Original Research Article

Efficacy of evening primrose oil and danazol in mastalgia–An observational study with respect to breast pain chart

Viruti[1*], Ashish Kumar[2], Sharique Nizami[3]

[1]Post Graduate, Department of General Surgery, MGM Medical College, KishanGanj, Bihar, India
[2]Post Graduate, Department of General Surgery, MGM Medical College, KishanGanj, Bihar, India
[3]Associate Professor, Department of General Surgery, MGM Medical College, KishanGanj, Bihar, India

Received: 28-11-2021 / Revised: 24-12-2021 / Accepted: 01-01-2022

Abstract

Background: Mastalgia is the most common symptom encountered in women who have gone under breast imaging, and 70% of women suffer from breast pain at least once in their lifetimes[1,2]. Mastalgia is defined as tension, discomfort and pain in one or both breasts[3]. **Materials and methods:** An Observational study was conducted upon 100 patients of Mastalgia receiving treatment in the Surgery Outpatient Department. Breast pain chart was initiated to classify mastalgia into cyclical or non-cyclical type and the response of respective drug monitored with Cardiff Breast Pain Score. These patients were either treated with Danazol (50mg BD) or Evening Primrose Oil (1000 mg BD). Duration of the study was from October 2018 to August 2020 in the Department of General Surgery, M. G. M. Medical College & L. S. K. hospital. **Results:** In this study overall mastalgia showed better useful response with Danazol (59. 2%) than with EPO (41. 2%) and this difference was statistically significant (Fisher's exact test2-tailed*p*value0. 05). Cyclical mastalgia showed better observed response with Danazol (69. 4%) than EPO (47. 2%), this difference coming out to be statistically significant, Fisher's exact test 2-tailed *p* value0. 02. Non-cyclical mastalgia showed slightly better observed response with Danazol (30. 8%) than EPO (26. 7%), this difference coming out to be statistically in significant, and Fisher's exact test2-tailed *p* value0. 40. **Conclusion:** No significant adverse effects were observed with the doses of Danazol and Evening Primrose Oil (EPO) during the observed period.

Keywords: Mastalgia, Evening Primrose Oil, Danazol, Observational study.

Introduction

Mastalgia could stem from breast tissue itself, extra-mammary tissues or psychological reasons. Some of these are macromastia, diet or lifestyle changes, hormone replacement therapy (HRT), ductal ectasia, mastitis, increased water and salt retention, and high-dose caffeine intake[3]. Slight premenstrual breast pain for1–4 days are considered normal[4].

Breast pain not only disrupts women's daily life quality, but also causes women to worry frequently over whether or not they have breast cancer[2]. As breast cancer is the most common cancer in women worldwide, the main goal is to exclude the diagnosis of cancer in women with mastalgia according to current examination methods[3]. This is because the incidence of breast cancer has recently increased based on the technological advances in screening methods and imaging technics[5].

Mastalgia is the most common breast symptom in patients attending abreast clinic [6]. Approximately 60 to 70 % of women experience some degree of breast pain at some stages of their lives, and in 10 to 20 % of cases, it is severe [7]. The two most common concerns of patients presenting with mastalgia are: the fear of breast cancer and the presence of severe pain affecting quality of life. The majority of patients with mastalgia can be managed with reassurance and simple drugs. The most important responsibility of the breast specialist is to convincingly rule out cancer and assiduously reassure the patient.

Mastalgia is often associated with breast nodularity that may be tender or without a discrete lump. Some amount of breast nodularity and mastalgia are found in normal population [8].

*Correspondence
Dr. Viruti
Post Graduate, Department of General Surgery, MGM Medical College, KishanGanj, Bihar, India
E-mail: drviruti@gmail.com

Classification of Breast Pain

Cyclical Mastalgia

Cyclical breast pain occurs 1 to 2 weeks prior to menstruation. The pain is commonly felt diffusely and bilaterally, with some radiation to the upper arm andaxilla. It can be more severe in one breast than the other and it is relieved by the onset of menstrual flow. These patients are usually aged between 30 and 40. Cyclical mastalgia may have spontaneous resolution in up to 22 % of patients and persists in up to 65 % of patients after treatment[9]. However, it can resolve with a hormonal event such as pregnancy or menopause, and because of this, it is postulated that cyclical mastalgia is due to hormonal stimulation of breast parenchyma particularly at the end of the luteal phase of the menstrual cycle[10]. For many, it may be a life long suffering toabateat menopause if left untreated[9].

Non cyclical Mastalgia

It is usually unilateral and localized to a particular quadrant of the breast. Patients are usually older, in their 40s or 50s, and are often perimenopausal[10]. There are several causes of non cyclical mastalgia including cysts, periductal mastitis, stretching of Cooper's ligaments, traumatic fat necrosis, Mondor's disease, diabetic mastopathy, and neoplasia[10]. Noncyclical mastalgia can resolve without treatment in up to 50% of cases but can also be more difficult to treat[8].

Finally, non-breast pain can mimic mastalgia. Common causes of chest wall pain include costochondritis (Teitze's disease), referred nerve root pain as in cervical spondylitis, and herpes zoster. Non-chest wall pain can arise from diverse causes such as ischemic heart disease, biliary pain, and peptic ulcer[10].

Evening Primrose Oil

For women with cyclic breast pain who elect treatment, evening primrose oil (gamma linolenic acid) has been widely advocated as an initial option[11]. Two small randomized, double-blind, place bo-

controlled studies of evening primrose oil have shown efficacy in the treatment of breast pain[20]. Also, several researchers have reported favorable response and adverse effect rates for evening primrose oil from sequential uncontrolled studies and clinical series[12]. A recent trial a randomized, double-blind factorial designs to evaluate evening primrose oil and fish oil for premenopausal women with chronic, severe cyclic or non cyclic mastalgia. Neither fish oil nor evening primrose oil showed benefit over corn and wheat germ oils. Fish oil was associated within creased gastrointestinal adverse effects, whereas evening primrose oil had no more adverse effects than control oils. Proposed explanations for these findings include lack of effect of any oil, similar effect of all the oils orthe vitamin E used with them to prevent oxidation, and the effect of time and care on improving pain[13].

Danazol

Danazol, the only medication approved by the Food and Drug Administration for treatment of mastalgia, is a derivative of 17-α-ethinyl testosterone that suppresses gonadotropin secretion, prevents luteinizing hormone surge, and inhibits ovarian steroid formation. Danazol relieves breast pain and tenderness in controlled clinical trials[14]. Overall, 59% to 92% of women treated with danazol experience relief of breast pain[14]. Typically, the initial dosage is 200 mg/d with eventual tapering to lower-dose, or luteal phase administration[15]. However, initial dosages of 50 to 400mg/d have been described[14]. Interestingly, danazol was associated with decreased mammographic breast volume and density Adverse effects are dose related and primarily androgenic, including acne, hair loss, decrease invoice pitch, weight gain, head ache, nausea, rash, anxiety, and depression. Menstrual irregularity or amenorrhea may occur in 50% to 85% of women taking danazol (200-400mg/d)[16].

Recently, luteal-phase administration of danazol relieved premenstrual breast pain in women with premenstrual syndrome without increased adverse effects compared with placebo[17]. Low-dose, luteal-phase administration may maintain symptom relief with few adverse effects in women with severe, relapsing cyclic mastalgia[18].

Aims and objectives of the study

- Maintenance of Breast Pain Chart by all mastalgia patients, differentiating mastalgia into cyclic al mastalgia and non – cyclic al mastalgia types.
- Observation of response of treating mastalgia with Evening Primrose Oil (1000mgBD) and Danazol (50mgBD)

Materials & methods

An Observational study was conducted upon 100 patient's of Mastalgia receiving treatment in the Surgery Outpatient Department. Breast pain chart was initiated to classify mastalgia into cyclical or non-cyclical type and the response of respective drug monitored with Cardiff Breast Pain Score. These patients were either treated with Danazol (50mg BD) or Evening Primrose Oil (1000 mg BD). Observation period for Danazol was for 2 months and for EPO was 4 months. However in some patients the period of observation was shorter. Duration of the study was from October 2018 to August 2020 in the Department of General Surgery, M. G. M. Medical College & L. S. K. hospital.

Some women were not taken in the study because they had certain set of conditions associated with them. All women had an initial clinical assessment and breast imaging and had maintained a proper breast pain chart.

Sample Design

All women in reproductive age group with regular menstrual history having mastalgia who had an initial clinical assessment and breast imaging and treated with Danazo land EPO in the dosage being used in the study. There was no control overall location of treatment to any particular patient.

Inclusion Criteria

- Patients of reproductive age group presenting with mastalgia in the Surgical Out patient 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 co morbid illness
- Age<18years

Parameters to be studied

- 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>45yrs.
- Side Effects (if any)

Study Tools

Clinical

- History, clinical examination, assessment of breast pain chart

Investigations

USGB/LBREAST

MAMMOGRAMB/L(AGE>45YEARS)

FNAC from radio logically detected suspicious cases MONTHLY PAIN CHART/CARDIFF BREAST SCORE

Study Techniques

After obtaining the approval of institute's ethical committee and written informed consent the patients of mastalgia who underwent evaluation and treatment in the Surgery Outpatient Department during the mentioned study period were observed for response. They were differentiated into responders and non-responders and an observational study of response of Danazol and EPO in this patient population was done. Analysis is explained inform of percentages and charts and observed response mentioned.

On initial presentation the consenting patients were provided with a breast pain chart on which they were requested to chart their breast pain for one month. On the basis of breast pain chart the patient was classified as a case of cyclical or non cyclical mastalgia. The response was measured using the Cardiff Breast Pain Score. The number of responders and non responders were calculated and observed response with Danazol and Evening Primrose Oil measured.

- Useful Response: C. B. S. I&II
- Not useful: CC. B. S. III&IV

Statistical Analysis

The data was analyzed using computer software Microsoft Excel and SPSS version 23. 0 for Windows. Mean and standard deviation (SD) was calculated and reported for quantitative variables. Chi square and Fisher's exact test2-tailed were performed by Epical 2000 software to evaluate statistical significance. Ap- value of<0. 05 was considered a statistically significance.

Results

Table 1: Type of Mastalgia

Type of Mastalgia	Frequency	Percentage
Cyclic	72	72. 0
Non-cyclic	28	28. 0
Total	100	100. 0

A total of 100 patients were included in the study. Out of 100 patients 72% had cyclical mastalgia while 28% had non-cyclical mastalgia. Data is tabulated in Table 1

Table 2: Age Distribution

Age Group(years)	Cyclic(n=72)		Non-cyclic(n=28)	
	Frequency	Percentage	Frequency	Percentage
15-25	59	81. 9	10	35. 7
26-35	10	13. 9	12	42. 9
>35	3	4. 2	6	21. 4
Total	72	100. 0	28	100. 0
Mean±SD	24. 736±5. 09		30. 392±7. 41	

Age distribution of the participants is shown in **Table 2**. The most common age group in cyclical mastalgia was 18-25 years involving 81. 9% 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 non cyclical mastalgia.

Table 3: Distribution according to drug given

Type of Drug	Frequency	Percentage
Danazol	49	49. 0
EPO	51	51. 0
Total	100	100. 0

Distribution of the study subjects according to the drugs given is mentioned in **Table3**. 49% of the study participants received Danazol while 51% of them Evening Primrose Oil.

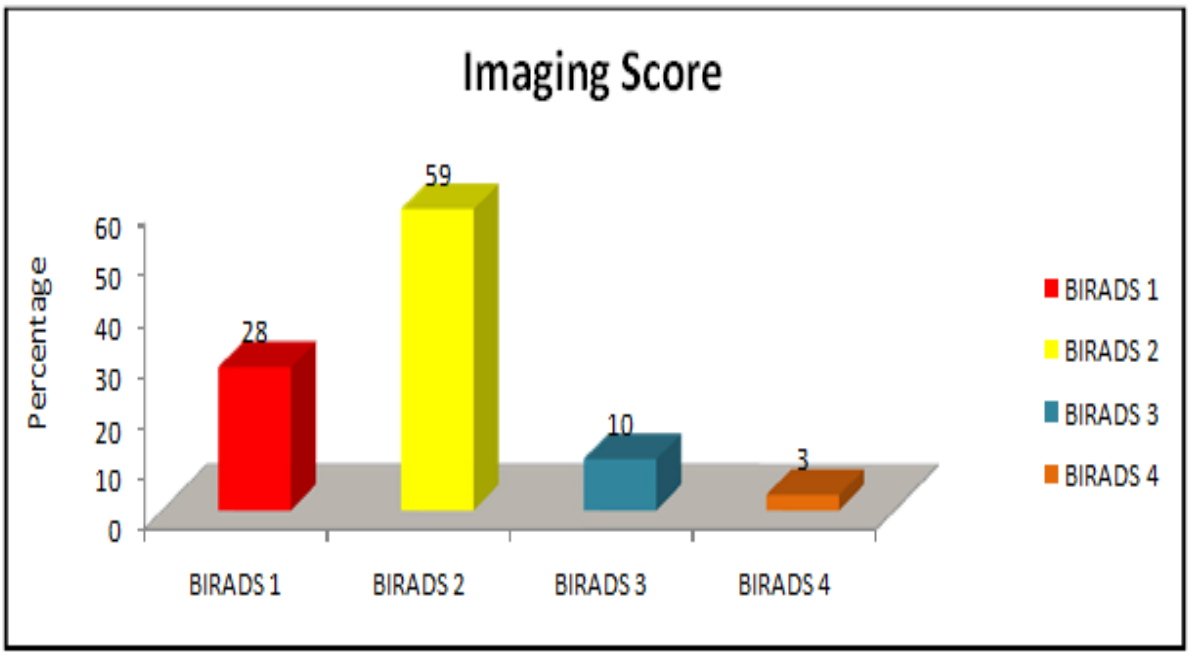

Figure1: Distribution according to Imaging Score

Figure 1 shows the distribution of the study subjects according to imaging score. Majority of the study subjects (59%) had imaging score of BIRADS 2 followed by BIRADS 1 involving 28% patients, BIRADS 3 involving 10% patients and BIRADS 4 involving 3% patients.

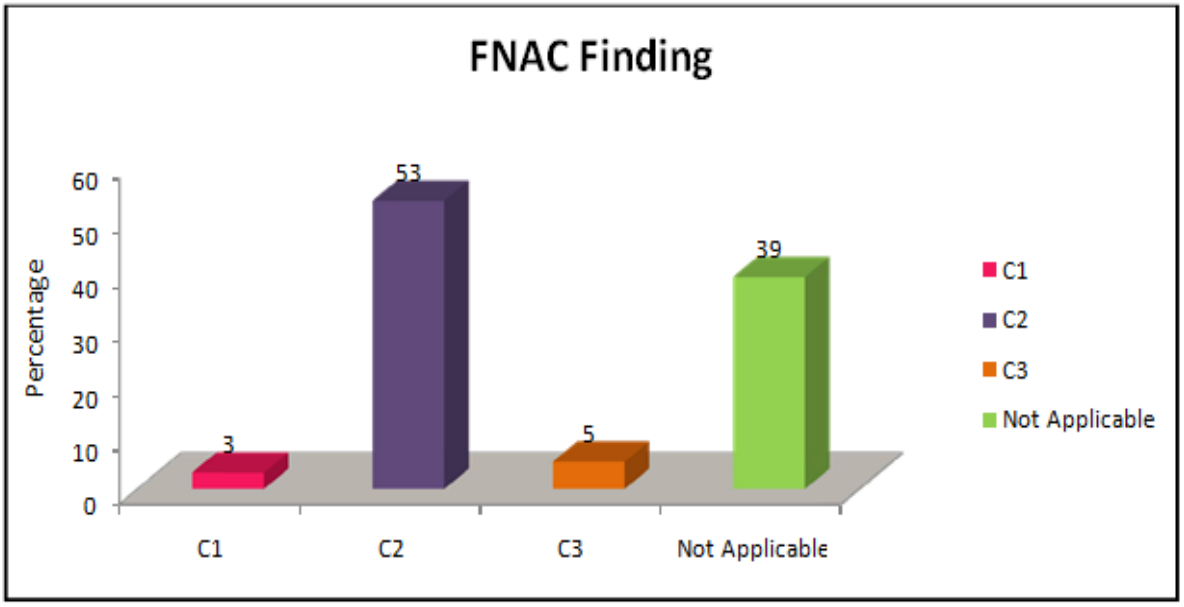

Figure 2: Distribution according to FNAC Finding

Figure 2 shows the FNAC finding of the study subjects. The most common finding was C2, C1 and C3 was found in 3% and 5% patients respectively while it was not applicable on 39% patients.

Table 4: Distribution according to Observation Period

Observation Period	Danazol(n=49)		EPO(n=51)	
	Frequency	Percentage	Frequency	Percentage
Completed	40	81. 6	41	80. 4
LeftOut	9	18. 4	10	19. 6
Total	49	100. 0	51	100. 0

Observation period of the drugs among study subjects is mentioned in **Table 4**. 81. 6% patients of Danazol group and 80. 4% of EPO group had completed the observation period.

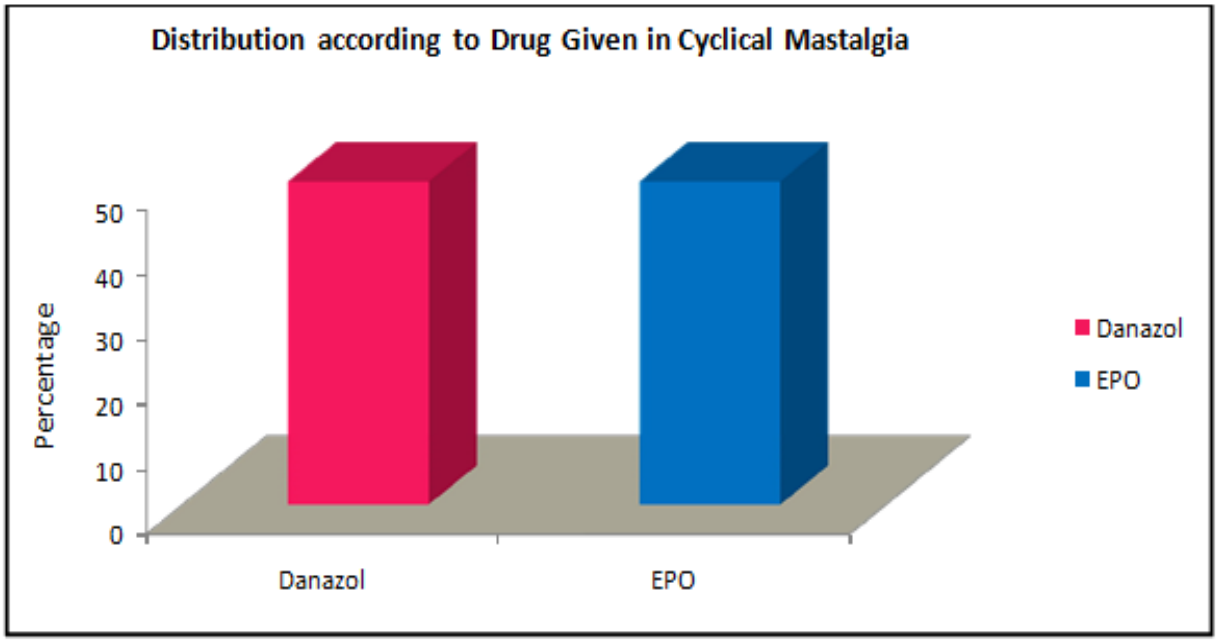

Figure 3: Distribution according to Drug Given in Cyclical Mastalgia (n=72)

Figure 3 shows the distribution study subjects in cyclical mastalgia group according to drug applied. The distribution of study participants was equal for both drugs.

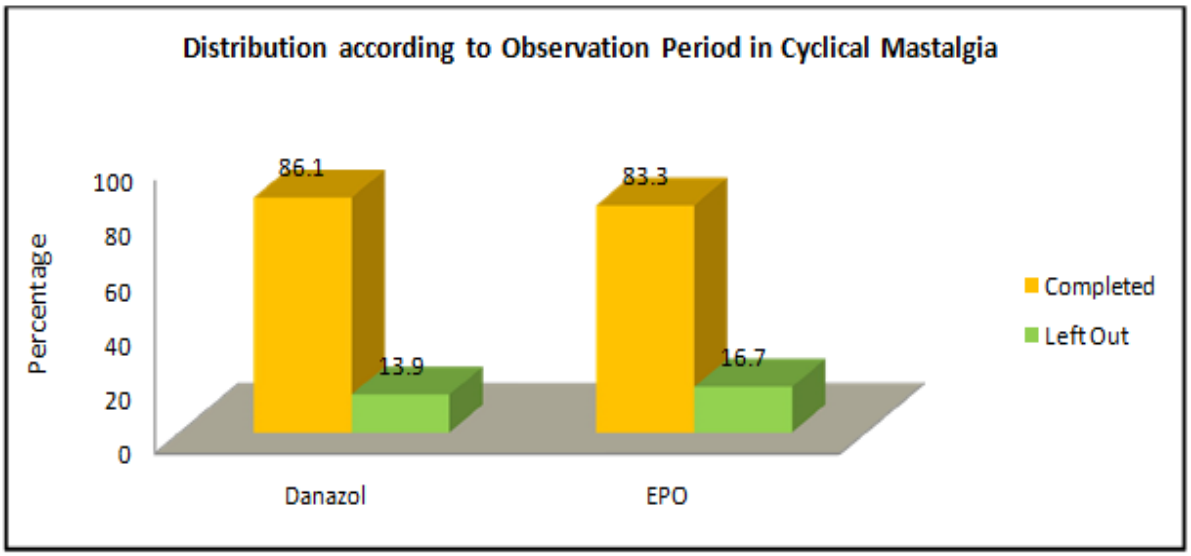

Figure 4: Distribution according to Observation Period in Cyclical Mastalgia (n=72)

Figure 4 shows the distribution study subjects in cyclical mastalgia group according to observation period and drug applied. In cyclical mastalgia 86.1% of Danazol group and 83.3% of EPO group had completed the therapy.

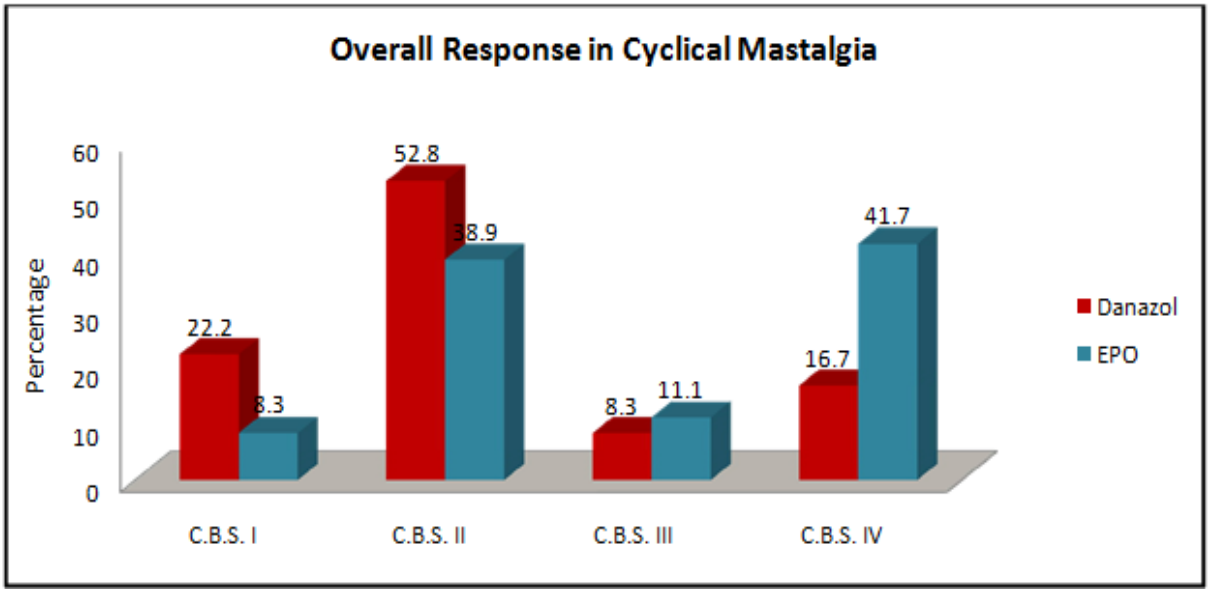

Figure 5 Overall Response in Cyclical Mastalgia (n=72)

Overall response in cyclical mastalgia according to drug applied is mentioned in **figure 5**. In Danazol group 75% were useful responders while in EPO group 47.2% were useful responders.

Table 5: Distribution according to Overall Response who completed Observation period in Cyclic Mastalgia (n=61)

	Danazol(n=31)		EPO(n=30)	
Overall Response	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Useful	25	80. 6	17	56. 7
Not Useful	6	19. 4	13	43. 3
Total	31	100. 0	30	100. 0

Table5 shows the distribution of study subjects according to over all response who completed observation period in Cyclic Mastalgia. 80. 6% of Danazol group and 56. 7% of EPO group were useful responders who completed the observation period.

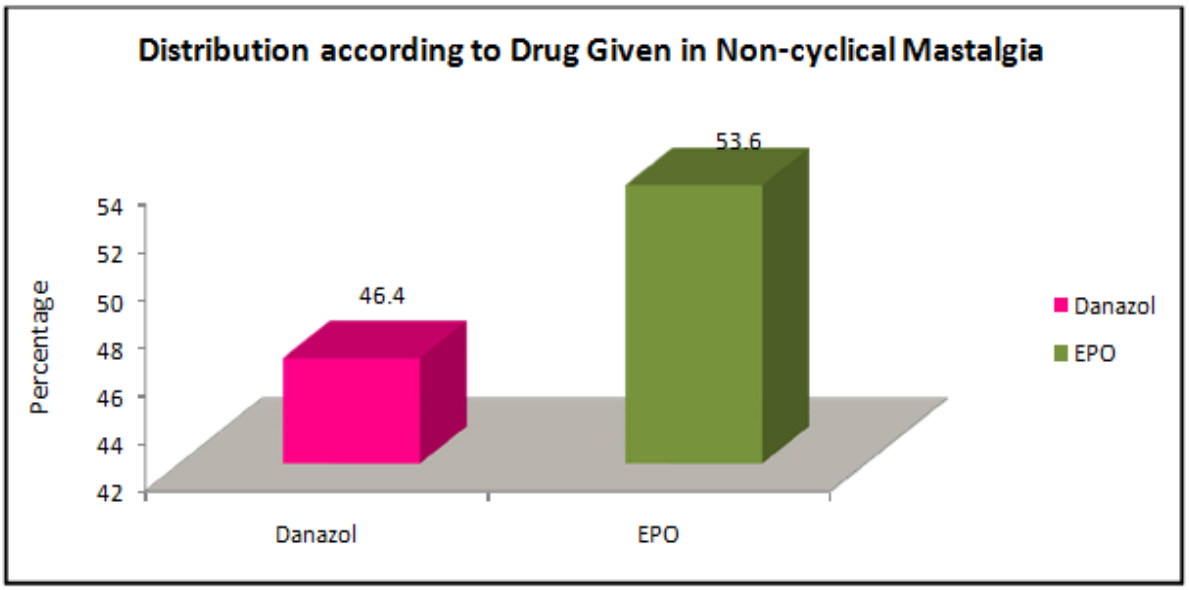

Figure6: Distribution according to Drug Given in Non-cyclical Mastalgia (n=28)

Figure 6 shows the distribution study subjects in non-cyclical mastalgia group according to drug applied. 46. 4% (13) received Danazol while 53. 6% received EPO.

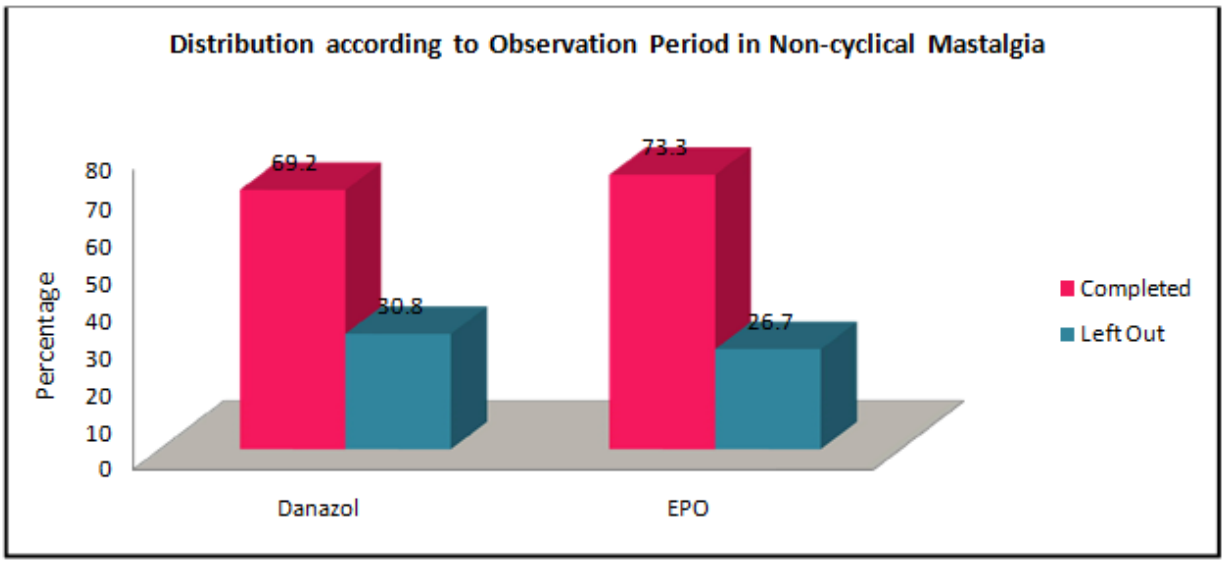

Figure 7 Distribution according to Observation Period in Non-cyclical Mastalgia (n=28)

Figure 7 shows the distribution study subjects in non-cyclical mastalgia group according to observation period and drug applied. In non-cyclical mastalgia 69. 2%of Danazol groupand73. 3% of EPO group had completed the therapy.

Table6: Overall Response in Non-cyclical Mastalgia(n=28)

Overall Response	Danazol(n=13)		EPO(n=15)	
	Frequency	Percentage	Frequency	Percentage
C. B. S. I	1	7. 7	1	6. 7
C. B. S. II	5	38. 5	5	33. 3
C. B. S. III	1	7. 7	5	33. 3
C. B. S. IV	6	46. 1	4	26. 7
Total	13	100. 0	15	100. 0

Overall response in non-cyclical mastalgia according to drug applied is mentioned in **Table 6**. In Danazol group 46. 2% were useful responders while in EPO group 40% were useful responders.

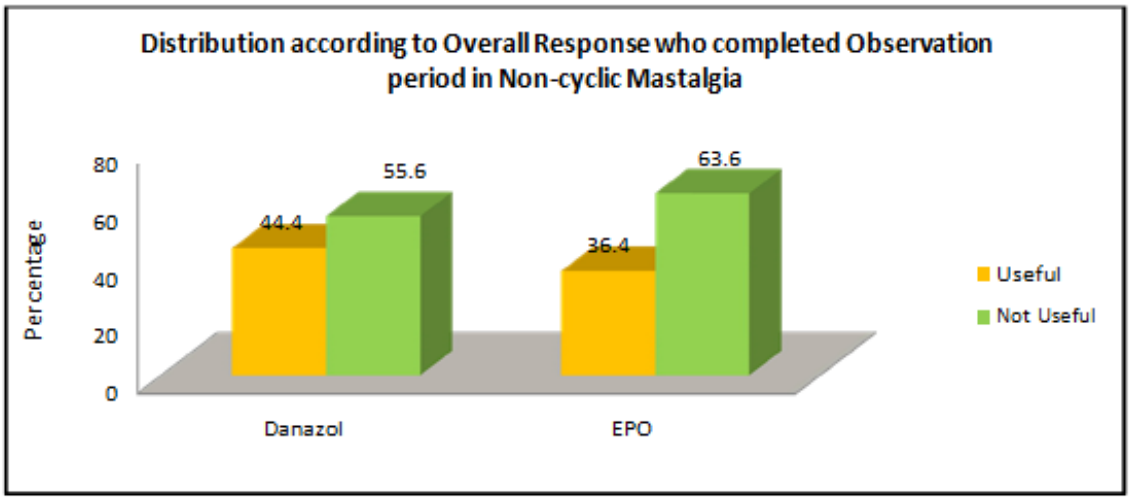

Figure 8: Overall Useful Response

Fig 8 shows the distribution of study subjects according to over all response who completed observation period in non-cyclic Mastalgia. 44.4% of Danazol group and 36.4% of EPO group were useful responders who completed the observation period.

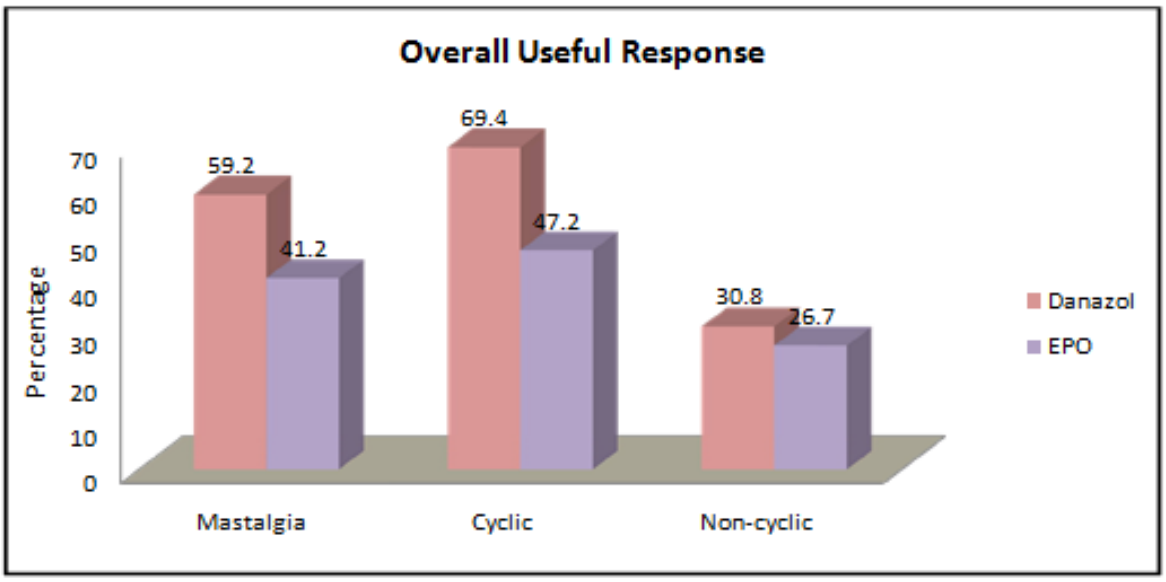

Figure 9: Overall Useful Response

Overall useful response is mentioned in **figure 9**. In our study overall mastalgia showed better useful response with Danazol (59. 2%) than with EPO (41. 2%) and this difference was statistically significant (Fisher's exact test 2-tailed*p*value0. 05). Cyclical mastalgia showed better observed response with Danazol (69.4%) than EPO (47.2%), this difference coming out to best artistically significant, Fisher's exact test 2-tailed *p* value0. 02. Non-cyclical mastalgia showed slightly better observed response with Danazol (30. 8%) than EPO (26. 7%), this difference coming out to be statistically insignificant, Fisher's exact test 2-tailed *p* value 0. 40.

Discussion

There was no control over the treatment allocation as this was purely an observational study. Breast pain chart was initiated to classify mastalgia into cyclical or non-cyclical type and the response of respective drug monitored with Cardiff Breast Pain Score.

In the present study out of the 100 patients, 72 were suffering from cyclical mastalgia and 28 from non-cyclical mastalgia.

A total of 49 patients had been given Danazol and the mean age of this group was 24. 7 years and a total of 51 patients had been given Evening Primrose Oil, the mean age of this group being 30. 3 years.

In our study we observed overall**, mastalgia** cases had better observed useful response with Danazol (29 responders out of 49 patients) (59. 2%) than with EPO (21 out of 51 patients had useful response) (41. 2%) and this difference came out to be statistically significant **(Fisher's exact test 2-tailed *p* value 0.5)** that Danazol has a better response in mastalgia than Evening Primrose Oil.

Gateley CA et al in their study named "**17 years experience in the Cardiff mastalgia clinic**" reported that overall 92% of cyclical mastalgia and 64% of non cyclical mastalgia obtain a clinically useful response to therapy, with Danazol being the most effective drug[19].

Out of the 72 patients of cyclical mastalgia taken for the study 36 each had been given Danazol and Evening Primrose Oil (EPO). The observation period was completed in 31 patients with Danazol and 30 patients with Evening Primrose Oil (EPO). In the Danazol group there were 25 responders out of 36 (useful response being 69. 4%)

and with EPO there were 17 responders out of 36 (useful response being 47. 2%). This difference came out to be statistically insignificant (Fisher's exact test 2- tailed *p* value 0.02) which can beat tribute to small size of the sample. However the observed response in cyclical mastalgia was better with Danazol though the difference was not significant.

According to **Gateley CA et al** clinically useful response was 79% with danazol and 58% with evening primrose oil[19].

Kataria K et al, in are view article in reported if no abnormality is found on assessment, then a combination of high quality reassurance, regular clinical assessments at follow-up, breast support garment and diclofenac gel are usually effective. For more severe cases, anti estrogen (centchroman /tamoxifen) is the drug of choice. Danazol use should be reserved for cases of severe mastalgia who have failed on 3 – 6 months of tamoxifen and centchroman treatment. Vitamins, diuretics, evening primrose oil, and gamolenic acid are obsolete and not effective[20].

Preece PE et al, in their article reported that patients with cyclical mastalgia had significant improvement in pain after 3 months on EPO, but not on place bo. Pain levels returned to base line by 6 months, despite continued therapy in the EPO group, and the placebo groups showed no reduction in pain when they were treated at" crossover" with open-label EPO[21].

Collins A et al, in their study found that EPO had no effect on breast pain. . However, they may not be generalize able to the mastalgia population because patients were selected from a pre menopausal group deemed to suffer from PMS[21].

Mansel RE *etal*, in their study reported that the Mean pains cores showed significant response to danazol [14].

O'Brien PM *et al*, in a **randomized controlled trial** showed that Danazol was found to reduce breast discomfort without any increase inside effects in comparison with placebo[15].

Kontostolis Eetal, reported in their study that treatment success was defined as> 50 % reduction in mean pain score and was achieved in 65% of those ondanazol, 72% of those ontamoxifen, and 38% of those on place bo. Statistically, tamoxifen and danazol were equivalent, and both were significantly better than placebo[22].

Ortiz-Mendoza CM et al in their study described a 79. 4% success rate in cyclical mastalgia[23].

In the present study out of the 28 patients of **non-cyclical mastalgia** observed in the study 13 had been given Danazol and 15 had been given Evening Primrose Oil (EPO). The observation period was completed in 7 patients of Danazol group and11 patients of EPO group. In the Danazol group there were 4 responders out of 13 (useful response being 30. 8%) and with EPO there were 5 responders out of 13(useful response being 26.7%). This difference came out to be statistically insignificant, Fisher's exact test 2-tailed *p* value 0. 40. The observed response in non-cyclical mastalgia patients treated with Danazol was slightly better than EPO.

The overall observed response with Danazol seems to be better than EPO in both cyclical and non-cyclical mastalgia. However the observed response of both Danazol and EPO in non –cyclical mastalgia does not appears to be as good as in cyclical mastalgia.

Gateley et al in their study observed that clinically useful response was 40 % in those treated with Danazol and 38% of those treated by EPO. Danazol appears to be the most effective drug. However patients taking evening primrose oil complained of very few significant adverse events, some 8 – fold less than the other agents. In view of this unless the severity of symptoms requires a rapid response, evening primrose oil should be considered as first line treatment. This low incidence of adverse events also makes evening primrose oil a good therapeutic option for patients requiring repeated courses of treatment because of recurrent pain[19].

Katariaetal reported that Tamoxifen appears to be the drug of choice with Danazol being used in refractory cases of mastalgia. Vitamins, diuretics, evening primrose oil, and gamolenic acid are obsolete and not effective[20].

Preeceetal[12]and **Manseletal**[14] conducted RCTs and found no significant response in non cyclical mastalgia to EPO.

Ortiz-Mendozaetal conducted a trial in which they found that there was a 77.7% success rate for non cyclical mastalgia subjects treated with Danazol[23].

Conclusion

At the end of the study we come to the conclusion that, Females in their reproductive system are more commonly affected by mastalgia. The prevalence of cyclical mastalgia is higher than that of 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. Evening Primrose Oil provides some pain relief in both cyclical and non-cyclical mastalgia to an extent. The effectiveness of Danazol and Evening Primrose Oil in non cyclical mastalgia is comparable. No significant adverse effects were observed with the doses of Danazol and Evening Primrose Oil (EPO)during the observed period.

References

1. ÖlçücüoğluE, YılmazG. Mastodynia:is imaging necessary in young patients? UlusCerrahiDerg. 2013;29:17–19.
2. Bilgin MG, Aydogan U, Bilgin S, Sarı O, Akbulut H, Doğaner YÇ, SağlamK, Tufan T. Breast cancer frequency among patients who applied to our out patient department for breast pain. TurkJ FamPrac. 2010;14:8–12.
3. Yıldırım AC, Yıldız P, Yıldız M, Kahramanca Ş, Kargıcı H. Mastalgia-cancer relationship: a prospective study. J Breast Health. 2015;11:88–91.
4. BaykalA. Fibrokistik Değişikliklerve Mastalji. In:Sayekİ, ÖzmenMM. , editors. Temel Cerrahi El Kitabı. Ankara:GüneşTıp;2009. pp. 314–317.
5. Özkan-OnurG, TarcanE, OnurA, CanH, AtahanMK, YiğitSC, Çakalağaoğlu F. Comparison between radiological and invasive diagnostic modalities in diagnosis of breast cancer. Asian PacJ Cancer Prev. 2015;16:4323–4328.
6. Barton MB, Elmore JG, Fletcher SW. breast symptom among women enrolled in a health maintenance organization: frequency, evaluation and out come. AnnIntern Med. 1999;130:651–657.
7. der DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: prevalence and associated health behavioral factors. J Psychosom Obstet Gynaecol. 2001;22:71–76.
8. Mansel RE, Webster DJT, Sweetland HM. Breast pain and nodularity. In:Mansel RE, Webster DJT, Sweetland HM, editors. Benign disorders and disease of the breast. 3. Philadelphia: Saunders Elsevier; 2009. pp. 107–138.
9. Kumar S, Rai R, DasV, Dwivedi V, KumarS, GG A. Visual analogue scale for assessing breast nodularity in non discrete lumpy breasts: the Lucknow Cardiff breast nodularity scale. The Breast. 2010;19:238–242.
10. Wisbey JR, Kumar S, Mansel RE, Preece PE, Pye JK, Hughes LE. Natural history of breast pain. Lancet. 1983;ii:672–674.
11. NorlockFE. Benign breast pain in women: a practical approach to evaluation and treatment. J Am Med Womens Assoc. Spring 2002;57:85-90.
12. Preece PE, Hanslip JI, Gilbert L, et al. Evening primrose oil (efamol) for mastalgia. In:Horrobin DF, ed. Clinical Uses of Essential Fatty Acids. Montreal, Quebec:Eden Press;1982:147-154.
13. Blommers J, de Lange-De Klerk ES, Kuik DJ, Bezemer PD, Meijer S. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. Am J Obstet Gynecol. 2002;187:1389-1394.
14. Manse lRE, WisbeyJR, HughesLE. Controlled trial of the antigonadotropin danazol in painful nodular benign breast disease. Lancet. 1982;1:928-930.
15. O'Brien PM, Abukhalil IE. Randomized controlled trial of the management of premenstrual syndrome and premenstrual

mastalgia using luteal phase-only danazol. Am J Obstet Gynecol. 1999;180(1, pt1):18-23.
16. Tobiassen T, Rasmussen T, Doberl A, Rannevik G. Danazol treatment of severely symptomatic fibrocystic breast disease and long-term follow-up—the H jarring project. Acta Obstet Gynecol Scand Suppl. 1984;123:159-176.
17. Cassidy A, Bingham S, Setchell KD. Biological effects of a diet of soy protein rich in isoflavoneson the menstrual cycle of pre menopausal women. Am JClin Nutr. 1994;60:333-340.
18. Maddox PR, Harrison BJ, Mansel RE. Low-dose danazol for mastalgia. Br J Clin PractSuppl. 1989;68:43-47.
19. Gateley C A, Miers M, Manse lRE, Hughes LE. Drug treatments for mastalgia: 17 years experience in the Cardiff mastalgia clinic; Journal of the Royal Society of Medicine Volume 85 January 1992.
20. Kataria K, Dhar A, Srivastava A, Kumar S, Goyal A; A Systematic Review of Current Understanding and Management of Mastalgia, Indian J Surg(May–June2014)76(3):217–222.
21. Collins A, Cerin A, Coleman G, Landgren B-M. Essential fatty acids in the treatment of pre menstrual syndrome. ObstetGynecol1993;81:93–8.
22. Kontostolis E, Stefanidis K, NavrozoglouI, LolisD. Comparison of tamoxifen with danazol for treatment of cyclical mastalgia. GynecolEndocrinol1997;11:393–397.
23. Ortiz-Mendoza CM, Olvera-Mancilla M. Danazol effectivity in control of moderate to severe Mastalgia. Cir 2004;72:479-82.