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General Surgery

A COMPARATIVE STUDY OF EFFICACY OF ORMILOXIFENE AND EVENING PRIMROSE OIL IN REGRESSION OF MASTALGIA AT A TERTIARY CARE CENTRE

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ABSTRACT **Background:** 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. Breast pain is classified as cyclical mastalgia, non-cyclical mastalgia and non-specific extra- mammary pain Cyclic mastalgia may resolve spontaneously in up to 22% of cases, or resolution may occur with a hormonal event. The condition may persist in up to 65% of cases after treatment. Noncyclic mastalgia can resolve without treatment in up to 50% of cases, but can it also be more challenging to treat and needs sufficient evaluation to define the causative factor and to rule out neoplasia. Most of the benign breast disease like mastalgia and fibrocystic diseases are treated conservatively with medications and rarely surgery. There is no satisfactory treatment for these benign diseases. Hence, this study was undertaken to compare the efficacy of Ormeloxifene and Evening Primrose oil in regression of mastalgia and fibrocystic breast disease **Methods:** A prospective study was conducted among 90 study subjects, 45 in each group, to compare the pain score between the group receiving evening primrose oil and the group receiving Ormeloxifene using VAS and CARDIFF scale **Results:** It was observed that mastalgia was more frequent in 26-35 years age group. Acyclic mastalgia outnumbered cyclic mastalgia in the study. Pain scores in both the groups showed a downward trend but the change in mean pain score at every visit was higher in the group receiving Ormeloxifene compared to the group receiving evening primrose oil. Mean pain score in the group receiving Ormeloxifene was significantly lower compared to the group receiving EPO at 3rd and 4th visit. **Conclusions:** Hence we conclude that Ormeloxifene shows rapid response and is superior to EPO in the treatment of mastalgia.

KEYWORDS : mastalgia, fibrocystic breast disease, evening primrose oil

INTRODUCTION

Mastalgia is the most common breast symptom in patients attending a breast clinic [1]. 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 [2, 3]. The peak age of incidence for cyclic mastalgia is 20 to 40 years of life. The incidence decreases with increasing age and early pregnancy and is less commonly found in postmenopausal women [4]. The prevalence of breast pain also varies depending on ethnicity. Studies conducted in the UK showed a 60% incidence in British women and US has showed prevalence of 70% [2, 5, 6]. In India, the Prevalence of mastalgia ranges from 41–60% [7].

Mastalgia should be treated when it is severe enough to interfere with a woman's lifestyle and occur for several days each month. The drugs available for the treatment of mastalgia are Danazol, Tamoxifen, Bromocriptine, Evening Primrose Oil, Gamolenic acid, LHRH analog Goserline, oral contraceptive pills (OCPs), diuretics and topical NSAIDs gels. All these agents have been tried with varying efficacy and side effects. There is no consensus about drug of choice for management of mastalgia [6].

Centchroman (Ormeloxifene) is a non-steroidal selective oestrogen receptor modulator (SERM) with strong anti-oestrogen action in uterus and breast and weak estrogen agonistic activity in bones. It is devoid of progestational, androgenic, and anti-androgenic activities. It was developed by the Central Drug Research Institute, Lucknow, India as once weekly OCP as an alternative to steroidal OCPs. It does not cause nausea, vomiting, dizziness, and break through bleeding and has no adverse effect on lipid profile and platelet function. There is an early return of fertility after stopping this drug, as it does not disturb ovulation. The only reported side-effect of centchroman is a prolonged menstrual cycle in <10% of women [8-10]. Because of the advantages of this drug with almost no side effects, it is used in the treatment of the benign breast diseases mastalgia and fibroadenoma [11].

Oenothera biennis with the common name of “evening primrose” grows in different parts of the world. Evening primrose oil with commercial name of 'EPO' is a valuable fixed oil extracted from the seeds of O.biennis. The oil's content of O.biennis is up to 25%. Evening primrose oil has two types of omega-6-fatty acid including linoleic acid (60%–80%) and γ-linoleic acid (8%–14%), which are considered as essential fatty acids, which they are not synthesized in the body [12]. Evening primrose oil is used in the management of various diseases such as atopic eczema, mastalgia, premenstrual syndrome etc. Evening primrose oil has been a special place for women in the management of female ailments during whole life [13-15]. Taking EPO orally is believed to restore saturated/unsaturated fatty acid balance and decrease sensitivity to steroidal hormones or prolactin causing mastalgia and its effectiveness is well documented [16-18].

Most of the benign breast disease like mastalgia and fibrocystic diseases are treated conservatively with medications and rarely surgery. There is no satisfactory treatment for this benign disease. So, a prospective study will be done to study the efficiency of Ormeloxifene and Evening primrose oil in the regression of mastalgia and fibrocystic disease.

OBJECTIVE OF THE STUDY

- To compare the efficacy of ormeloxifene and Evening Primrose oil

a. In regression of mastalgia
b. In regression of fibrocystic breast disease

METHODOLOGY

- **Study Design:** Prospective hospital-based study
- **Study Duration:** 18 months (January 2021 - June 2022)
- **Study Area:** Hassan institute of medical sciences, Hassan.
- **Study Participants:** All female patients aged 16 - 45 years with a history of breast pain with or without tender nodularity attending the surgery OPD/IPD of Hassan institute of medical sciences, Hassan.

- **Inclusion Criteria**

1. History of mastalgia with or without nodularity
2. Age between 16 – 45 years

- **Exclusion Criteria**

1. Polycystic ovarian disease
2. Liver disease
3. Pregnancy
4. Lactation period for first 6 months

5. Patients wishing to conceive in near future
6. Patients on other oral contraceptive pills
7. History of breast carcinoma or family history of breast carcinoma

Estimation Of Sample Size

On the basis of statistics obtained from Department of Surgery, Hassan institute of Medical Sciences, an average of 6 cases per month fitting the criteria of the study with study duration of 18 months, we can expect to have N=108. Based on this population size, using YAMANE equation, for a known population size, sample size (n) equal to

n =N/1+Ne2

n=sample size

N=population size

e= margin of error (for 95% of confidence level, margin error =0.05)

n=108/1+108*0.05*0.05 = 108/1.27 = 85

Therefore, after approximating, the sample size of the study participants was fixed at 90. The study participants were divided into two groups of 45 each with

Group 1 receiving ormiloxifene 30mg.

Group 2 receiving evening primrose oil 1000mg.

Method Of Collection Of Data

All female patients between 16 – 45 years of age diagnosed with a history of breast pain with or without tender nodularity attending the surgery OPD/IPD of Hassan institute of medical sciences, Hassan were included in the study. Clearance from the institutional ethical committee was taken before starting the study. Study participants were included in the study by Purposive Sampling technique.

The study participants with a history of breast pain with or without tender nodularity were included in the study, till the sample size was reached. Written informed consent was taken from the study participants before collecting the data. A pre-tested, semi-structured questionnaire was used to collect information on socio-demographic variables and clinical history related to Mastalgia by interview method. Relevant Laboratory and Radiological investigations were done. The breast nodularity was graded using the Lucknow – Cardiff Breast Nodularity Scale. Pain was evaluated using a standard 10 cm linear Visual Analog Scale (VAS). The patients were divided into 2 groups by computerised randomisation with group 1 receiving ormiloxifene 30mg and group 2 receiving evening primrose oil 1000mg. Follow-up was done on the end of 1st, 2nd, 3rd and 4th month and corresponding VAS scores were documented

Statistical Analysis

The data was collected and compiled in MS Excel. Descriptive statistics has been used to present the data. To analyse the data SPSS (Version 26.0) was used. Significance level was fixed as 5% ($\alpha = 0.05$. Qualitative variables are expressed as frequency and percentages and Quantitative variables are expressed as Mean and Standard Deviation. To compare the mean values between groups chi-square test was applied

RESULTS

14 (31.1%) belonged to 18-25 years age group, 23 (51.1%) belonged to 26-35 years age group and 8 (17.8%) belonged to 36-45 years age group in Group EPO. 13 (28.9%) belonged to 18-25 years age group, 22 (48.9%) belonged to 26-35 years age group and 10 (22.2%) belonged to 36-45 years age group in Group OXE. No significant association was found between age and type of treatment received.

14 (31.1%) had bilateral mastalgia, 20 (44.4%) had left sided mastalgia and 11 (24.4%) had right sided mastalgia in Group EPO. 16 (35.6%) had bilateral mastalgia, 16 (35.6%) had left sided mastalgia and 13 (28.9%) had right sided mastalgia in Group OXE. No significant association was found between side involved and type of treatment received.

28 (62.2%) had acyclic pain in the breast and 17 (37.8%) had cyclic pain in the breast in Group EPO. 22 (48.9%) had acyclic pain in the breast and 23 (51.1%) had cyclic pain in the breast in Group OXE. No significant association was found between pain in the breast and type of treatment received

42 (93.3%) took no analgesics for relieving pain and 3 (6.7%) took analgesics additionally for the relief of pain in Group EPO. 45 (100%) took no analgesics for relieving pain in Group OXE. No significant association was found between analgesics and type of treatment received.

Among those who received primose oil, 12 (26.7%) had mastalgia due to menstrual cycles and 33 (73.3 %) had mastalgia due to other reasons. Among those who received ormiloxefene 30 mg, 45 (100%) had mastalgia due to other reasons. No significant association was found between menstrual cycle related mastalgia and type of treatment received.

24 (53.3%) showed normal findings on USG and 21 (46.6%) showed abnormal findings. Among these 21, majority i.e., 13 (28.9%) showed fibrocystic breast disease, 7 (15.6%) showed fibradenoma, and 1 (2.2%) showed benign breast disease in Group EPO. 25 (55.6%) had normal USG breast and 20 (44.4%) had abnormal USG breast. Among these 20, majority i.e., 9 (20%) had fibroadenoma breast, 6 (13.3%) had fibrocystic breast disease, 5 (11.1%) had fibroadenosis in Group OXE. Statistically significant association was found between USG breast finding and type of treatment received ($P<0.05$).

Mean VAS score before treatment was higher among subjects in Group-2, mean CARD score before treatment was almost similar in both the groups. Mean VAS-1, VAS-2, VAS-3, VAS-4, CARD-1, CARD-2, CARD-4 scores were higher in Group-EPO than in Group-OXE. Only CARD 3 score was higher for group-2. No Significant difference was observed in the mean scores between the groups except for VAS-3 and VAS4 which were significantly higher in Group-1 than group-2 ($P<0.05$).

DISCUSSION

The women of 70% complain of breast pain at some stages of their life. Breast pain or mastalgia is a common distressing ailment among ladies in reproductive ages. Mastalgia should be treated when it is severe enough to interfere with a woman's lifestyle and occur for several days each month. This study included 90 study participants, 45 in each group receiving EPO and OXE respectively.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 VAS score and Cardiff Breast Pain Score.

In our study, 14 (31.1%) belonged to 18-25 years age group, 23 (51.1%) belonged to 26-35 years age group and 8 (17.8%) belonged to 36-45 years age group in Group EPO. 13 (28.9%) belonged to 18-25 years age group, 22 (48.9%) belonged to 26-35 years age group and 10 (22.2%) belonged to 36-45 years age group in Group OXE. No significant association was found between age and type of treatment received. In a study by Nirhale et al.,[19] 42 patients (52.5%) were in the age group of 31-40 years, followed by 28 patients (35%) below the age of 30 years which was in accordance with this study.

In our study, 14 (31.1%) had bilateral mastalgia, 20 (44.4%) had left sided mastalgia and 11 (24.4%) had right sided mastalgia in Group EPO. 16 (35.6%) had bilateral mastalgia, 16 (35.6%) had left sided mastalgia and 13 (28.9%) had right sided mastalgia in Group OXE. No significant association was found between side involved and type of treatment received.

28 (62.2%) had acyclic pain in the breast and 17 (37.8%) had cyclic pain in the breast in Group EPO. 22 (48.9%) had acyclic pain in the breast and 23 (51.1%) had cyclic pain in the breast in Group OXE. No significant association was found between pain in the breast and type of treatment received. In a study by Lakhmichand et al.,[20] 25% and 17% had acyclic and cyclic mastalgia respectively in the group OXE which was less compared to this study.

In our study, 42 (93.3%) took no analgesics for relieving pain and 3 (6.7%) took analgesics additionally for the relief of pain in Group EPO. 45 (100%) took no analgesics for relieving pain in Group OXE. No significant association was found between analgesics and type of treatment received. Among those who received primose oil, 12 (26.7%) had mastalgia due to menstrual cycles and 33 (73.3 %) had mastalgia due to other reasons. Among those who received ormiloxefene 30 mg, 45 (100%) had mastalgia due to other reasons. No significant association was found between menstrual cycle related mastalgia and type of treatment received.

In our study, 24 (53.3%) showed normal findings on USG and 21 (46.6%) showed abnormal findings. Among these 21, majority i.e., 13 (28.9%) showed fibrocystic breast disease, 7 (15.6%) showed

fibradenoma, and 1 (2.2%) showed benign breast disease in Group EPO. 25 (55.6%) had normal USG breast and 20 (44.4%) had abnormal USG breast. Among these 20, majority i.e., 9 (20%) had fibroadenoma breast, 6 (13.3%) had fibrocystic breast disease, 5 (11.1%) had fibroadenosis in Group OXE. Statistically significant association was found between USG breast finding and type of treatment received (P<0.05).

In a study by Nirhal et al., [19] 37 (46.25%) had fibroadenosis, 10 (12.5%) had fibroadenoma, 08 (10%) had mastitis, 06 (7.5%) had breast abscess, 03 (3.75%) had duct ectasia, 02 (2.50%) had galactocoele, 02 (2.50%) had breast carcinoma and 12 (15%) had non-specific extra-mammary cause.

In our study, Mean VAS score before treatment was higher among subjects in Group-2, mean CARD score before treatment was almost similar in both the groups. Mean VAS-1, VAS-2, VAS-3, VAS-4, CARD-1, CARD-2, CARD-4 scores were higher in Group-EPO than in Group-OXE. Only CARD 3 score was higher for group-2. No Significant difference was observed in the mean scores between the groups except for VAS-3 and VAS4 which were significantly higher in Group-1 than group-2 (P<0.05).

The pain scores of this study were lesser compared to a study by Ahluwalia e tal.,[120] in which initial pain score was 7.85±0.80 in group receiving primosa oil and 7.20±1.24 in group receiving Ormiloxefene 30 MG. In a study by Balci et al [18], Pain score at the time of admission in EPO group was 6.73 ± 1.03 which was similar to this study. In a study by Lakshmichand et al.,[20] baseline pain score in Ormiloxefene 30 was 6.69 which was similar to this study. At 12 weeks scores were 3.63±1.05 and 2.63±0.92 in the respective groups in a study by Ahluwalia et al., [21] whereas in the present study score a t 12 weeks were 6.22+1.744 and 5.93+1.629 respectively. The change in mean score was observed to be more in the previous study compared to the present one. Group-1 v/s Group-2 mean VAS scores at 16, 20 and 24 weeks in the present study were 4.33+1.552 v/s 3.80+1.440, 3.09+1.505 v/s 2.29+1.424 and 1.53+1.036 v/s 0.82+0.936 respectively. Pain scores in the present study were higher compared to a study by Ahluwalia etal., [21] in which scores were 2.75±1.05 v/s 1.65±1.16 at 12 weeks, 1.75±1.12 v/s 0.90±0.98 at 20 weeks, 1.18±1.07 v/s 0.43±0.90 at 24 weeks. In group 1 (Primosa oil), decrease in pain as compared to initial pain was statistically significant (p value <0.05) at 2nd, 3rd and 4th visits. Similarly, in group 2 (Ormiloxefene 30 MG), decrease in pain was statistically significant (p value <0.05) at all visits. Patients in group 2 experienced early relief of mastalgia as compared to group B. The mean change in VAS score was better in group 2 than group 1 in all visits. In a study by Ahluwlia etal.[21] in group A (Ormiloxefene 30 MG), decrease in pain as compared to initial pain was highly statistically significant (p value 0.00) at all visits. Similarly, in group B, decrease in pain was highly statistically significant (p value 0.00) at all visits. Patients in group A experienced early relief of mastalgia as compared to group B. the findings of this study were consistent with the present study. Similarly in studies by Dhar and Srivastava et al., [22] and Kumar et al. [23], mean pain level significantly reduced in the active group (Ormiloxefene 30 MG) compared to that in the placebo group which confirmed the rapid response and early efficacy of the Ormiloxefene 30 MG in mastalgia. In a study by Lakhmichand et al., [20], Centchroman was found to have response rate of 89.7 % (reduction of pain to less than or equal to 3 on VAS) at the end of 12 weeks whereas Danazol achieved 69.44% response rate at 12 weeks. The response of pain relief was 29% better with Centchroman at 24 weeks which showed that Centchroman was non-inferior to Danazol.

In a study conducted by Anjana Nigam et al.,[24] at the time of enrolment, patients had VAS score ranging from three to seven; gradual reduction of pain was seen in both the groups. After the first month of treatment 60% of the patients reported VAS score reaching to zero and the percentage increased to 87% after third month of the treatment. After one month of treatment reduction in pain which was recorded on visual analogue scale was similar in both the groups. But patients in group 1 (ormeloxifene) recorded a greater reduction in pain on VAS pain scale at the end of second and third month when compared to patients in group 2 (evening primrose oil). The results of this study were consistent with the current study.

In a study by Rathi etal.,[25] a systematic downward trend in the pain score was observed. The median pain score was significantly reduced over successive visits (1, 4, 12, and 24 weeks) whereas in this study a downward trend in the pain score was observed but it was significant only at 20 and 24 weeks which was different from the previous study.

Table 1: Patient Characteristics

PATIENT CHARACTERISTICS		Evening Primrose Oil	Ormiloxefene 30 Mg	P value
AGE	18-25 YEARS	14 (31.1%)	13 (28.9%)	0.923
	26-35 YEARS	23 (51.1%)	22 (48.9%)	
	36-45 YEARS	8 (17.8%)	10 (22.2%)	
SIDE	LEFT	20 (44.4%)	16 (35.6%)	0.771
	RIGHT	11 (24.4%)	13 (28.9%)	
	BILATERAL	14 (31.1%)	16 (35.6%)	
BREAST PAIN	CYCLIC	17 (37.8%)	23 (51.1%)	0.144
	ACYCLIC	28 (62.2%)	22 (48.9%)	
PAIN RELIEVED BY ANALGESIC	YES	42 (93.3%)	45 (100%)	0.121
	NO	3 (6.7%)	-	
MENSTUAL CYCLE REALATED TO MASTALGIA	YES	12 (26.7%)	-	<0.0001
	NO	33 (73.3 %)	45 (100%)	
USG BREAST	NORMAL	24 (53.3%)	25 (55.6%)	0.048*
	ABNORMAL	21 (46.6%)	20 (44.4%)	

Table 2: Vas Score During Follow-up

VAS SCORE	GROUP EPO	GROUP OXE	P VALUE
BEFORE TREATMENT	6.36+1.654	6.73+1.615	0.276
VAS-1	6.22+1.744	5.93+1.629	0.419
VAS-2	4.33+1.552	3.80+1.440	0.095
VAS-3	3.09+1.505	2.29+1.424	0.011*
VAS-4	1.53+1.036	0.82+0.936	0.001*

Table 3: Cardiff Scale During Follow-up

CARDIFF SCALE	GROUP EPO		GROUP OXE		P VALUE
BEFORE TREATMENT	1.18	1.435	1.18	1.419	1.000
CARDIFF -1	1.24	1.433	1.11	1.434	0.660
CARDIFF -2	1.16	1.507	1.11	1.434	0.886
CARDIFF -3	0.69	1.062	0.84	1.296	0.535
CARDIFF -4	0.47	0.842	0.27	0.720	0.229

CONCLUSION

This study was conducted to compare the pain score between the group receiving evening primosa oil and the group receiving ormeloxifene using VAS and CARDIFF scale. It was observed that mastalgia was more frequent in 26-35 years age group. Acyclic mastalgia outnumbered cyclic mastalgia in the study. Pain scores in both the groups showed a downward trend but the change in mean pain score at every visit was higher in the group receiving ormeloxifene compared to the group receiving evening primosa oil. Mean pain score in the group receiving ormeloxifene was significantly lower compared to the group receiving EPO at 3rd and 4th visit. Hence, we conclude that ormeloxifene shows apid response and is superior to EPO in the treatment of mastalgia.

REFERENCES

1. Barton MB, Elmore JG, Fletcher SW. Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. Ann Intern Med. 1999 Apr 20;130(8):651–7.
2. Ader DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: prevalence and associated health and behavioral factors. J Psychosom Obstet Gynaecol. 2001 Jun;22(2):71–6.
3. Mansel RE, Webster DJT, Sweetland H, Hughes LE. Hughes, Mansel & Webster's benign disorders and diseases of the breast. 3rd ed. Edinburgh: Saunders; 2009.
4. Scurr J, Hedger W, Morris P, Brown N. The prevalence, severity, and impact of breast pain in the general population. Breast J. 2014;20(5):508–13.
5. Johnson KM, Bradley KA, Bush K, Gardella C, Dobie DJ, Laya MB. Frequency of mastalgia among women veterans. J GEN INTERN MED [Internet]. 2006 Mar 1 [cited 2023 Jan 16];21(3):S70–5. Available from: https://doi.org/10.1111/j.1525-1497.2006.00378.x
6. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. Mayo Clinic Proceedings [Internet]. 2004 Mar 1 [cited 2023 Jan 16];79(3):353–72. Available from: https://www.mayoclinicproceedings.org/article/S0025-6196(11)62869-3/fulltext
7. Raghunath S, Raghuram N, Ravi S, Ram N, Ram A. Prevalence of mastalgia in young Indian females. J Health Res Rev [Internet]. 2015 [cited 2023 May 2];2(3):108. Available from: http://www.jhrr.org/text.asp?2015/2/3/108/168368
8. Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders. Med Res Rev. 2001 Jul;21(4):302–47.
9. Kamboj VP, Setty BS, Chandra H, Roy SK, Kar AB. Biological profile of Centchroman--a new post-coital contraceptive. Indian J Exp Biol. 1977 Dec;15(12):1144–50.

10. Rajswaroob U, Kannan R, Kannan NS, Tirouaroul T. Effectiveness of centchroman on regression of fibroadenosis and mastalgia. J Clin Diagn Res [Internet]. 2016 Oct [cited 2023 Jan 16];10(10):PC10–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5121728/
11. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg [Internet]. 2007 Jun 1 [cited 2023 Jan 16];31(6):1180–6. Available from: https://doi.org/10.1007/s00268-007-9040-4
12. Krueger RJ. The handbook of clinically tested herbal remedies, vols. I and ii edited by m. Barrett (Pharmacognosy consulting). Haworth press, inc. , birmingham, ny. 2004. Xxvii + 1435 pp. 16 × 22 cm. $129. 95. Isbn 0-7890-1068-2. J Nat Prod [Internet]. 2005 Jan 1 [cited 2023 Jan 16];68(1):154–5. Available from: https://pubs.acs.org/doi/10.1021/np0307791
13. Bamford JTM, Ray S, Musekiwa A, van Gool C, Humphreys R, Ernst E. Oral evening primrose oil and borage oil for eczema. Cochrane Database Syst Rev. 2013 Apr 30;2013(4):CD004416.
14. Joe LA, Hart LL. Evening primrose oil in rheumatoid arthritis. Ann Pharmacother. 1993 Dec;27(12):1475–7.
15. Mahboubi M. Evening primrose (Oenothera biennis) oil in management of female ailments. Journal of Menopausal Medicine [Internet]. 2019 Aug 1 [cited 2023 Jan 16];25(2):74–82. Available from: https://doi.org/10.6118/jmm.18190
16. Gateley CA, Maddox PR, Pritchard GA, Sheridan W, Harrison BJ, Pye JK, et al. Plasma fatty acid profiles in benign breast disorders. Br J Surg. 1992 May;79(5):407–9.
17. Pruthi S, Wahner-Roedler DL, Torkelson CJ, Cha SS, Thicke LS, Hazelton JH, et al. Vitamin E and evening primrose oil for management of cyclical mastalgia: a randomized pilot study. Altern Med Rev. 2010 Apr;15(1):59–67.
18. Balci FL, Uras C, Feldman S. Clinical factors affecting the therapeutic efficacy of evening primrose oil on mastalgia. Ann Surg Oncol [Internet]. 2020 Nov [cited 2023 Jan 16];27(12):4844–52. Available from: https://link.springer.com/10.1245/s10434-020-08949-x
19. Nirhale DS, Dhende M, Shingade P, Chavan S, Sonawane T, Kulkarni G. A study on clinical profile and management of mastalgia. Int Surg J 2018;5:1889-93
20. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, Thulkar S, Chumber S, Kumar S. Centchroman regresses mastalgia: a randomized comparison with danazol. Indian Journal of Surgery. 2011 Jun;73(3):199-205.
21. Ahluwalia AS, Bhatia P, Chhabra AS. A comparative study of centchroman versus evening primrose oil in treatment of mastalgia. Int Surg J 2021;8:331-8.
22. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World journal of surgery. 2007 Jun;31(6):1180-6.
23. Kumar S, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V. A randomized, double-blind, placebo-controlled trial of ormeloxifene in breast pain and nodularity. Natl Med J India 2013;26:69–74
24. Nigam A, Goenka A, Shrivastava N. A Comparative Study of Effect of Ormeloxifene and Evening Primrose Oil in Treatment of Mastalgia. Ind J Surg.2019;81(3):259-64
25. Rathi J, Chawla I, Singh K, Chawla A. Centchroman as First□line Treatment for Mastalgia: Results of an Open□label, Single□arm Trial. The breast journal. 2016 Jul;22(4):407-12.