

## COMPARATIVE EFFECT OF DANAZOL VS EVENING PRIMEROSE OIL IN THE MANAGEMENT OF MASTALGIA IN WOMEN IN A TERTIARY CARE HOSPITAL

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### Abstract

**Background:** The objective is to study the recent outcomes of management of mastalgia treated by Danazol and Evening Primerose oil. Study design is descriptive observational study. Study setting is department of General Surgery, Bhima Bhoi Medical College and Hospital, Balangir, Odisha. Duration for a period of 24 months: from December 2020 to December 2022. **Materials and Methods:** The candidates were selected on basis of double blinded, consecutive sampling. Females with complains of Mastalgia, coinciding with our inclusion criteria were administered danazol, evening primerose oil in divided doses for a period of 6 weeks and they were assessed for pain alleviation by the Cardiff Breast Pain score. **Result:** In our study the results showed Danazol to be significantly effective in the management of Mastalgia as compared to the efficacy of evening primrose oil. In Group-A, the average Cardiff breast pain score of those candidates receiving Danazol at 4 weeks was 2.19 and at 12 weeks was 1.23, which signifies the efficacy of the drug in relieving pain. The Mean Cardiff breast pain score of group-B at 4 weeks was 2.77 and at 12 weeks was 2.03 reinforcing its use not strongly beneficial for patients in mastalgia. **Conclusion:** We concluded that although with mild, tolerable and reversible adverse effects Danazol has a promising role in management of cyclical in women.

## INTRODUCTION

Mastalgia, commonly termed as breast pain, is one of the most common benign conditions of the breast. It is a frequent complain of female patients visiting the breast clinics and surgical outpatient departments worldwide. The cause of mastalgia could be variable, the common being cyclical and non-cyclical. Cyclical mastalgia is termed as breast pain with either only premenstrual exacerbation or pain throughout the month with premenstrual exacerbation. There is increase in breast tissue volume prior to menstruation which results in pressure on pain nerve endings causing cyclical pain. Just prior to menstruation as the estrogen and progesterone levels decline, there is a reduction of cellular proliferation in the early follicular phase and consequent relief of pain and engorgement.<sup>[1,2]</sup> The factors leading to mastalgia may be due to increased estrogen secretion from ovary, deficient progesterone production or increased prolactin secretion. Non-cyclical mastalgia is defined as intermittent or continuous breast pain without premenstrual exacerbation and no obvious source of

musculoskeletal disease.<sup>[3,4]</sup> Non-cyclical mastalgia can be true i.e. arising from breast tissue or it can arise from chest wall e.g. Tietze's syndrome and lateral chest wall. The extra-mammary causes are those that are perceived as breast pain by the patient although they do not have any relation to the breast itself. The pattern and severity of pain is also variable therefore has to be assessed with the help of a specialized breast pain score.<sup>[1]</sup>

The important factors in the evaluation of breast pain depends on taking a good and elaborate history and examination. Followed by appropriate investigations to rule out other pathologies that might lead to breast pain like trauma, breast lumps, abscess, mastitis any more.<sup>[2]</sup> Mastalgia has always been a under researched, under managed symptom in the domain of breast diseases the reason being that its cause has never been established firmly. Various drugs and herbal remedies have gained popularity and their effectiveness has died down with time. NSAIDS have been one of the most popular initial drugs of management for short duration, but they play no effective role in cyclical mastalgia although their

effectiveness in non-cyclical causes has been in the limelight.<sup>[1]</sup> Other alternative drugs like Danazol, evening primrose oil, tamoxifen have been used off and on but time to time their compliance and efficacy has always been questioned in terms of side effects. Evening oil of primrose is extracted from the seeds of evening primrose plant (*OenotheraBennis*). It is referred as evening primrose because the flower blooms in the evening. Its oil is a natural product rather than a drug, which is rich in essential fatty acids like linolenic acid. Our body converts linolenic acid into a hormone like substance prostaglandin (PG) especially PgE1,14 that leads to reduction of inflammatory cells. The product is usually prescribed in a dose of 1,000mg bid per oral1 or 500mg Bid, though various international studies have used 2-3grams daily. The optimal dose and duration of treatment with EOP is not known.<sup>[3-5]</sup> On the other hand, Danazol is a synthetic testosterone which binds to the progesterone and androgen receptors, though the exact mechanism of action in the treatment of mastalgia is unknown. The main factors limiting the use of Danazol is its spectrum of side effects. Majority (59%- 92%) of women treated with Danazol (200mg orally per day) in controlled clinical trials gets relief in breast pain and tenderness.<sup>[4,6]</sup> Our study aims to compare and select a better drug amongst Danazol and evening primrose oil for mastalgia management, which will have least dis-agreeable side effects making it a complaint drug for patients for long term use.

## MATERIALS AND METHODS

We conducted a prospective study in the Department of General Surgery, Bhima Bhoi Medical College and Hospital, Balangir, Odisha for a period of 24 months, from December 2020 to December 2022. We included females with ages above 15 years presenting with complains of cyclical or non-cyclical mastalgia refractory to oral or topical analgesics. Patients with extra mammary pain/ Tietze's Syndrome, nipple discharge, lactation, pregnancy, breast abscess, malignant breast diseases were excluded. Patients on oral contraceptive pills were also not enrolled in our study. Patients consenting participation in the study went through clinical and radiological assessment. Candidates coinciding our inclusion criteria were managed for medically for mastalgia and assessed in our study. Patients were selected for allocated into two groups A and B, drug administration was done by a blind random sequence by a co- researcher who was not actively involved in the study. Group-A comprised of every even number patient was given oral Danazol 200mg daily and group-B had every odd number patient was given oral evening primrose oil 1000mg bid. Both the drugs were given for a period

of three months. Patients were advised to follow-up after 4 and 12 weeks for assessment of mastalgia. Patients were advised not to plan a conception during this period of drug administration. All the cases were recorded in a predesigned and pretested proforma. Patients were then assessed by the primary researcher for improvement of mastalgia using the Cardiff Breast Pain score. Common adverse effects during therapy were also recorded.

## RESULTS

In our study of 12 months, 53 patients were enrolled in the study, had an average age of 33.6 years. The mean age of group-A was 33.5 years and that of group-B was 33.6 years. Amongst these patients 32 women were married and 21 were single. Group-A contained 26 females 14 married and 12 were single, they were given danazol. Group-B comprised of 27 females 20 married and 7 singles were administered evening primrose oil for a period of three months. In Group-A, the average Cardiff breast pain score of those candidates receiving danazol at 4 weeks was 2.19 and at 12 weeks was 1.23, which signifies the efficacy of the drug in relieving pain. The patients whom were administered danazol experienced a few reversible and tolerable adverse effects. 8-patients experienced menstrual disturbances, 3 had bloating, 4 complained of acne, 2 hirsutism and 2-patients also had nausea. The mean Cardiff breast pain score of group-B at 4 weeks was 2.77 and at 12 weeks was 2.03 reinforcing its use not strongly beneficial for patients in mastalgia. [Table 1] The adverse effects of danazol, which were experienced in 73.07 % patients in group-A in comparison to very low side effects of evening primrose oil that is 11%, in group-B which was nausea experienced by only 2 patients. These adverse effects are bearable and mild. Patients easily comply to them as they are reversible. An increasing trend of relief of symptoms was noted in patients administered with danazol as compared to evening primrose oil despite of these undesirable adverse effects. usage of danazol in the management of mastalgia.

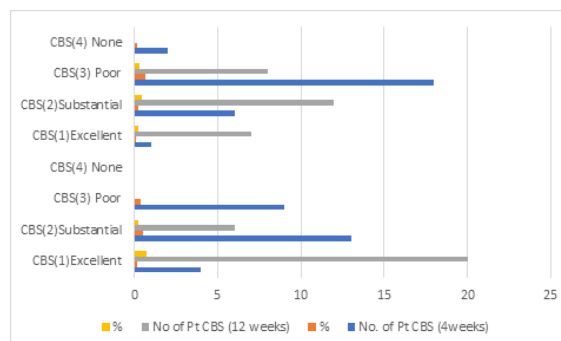


Figure 1:

Table 1:

Drugs	Score	No. of Pt CBS (4weeks)	%	No of Pt CBS (12 weeks)	%
Danazol	CBS(1)Excellent	4	15.38%	20	74.07%
	CBS(2)Substantial	13	50%	6	22.2%

	CBS(3) Poor	9	34.6%	-	-
	CBS(4) None	0	-	-	-
Evening Primrose Oil	CBS(1)Excellent	1	3.7%	7	25.9%
	CBS(2)Substantial	6	22.2%	12	44.4%
	CBS(3) Poor	18	66.6%	8	29.62%
	CBS(4) None	2	14.8%	-	-

## DISCUSSION

The management of mastalgia has always been an unsolved dilemma as its pathophysiology is difficult to establish. A single drug of choice has never been decided for mastalgia. A wide array of medicines like NSAIDS, danazol, evening primrose oil, Tamoxifen have been under trial for quite a long time. NSAIDS have served as a first line treatment in the management of mastalgia for ages. Oral NSAIDS being more popularly prescribed as compared to topical gels. But as stated by Afsheen et al they provide instant pain relief to the patient but has short term effectiveness. In this study they do not agree to advise long term pharmacological treatment for mastalgia. In patients with mastalgia, these episodes seem to wax and wane, and relapse after months therefore they have to be managed long term. Patients with no known organic cause are indicated to be managed for a long duration, and NSAIDS are definitely not the recommended drug for these cases due to their severe side effects due to chronic use.<sup>[7]</sup> The two agents used for comparison in our study included danazol and evening oil of primrose (EOP). Our results were consistent with the study conducted in 2007 by Parveen et al, in which the use of danazol for management of mastalgia was recommended over evening primrose oil supplements. The adverse effects of these two drugs were also observed. Although danazol had disturbing adverse effects, but the effects were temporary and reversible.<sup>[8]</sup> As stated by Kataria, if no pathology is found in the breast on assessment, then a combination of reassurance, breast support, and topical NSAID gel massage are usually effective for management of mastalgia. Anti-estrogen drugs like (centchroman/tamoxifen) therapy for 3 to 6 months was termed as the second-line treatment of choice. They advised treatment by danazol in resistant cases. Gamma-linolenic acid or evening primrose oil though commonly prescribed is not effective. Similar results of administration of danazol and EPO was observed in our study stating EPO less effective as compared to danazol.<sup>[9]</sup> Severe cyclical mastalgia runs a long course especially if it begins in third or fourth decade of life. It may last the complete menstrual age of female and the only chance of relief may be menopause. There is a strong relationship of the menstrual cycle to the female sex hormones. This type is amenable to hormonal manipulation comparatively non-cyclic mastalgia has a lesser response rate to hormonal preparations. Several hormonal modalities may be attempted for pain in such cases. Tamoxifen is well known option and is also acceptable to patients at a low dose for

management of mastalgia but holds a risk of potentially serious adverse effects like deep venous thrombosis and endometrial cancer along with hot flashes, nausea, menstrual irregularity, vaginal dryness and weight gain. Therefore, it is not recommended initially. Prashant et al carried out a study showing danazol treatment is more effective in treatment of cyclic mastalgia.<sup>[10]</sup> In another study conducted in India danazol was compared to Centchroman (Ormeloxifene) which is a non-steroidal selective estrogen receptor modulator (SERM) for treatment of mastalgia. They found centchroman to be a cheap and effective relief of symptoms but its drawback being the fact that danazol acts faster, centchroman is more efficacious in reduction of pain score at 12 weeks. The mean Cardiff breast pain score in our study too was appreciable at 4 weeks as compared to EPO at 4 weeks reinforcing the fact that danazol provides early relief. In the group of patients given danazol at 100mg per day. Androgenic side effects were observed like acne, voice change, hirsutism while on treatment were noted. Menstrual irregularities were noted in the form of delayed menses in 2 patients, scanty menses in 1 patient and menorrhagia in 3 patients at the end of 3-months. All patients resume normal menses after discontinuing danazol in 2 to 3 months.<sup>[11]</sup> Similar reversible adverse effects were observed in our study too, therefore reassurance and preempted counseling of these temporary adverse effects improved the patients compliance.

## CONCLUSION

Danazol is a relatively safe and effective drug for the management of mastalgia of women, with reversible and mild adverse effects.

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