International Journal of Enhanced Research in Medicines & Dental Care, ISSN: 2349-1590
Vol. 3 Issue 4, April-2016, Impact Factor: 1.102

Centchroman vs Danazol for regression of cyclical mastalgia: A randomized control trial

Dr. R.K. Karwasra[1], Dr. Rajat Batra[2], Dr Hans Raj Ranga,[3] Dr Jyotsna Sen[4]

[1] Senior professor and head of department of surgery Pt BDS University of Health Sciences, PGIMS, ROHTAK-124001
[2] Junior resident, department of surgery, PGIMS, ROHTAK-124001
[3] Associate professor, department of surgery PGIMS, ROHTAK-124001
[4] Professor, Department of radio diagnosis, PGIMS, ROHTAK-124001

ABSTRACT

Breast pain or mastalgia is one of the most common benign disorders of breast. Several agents have been tried in the treatment of mastalgia. Centchroman (Ormeloxifene) is a selective estrogen receptor modulator, has recently been used in treatment of mastalgia.

Methods: Eligible patients of cyclical mastalgia were randomly divided into two groups A and B of 25 each. In group A Centchroman 30 mg per day and in group B danazol 100 mg per day were given for 3 months, followed up every month and at 6 month (after stoppage of treatment) to see the relapse. Severity of pain was measured on visual analogue scale (0-10). Patients were considered relief of pain when VAS was ≤3.

Results: There was gradual improvement in mean VAS in both groups. At the end of 3 months, 92% of women achieved reduction in pain score to ≤3 in centchroman group and in danazol group 66.66% women achieved reduction in pain to ≤3 ($p<0.007$). Mean VAS was decreased to 2.09 and 3.04 in group A and B respectively ($p<0.0001$) at the end of treatment. Centchroman was more effective in sustaining pain relief than danazol after stoppage of drugs for 3 months ($p<0.0001$). Centchroman is more effective, safe and in expensive than danazol in the treatment of cyclical mastalgia.

Key words: Mastalgia, Centchroman, Danazol, VAS

INTRODUCTION

Mastalgia or breast pain was described in the medical literature as early as 1829.[1] It is the commonest breast related complaint for which a woman seeks medical attention. The reported prevalence of mastalgia in western literature is 41-79%.[2]Mastalgia may be cyclical or non-cyclical.[3]

Cyclical mastalgia is defined as breast pain that is related to menstrual cycles and occur 1 to 2 weeks prior to menses. It is relieved by onset of menstrual cycles. Non-cyclical mastalgia is defined as intermittent or continuous breast pain without premenstrual exacerbation and having no relationship with menstrual cycles. Cyclical mastalgia is the most common type of breast pain accounting for two-thirds of cases.[4] Several factors have been implicated by various workers; however no consistent opinion has emerged.[4] Treatment of mastalgia is as controversial as its etiopathogenesis. Non medical therapy includes reassurance and good external breast support "sports brassier". There are number of drugs which have been tried in the treatment of mastalgia such as tamoxifen, danazol, evening primrose oil, topical as well as oral non steroidal anti inflammatory drugs and more recently centchroman. Centchroman (Ormiloxifene) is a selective estrogen receptor modulator.[5] It is primarily used as an oral contraceptive pill and is being distributed in India free of cost under National Family Welfare Program. Dhar et al. in a pilot study of centchroman in mastalgia, showed 100% response rate in pain relief after 12 weeks of treatment while nodularity and tenderness disappeared in all patients after 4 weeks.[5] In a randomized controlled trial comparing centchroman with Danazol. Tejwani et al. showed that centchroman was more effective in reducing pain on visual analouge scale[6]. Menstrual irregularities were reported as the most common side effects in both

these studies. Considering encouraging result of Centchroman in the treatment of matalgia, this randomized study was done to compare centchroman (recently used) and danazol (established drug) in the treatment of cyclical mastalgia.

METHODS

Study design: The present prospective study was randomized control trial of centchroman and danazol conducted in Department of General Surgery, Pt. B. D. Sharma Institute of Medical Sciences, Rohtak. Patients having complaint of breast pain were screened and divided into cyclical and non cyclical mastalgia. A minimum of 50 patients were taken. Patients having cyclical mastalgia were allocated randomly into two groups of 25 each. In group A centchroman (30mg/day) was given for three months. In group B danazol (100mg/day) was given for three months. Patients with non cyclical mastalgia were excluded from study.

Patient selection : All patients having complaint of breast pain with or without nodularity for more than 3 months duration and having pain severity of >3 on VAS were assessed for inclusion in the study. A detailed history was taken from all the patients followed by physical examination. Ultrasonography was carried out in all cases to find out any lump. Mammography was done in age group ≥35 and in patients with high risk group like positive family history of breast cancer. Patients were excluded if they met any of the following criteria: patients with non cyclical mastalgia, patients with cyclical mastalgia with visual analogue pain score <3, patients who present with mastalgia and found to have clinically palpable or ultrasonograhically detected lump.

Randomization and trial flow: Patients were given with Centchroman 30 mg per day and Danazol 100 mg per day randomly. Patients were followed at 4, 8, 12 weeks and again at 24 weeks after stoppage of drugs to see the decrease in mean visual analogue score and considered positive with VAS score of ≤3. The data were tabulated and analyzed by using SPSS version 20. Significance difference were considered when p value was less than 0.05.Each group was assessed for homogeneity of variances at base line using t test and chi square test. Side effect of drugs were noted in both groups at every follow up and tabulated.

RESULTS

In present study 50 patients presenting with cyclical mastalgia in outpatient department of surgery at Pt. B. D. Sharma Institute of Medical Sciences, Rohtak were randomized into two groups Group A (Centchroman) and Group B (Danazol) of 25 each. There was no significant difference between two groups with respect to age, marital status, parity, duration of symptoms and pretreatment severity of mastalgia. In group A all patients reported at 1, 2, 3 months of follow up and one patient did not report for follow up at six months. In group B, one patient lost follow up at three months and two more at six months. There was gradual improvement in the breast pain in both the groups. However means VAS worsened to 3.83 at 6 months of follow up after completion of therapy in group B as shown in table 1.

Table 1: Percentage improvement in the VAS of group A and B

Time	Mean VAS (Group A)	Mean VAS (Group B)	p value
At the start of study	7.18±0.86	7.11±0.86	0.38
At 1 month	4.20±0.61	3.95±0.63	0.08
At 2 month	2.96±0.37	3.12±0.54	0.18
At 3 month	2.09±0.55	3.04±0.35	0.0001
At 6 month	2.09±0.55	3.83±0.44	0.0001

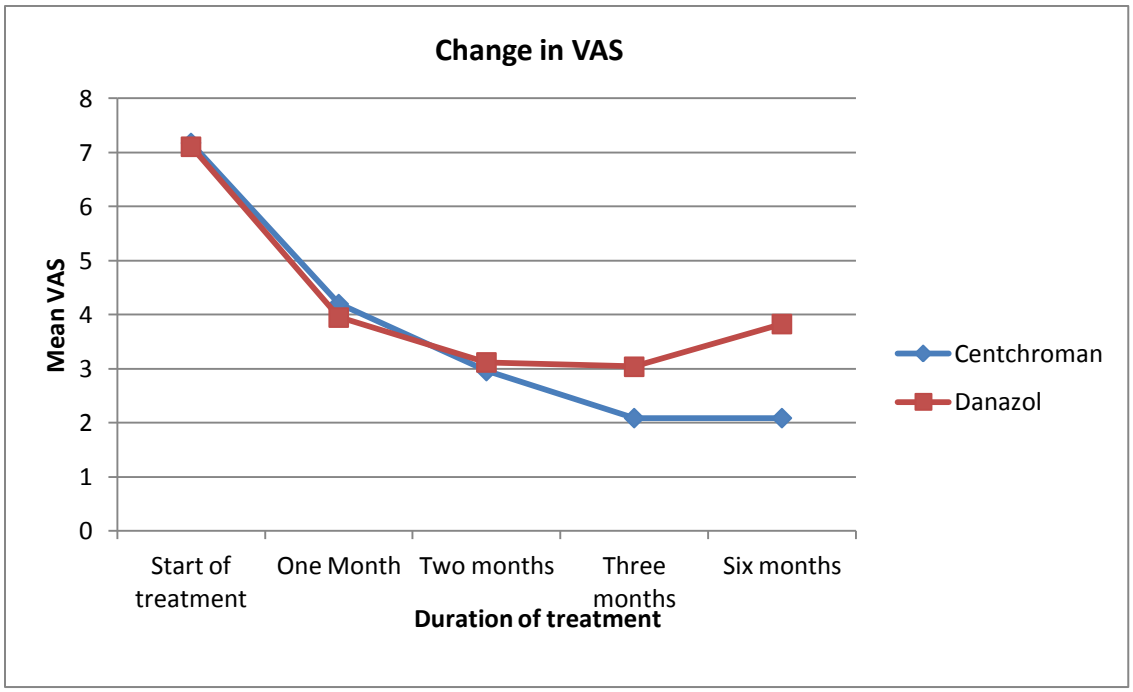
The difference in the mean VAS was most marked at 1 month of drug therapy The decrease in VAS in group A was 3.98 and decrease in VAS in group B was 4.16 (41.5% vs. 44.44%). The change was more marked with danazol. At the end of second and third month, change in VAS was more in group A than group B as shown in table above. After stoppage of therapy for three month, there was no change of VAS in group A and increased of 0.79 mean VAS noted in group B.

Table 2: Proportion of women having pain relief VAS ≤3

Time	Group A	Group B	p value
1 months	1/25(4%)	3/25(12%)	0.30

2 months	16/25(64%)	13/25(52%)	0.74
3 months	23/25(92.00%)	16/24(66.66%)	0.074
6 months	22/24 (91.66%)	10/22(45.45%)	0.0004

There was gradual increase in the number of women having pain relief (VAS ≤3) over three month's period. Initial good response was seen with danazol (group B) at the end of one month. But later on response was good with centchroman (group A). At the end of three months 92.00% of women had pain relief (VAS≤3) in group A and 66.66% in group B. Three months after stopping therapy, centchroman was more effective in sustaining pain relief than danazol (91.66% vs 45.45%) as shown in table 2.



Side effects

In group A (Centchroman 30 mg per day), 08 patients had scanty menstruations, 4 had delayed menses by 10-12 days. In group B patients were given Danazol at 100 mg per day. At this no androgenic side effects like acne, facial hair, voice change or other stigmata of hirsutism while on treatment were noted. The most common side effect noted was menstrual irregularities in the form of delayed menses in 4 patients and menorrhagia in 1 patient at the end of 3 months. All patients resume normal menses after stopping danazol in 2 to 3 month. Allergic reaction in the form of utricaria was noted in one patient after 2 months of start of treatment. The drug was immediately stopped and we lost follow up of that patient.

DISCUSSION

Several drugs are available for treatment of mastalgia namely Danazol, Tamoxifen, Bromocriptine, evening primrose oil, topical non steroidal anti inflammatory gels. Evening primrose oil, flaxseed, topical non steroidal drugs are generally used as first line drug for mild cases of mastalgia. Hormonal agents like danazol, tamoxifen , bromocriptine are used as second line of drugs. The present study evaluated and compared centchroman (recently used) and danazol (already established) in the treatment of cyclical mastalgia. The dose of centchroman was 30 mg per day and danazol 100 mg for three months. The response was assessed in terms of change in VAS (VAS≤3). Currently only one study is available comparing centchroman and danazol for mastalgia done by Tejwani et al at All India institute of Medical Sciences in 2010.[6] A few studies are available in which one of the two drugs are compared with other drugs like evening primrose oil, non steroidal anti inflammatory drugs, tamoxifen or placebo.

In the present study, patients in both group showed gradual improvement in symptoms in terms of decrease in mean VAS during 3 months period of treatment. Decrease in mean VAS was more in group A (Centchroman) than group B (Danazol)

at the end of three months of treatment (2.09 vs 3.83). In group A 92.00% of patients and in group B 66.66% reported pain relief (VAS≤3).The difference between VAS in both groups was statically significant (p value = 0.0001).Tejwani et al 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. These results are almost similar to our study. The pain score was also assessed at 6 months (three months after completion of therapy). There was no change in mean VAS in group A and increased (0.79) in group B and its statically significant with p value of 0.0001. In study conducted by Dhar et al [5] in 2007 and Kumar S et al [7] 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. In a recent study comparative conducted by Jain B K et al [8] 2015 between centchroman and tamoxifen, our results for group A are better than Tejwani et al study as in them both cyclical and non cyclical cases (17/22) were included and hormonal agents used in mastalgia have better response to cyclical than non cyclical cases.

Centchroman was given alternate day basis in the initial part of their study and was given on daily basis in our study. This shows that results are better with daily administration of centchroman as compared to alternate day basis. While comparing ours results with Jain BK et al study at the end of one month, there was decrease in mean VAS of 2.98 in our study vs 2.33 in their study. Probable explanation for this is inclusion of more number of non cyclical cases of mastalgia than cyclical (23/7) cases in Jain B K et al study as explained above. In Kumar et al study mean change in VAS was only 1.65 as Centchroman was given twice a week in their study. In group B (danazol), mean VAS drops from 6.92 to 4.0 in Tejwani et al study and from 7.11 to 4.0 in our study at the end of one month of treatment. Results in our study are slightly better than Tajwani et al study. This is probably because of better follow up of patients in our study than Tejwani et al study. In Kumar S et al study group B is placebo group and in Jain BK study in group B tamoxifen was given, so we cannot compare our result of danazol with Kumar S et al and Jain BK et al study.

Side effects

Table 3: Side effects in different studies

Group A

Study	Menstrual irregularities			Dizziness	Utricaria	Ovarian cysts
	Scanty Menses	Delayed menses	Menorrhagia			
Tejwani et al[6]	31/41	6/41	2/41	0/41	0/41	0/41
Kumar et al[5]	12/75	0/75	0/75	0/75	0/75	0/75
Jain B K et al[8]	2/30	2/30	0/30	8/30	0/30	5/30
Present study	8/25	4/25	0/25	0/25	0/25	0/25

Group B

Study	Menstrual irregularities			Dizziness	Utricaria	Androgenic side effects
	Scanty menses	Delayed menses	Menorrhagia			
Tejwani et al[6]	0/39	3/39	1/39	0/39	1/39	0/24
Present st.	0/24	4/24	1/24	0/24	1/24	0/24

In group A patients on Centchroman 30 mg per day, 08 patients had scanty menstruations, 4 had delayed menses by 10-12 days. All these menstrual irregularities subsided after stopping the drugs. All most similar incidence of side effects reported by Tejwani et al [6] reported scanty menses in 31 out of 41 patients, 6 had by 10-15 delayed menses by 10-15 days and 2 had menorrhagia. Studies conducted previously on the effect of centchroman on regression of mastalgia by Kumar S et al [7] in 2013 and Dhar et al [5] in 2007, incidence of menstrual irregularity was less as compared to our study. It seems that menstrual irregularity 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) and twice weekly (Kumar et al). Dizziness was reported by Jain et al study in 8 patients that was completely resolved on stopping drug for one month. Dizziness was not reported by any other studies including ours, using centchroman for mastalgia. Ovarian cyst was detected during ultrasonography in

five out of 26 patients (19.2%) who completed 24 weeks follow up in study conducted by Jain B K et al.[8] All the ovarian cysts had resolved after stopping of treatment (centchroman 30 mg). Ovarian cysts had not been reported in any other study including ours as ultrasonography of pelvis was not a part of their research protocol. These cysts has been reported when using centchroman at 60 mg doses in 7.1% of cases in one study.[8] There is doubtful association of benign ovarian cysts with its use.

In group B patients were given Danazol at 100 mg per day. At this no androgenic side effects like acne, facial hair, voice change or other stigmata of hirsutism while on treatment were noted. The most common side effect noted was menstrual irregularities in the form of delayed menses in 4 patients and menorrhagia in 1 patient 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 study. Allergic reaction in the form of utricaria was noted in one patient after 2 months of start of treatment. The drug was immediately stopped and we lost follow up of that patient.

COST OF TREATMENT

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

Centchroman is a safe non steroidal drug .It has shown good results and is effective, inexpensive and safer than danazol in the treatment of cyclical mastalgia.

REFRENCES

[1]. Cooper A. Illustration of disease of breast, Part 1. London (England): Longman; 1829. P. 78-9.
[2]. Johnson KM, Bradley KA, Bush K, Gardella C, Doble DJ, Laya MB. Frequency of mastalgia among women veterans. Association with psychiatric conditions and unexplained pain syndromes. J Gen Intern Med. 2006; 21:70-5.
[3]. K Kataria, A Dhar, Srivastava A, S Kumar, Goyal A. A systemic review and current understanding and management of mastalgia. Indian J Surg. 2014; 76: 217-22.
[4]. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. Mayo Clin Proc 2004; 79:353-72
[5]. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg.2007; 31:1178-84.
[6]. Tejwani PL, Srivastava A, Nerker H, Dhar A, Hari S, Thulkar S et al. Centchroman regress mastalgia: a randomized comparision with Danazol. Indian J Surg. 2011; 73:199-205.
[7]. Kumar S, Rai R, Randomized controllled trial of ormeloxifene in breast pain and nodularity.National Med J of India 2013; 26: 69-73.
[8]. Jain BK, Bansel A, Choudhary D, Garg PK, Mohtany D. Centchroman vs tamoxifen for regression of mastalgia: a randomized controlled trial. Int J Surg. 2015; 15:11-6.
[9]. Grover,Chhabra, Bindu. A Study of ormeloxifene in case of dysfunctional uterine bleeding. IJMDS.2013; 2:2.