Original Research Article

A comparative study of Centchroman, Tamoxifen and Danazol in management of cyclical mastalgia

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ABSTRACT

Background: Mastalgia is a common problem and 60-70% women encounter it at least once in their lifetime. Many drugs have been used and are been used with varying response, like Tamoxifen, Danazol, primrose oil, topical analgesics and recently Centchroman. The objective of the present study was to compare the three most commonly used drugs in the treatment of mastalgia, namely Centchroman, Tamoxifen and Danazol with a placebo.

Methods: All consecutive female patients more than 25 years of age with history of mastalgia for more than 3 months were taken up for the study. Patients were distributed into four groups and administered Centchroman, danazol, tamoxifen and placebo, respectively.

Results: In present study of 78 patients, the median visual analogue score (VAS) in Centchroman group were 3, 1 and 3 after treatment of 4, 12 and 24 weeks, respectively with a pre-treatment VAS of 8. Similarly, in the danazol group, VAS at 4, 12 and 24 weeks were 4, 1.5 and 5, respectively. In the Tamoxifen group it was 4, 1 and 3 after treatment for 4, 12 and 24 weeks. On comparison, Centchroman and Tamoxifen both had better pain relief than danazol at 24 weeks ($p < 0.001$) while Centchroman and Tamoxifen had comparable results ($p > 0.05$) despite Centchroman having a lower mean VAS score.

Conclusions: Mild cyclical mastalgia can be treated with reassurance and lifestyle measures. Moderate to severe mastalgia usually require drug treatment. Centchroman, Danazol and Tamoxifen are effective. Centchroman appears to have better pain relief relative to the rest.

Keywords: Breast, Centchroman, Danazol, Mastalgia, Tamoxifen, VAS

INTRODUCTION

Mastalgia is one of the commonest symptoms in patients attending a breast clinic throughout the world and it is estimated that approximately 60-70% of women experience breast pain at some time of their life. However, there is no established cure for this common problem. Many drugs have been used with varying response, like Tamoxifen, Danazol, oil of evening primrose, topical analgesics and much recently, at least in

India, a very commonly used, cheap oral contraceptive pill, Centchroman (distributed as 'Saheli'). Pharmacologically, Centchroman is Ormeloxifene, a non-steroidal selective oestrogen receptor modulator (SERM) used primarily as an oral contraceptive. In a study by Dhar et al, for Centchroman in mastalgia, they found a 100% relief after 12 weeks of treatment with this drug.¹ On the other hand, in a meta-analysis done by Srivastava et al, it was found that Tamoxifen is the most effective form of treatment of mastalgia when compared with

bromocriptine, Danazol and oil of evening primrose. Centchroman was not included in this study.² Rathi et al, reported 88% pain relief after 12 weeks of initiation of therapy with Centchroman.³ Tejwani et al, found Centchroman to be better than Tamoxifen in reducing breast pain using the Visual Analogue Scale (VAS) in a randomized trial.⁴ This study however did not include danazol as another comparative index. This present study was done, to compare the three most commonly used drugs in the treatment of mastalgia, namely Centchroman, Tamoxifen and Danazol with a Placebo.

METHODS

This study was conducted at a tertiary care teaching hospital of Central India from August 2016 to September 2017. All consecutive patients with age more than 25 years and mastalgia for more than three months were inducted in the study. A detailed history and clinical examinations were done, followed by sonomammography or digital mammography. Patients were also sent for Gynaecological assessment and an ultrasound pelvis was done to rule out any pelvic pathology.

Patients with breast lump or pelvic pathology were excluded from the study. Also, patients planning to conceive in the next 6 months were excluded from the study. Patients willing to take part in the study were registered after taking a detail informed consent.

A total of 78 patients fulfilled the study criteria and were enrolled in the study.

The patients thus chosen were divided into four groups using randomization by sealed envelope technique, handed over by the OPD sister in charge. Group A received Centchroman 30 mg daily, group B received danazol 200 mg daily, group C received Tamoxifen 20 mg daily and group D received a placebo (Vit B complex multivitamin) for a period of 3 months each.

Patients were asked to keep a record of breast pain for this duration. The patients were asked to fill in the occurrence of pain on a day to day basis with severity of mastalgia assessed by Visual Analogue Scale.

All subjects were followed after one week and tolerance to the drug assessed. Subsequently patients were followed at 4 weeks, 12 weeks and 24 weeks of starting treatment and response to therapy assessed.

RESULTS

A total of 78 patients enrolled for the study. 5 patients did not turn up or refused to continue in the study. So, the final outcome was studied on 73 patients; 23 patients in group A, 17 in group B, 14 in group C and 19 in group D. There was no statistically significant difference in the four groups, with respect to age, parity and the menstrual cycles (Table 1).

Table 1: Numbers enrolled, mean age and mean menstrual cycle length.

	No. of patients (n=73)	Mean age (in years)	Mean duration of menstrual cycle (in days)
Group A (Centchroman)	23	30.69	28.76
Group B (Danazol)	17	30.70	27.76
Group C (Tamoxifen)	14	30.43	28.14
Group D (Placebo)	19	30.47	28.58

Pain relief as primary outcome measure

There was improvement in mastalgia in all groups, including the Placebo group. At 4 weeks, the pain relief was most marked in Centchroman (group A), with a median VAS score of 3, as compared to a VAS score of 4 for both Danazol and Tamoxifen group. Pain relief was more pronounced at 12 weeks of treatment, when the VAS scores further reduced to 1 in the Centchroman and Tamoxifen group, with a median VAS of 1.5 in the Danazol group. Whereas a VAS score of 7 remained unchanged in the placebo group. However, after stopping treatment, assessment was done at 24 weeks, when the median VAS scores in group A and group C went up to 3, while the median score in the Danazol group went up to 5. placebo group remained unchanged at 7 (Table 2).

The relative risk for significant pain relief, i.e. VAS score of less than 3, with Centchroman as exposed and Danazol as reference category was calculated at 4, 12, and 24 weeks of follow up. The relative risk of good pain relief at 4 weeks was 1.62 and at 12 weeks was 1.16 and at 24 weeks was 1.83. The relative risk for significant pain relief with Centchroman as exposed and Tamoxifen as reference category was calculated at 4, 12, and 24 weeks. The relative risk of good pain relief at 4 weeks was 1.47 at 12 weeks and at 24 weeks was 1.11. With Tamoxifen as exposed and Danazol as reference, the relative risk at 4 weeks was 1.10, at 12 weeks, 1.12 and at 24 weeks was 1.65.

Therefore, comparing Centchroman vs Danazol, authors did not find a significant difference in Pain relief during treatment period of 12 weeks, but the difference was significant ($p < 0.001$) after stopping the treatment and assessing at 24 weeks. Comparing Centchroman and Tamoxifen there was no difference in pain relief, all along the treatment period and even after treatment was stopped, and assessment done at 24 weeks. These two drugs would classify to be comparable in their efficacy ($p > 0.05$). Lastly comparing Tamoxifen with Danazol, not much difference during the treatment period of 12 weeks but significantly better pain relief with Tamoxifen as compared to Danazol at 24 weeks follow up ($p < 0.001$). On comparison of all 3 drugs with placebo, there was no

difference in pain relief at 1 week, but all the three scored better in Pain relief subsequently at 4, 12, and 24 weeks (Table 3).

Side effects as secondary outcome measure

Maximum side effects were seen in the Danazol group. Of the 17 patients in the Danazol group, 8 patients had some or other form of menstrual irregularity, in the form

of scanty menses, delayed menses, hot flushes or menorrhagia.

In the Centchroman group, 4 patients had oligomenorrhea, while 2 had delayed periods.

Whereas in the Tamoxifen group, 4 patients had delayed periods and 2 complained of hot flushes.

Table 2: Effect of Centchroman, Tamoxifen, Danazol and placebo on cyclical mastalgia.

Weeks	Centchroman (median VAS)	Danazol (median VAS)	Tamoxifen (median VAS)	Placebo (median VAS)
0	8	8	8	8
4	3	4	4	6
12	1	1.5	1	7
24	3	5	3	7

Table 3: Comparison of P-value of Centchroman, Danazol, Tamoxifen and placebo with relation to VAS.

Weeks	Centchroman-danazol (P-value)	Centchroman-tamoxifen (P-value)	Tamoxifen-danazol (P-value)	Centchroman-placebo (P-value)	Danazol-placebo (P-value)	Tamoxifen-placebo (P-value)
0	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
4	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001
12	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001
24	<0.001	>0.05	<0.001	<0.001	<0.001	<0.001

DISCUSSION

The problem of cyclical mastalgia is grossly underestimated despite a significant detrimental effect on quality of life.⁵ In present study we compared the effect of Centchroman, Tamoxifen, Danazol and Placebo on cyclical mastalgia.

The median and mean ages in present study were 30 and 30.57 years, respectively. This correlates with the median age of 34 years for cyclical mastalgia in the study done by Davies et al.⁶

In the first week, there was no effect on pain with any of the drugs relative to placebo. But after 4 weeks, Centchroman was the most effective, followed by Tamoxifen and Danazol with the Placebo being the least effective. After 12 weeks and 24 weeks of treatment, Centchroman and Tamoxifen were together most effective compared to Danazol and Placebo. This result of present is supported by Dhar et al, who also found Centchroman to be more effective than Danazol and evening primrose oil for pain relief.⁷

On comparison between Centchroman and Danazol, the pain relief was significantly better with Centchroman only at the 24th week of treatment. Though pain relief was

comparable at 4 and 12 weeks, Centchroman is cheapest among the three drugs, has a better side effect profile in contrast to Danazol, and hence would be a better choice than Danazol.

On comparison between Centchroman and Tamoxifen, the difference in pain relief was not statistically significant at any time during the study. Even though the difference in pain relief was equivocal, Centchroman had a lesser mean VAS score in the study. Jain et al, also found Centchroman and Tamoxifen to be equally effective for pain relief in mastalgia.⁸

On comparison between Tamoxifen and Danazol, statistically significant pain relief was seen after 24 weeks. The difference in pain relief was again equivocal after 4 or 12 weeks.

All the three drugs were found to be superior to a placebo for pain relief for the whole duration of present study.

Centchroman overall had the best pain relief with the lowest mean VAS scores throughout present study, even though it was not found to be statistically better than Tamoxifen. In the study conducted by Tejwani et al, on 39 patients and after 12 weeks of treatment with Centchroman, 89.7% were relieved of pain similarly.⁴

Bansal V et al, studied effect of Centchroman on 203 patients and reported that after 12 weeks of treatment the mean VAS was similarly found to be 1.21.⁹ In two separate studies Rathie et al, and Srivastava et al, reported more than 85% relief in pain after 12 weeks of treatment with Centchroman which supports present study.^{3,10} More multicentric studies with a larger sample size are required to validate Centchroman as a more effective drug over the now more traditionally used Tamoxifen.

CONCLUSION

Cyclical mastalgia is commonly encountered in the premenstrual phase in women most commonly 30-40 years of age. Mild cyclical mastalgia can be treated with reassurance and life style modifications. Moderate to severe mastalgia usually require drug treatment. Centchroman is non-steroidal and effective in providing relief with minimal side effects in cyclical mastalgia. Tamoxifen is another effective drug that can be used. Danazol is inferior to both Centchroman and Tamoxifen with regards to pain relief offered and anticipated side effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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