

Role of LHRH analogue in cases of refractory mastalgia

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Abstract

Background: Mastalgia is the commonest cause of visit to the breast clinic. The present study was conducted to assess the efficacy of complete estrogen blockade (CEB) with centchroman and LHRH analog goserelin in the treatment of refractory mastalgia. **Aim:** To study the effect of LHRH analogue in refractory mastalgia and to increase pain free period in patients with refractory mastalgia. **Methods:** This is a prospective cohort study conducted in the Dept. Of Gen. Surgery IGIMS, Patna over a period of six months. The reduction of pain score (as measured by a visual analog scale (VAS) recorded on a breast pain chart) to 3 or less at 6 weeks of initiation of treatment was taken as primary objective. **Results:** Fifty patients were enrolled in the study. The mean age of the patients was 28 years (15–45 years). The median duration of symptoms was 6 months (4–8). All of them had bilateral mastalgia. The mean pain score at start of study was 7. **Conclusion:** Complete estrogen blockade by means of GNRH analogue is safe and effective for treatment of refractory mastalgia.

Keywords: Mastalgia, Complete estrogen blockade, GNRH analogue.

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Introduction

Mastalgia is the commonest breast disorder bothering young women and is a source of anxiety and discomfort to them. It is hypothesized to occur due to increased estrogen or deficient progesterone paving the way for various modalities of hormonal treatment [1]. There are two patterns of breast pain, cyclical and non-cyclical. The cyclical pain is associated with occurrence of breast pain about 1 to 2 weeks prior to menstruation and relieved by onset of menstrual flow. This type of pain responds better to hormonal manipulation. Various hormonal agents like tamoxifen, centchroman, danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analog (goserelin) have been used for treating mastalgia with significant improvement in pain scores. Tamoxifen is considered as the drug of choice by most in the west because of favorable side effect profile and good clinical improvement [2]. However, most of the above mentioned drugs have a response rate varying from 60 to 80% [2], implying that around 20% of women still have symptoms bothering them. Complete estrogen blockade (CEB) using LHRH analog and an anti-estrogen or selective estrogen receptor modulator (SERM) may be more efficacious in estrogen blockade than either of these drugs used alone. With this understanding, the present study was conducted to assess the efficacy of complete estrogen blockade with centchroman and LHRH analogue goserelin in the treatment of refractory mastalgia with centchroman.

Aim and objectives

To study the effect of LHRH analogue in refractory mastalgia and to increase pain free period in patient with refractory mastalgia.

Methodology

This is a prospective study done over 50 patients in the Department Of Gen. Surgery of IGIMS, Patna over a period of six months. The reduction of pain score (as measured by a visual analog score (VAS) recorded on a breast pain chart) to 3 or less at 4 weeks of initiation

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of treatment was taken as the primary objective. For the purpose of this study, refractory mastalgia was defined as bothersome breast pain with pain scores of six or more on breast pain chart, lasting for at least 7 days in a month even with centchroman therapy for 3 months. Women with recalcitrant mastalgia consenting to participate were included in the study. Women who were pregnant or desiring pregnancy in the next 6 months, having irregular menstrual cycles, breast lump, and personal or family history of breast/ovarian cancer were excluded from the study. The patients were evaluated at baseline taking note of their symptoms (duration of symptoms, nature of mastalgia-cyclical vs. non-cyclical, unilateral vs. bilateral, VAS pain score, and treatment history for mastalgia), previous breast biopsy or surgery, menstrual history, and personal or family history of breast or ovarian cancer. The ladies were taught and instructed to use breast pain chart for the entire duration of the study [3]. Breast and systemic examination was done. A urinary pregnancy test and USG breast/mammogram were done prior to start of therapy.

All patients meeting the inclusion criteria received LHRH analog (goserelin 3.6 mg subcutaneous depot injection at 0, 1, and 2 months) along with tablet centchroman 30 mg daily. After the treatment, the patients were followed for 3 months to see for their symptom relief/recurrence. The pain scores were recorded. Side effects of the drug (hypersensitivity, amenorrhea, unwanted pregnancies, nausea, vomiting, hot flushes, jaundice, etc.) were noted.

Inclusion criteria

1. Women with recurrent mastalgia to centchroman.
2. Women age group 15 – 45 years.

Exclusion Criteria

1. Pregnant women
2. Female desiring pregnancy in next 6 months.
3. Women with discrete breast lump.
4. Personal or family h/o breast/ovarian cancer.
5. Covid positive women.

Result

Fifty patients were enrolled in the study. The mean age of the patients was 28 years (15–45 years). The median duration of symptoms was 6

months (4–8). All of them had bilateral mastalgia. The symptoms were cyclical in 30 women and noncyclical in 20. All were pre-menopausal except one patient who had undergone abdominal hysterectomy for menorrhagia 4 years ago. Since the status of her ovarian function was not known, serum LH, FSH, and estradiol were done which confirmed her physiological pre-menopausal status. Twenty women were multiparous. All women had taken the tablet centchroman 30 mg daily for minimum of 3 months, without significant relief of their symptoms. The mean pain score at start of study was 7. At 4 weeks of initiation of treatment, pain score became zero in 20 patients and reduced to less than three (but not zero) in 15 patients. There was no rise in pain scores to more than 3 in any of these

patients during the entire study period. The other 15 patients also had reduction in pain scores to 4 in one and 5 in the other two. The maximum pain scores of these three patients were 5, 6, and 7, respectively, during the follow-up period.

There was no difference in the characteristics of patients who responded from those who did not. This is shown in Table 1. No differences were seen among women with cyclical or noncyclical mastalgia.

The side effects are shown in Table 2. All menstruating women had amenorrhoea. None of the patients had adverse effect of the magnitude to request cessation of the treatment. Menstruation returned in all the patients within 2 months of stopping the treatment.

Table 1: Characteristics of patients (responders vs nonresponders)

	Responder (n = 35)	Nonresponder (n = 15)
Age	28 years	27 years
Mean duration of symptoms	6 months	6.5 months
Nature of mastalgia	Cyclical, 30; noncyclical, 10	Cyclical, 5; noncyclical, 5
Previous treatment	Centchroman, 35; danazol, 10; Evion, 10	Evening primrose oil, 5; centchroman, 15; tamoxifen, 5

Table 2: Side effect profile

Side effect	Percentage of patients
Amenorrhoea	100%
Hot flushes	70%
Vaginal dryness	30%

Discussion

Mastalgia is the commonest cause of visit to the breast clinic. While most cases are mild and often require no more than counseling and reassurance, around 15% of these ladies have troublesome symptoms requiring drug treatment[4]. The medications that decrease the level of estrogen in the body, such as tamoxifen, danazol, centchroman, and LHRH analog (goserelin), have been tried with varying success in the management of breast pain. Presently, danazol is not commonly used in most breast clinics because of several side effects[2]. Tamoxifen is considered the drug of choice in most breast clinics in the west for treatment of mastalgia. Srivastava et al. have also suggested in their meta-analysis that tamoxifen may be the drug of choice because of good efficacy and low incidence of side effect[2]. Later on, an Indian nonsteroidal SERM was evaluated for the treatment of mastalgia at our institute and subsequently at other Indian centers[5–7]. These drugs, however, have an efficacy ranging from 60 to 80%, suggesting that still a subset of patients have refractory and recalcitrant mastalgia. Previously, LHRH analog goserelin has been given for severe and refractory mastalgia[8, 9].

Goserelin (Zoladex), a potent synthetic analog of luteinizing hormone-releasing hormone (LHRH), induces reversible ovarian suppression with castrate levels of ovarian hormones being attained within 72 h. LHRH analogs result in an initial stimulation of gonadotrophin release, which is quickly followed by a fall in gonadotrophin secretion and a subsequent decrease in the circulating estrogen concentrations to postmenopausal levels. Centchroman is a novel SERM developed by the CDRI Lucknow. While LHRH provides central suppression of estrogen production, centchroman provides peripheral blockade by acting on the target organ.

LHRH has been studied previously by Hamed et al. in 1990 and Mansel et al. in 2004. Hamed et al. gave LHRH depot injections to 21 women with mastalgia and defined successful treatment as 50% reduction of pain scores following depot injection. They found that 28%, 71%, and 81% were having successful response to treatment at 1, 3, and 6 months following treatment. They also reported that five of the patients who responded to Zoladex had failed to respond to previous hormonal treatment, and all 12 patients with recurrent pain responded to treatment. They also reported that 56% (5/9) of patients responded in the refractory group. In those with recurring mastalgia, they found that all patients responded[8]. Mansel et al. reported a response rate of 67% in patients with mastalgia.

However, they saw that the pain did recur in the follow-up as the estrogen levels started rising. This also supported the fact that mastalgia does have a hormonal basis and that the subset of patients not having improvement with mastalgia need to have their concerns addressed [9]. Both these authors recommended the use of LHRH analog as a second-line drug for treatment of refractory mastalgia.

Goserelin was associated with menopausal symptoms such as vaginal dryness, hot flushes, decreased libido, oily skin or hair, and a decrease in breast size. Mansel et al. reported dropout of nine patients (almost 7%) due to side effects[9]. Hamed et al., however, reported no dropout because of side effects and also re-emphasized that mastalgia is indeed a bothersome problem with hormonal basis [8]. While this study addresses the safety and efficacy of a novel treatment option for refractory mastalgia, the topic does warrant further clinical trials in the setting of a larger sample size.

Conclusion

Complete oestrogen blockage by means of LHRH therapy definitely has beneficial role in refractory mastalgia with significant pain relief but further randomized control trials on larger sample size are required to further substantiate its role in refractory mastalgia treatment.

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