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Research Article

Role of Ormeloxifene (Centchroman) in Benign Mastalgia of Diverse Origin

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Abstract

Mastalgia is a commonly encountered complaint in everyday gynaecological practice. Although various options were suggested by different authorities none of them stood the test of time and mastalgia remains a treatment quandary. We have selected Ormeloxifene as a treatment modality for mastalgia of benign origin because of its selective anti-estrogenic property. Women with mastalgia attending the Gynaecology OPD between ages 20-50yrs fulfilling the inclusion criteria were registered for the study. The patients were started on Ormeloxifene 60mg twice weekly for three months after excluding the possibilities of malignancy. The results were recorded on a pain score of grade 0 to 4 which was devised by the author. Out of total 84 patients studied between August 2009 and August 2011, severe pain was recorded in 72.6%patients (grade 3 & 4). The rest 27.4%patients had less severe pain (grade 1 & 2). The mammographic lesions noted either singly or in combinations were fibroadenosis 69%, fibroadenoma 11.9%, duct ectasia 4.8%, benign cysts 10.7%, and benign micro calcifications of 11.9%. 21.4% had normal mammography. Excellent response to the treatment was noticed in most. 57.14% were pain free at the end of one month; 82.14% by the end of second month, and a whopping 92.8% had no pain by the end of third month. 4.8% persisted with mild pain. In 2.4% no change in the severity was noted. The adverse effects noted were 8.33% of either oligomenorrhoea or hypo-menorrhoea, 2.38% of menorrhagia and 2.38% of hot flushes. This study suggests that Ormeloxifene may be considered as a safe, efficient and cost-effective non-steroidal drug for the treatment of mastalgia with minimal adverse effects.

Keywords: Mastalgia, Benign breast disease, Ormeloxifene, Centchroman

Introduction

Mastalgia is the most common presenting symptom among benign breast conditions. Although very few of them are sinister of malignancy, majority are of benign aetiology, needing symptomatic relief only. As mastalgia strongly affects a woman's personal and sexual life there is a great expectation from the treating doctor. Mastalgia proves notorious in posing a challenge to treat it. Not just the aetiology but also the management of mastalgia has provided enough reasons for on-going research. Although as clinicians we are eager to make our patient pain free with a wide array of products ranging from analgesics to evening primrose oil, we always knew most of them were just empirical and gave varied responses with no proven benefits over a placebo [1]. Danazol, bromocriptine, tamoxifene and LHRH analogue have all been in use in the recent times for mastalgia but most of them are known for their significant side effects. In the quest for a better remedy there have been few attempts to try selective oestrogen receptor modulator (SERM). Ormeloxifene is a SERM synthesized by the Central Drug Research Institute, Lucknow, India. It was introduced as an oral contraceptive in the National Family Welfare Program India, in 1995. Ormeloxifene had an advantage over the other steroidal oral contraceptives in not having side effects like nausea, vomiting, weight gain and dizziness. The other added benefit was its less frequent administration of twice weekly regimen. Return of fertility was not delayed. Owing to its low dosage and less frequent administration, any effect over the hypothalamic-pituitary axis is minimal; hence normal ovulatory cycles are resumed after withdrawal of the drug. Having been convinced of the very minimal side effects and considering of the few studies available with this drug, it was decided to assess its efficacy in the treatment of mastalgia. A clinical study was conducted in Visakha Steel General Hospital to evaluate

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the effectiveness of Ormeloxifene in alleviating mastalgia of benign origin.

Materials and Methods

Our observational study was prospectively conducted in the Gynaecology out-patient department of Visakha Steel General Hospital, Visakhapatnam Steel Plant between August 2009 and August 2011. All women presenting with mastalgia between the ages 21 to 55 years were subjected to evaluation. A written informed consent was taken from the patients before including in the study. Clinical history and examination findings were recorded. A baseline haematological and biochemical workup was conducted in all. All women before inclusion in the study were subjected to imaging studies either ultrasound examination or mammography as indicated. FNAC of any lumps detected and cytological studies of the breast secretions if present were also carried out to rule out malignancy.

The exclusion criteria

1. Women suspected or diagnosed of malignancy.
2. Women who were planning pregnancy in the near future and pregnant women.
3. Women with abnormal and undiagnosed uterine bleeding.
4. Recent history of jaundice or hepatic impairment.
5. Severe allergic states.
6. TB.
7. Renal impairment.
8. History of thrombosis.

Only women with mastalgia of benign origin were included in the study after screening. Irrespective of the history of previous treatment with other drugs patients were enrolled. It was a consecutive cohort and all the eligible patients participated in the study. All data pertaining to the study was recorded on a special proforma designed for the purpose, and each case was given a unique identification number for easy retrieval of the data during follow up. What was unique to this study was the method by which the pain score was recorded. We did not follow the conventional VAS score but had recorded pain on a special score devised by the author. The pain score was ranging from grade 0 to grade 4. In this system we were able to eliminate the subjective variation of the pain threshold and could record a definitive and objective result during follow up .The end point of the study was the pain score assessed using a scale ranging from grade 0 to 4 and the adverse effects of the drug.

The pain score was as follows:

Grade 4- Breast Pain at Rest

Grade 3- Breast Pain on Movement

Grade 2- Pain on Light Palpation of Breast

Grade 1- Pain on Deep Palpation of Breast

Grade 0- No Pain Even on Deep Palpation of Breast

The pain score was recorded at the beginning of the study and patients were started on Ormeloxifene 60 mg twice weekly on day 1 and day 4 of the week (e.g. Monday and Thursday). It was a fixed dosage schedule for 3 months of period. The drug was stopped after completion of 3 months. The pain score was recorded at the end of first, second and third month of the treatment. Statistical calculations were done using chi square test and Spearman's correlation.

Observations

The study included 84 women with age range of 21 to 55 years .Majority of the women 41.7 %(34) were between 36 to 40 years of age (Table 1).

Out of all women 32.14 %(27) reported between 1 to 3 months of their symptoms followed by 28.57% (24) reporting before 1 month. Surprisingly few women 4.76 %(4) gave a history of mastalgia for more than 3 years of duration (Table 2). 63%(53) of women had non-cyclical mastalgia whereas the rest had cyclical mastalgia (Figure 1). Clinically bilateral nodularity was detected in 73.8% (62) of cases whereas unilateral nodularity was present in 23.8%(20).In 13.09% (11)of cases breast secretion was noted whereas 2.38% (2)only had breast lumps and nodules (Table 3).

At the time of booking 42% (35) women presented with grade 4 pain and 31%(26) presented with grade 3 pain. 18% (15) patients had grade 2 and 9%(8) had grade 1 pain (Figure 2). The imaging results showed various finding either existing singly or in combination with other findings. 21.43 %(18) women had normal findings, in 69.05 %(58) women fibroadenosis was reported

Age in years	No of patients	percentage
21-25	1	1.2%
26-30	7	8.3%
31-35	22	26.2%
36-40	35	41.7%
41-45	15	17.8%
>45	4	4.8%

Table 1: Age distribution of the patients.

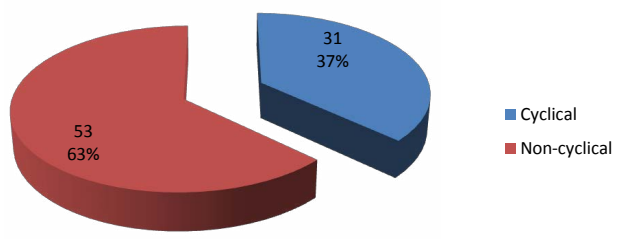

Figure 1: Types of mastalgia.

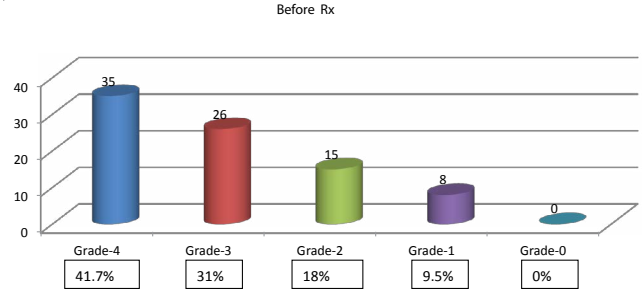

Figure 2: Pain scores at the time of booking.

Duration	<1 month	1-3months	4-6months	7-9months	10-12month	1-3 yrs	>3yrs
No. of patients	24	27	13	2	2	12	4
% of patients	28.6%	32.1%	15.5%	2.4%	2.4%	14.2%	4.8%

Table 2: Symptom duration of the patients.

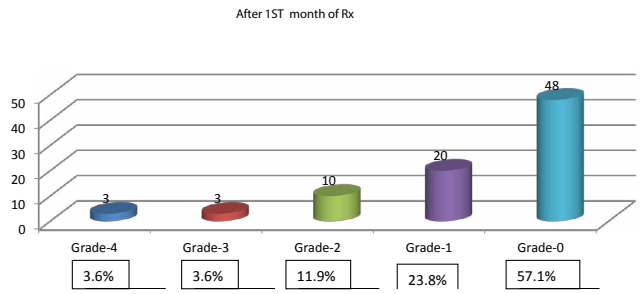

Figure 3: Pain scores after 1st month of treatment. * p=<0.0001, N=84.

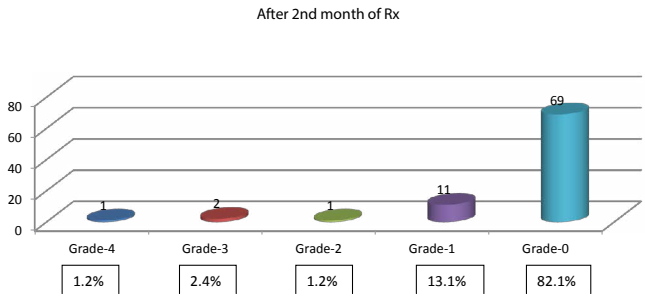

Figure 4: Pain scores after 2nd month of treatment * p=<0.0001, N=84.

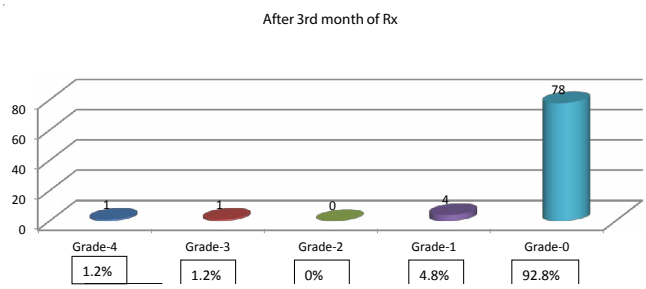

Figure 5: Pain scores at the end of the study (after 3rd month) * p=<0.0001, N=84 .

Clinical finding	No. of patients	% of patients
Bil. nodularity	62	73.8%
Unilat. Nodularity	20	23.8%
Breast Secretions	11	13.1%
Lumps/nodules	2	2.4%

Table 3: Common findings on clinical examination.

and 11.9 %(10) had fibro-adenomas. Micro-calcifications were reported in 11.9 %(10); ectatic ducts in 4.76 %(4) and 10.71 %(9) women had cysts (Table 4).

All women were given Ormeloxifene 60mg twice weekly and asked to report back after one month. At the end of one month of treatment 57.14 %(48) women were pain free; in 23.8 %(20) the severity reduced to only pain on deep palpation (grade 1) and only 3.6 %(3) women were left with grade 4 pain. After the second month of treatment 82.14%women were pain free, and 13.09 %(11) had grade 1 pain (pain on deep palpation). Only one patient had persisting pain at rest. The end of the third month marked the end point of the study. The results were extremely promising and significant as 92.85 %(78) women were absolutely pain free and 4.76 %(4) were having grade 1 pain only (P=<0.0001 chi square test). There was only one patient who had remained unresponsive throughout the treatment (Table 5) (Figures 2-6). One patient dropped out after 1 month of treatment. Follow up revealed that she remained pain free afterwards hence did not take the full course. One patient was allergic to Ormeloxifene and hence excluded from study. During subsequent 6 months follow up after full course of treatment 91.7%(77)patients remained pain free.

Spearman's correlation was used to find out the pain score improvement versus duration of therapy (Figure 6 and Table 5). Grade 2 and Grade 3 pains were showing r value 1 and p value 0 which indicates a steady decrease in the level of pain with duration of therapy. Grade 4 pain with r value of -0.95 and p value 0f 0.05 is also indicating significant decrease with duration. Grade-0 pains, which is showing a positive correlation with r value 1 and p value

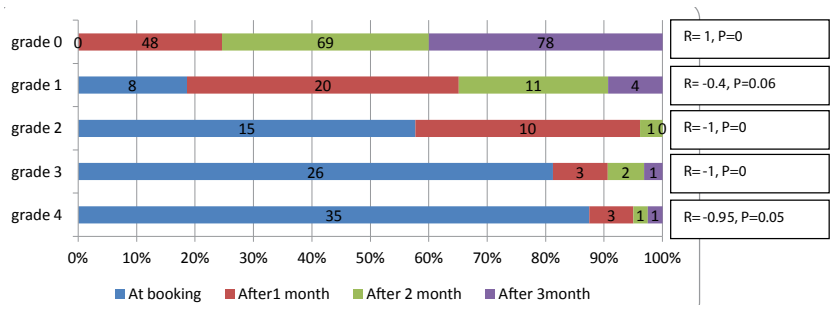

Figure 6: Pain score change compared month wise (Spearman's Correlation).

Imaging results	Normal study	Fibroadenosis	Fibroadenoma	Microcalcifications	Ectatic ducts	Cysts
No of pts	**18**	**58**	**10**	**10**	**4**	**9**
% of pts	21.4%	69.1%	11.9%	11.9%	4.8%	10.7%

Table 4: Imaging results.

	Grade-4 (PAIN AT REST)	Grade-3 (PAIN ON MOVEMENT)	Grade-2 (PAIN ON LIGHT PALPATION)	Grade-1 (PAIN ON DEEP PALPATION)	Grade-0 (NO PAIN)
BEFORE Rx	35	26	15	8	0
After 1ST MONTH OF Rx	3	3	10	20	48
After 2ND MONTH OF Rx	1	2	1	11	69
After 3RD MONTH OF Rx	1	1	0	4	78
	R= -0.95, P=0.05	R= -1, P=0	R= -1, P=0	R= -0.4, P=0.06	R= 1, P=0

Table 5: Pain score change compared month wise (Spearman's Correlation).

Adverse effects/side effects	NO OF CASES	PERCENTAGE
TOTAL NO OF CASES SHOWING SIDE EFFECTS	14	16.7%
REGULARISED CYCLES	4	4.8%
AMENORRHOEA	5	5.9%
HYPOMENORRHOEA	3	3.6%
OLIGOMENORRHOEA	1	1.2%
HOT FLUSHES	2	2.4%
VAGINAL DRYNESS	1	1.2%
DYSURIA	1	1.2%

Table 6: Adverse effects/side effects.

0 indicates steady increase in the number of pain free patients with time. However grade 1 pain with r value of-0.4 and p value of 0.6 did not show statistical significance by normal standards.

Adverse effects

The side effects were trivial and not interfering with the women's routine. Only 16.67% (14) women reported side effects. Most of the side effects were menstruation related. In 4.76%(4) women it proved advantageous in their cycles getting regularised. 3.57 %(3) had hypo-menorrhea and 1.19 %(1) had oligo-menorrhoea. 5.95%(5) women reported amenorrhoea all of whom were pregnancy negative. 2.38%(2) complained of hypo-estrogenic symptoms like hot flashes and one complained of vaginal dryness and another 1.19%(1) reported dysuria (Table 6).The menstrual problems were treated by reassurance as it was temporary and patients recovered their original cycles after stopping the drug. Hot flashes could be treated with short course of anxiolytics like alprazolam. Dysuria was managed with alkaline citrate oral administration.

Discussion

The commonest breast related symptoms in women attending the gynaecological OPD is mastalgia [2]. Mastalgia has been broadly classified into cyclical, non-cyclical and extra-mammary [3]. The names themselves are self -explanatory. In cyclical mastalgia discomfort most commonly occurs around the menstrual cycle or ovulation. It is usually seen 2 to 3 days premenstrual. This is typically characterised by fine nodularity of breast prior to menstruation which subsides post menstrually. Premenstrual breast tenderness and heaviness without any restriction of activity of the woman is considered normal. When the pain or discomfort lasts for more than a week per cycle and restricts her activities it is considered significant. Non-cyclical mastalgia has no relationship with the menstrual cycle. This falls into two categories- true non-cyclical mastalgia and musculoskeletal pain. True non-cyclical mastalgia occurs in both premenopausal and postmenopausal women. This pain is well localised to the breast especially in the sub-areolar and upper outer quadrants of the breast. Normally the intensity and nodularity is less pronounced than in the cyclical mastalgia. Non-cyclical mastalgia in fact responds better to hormonal therapy than musculoskeletal pain [4].

Musculoskeletal pain is further categorised under two groups: Tietze's syndrome and lateral chest wall pain.

Musculoskeletal pain is essentially unilateral (92%). Tietze's syndrome is characterised by pain in the medial aspect of the breast along with tenderness over the affected costo-chondral junction.

Aetiology of mastalgia has always been a mystery but various theories have been put forward to explain it. One of the earliest being oedema due to water retention but Peerce, et al. had found no correlation between women with mastalgia and controls on determining the total body water. Therefore there was no role of either diuretics or sodium restriction in the management of mastalgia; hence this theory has been discarded [5]. Later the three hormonal theories were regarded as the aetiology of mastalgia and nodularity.

Increased oestrogen secretion from the ovary, deficient progesterone production (relative hyper-estrogenism) [6] and hyper-prolactinemia were put forward. The first two theories did not stand as early studies showed that there was no difference in the hormonal levels between the patients and the controls [7-9]. A small but statistically significant difference in the prolactin levels between women with cyclical mastalgia and controls was recorded in a study in which daily sampling of prolactin at a fixed time throughout the menstrual cycle was done [10]. In a study by Peters et.al, who examined the stimulated prolactin response to thyrotropin-releasing hormone found that those with mastalgia had a significantly greater rise in prolactin compared to controls. However the difference in the basal prolactin levels was not statistically significant between the groups, thus, strongly suggesting a disturbance of hypothalamic control in women with cyclical mastalgia [11,12]. A definite role of oestrogen receptor (ER) in the pathogenesis of benign breast diseases is suspected based on a study done to estimate the value of ER. It was found that the patients with ER-positive breast disease responded better to danazol than patients with

ER-negative breast disease [13]. An abnormal prostaglandin synthesis secondary to inadequate intake of essential fatty acid (EFA) in the diet of affected women was proposed in yet another hypothesis according to Horrobin DF, et.al. [14]. Abnormal plasma fatty acid profiles [15] with increased saturated fatty acids, and reduced EFA were confirmed in patients with mastalgia. The EFA deficiency results in decreased production of prostaglandin E1 which finally augments prolactin effects on breast cells. Elevation of HDL-C (high density lipoprotein-C) has been reported in patients with cyclical mastalgia but not in those with non-cyclical pain [16]. A relatively recent study on 335 women in Germany (212 had mastalgia) investigated the morphological structures by ultrasound. A significant positive correlation between the width of the milk ducts and intensity of pain was noted suggesting an association between duct ectasia and mastalgia. Moreover, the site of pain positively correlated with the site of ductal dilatation in the noncyclical type [17].

Management

Management of mastalgia is a challenging task to the treating physician. Elevated anxiety and depression was noted in women with mastalgia in a couple of studies [18,19]. Psychological assessment and support forms an integral part of the management of mastalgia owing to these stress levels.

Non-Medical Management

Education and reassurance proved to be beneficial in most mild and moderate mastalgia cases according to Barros AC, et al. [20].

The use of a well-fitting brassiere or a sports bra that provides good support had actually proved beneficial to 75-85% women with mastalgia according to two prospective studies hence can be considered for relief of both cyclical and non-cyclical mastalgias [21,22]. Although numerous dietary measures had been advocated initially subsequent randomized trials have failed to prove any definite advantage [23-25].

Medical Management

Topical application of NSAIDs was effective in mild type of mastalgias according to one study conducted in 2003, where diclofenac-diethyl-ammonium 2% gel was used [26].

Vitamin E

Three RCTs had been conducted, which showed that vitamin E was no better than placebo in the treatment of benign breast disease. In the first study 40% reported improvement in pain after 2-3 months of therapy [27]. The second trial did not assess the breast pain, but they found no improvement in nodularity [28]. There was no improvement in nodularity or mammographic density in the last study, but a larger proportion of women in the vitamin E group reported improvement in breast tenderness, which was not statistically significant [29]. Hence, Vitamin E is not recommended for the treatment of mastalgia.

Gamolenic acid or gamma-linolenic acid (GLA)

Evening primrose oil (EPO) had been introduced into the management of mastalgia based on the fatty acid deficiency hypothesis. EPO is rich in 7% linolenic and 72% linoleic acid which represent the richest natural source of essential fatty acids. A number of trials have showed beneficial effects in mild and moderate mastalgia [30]. GLA is an essential polyunsaturated fatty acid (PUFA) present in large quantities in evening primrose oil. Women with cyclical mastalgia were found to have low levels of the metabolites of GLA [1]. As PUFA is thought to be denatured in the body by oxidation, adding antioxidants to PUFA was thought to enhance clinical response of PUFA. A study from Cardiff University in 2005, on patients with mastalgia treated with GLA and placebo concluded that GLA efficacy did not differ from placebo, regardless of whether antioxidant vitamins were present.

Danazol

Danazol is a synthetic testosterone which binds to progesterone and androgen receptors, but the precise mechanism of action in the treatment of mastalgia is unknown [31]. Danazol in humans interferes with follicle stimulating hormone and luteinising hormone at high doses. Thereby it results in a low luteal progesterone level (suggesting anovulation) during treatment [32,33]. With an overall improvement rate of 70% in cyclical mastalgia and 31% in non-cyclical mastalgia, danazol appears to be a very good agent for severe breast pain and nodularity [31]. Although it is superior to bromocriptine in the treatment of cyclical breast pain, the main limiting factor is its spectrum of side effects [34]. It is notorious for its unpleasant side effects like amenorrhea and various androgenic effects. The incidence of amenorrhoea increases with dose, and the androgenic effects being weight gain, acne, and hirsutism are very unwelcome by the women. It has also been proved to be a potential teratogen [35]. Hence limiting the drug to only luteal phase has proven beneficial by providing relief of cyclical mastalgia and limiting the side effects to the minimum, according to a study by O'Brien, et al. [36].

Bromocriptine

Significant reduction of cyclical mastalgia has been observed with bromocriptine 5 mg daily when compared to placebo according to two studies [37,38]. It blocks the release of prolactin from the pituitary gland by dopaminergic receptor stimulation. Severe side effects have been noted in most women, the commonest being nausea, vomiting, dizziness, headache and postural hypotension. This could be overcome by increasing the drug doses gradually, and avoiding higher doses.

Tamoxifen

A daily dosage of tamoxifen 10mg had proved beneficial in both cyclical and noncyclical mastalgia, with 98% response rates in the former and 56% in the latter according to a double blind study [39]. Two other RCTs found tamoxifen superior to placebo in treatment of both cyclical and noncyclical mastalgia in premenopausal women.

Though each used a different dosage of 20mg and 10mg; when both these doses were compared directly the response rates were almost similar [40,41]. Prolonging the treatment beyond three months neither increased the response rates nor did it reduce the relapse rates. With this background a daily dose of 10mg is usually preferred for three months and repeated for any further relapses only after considering the possible long term side effects. Side effects characteristically noted with short-term treatment

include hot flashes, menstrual disturbances, weight gain, nausea, vaginal dryness and bloating. A few rare yet serious side effects like thromboembolic events, endometrial cancer and cataracts have been reported in the literature; but their incidence in short term, low-dose treatment regimens for mastalgia is unknown.

Luteinising hormone releasing hormone (LHRH) analogue

A randomized multicenter study on 147 premenstrual women with mastalgia who were treated with goserelin (LHRH analogue) injection 3.6mg/month for six months showed better outcome when compared to the placebo. Although it proved to be an effective short term treatment for mastalgia the side effects and cost have been a huge setback in its common use. Patients receiving goserelin experienced vaginal dryness, hot flushes, decreased libido, oily skin or hair, and a decrease in breast size more frequently than patients treated with placebo, thus making it the last resort in most refractory cases [42].

Ormeloxifene

Ormeloxifene (Centchroman -$C_{30}H_{35}NO_3$) is a non-steroidal, third generation selective oestrogen receptor modulator (SERM) that antagonises the effect of oestrogen on uterine and breast tissue and agonises its effects on vagina, bones, CVS and CNS. Ormeloxifene binds competitively to the oestrogen receptors and antagonises oestrogen induced gene expression [43]. It elicits weak oestrogen agonistic and potent antagonistic activities but is devoid of progestational, androgenic, and antiandrogenic activities [44-48]. There is an early return of fertility after stopping this drug; therefore it is safe in the treatment of unmarried women and those who wish to conceive after treatment. No teratogenic effect has been observed yet. Women who conceived while on treatment gave birth to healthy children in the phase III multicentric contraceptive trials during research [45-48].

In our study we tried to figure out the efficacy of Ormeloxifene in relieving mastalgia of diverse origin. We have restricted the study to benign breast pain which is an ordeal in a women's day to day life socially and sexually. It was a consecutive cohort and all the eligible patients participated in the study. In our study Ormeloxifene was found to be very useful in relieving mastalgia effectively irrespective of the etiology. The efficacy is evidenced by the fact that 57.14%(48) of patients were pain free and in 23.8%(20) the pain score went down to grade 1at the end of 1st month. Only 3.6%(3) were left with grade 4 pain during this period. Subsequently the cumulative effect was also wonderful .Analysis at the end of 2nd month indicates that 82.3% participants became pain free, whereas only 13.1%(11) had grade1 pain and 1 patient was continuing with grade 4 pain. By the end of 3rd month the results were far more encouraging where 92% of the participants were absolutely pain free (grade-0) and in 4.8%(4) there was substantial relief of pain reaching Grade 1. At the end of the study period only 1 patient was unresponsive to the drug and continued with grade 4 pain through-out the period. Spearman's correlation was used to find out the pain score improvement versus duration of therapy .It shows statistically significant shift of higher grade of pain in to lower grade with increasing duration of therapy. However grade 1 pain did not show statistical significance .This could be due to majority of higher grade pain like 4, 3 and 2 moved to grade 1 transiently increasing its number in subsequent months which is clearly evidenced by the fact that grade 0 pain shows a steady increase with time which is statistically significant. Actually the major swing which was seen in these groups is in the 1st month itself, therefore linear correlation was not found in the time scale for grade 1 pain.

A study by Anita Dhar, et al. using Ormeloxifene 30mg alternate day have reported drastic pain reduction in 1 week period in 90% of the cases and at the end of 1 month almost all patients (n=60) were painless [49]. Bhupendra K Jain et al reported a study of 60 cases where comparison was done between Ormeloxifene 30 mg daily versus tamoxifen 10mg daily. More than 70% in both the group had complete pain relief by 3months.There was no statistical difference in both groups [50]. They had reported ovarian cyst in Ormeloxifene groups which was not substantiated either by our study or the study by Anita Dhar, et al. This could be due to use of Ormeloxifene in a very high dosage by them i.e. 210 mg weekly compared to 105 mg/week by Anita Dhar, et al. and 120mg /week in our study. In another randomized trial combining both alternate and daily dosage, Prakash Lakhmichand Tejwani, et al. reported Centchroman (Ormeloxifene) to have response rate of 89.7 % (reduction of pain to less than or equal to 3 on VAS) at the end of 12 weeks whereas Danazol achieved 69.44% response rate at 12 weeks [51].

Most of the side effects in our study were menstruation related (15.48%). 3 had hypo-menorrhea and 1 had oligo-menorrhoea. 5 women reported amenorrhoea all of whom were pregnancy negative. Menstrual irregularities were short lived and patients recovered their original periods after stopping the drug.

Other side effects like hypo-estrogenic symptoms hot flashes accompanied by vaginal dryness were reported by 2.4% only which responded well to anxiolytics like alprazolam and vaginal lubricants. The dysuria reported by 1.2% of the patient was relieved by symptomatic treatment with alkaline citrate.

Conclusion

Ormeloxifene appears to be a safe non-steroidal non-hormonal drug for the treatment of mastalgia. Promising results, lack of major side effects, low cost and a convenient twice weekly regimen in our protocol makes it more patient friendly. Better compliance is due to twice weekly dosage where patient psychologically feels using less quantity of drug therefore not unnecessarily worried about the adverse effects. Though small in number, available studies greatly favour this drug as a treatment of choice in mastalgia. Nevertheless more prospective studies (large scale multicentric) are recommended to fully establish the role of this drug as a prime therapy for mastalgia.

Conflict of Interest

Dr. Subrat Kumar Mohakul, Dr. Sujatha Guttala and Dr. Purnima Tiru, declare that they have no conflict of interest.

Ethical standard statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Authors Contribution

S. K. Mohakul: Project development, Data Collection, Manuscript writing

P. Tiru: Data collection

S. Guttala: Manuscript writing

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