 3 on VAS) at the end of 12 weeks. Danazol achieved 71.1% response rate at 12 weeks. A greater proportion of women in Ormeloxifene group continue to enjoy pain free life even after stopping the drug, suggesting a longer carry-over effect. Ormeloxifene scores over Tamoxifen in being nonsteroidal molecule hence devoid of steroid like side effects in the long term therapy. It is also cheaper than Tamoxifen and Danazol. Moreover, there are no reports of endometrial carcinoma or thromboembolic side-effects with long term use of Ormeloxifene as compared to Tamoxifen.

Conclusion

This trial has demonstrated that Ormeloxifene therapy offers an effective alternative to Danazol for the regression of mastalgia and nodularity.

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