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RANDOMIZED CONTROL DOUBLE BLIND TRIAL TO EVALUATE EFFECTIVENESS OF CENTCHROMAN IN CONTROL OF MASTALGIA IN COMPARISON TO DANAZOL.

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ABSTRACT **Objectives:** To study the efficacy, cost effectiveness and side effect profile of centchroman in comparison to danazol in women with pain in the breast. **Methodology:** A double blind (investigator assessing the response and patient both was blinded) two arm parallel designs randomized controlled trial. Block randomization with a block size of 4 was employed to generate a list of random numbers. **Results:** patients in both group showed gradual improvement in symptoms in terms of decrease in mean VAS during 3 months period of treatment while after three months after stopping therapy, centchroman was more effective in sustaining pain relief than danazol. **Conclusion:** This trial has demonstrated that Centchroman therapy offers a safe, at least equally effective and inexpensive alternative to Danazol for treatment of mastalgia.

KEYWORDS : Centchroman, mastalgia, randomized controlled trial

Introduction

Mastalgia is the most common type of breast pain which may be associated with menstruation. It is cyclic in two-thirds of patients so also called a premenstrual or cyclic mastalgia. It is bilateral and usually most severe in the upper outer quadrants of the breast, and may be referred to the upper arm and axilla[1,2]. Mastalgia could be noncyclic which is described as a constant or intermittent breast pain with irregular exacerbations and no relationship to menstruation. Noncyclical mastalgia is usualy bilateral and located within single quadrant of the breast[3].Cyclic mastalgia is more common in Western world.[4,5]

Aim: Randomized control double blind trial to evaluate effectiveness of centchroman in control of mastalgia in comparison to danazol.

OBJECTIVES: To study the efficacy, cost effectiveness and side effect profile of centchroman in comparison to danazol in women with pain in the breast.

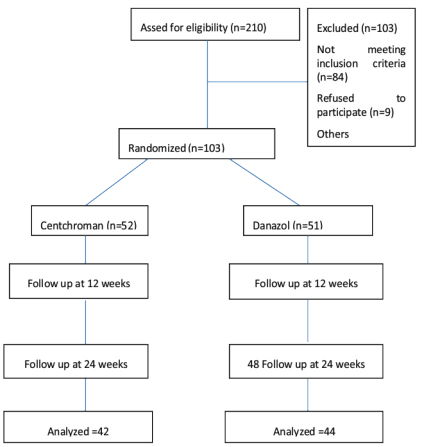

Fig: consort diagram

Methodology:

A double blind (investigator assessing the response and patient both was blinded) two arm parallel designs randomized controlled trial. Block randomization with a block size of 4 was employed to generate a list of random numbers.

Study subject: Women in the reproductive age group with regular menses presenting with cyclical and noncyclical breast pain.

Exclusion criteria: Patients taking alternative treatment, lactating women, those planning a pregnancy or currently pregnant or taking other oral contraceptive pills, past history of breast carcinoma or family history of breast carcinoma.

Study Period: September 2014 to October 2016.

Sample Size: We put forth the assumption that, Centchroman therapy would achieve pain relief similar to or slightly less than that achieved by Danazol. The clinically meaningful difference in the proportion of cases getting pain relief in between the two arms is represented by delta-(δ) which is the non-inferiority margin in calculating the sample size with the following null hypothesis (H0). p1 (50%) = pain response proportion with Centchroman therapy, p2 (60%) = pain response proportion with Danazol therapy. Allowing the 15% of difference between results of two therapies as the clinically meaningful difference, the value of δ has been chosen as 0.15. The values of other factors were taken as follows:- Z=1.645 for =0.05 for one tailed hypothesis Zβ=0.84 for power=80% for one or two tailed hypothesis With all these values the formula used in calculation of sample size for one group was as follows: $N = (Z\alpha + Z\beta)^2 [p1(1-p1) + p2(1-p2)/[(p1-p2)-\delta]^2$

$N = (1.645+0.84)^2 [0.5(1-0.5) + 0.6(1-0.6)] / [0.1-0.12]^2$ .The value of N (i.e. the sample size for one group) was calculated to be 48. Expecting 10% of withdrawal of the volunteers from the groups, the total numbers of patients to participate were considered 110. The study presents the result on 86 subjects.

Daily Breast Pain Charting: Patients were requested to record their daily pain experience on a chart asked to keep a record of their breast pain in a "pain diary". The drug treatment was continued for a total of 12 weeks and then the patient was followed for another 12 weeks without medication to assess sustained response or recurrence of mastalgia.

Procurement of drug: By supervisor: Ormeloxifene: Brand name: Saheli (30mg), company: Kerala state drug and pharmaceutical ltd. Danazol: Brand name: Gonablok (100mg), company: win Medicare. Separate white coloured envelops are prepared under guidance of supervisor and allocated number case 1 and case 2 respectively.

Statistical Analysis: Data was analyzed by using SPSS version 17.

Ethical clearance and consent Approved by the Institute ethics committee of Government Medical College Haldwani.

Observation and Results: Mean age of study subjects receiving Centchroman and danazol for treatment was 29.95 years and 28.56 years respectively. Mean pain score by VAS scale was 7.40 for centchroman while it was 7.29 for danazol group. Mean duration of menses for centchroman and danazol and centchroman group was 6.52 days and 6.72 days respectively. Fig: 1 Patients in centchroman arm experienced early relief of mastalgia as compared to patients in danazol arm. VAS score of ≤3 was considered as relief from mastalgia. Pain score at one month for danazol was found to be more (5.20±0.66), then centchroman (4.00±0.79), similarly pain score of danazol was found (2.70±0.59) as compared to centchroman (2.14±0.41), follow up at 6 month there was an increase in pain score of danazol (3.66±1.01) from third month and as compared to centchroman (2.02±0.15). Table: 3 Depicts that acne as a side effect was seen in 10 subjects out of 86 subjects from this 90% of cases were seen in danazol group while only 10% cases were seen in centchroman group hirsutism as a side effect was seen in eight subjects and 100% of them belong to danazol group.

Table 1: Comparison of baseline characteristics of study subjects

Variable	Centchroman (mean) (n=42)	Danazol (mean) (n=44)	p Value
Age(years)	29.95	28.56	0.34
VAS(pain)	7.40	7.29	0.36
Duration Of Menses(days)	6.52	6.72	0.08
Cases With Cyclical Mastalgia	30	34	0.62
Cases With Non-Cyclical Mastalgia	12	10	0.62
Weight(Kg)	61.94	55	0.11

Figure 1: Depicting the change in Median VAS pain score up to 24 weeks

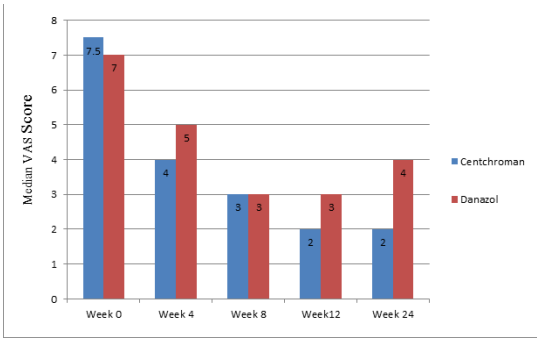

Table 2: Comparison of pain at different time intervals between danazol and centchroman group

VARIABLE	Drug Given	n	Mean±SD	p VALUE
Pain at initial visit	Centchroman	42	7.40±0.85	.518
	Danazol	44	7.30±0.70	
Pain at 1 month	Centchroman	42	4.00±0.79	.000
	Danazol	44	5.20±0.66	
Pain at 2nd month	Centchroman	42	2.79±0.64	.000
	Danazol	44	3.50±0.79	
Pain at 3rd month	Centchroman	42	2.14±0.41	.000
	Danazol	44	2.70±0.59	
Pain 6th month	Centchroman	42	2.02±0.15	.000
	Danazol	44	3.66±1.01	

Table 3: Comparative Side Effect Profile of danazol and centchroman

Variable	Danazol	Centchroman	Total	Chi Square/P Value
Acne				
No	35(46.1)	41(53.9)	76(100)	6.83/0.015
Yes	9(90)	1(10)	10(100)	
Deeping Of Voice				
No	42(50)	42(50)	84(100)	1.95/0.49
Yes	2(100)	0(0)	2(100)	
Hirsutism				
No	36(46.2)	42(53.8)	78(100)	8.42/0.006
Yes	8(100)	0(0)	8(100)	
Deranged Lipid Profile				
No	37(48.1)	40(51.9)	77(100)	2.85/0.15
Yes	7(77.8)	2(22.2)	9(100)	

DISCUSSION: The dose of centchroman was 30 mg per day and danazol 100 mg for three months. Mean age of the study participant in our study was 29.24years, similarities in mean age was seen in studies conducted by Kumar et al[6] (33.7years), and Bansal et al[7] (32.8years). Decrease in mean VAS was more in group A (Centchroman) than group B (Danazol) at the end of three months of treatment (2.14 vs 2.70) and was statically significant (p value = 0.0001). In group A 97.18% of patients and in group B 91.18% reported pain relief (VAS≤3).The difference between VAS in both groups Tejwani et al[8] in 2011 in a similar study reported relief of breast pain in 89.7% as compared to 69.44% in group B at 12 weeks of treatment. The pain score was also assessed at 6 months (three months after completion of therapy). In group A mean VAS decreased from (2.14 to 2.02) while got increased from (2.70 to 3.66) in group B and it's statically significant with p value of 0.0001. In study conducted by Dhar et al[9] in 2007 and Kumar S et al[6] in 2013 to see the effect of centchroman in mastalgia, there was 100% and 93.3% improvement in mastalgia at the end of 3 months and decrease in mean VAS to 0.00 and 1.39 respectively. Our results for group A are better than Tejwani et al[8] study because in their study centchroman was given alternate day basis in the initial part of their study and was given on daily basis in our study. In group A patients on Centchroman 30 mg per day, 07 patients had scanty menstruations, 3 had delayed menses by 9-13days and menorrhagia in 01 case. All these menstrual irregularities subsided after stopping the drugs except one case of menorrhagia. It seems that menstrual irregularities are more frequent in patients receiving 30 mg of centchroman daily as in our study as compared to patient receiving centchroman on alternate days (Dhar et al[9]) and twice weekly (Kumar et al[6]). In group B patients were given Danazol at 100 mg per day. At this androgenic side effects were observed like acne (09), voice change (02), hirsutism (8) 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 stopping danazol in 2 to 3 months. Similar incidence of side effects noted with Tejwani et al[69] study. The cost of centchroman is 2.00 rupee per tablet, which computes to a cost of 180 rupee for a period of 3 months. The cost of Danazol is 15 rupee per tablet, which computes to a cost of 1350 rupee for a 3 month course. The cost of treatment of mastalgia with centchroman was much cheaper than danazol.

Conclusion and recommendation

This trial has demonstrated that Centchroman therapy offers a safe, at least equally effective and inexpensive alternative to Danazol for treatment of mastalgia. It is a pride molecule for Mother India as it is developed, manufactured and marketed by Indian Government.The cost-effectiveness and quality of life with Centchroman therapy should be assessed in comparison with other drugs on a larger multi centre randomized trial, based on superiority hypothesis.

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