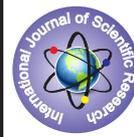


A COMPARATIVE STUDY OF CENTCHROMAN VS DANAZOL VS EVENING PRIMROSE OIL IN THE MANAGEMENT OF MASTALGIA AND FIBROADENOMA



General Surgery

KEYWORDS: Centchroman, Danazol, EPO, Mastalgia, Fibroadenoma

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ABSTRACT

We conducted an prospective nonrandomized interventional study to compare the efficacy of a newer therapeutic agent Centchroman with established therapeutic agents Danazol and Evening Primrose Oil (EPO) in the treatment of mastalgia and fibroadenoma. Total 117 patients have been participated in the study (mastalgia-68, fibroadenoma-54 and 5 patients have both). In mastalgia group 28, 18 and 22 patients were treated with Centchroman, Danazol and EPO respectively. In fibroadenoma group 17, 18 and 19 patients received Centchroman, Danazol and EPO respectively. Centchroman was found to be the most effective drug with the post intervention pain scores <2 in 71% patients (50% with Danazole, 0% with EPO). In fibroadenoma group complete response rate was highest in Centchroman arm (29%) in comparison to Danazol (17%) and EPO (0%) respectively. Side effects are maximum with Danazole and Centchroman is the cheapest.

Introduction: Mastalgia and fibroadenoma are the two major causes of morbidity amongst Indian women presenting with benign breast diseases. Incidence of these are sparsely documented in literature and probably quiet underestimated. Conventional conservative treatment of these diseases are less rewarding and sometime with lots of untoward effects. So cost and side effects are the limiting factors for the conventional conservative therapies in our country. Finding a efficacious drug with low cost and less side effects is a challenge in Indian subcontinent.

Method: We have conducted an prospective nonrandomised interventional study on 117 patients attending the outpatient department of a tertiary care teaching hospital in eastern India over a period of one and half year. The aim of the study is to compare the efficacy of the newer therapeutic agent Centchroman with the established therapeutic agents Danazol and Evening Primrose Oil (EPO) in the treatment of mastalgia and fibroadenoma. All premenopausal women with mastalgia with or without nodularity and fibroadenoma, after performing triple assessment, were included in the study. The exclusion criteria were 1. All malignant breast diseases 2. Dysplastic lesion which mandate compulsory surgical intervention 3. Simple breast cysts 4. Fibroadenoma of more than 5 cm size 5. Patients on oral contraceptive pills 6. Patients desirous to remove the lump 7. Patients unwilling to enrol herself in the study 8. Contraindications of Centchroman : i. Pregnancy ii. Polycystic ovarian diseases (PCOD) iii. Cervical hyperplasia iv. Recent history or clinical evidence of jaundice or liver diseases v. Conditions like severe allergic states, chronic illness such as tuberculosis, renal diseases etc. vi. Patients willing to conceive within six months. An ethical committee clearance has been taken before initiation of the study and prior informed consent was obtained in all the cases. Ultrasound guided fine needle aspiration cytology was done in fibroadenoma and dominant nodule in patients with nodularity of the breast. All sexually active women were sent for a detailed gynaecological examination, as well as ultrasound of the pelvis to rule out polycystic ovarian disease. Cases of mild mastalgia were treated with supportive care only and not included in the study.

All the patients received the same supportive care that included reassurance, breast support and stopping of methyl xanthenes in diet (abstinence from coffee, tea etc). Two groups (mastalgia and fibroadenoma) of the patients were divided into three arms, the first arm treated with Evening Primrose Oil (EPO), the second arm with Danazol and third with Centchroman. All the cases were recorded in a predesigned and pretested schedule. Patients with mastalgia were asked to maintain breast pain chart. After 3 months all patients were evaluated by 0-10 visual analogue score (VAS) and by ultrasound (USG). Evaluation of response of fibroadenoma by ultrasound are categorised in 3 groups, namely no response (no change in size or increase in size), partial response (some decrease in size but not to zero) and complete response (lump vanished).

Results:

Majority of the patients are in the range of 20-35 years.

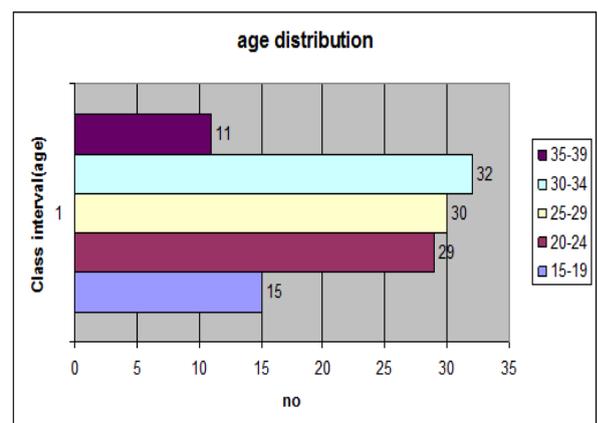


Figure 1: Distribution of age

Patient distribution

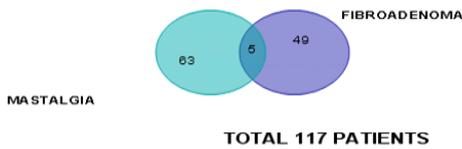


Figure 2: Distribution of patient according to disease

Out of 117 patients, participated in the study, 68 (58 %) had mastalgia and 54 (46%) patients had fibroadenoma. Five patients had both fibroadenoma and cyclical mastalgia. In mastalgia group 28, 18 and 22 patients were treated with Centchroman, Danazol and EPO respectively. In fibroadenoma group 17 , 18 and 19 patients received Centchroman, Danazol and EPO respectively.

Table 1: Distribution of patients according to drug treatment

	Fibroadenoma	Mastalgia
EPO	19	22
Danazol	18	18
Centchroman	17	28

Out of 68 patients presented with mastalgia, 56 (82%) were suffering from cyclical mastalgia and 12 (18%) patients from non cyclical mastalgia. A pre-intervention VAS score of ≥ 7 was recorded in 52 (76.47%) and remaining 16 patients had VAS score of less than 7.

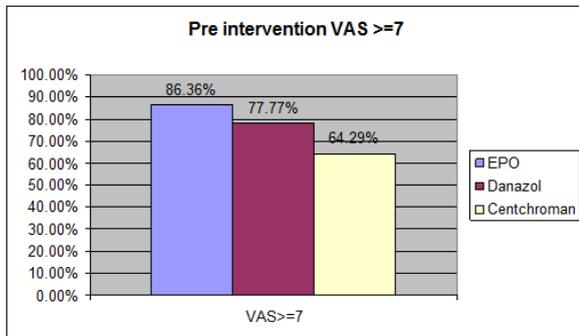


Figure 3: Pre intervention VAS score ≥ 7 in different arms

18 (64%), 14 (78%) and 19 (86 %) patients having a pre intervention VAS score greater than or equal to 7 received Centchroman, Danazol and EPO respectively. Difference in mean initial VAS in 3 different arms was not significant ($p=0.935$). Post ad hoc multiple comparison also gave same type of result ($p = 0.717\&0.887$). Post intervention (at the end of 3rd month) VAS reduced to less than or equal to 3 in 26 (93%), 17 (94%) and 9 (41%) cases with Centchroman, Danazol and EPO respectively. Similarly post intervention VAS ≤ 2 occurred in 20 (71 %), 9 (50 %), and 0 (0 %) with Centchroman, Danazol and EPO respectively. Centchroman was found to be the most effective drug with the post intervention pain scores <2 in more than 70% patients. But post intervention pain score <3 was maximum in patients treated with Danazol (94.44%) when compared to Centchroman (93%). Difference in mean final VAS in 3 different arms was statistically significant ($p = 0.000$). Comparison between final VAS of each 2 arms of patients receiving EPO or Centchroman revealed statistically significant ($p = 0.000$) difference. Difference between 2 arms on Danazol or Centchroman therapy did not show significant difference.

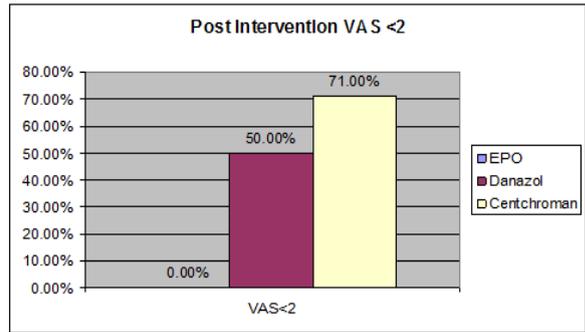


Figure 4: Post intervention VAS <2 in different arms

Size of Fibroadenoma ranged from 9.3 to 40 mm, single or multiple in one or both breasts. Complete response rate was highest in Centchroman arm (29%) in comparison to Danazol (17%) and EPO (0%).

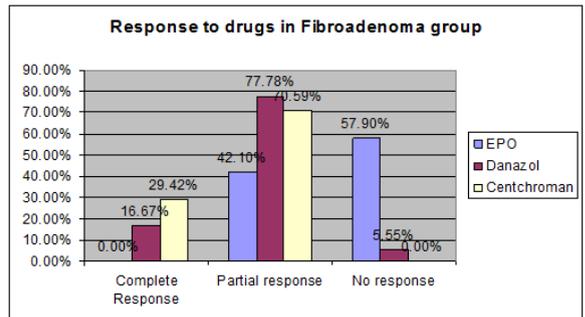


Figure 5: Response of fibroadenoma in different arms

Partial response was observed in 71 % , 78%, 42% cases receiving Centchroman, Danazol and EPO respectively and no response occurred in 0%, 6%, 58% respectively. Difference in average initial size of fibroadenoma in 3 different arms were not statistically significant ($p = 0.165$). Post hoc multiple comparison also did not reveal statistical significance ($p = 0.208 \& 0.063$). Difference in average final size of fibroadenoma in 3 different arms were statistically significant ($p = 0.000$). Comparison between two arms of patients on EPO and Centchroman showed statistically significant ($p = 0.000$) difference in final size of fibroadenoma. On the other hand arms with Danazol or Centchroman did not reveal any statistically significant difference ($p = 0.071$).

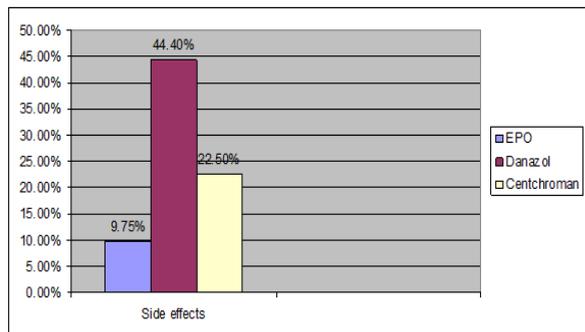


Figure 6: Side effects of different drugs

Maximum side effects (44 %) were observed with Danazol which was mainly menstrual irregularities. Centchroman usage was associated mostly with oligomenorrhea in about 23 % of patients. Inter group X2 test between arm on EPO & arm on Centchroman was significant ($p = 0.118$) whereas significant value ($p = 0.042$) of X2 between arms on Danazol and Centchroman was not supported by relative risk ($RR=0.51$ which falls within the range).

Table 2: Cost of therapy with different drugs

Drug	Cost (Rs) per month (approx)
EPO	800
Danazol	700
Centchroman	35

Centchroman is the cheapest (Rs 35/month) & EPO is the costliest (Rs 800/month) whereas cost of Danazol (Rs 700/month) is less but close to EPO.

Discussion :

The vast majority of lesions that occur in the breast are benign. Benign breast diseases in comparison to its much heavyweight counterpart malignant breast disease received less attention academically. In western population prevalence of cyclical mastalgia ranges from 45 - 79%.^{1,2} Cyclical mastalgia, though often underestimated, has been found to significantly interfere with sleep (10%), work, social functioning (6-13%), physical activity (36%) and sexual activity (48%).^{2,3,4} Only 14% of women with cyclic mastalgia experience spontaneous resolution; however, 42% experience resolution at menopause.² Benign breast disease deserves attention because of its high prevalence, its impact on quality of life, and for malignant potential of some histological variants.⁵ There are evidences that high concentration of saturated fatty acids and reduced proportions of essential fatty acids, especially gamma-linolenic acid (GLA), is quiet common in patients of mastalgia and nodularity.⁶ EPO, rich source of essential fatty acids, was considered an effective agent for treating mastalgia with or without nodularity. Though some study reported some response with EPO⁷, results are not always satisfactory; more so with non cyclical mastalgia⁸ and the cost of therapy is again very high.^{9,10,11} A double-blind, randomized, placebo-controlled trial, conducted at two U.S. academic medical centres on 85 women with premenstrual cyclical breast discomfort failed to establish any advantage of using vitamin E and EPO over placebo.¹² Influences of hormonal abnormality on cyclical mastalgia and nodularity is now well established and evidenced by its temporal relationship with menstrual cycle and well documented response to hormonal manipulation, but etiology of non cyclical mastalgia still lacks documentation.¹⁰ Greenblatt incidentally noticed alleviation of breast pain, nodularity and premenstrual breast engorgement while employing Danazole in the management of endometriosis and on further study he experienced Danazole as an excellent hormonal agent in the treatment of nodularity and breast pain in 75% of the patients.^{13,14} Our study also revealed Danazole as a very effective drug for managing mastalgia and there are many other studies to support.^{16,17,18} Unfortunately, adverse effects are very frequent (30-00%) with the use of Danazol. They are dose related and primarily androgenic, including menstrual irregularity or amenorrhea (50-100%), acne, hair loss, decrease in voice pitch, weight gain, headache, nausea, rash, anxiety and depression.^{26,19} Presently in most breast clinics Danazol is reserved as a second line drug for mastalgia.²⁰ Tamoxifen, a selective estrogen receptor modulator, is effective in reducing pain in 71% to 96% of women with cyclic mastalgia and 56% of women with noncyclic mastalgia in controlled trials.² Tamoxifen is well tolerated in low dose but has a risk of potentially serious adverse effects like deep venous thrombosis and endometrial cancer along with hot flashes, nausea, menstrual irregularity, vaginal dryness or discharge, and weight gain.^{26,20} Centchroman (Ormeloxifene) is a nonsteroidal selective estrogen receptor modulator (SERM) and is in use as oral contraceptive in India for last two decades.²¹ In a pilot study conducted in All India Institute of Medical Sciences on 60 patients experienced complete response in 39% and partial response in 61% of cases with mastalgia at the end of two weeks.¹⁹ In their study all the patients with mastalgia responded completely after 12 weeks but during the follow-up period 4% returned with pain, with VAS scores of 2 and 5 only.¹⁹ In the same study nodularity regressed completely in all the cases at the end of 12 weeks and there were no recurrences at the end of 6 months.¹⁹ This group also observed that at the end of 12 weeks 41% cases of fibroadenoma disappeared, 24% reduced in size but there was no change in size in 35% of the cases.¹⁹ A

randomised trial comparing efficacy of Centchroman with Danazole in relieving mastalgia showed that, though Danazole acts faster, Centchroman is more efficacious in reduction of pain score at 12 weeks (89.7% vs. 69.44%; p=0.001).²⁰ There are other studies including a randomized, double-blind, placebo-controlled trial which also showed efficacy of Centchroman in breast pain and nodularity.^{21,22} In our study, though Danazol is very effective in pain relief, it is maximum with Centchroman (post intervention VAS <= 2 occurred in 71 % with Centchroman and 50 % with Danazol). We found a good response in mastalgia group where 71 % of patients receiving Centchroman finally showed a VAS score of less than 2 after 3 months of treatment compared to 50 % in Danazol group and 0 % in EPO group. In 29 % of patients receiving Centchroman showed complete resolution of nodularity whereas 17 % in Danazol group and 11 % in EPO group. So Centchroman is an efficient and safe as well as cheap alternative to conventional agents in treatment of mastalgia and fibroadenoma and can be used as the first line drug in the management of mastalgia.

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