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A Comparative Study of Danazol alone with Danazol Combined with Evening Primrose Oil in the Treatment of Fibrocystic Breast Disease

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Abstract **Original Research Article**

Introduction: Mastalgia was described in the medical literature as early as 1829 and is the most common complaint among women of child bearing age. Breast pain among women with or without lump is a common complaint and a cause of significant anxiety and fear of breast cancer. Objective: To assess the Danazol alone with Danazol combined with Evening Primrose Oil in the treatment of Fibrocystic Breast Disease. ***Methods:*** The study was conducted in the department of surgery, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh from January to July 2022. A total 110 women were selected an initial clinical assessment and breast imaging and had maintained a proper breast pain chart. The registers of the Surgery outdoor Patient department were crosschecked and the list of all females presenting with mastalgia treated with Danazol and Evening Primrose Oil in dosage mentioned for this study was made. A total 100 women were selected an initial clinical assessment and breast imaging and had maintained a proper breast pain chart. ***Results:*** The most common age group in cyclical mastalgia was 18-25 years involving 73.2% patients while in non-cyclical mastalgia the most common age group was 26-35 years involving 42.4% patients. 24.7 years and 30.3 years was the mean age for cyclical and noncyclical mastalgia. In our study overall mastalgia showed better useful response with Danazol (59.2%) than with EPO (41.1%) and this difference was statistically significant (Fisher's exact test 2-tailed p value 0.05). Cyclical mastalgia showed better observed response with Danazol (68.4%) than EPO (46.2%), this difference coming out to be statistically significant, Fisher's exact test 2- tailed p value 0.02. Non-cyclical mastalgia showed slightly better observed response with Danazol (33.3%) than EPO (27.7%), this difference coming out to be statistically insignificant, Fisher's exact test 2-tailed p value 0.40. ***Conclusion:*** Mastalgia is more common in females in their reproductive system. Cyclic mastalgia has a higher prevalence than non-cyclical mastalgia. Danazol (Danocrine) offered good pain control in mastalgia than Evening Primrose Oil (EPO). Danazol appears to be a better pain reliever in cyclical mastalgia compared to non-cyclical mastalgia.

Keywords: Breast pain, Cyclic, Non-cyclic, Danazol, Mastalgia.

INTRODUCTION

Mastalgia was described in the medical literature as early as 1829 and is the most common complaint among women of child bearing age [1]. Breast pain among women with or without lump is a common complaint and a cause of significant anxiety and fear of breast cancer [2]. Mastalgia may be cyclic or non-cyclical and extra mammary cause like Trietz syndrome [3]. Mastalgia can be caused by breast tissue, extra-mammary tissues, or psychological factors. Macromastia, dietary or lifestyle changes, hormone replacement therapy (HRT), ductal ectasia, mastitis, increased water and salt retention, and high-dose caffeine use are a few examples [4]. Cyclic mastalgia is related to menstrual cycle and it starts in leuteal phase. The symptoms of cyclic mastalgia include congestion of breast, soreness and feeling of fullness, heaviness and tenderness [5]. It appears 7-10 days before menstruation and lasting 1-4 days and causes slight pain and is seen in 8-10% premenopausal women. Non-cyclic mastalgia is another type of mastalgia the pain of which does not correlate with menstruation as in cyclic mastalgia and is felt throughout [6]. Premenstrual breast soreness lasting 1–4 days is considered normal [7]. Mastalgia is a chronic issue that affects physical and social activity, work-school activities, and sexual activity and can last for years [8]. Mastalgia is the most prevalent breast symptom among women who visit a breast clinic [9]. Approximately 60 to 70 percent of

women suffer some degree of breast pain at some point in their life, with severe pain occurring in 10 to 20% of cases [10]. The majority of mastalgia sufferers can be treated with reassurance and inexpensive medicines. Most non-cyclic breast pain arises for unknown reasons, yet is believed more likely to have an anatomical rather than hormonal cause. Approximately 16 and 32% of women report breast pain as an adverse effect of estrogen and combined hormonal therapies respectively [11]. Various modalities like wearing of proper fitting and supportive bra, heat cold therapy, non-medical means like dietary measures like fat restrictions, avoidance of methyl xanthine and reassurance. Various drugs have been tried so far for mastalgia. Danazol is anti-gonadotrophic that has unique action on pituitary ovarian axis. It is labeled as impedal androgen and had been most popular drug for the treatment of benign breast disorders. Mastalgia is frequently linked with breast nodularity, which may be painful or absent of a distinct lump. Breast nodularity and mastalgia are common in the general population [12].

METHODS AND MATERIALS

The study was conducted in the department of surgery, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh from January to July 2022. A total 110 women were selected an initial clinical assessment and breast imaging and had maintained a proper breast pain chart. The registers of the Surgery Outdoor Patient Department were crosschecked and the list of all females presenting with mastalgia treated with Danazol and Evening Primrose Oil in dosage mentioned for this study was made. Detailed history , clinical examination, Pain –site, character, intensity, nature, relation to periods, Menstrual History, Family History, General health History, Current medications (especially hormones), USG both breasts, Mammogram bilateral in age>45 yrs.

Inclusion Criteria

- Patients of reproductive age group presenting with mastalgia in the Surgical Outpatient Department.
- Patients giving informed consent.

Exclusion Criteria

- Past history of breast carcinoma or family history of breast carcinoma.
- Patients with polycystic ovarian diseases and uterine cervical hyperplasia.
- First six months of Lactation.
- Pregnancy.
- Patients having irregular menstrual cycle.
- Patients taking hormonal drugs like Oral contraceptives / Hormone replacement therapy.
- Female habitual of smoking, alcohol or any other drugs.
- Females suffering from other comorbid illness.
- Age<18 years.

Patients with mastalgia who underwent examination and therapy in the Surgery Outpatient Department during the study period were evaluated for response after receiving approval from the institute's ethical committee and provided informed consent. They were divided into responders and non-responders, and an observational study of Danazol and EPO response in this patient population was conducted. The analysis is presented in the form of percentages and charts, with the observed reaction noted. At the initial presentation, consenting patients were given a breast pain chart on which they were asked to record their breast pain for one month. The patient was categorised as having cyclical or non-cyclical mastalgia based on the breast pain chart. The Cardiff Breast Pain Score was used to assess the response. The number of responders and no responders was determined, and the observed response to Danazol and Evening Primrose Oil was recorded.

Statistical Analysis

The data was analyzed using computer software Microsoft Excel and SPSS version 21.0 for Windows. Mean and standard deviation (SD) was calculated and reported for quantitative variables. Chi square and Fisher's exact test 2-tailed were performed by Epical 2000 software to evaluate statistical significance. A p-value of <0.05 was considered a statistically significance.

RESULTS

Table 1: Type of Mastalgia (N=110)

Type of Mastalgia	Frequency	Percentage
Cyclic	77	70.0
Non-cyclic	33	30.0
Total	**110**	**100.0**

A total of 110 patients were included in the study. Out of 110 patients 70.0% had cyclical mastalgia while 30.0% had non-cyclical mastalgia (Table-1).

Table 2: Age Distribution (N=110)

Age Group (years)	Cyclic (n=77)		Non-cyclic (n=33)	
	Frequency	Percentage	Frequency	Percentage
15-25	61	73.2	12	36.3
26-35	12	15.5	14	42.4
>35	4	5.1	7	21.1
Total	**77**	**100.0**	**33**	**100.0**
Mean±SD	24.736±5.09		30.392±7.41	

The most common age group in cyclical mastalgia was 18-25 years involving 73.2% patients while in non- cyclical mastalgia the most common age group was 26-35 years involving 42.9% patients. 24.7 years and 30.3 years was the mean age for cyclical and noncyclical mastalgia (Table-2).

Table 3: Distribution according to drug given (N=110)

Type of Drug	Frequency	Percentage
Danazol	54	49.1
EPO	56	50.9
Total	**110**	**100.0**

49.1% of the study participants received Danazol while 50.9% of them Evening Primrose Oil (Table-3).

Table 4: Distribution according to Imaging Score (N=110)

Imaging Score	Frequency	Percentage
BIRADS 1	31	28.1
BIRADS 2	63	57.2
BIRADS 3	12	10.9
BIRADS 4	4	3.6
Total	**110**	**100.0**

Majority of the study subjects (57.2%) had imaging score of BIRADS 2 followed by BIRADS 1 involving 28.1% patients, BIRADS 3 involving 10.9% patients and BIRADS 4 involving 3.6% patients (Table-4).

Table 5: Distribution according to FNAC Finding (N=110)

FNAC Finding	Frequency	Percentage
C1	3	2.7
C2	58	52.7
C3	6	5.4
Not Applicable	43	39.1
Total	**110**	**100.0**

The most common finding was C2, C1 and C3 was found in 2.7% and 5.4% patients respectively while it was not applicable on 39.1% patients (Table-5).

Table 6: Distribution according to Observation Period in Cyclical Mastalgia (n=77)

Observation Period	Danazol (n=39)		EPO(n=38)	
	Frequency	Percentage	Frequency	Percentage
Completed	33	84.6	32	84.2
Left Out	6	15.4	6	15.8
Total	**39**	**100.0**	**38**	**100.0**

The distribution study subjects in cyclical mastalgia group according to observation period and drug applied. In cyclical mastalgia 84.6% of Danazol group and 84.2% of EPO group had completed the therapy (Table-6).

Table 7: Distribution according to Overall Response who completed Observation period in Cyclic Mastalgia (n=67)

Overall Response	Danazol (n=34)		EPO(n=33)	
	Frequency	Percentage	Frequency	Percentage
Useful	27	79.4	19	57.5
Not Useful	7	20.5	14	42.5
Total	**34**	**100.0**	**33**	**100.0**

The distribution of study subjects according to overall response that completed observation period in Cyclic Mastalgia. 79.4% of Danazol group and 57.5% of EPO group were useful responders who completed the observation period (Table-7).

Table 8: Distribution according to Observation Period in Non-cyclical Mastalgia (n=33)

Observation Period	Danazol (n=15)		EPO(n=18)	
	Frequency	Percentage	Frequency	Percentage
Completed	10	66.6	13	72.2
Left Out	5	33.4	5	27.8
Total	**15**	**100.0**	**18**	**100.0**

The distribution study subjects in non-cyclical mastalgia group according to observation period and drug applied. In non-cyclical mastalgia 66.6% of Danazol group and 72.2% of EPO group had completed the therapy (Table-8).

Table 9: Overall Useful Response (N=110)

Type of Mastalgia	Danazol (n=54)		EPO (n=56)		p value
	Frequency	Percentage	Frequency	Percentage	
Mastalgia	32/54	59.2	23/56	41.1	0.05
Cyclic	26/38	68.4	18/39	46.2	0.02
Non-cyclic	5/15	33.3	5/18	27.7	0.40

In our study overall mastalgia showed better useful response with Danazol (59.2%) than with EPO (41.1%) and this difference was statistically significant (Fisher's exact test 2-tailed *p* value 0.05). Cyclical mastalgia showed better observed response with Danazol (68.4%) than EPO (46.2%), this difference coming out to be statistically significant, Fisher's exact test 2- tailed *p* value 0.02. Non-cyclical mastalgia showed slightly better observed response with Danazol (33.3%) than EPO (27.7%), this difference coming out to be statistically insignificant, Fisher's exact test 2-tailed *p* value 0.40 (Table-9).

DISCUSSION

The current study included 110 Mastalgia patients who were being treated at the Surgery Outpatient Department. In the current study, 77 of the 110 patients had cyclical mastalgia and 33 had non-cyclical mastalgia. A total of 54 patients were administered Danazol, with a mean age of 24.7 years, and a total of 56 patients were given Evening Primrose Oil, with a mean age of 30.3 years. The observation period was based on the entire course of pharmacological treatment, which was set at two months for Danazol and four months for Evening Primrose Oil. Cardiff Breast Scores I and II were recognised as useful responses, whilst III and IV were considered nonresponders. In our study, we found that Danazol (29 responders out of 49 patients) had a better observed useful response than EPO (21 out of 51 patients had useful response) (41.2 percent), and this difference was statistically significant (Fisher's exact test 2-tailed p value 0.5) that Danazol has a better response in mastalgia than Evening Primrose Oil. In their study titled "17 years' experience in the Cardiff mastalgia clinic," Gateley CA *et al.*, observed that 92 percent of cyclical mastalgia and 64 percent of non-cyclical mastalgia received a clinically useful response to therapy, with Danazol being the most effective drug [13]. Danazol and Evening Primrose Oil were given to 39 of the 77 patients with cyclical mastalgia who were enrolled in the trial (EPO). The study included 33 individuals who received Danazol and 32 patients who received Evening Primrose Oil (EPO). There were 25 responders out of 36 in the Danazol group (69.4 percent useful response), and 17 responders out of 36 in the EPO group (useful response being 47.2 percent). This difference was statistically insignificant (Fisher's exact test 2-tailed p value 0.02), which can be attributable to the limited sample size. However, in cyclical mastalgia, the observed response was better with Danazol, while the difference was not statistically significant. According to Gateley CA *et al.*, clinically meaningful response with danazol was 79 percent and 58 percent with evening primrose oil [13]. Preece PE *et al.*, observed in their article that individuals with cyclical mastalgia experienced significant pain relief after 3 months on EPO but not on placebo. Despite continuous therapy in the EPO group, pain levels reverted to baseline after 6 months, and the placebo groups exhibited no improvement in pain when treated at "crossover "with open-label EPO [14]. In their investigation, Mansel RE *et al.*, observed that the mean pain scores indicated a substantial response to danazol [15]. In a randomised controlled trial, O'Brien PM *et al.*, discovered that Danazol reduced breast tenderness without increasing adverse effects when compared to placebo [16]. In their study, Kontostolis E *et al.*, stated that treatment effectiveness was defined as a reduction in mean pain score of more than 50%, which was achieved in 65 percent of those on danazol, 72 percent of those on tamoxifen, and 38 percent of those on placebo. Tamoxifen and danazol were statistically comparable, and both were considerably better than placebo [17]. In their study, Ortiz-Mendoza CM *et al.*, colleagues reported a 79.4 percent effectiveness rate in cyclical mastalgia [18]. In the current study, 15 of the 33 patients with non-cyclical mastalgia were given Danazol and 17 were given Evening Primrose Oil (EPO). The observation period was completed in 7

Danazol group patients and 11 EPO group patients. There were 4 responders out of 13 in the Danazol group (30.8 percent useful response), and 5 responders out of 13 in the EPO group (useful response being 26.7 percent). This difference was statistically insignificant, with a Fisher's exact test 2-tailed p value of 0.40. Danazol produced a little better response than EPO in non-cyclical mastagia patients. Danazol appears to provide a superior overall response than EPO in cyclical and non- cyclical mastalgia. However, the response to Danazol and EPO in non-cyclical mastalgia does not appear to be as good as in cyclical mastalgia. In their study, Gateley *et al.,* [12] discovered that clinically relevant response was 40% in those treated with Danazol and 38% in those treated with EPO. The most effective medicine appears to be danazol. Patients taking evening primrose oil, on the other hand, reported far fewer serious side effects, up to eight times fewer than those on the other medicines. As a result, unless the severity of the symptoms necessitates a speedy response, evening primrose oil should be considered as a first-line treatment. Because of the low frequency of side events, evening primrose oil is a good therapeutic alternative for patients who require repeated rounds of treatment due to recurring pain [13]. Tamoxifen appears to be the treatment of choice, according to Kataria *et al.,* with Danazol used in refractory cases of mastalgia. Vitamins, diuretics, evening primrose oil, and gamolenic acid are all out dated and ineffective [19]. Preece *et al.,* [14], as well as Mansel *et al.,* [15] conducted RCTs and found no significant response to EPO in non-cyclical mastalgia. Ortiz-Mendoza *et al.,* ran a trial and discovered a 77.7 percent success rate for non-cyclical mastalgia patients treated with Danazol [18].

CONCLUSION

Mastalgia is more common in females in their reproductive system. Cyclic mastalgia has a higher prevalence than non-cyclical mastalgia. Danazol (Danocrine) provided better pain relief in mastalgia patients than Evening Primrose Oil (EPO). It was more effective pain reliever in cyclical mastalgia than in non-cyclical mastalgia. Evening Primrose Oil may provide some pain relief in both cyclical and non-cyclical mastalgia. The efficacy of Danazol and Evening Primrose Oil in non-cyclical mastalgia is equivalent. During the observation period, no major side effects were noticed with the dosages of Danazol and Evening Primrose Oil (EPO).

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