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Research Paper

Efficacy of Treatment Protocols for Mastalgia in A Speciality Breast Clinic.

Medical Science

KEYWORDS : Mastalgia; Breast Clinic; Gamma linolenic Acid

*** Prof. Shilpa Rao**	(M.S., MRCSEd, FACRSI), Professor and Unit Head, In- charge Breast Clinic, Department of General Surgery, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, India. * corresponding author
Dr. Aditya Kunte	(M.S.), Speciality Medical Officer, Department of General Surgery, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, India.
Dr. Tejas Vaja	Surgical resident, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, India.

ABSTRACT

Mastalgia is the most common presenting breast complaint. Hormonal agents are effective but have side effects. We observed 60 women with mastalgia presenting to a speciality breast clinic over 10 weeks. 46.66 % patients were between 31 and 40 years old. Pain scores were significantly reduced over 6 weeks (6.73 v/s 5.67; p=0.03261) and at 10 weeks (6.73 v/s 4.06; p=0.000003136) in patients of cyclical and non- cyclical mastalgia [(7.66 v/s 5.86; p=0.003436); (7.66 v/s 4.6; p=<0.0000001)] when treated with Gamma- linolenic acid (GLA).

GLA therapy over 10 weeks reduced the number of women with clinically significant levels of mastalgia, of cyclical as well as non- cyclical type [23 (76.66%) v/s 16 (53.33%); p=0.03313; 29 (96.66%) v/s 21 (70%); p=0.006490].

Mastalgia decreases quality of life and requires definitive management. GLA therapy significantly decreases its severity and improves quality of life.

Introduction

Mastalgia has become one of the most frequent reasons for medical consultation in a breast clinic [1] with an estimated prevalence of 69 % and significant impact on the quality of life of women [2]. Ader DN et al. observed that 30% of premenstrual women suffered from cyclical mastalgia lasting for more than 5 days a month, which was severe enough to interfere with sexual, physical, social and work-related activities [3]. Although a majority of women can be reassured after a clinical evaluation, approximately 15% require pain-relieving therapy. Supportive therapies are usual first-line treatments, however, not always effective. Hormonal agents, such as bromocriptine, tamoxifen and danazol are effective but limited by side effects. Gamma-linolenic acid (GLA) has recently been found to be beneficial in the treatment of mastalgia [4]. Good symptom relief and lack of side effects makes GLA a very promising therapy in the treatment of mastalgia. In this prospective study, we aim to study the clinical and radiological features of mastalgia and the impact that its treatment has on the lives of women.

Methods

1. This was a prospective observational study in which women presenting to the Breast Clinic OPD over a period of two months were screened.
2. Inclusion criteria:
3. Female patients between the ages 18 to 60 years.
4. Presenting complaints of unilateral or bilateral breast pain.

Exclusion criteria

1. Carcinoma of the breast.
2. Patients with a history of psychiatric illness or ongoing medications for the same.
3. Extra mammary chest pain.
4. Patients with a palpable breast lump.

Study protocol

On the day of screening (Visit 1), a detailed clinical history along with a thorough physical examination was performed on the patients. Height, weight and body mass index (BMI) was recorded of all the included patients.

Laboratory investigations such as complete haemogram, erythrocyte sedimentation rate (ESR) and thyroid function tests (T3, T4 and TSH) were noted.

Pain scores of the patients were recorded on a Wong- Baker faces pain scale, at the time of inclusion, 6 weeks after inclusion and 10 weeks after inclusion into the study.

The patients were followed up for a total period of 10 weeks after induction into the study. During this period, they had 2 scheduled visits after the initial visit; 1st follow-up visit at 6 weeks (Visit 2) and the 2nd follow- up visit at 10 weeks (Visit 3).

During these visits, the ongoing medications of the patients were reviewed and their pain scores recorded on the Wong- Baker faces pain scale.

A value of >4 on the Wong- Baker faces pain scale was taken as a clinically significant degree of mastalgia [3, 5-7].

Statistical analysis

Qualitative data was analysed by Fisher or Chi- square tests. Parametric data was analysed by the paired t- test. A p value of <0.05 was considered as statistically significant.

Results

A total of 60 female patients with mastalgia, of which 30 had cyclical and 30 had non- cyclical mastalgia were included in the study, and observed for a period of 10 weeks.

Demographic characteristics **[***Graph 1***]**

28 out of the 60 women (46.66%) of the women with mastalgia were in the age group of 31 to 40 years. This pattern of distribution was similar for the sub- group analysis of cyclical and non- cyclical mastalgia, with 15 out of 30 (50%) women with cyclical mastalgia and 13 out of 30 (43.33%) of women with non- cyclical mastalgia being in the age group of 31 to 40 years.

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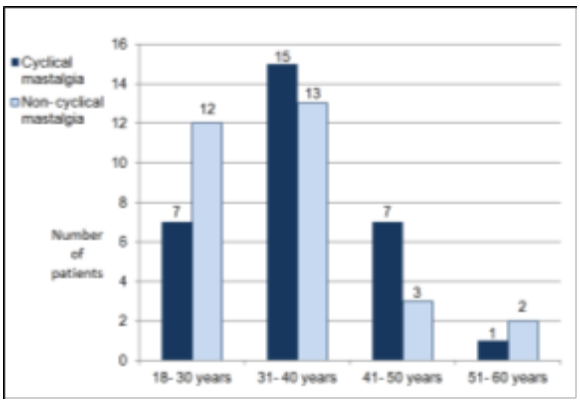
Graph 1. Distribution of patients of mastalgia according to age

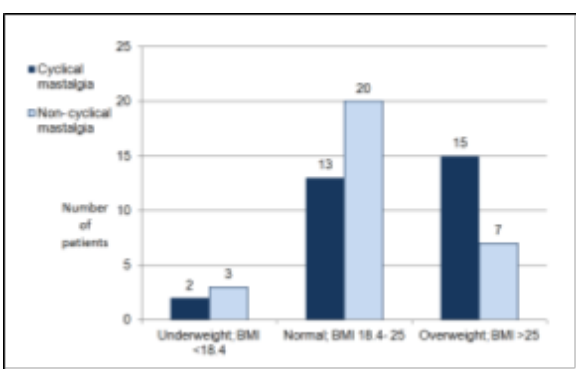


Body mass index (BMI) and mastalgia **[***Graph 2***]**
Among the patients having cyclical mastalgia, 13 out of 30 (43.33%) patients had a normal BMI (BMI 18.5- 24.9) and 15 out of 30 (50%) patients were overweight (BMI >25).

Among the patients with non- cyclical mastalgia, 20 out of 30 (66.67%) patients had a normal BMI, whereas 7 out of 30 (23.33%) patients were overweight.

There were a significantly higher number of patients with cyclical mastalgia who were overweight than those with non- cyclical mastalgia (p= 0.03729).

Graph 2. Distribution of patients of mastalgia according to BMI.



Leukocytosis and mastalgia **[***Graph 3***]**
Leukocytosis was defined as total leucocyte counts >11,000/cu.mm.

Only 22 out of 60 (36.66%) patients had mastalgia associated with leucocytosis., out of which 12 (54.54%) had cyclical and 10 (45.45%) had non- cyclical mastalgia.

Neutrophilia was defined as neutrophils >60/100 cells in patients with leucocytosis.

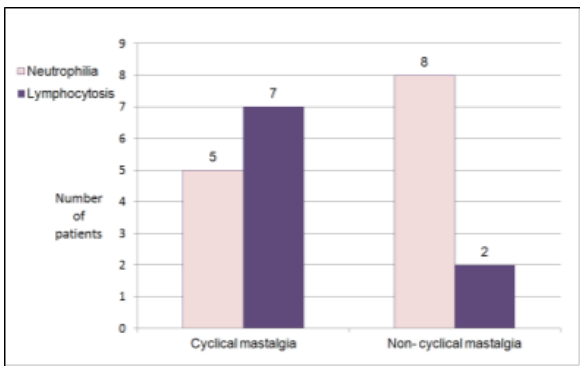
Lymphocytosis was defined as lymphocytes >30/100 cells in patients with leucocytosis.

Among the 12 patients of cyclical mastalgia associated with leucocytosis, 5 (41.66%) had neutrophilia and 7 (58.33%) had lymphocytosis.

Among the 10 patients of non- cyclical mastalgia associated with leucocytosis, 8 (80%) had neutrophilia and 2 (20%) had lymphocytosis.

The number of patients of non- cyclical mastalgia associated with a neutrophilic leucocytosis were significantly higher than those with a lymphocytic leucocytosis (p= 0.01205).

Graph 3. Association of mastalgia with type of leucocytosis

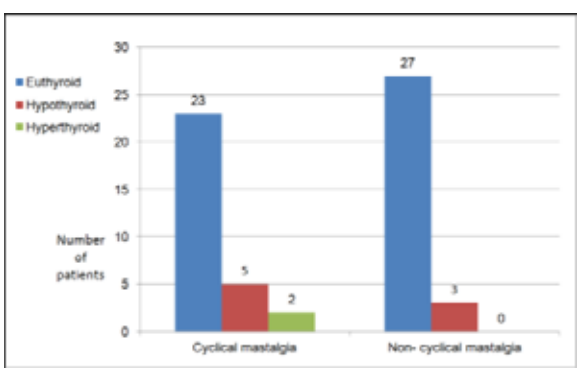


ESR and mastalgia
An elevated ESR was defined as >20mm/hr.

6 (20%) out of 30 patients with cyclical and 8 (26.66%) out of 30 patients with non- cyclical mastalgia were associated with an elevated ESR.

Thyroid functions and mastalgia **[***Graph 4***]**
7 (23.33%) out of 30 patients with cyclical and 3 (10%) out of 30 patients with non- cyclical mastalgia were associated with altered thyroid functions.

Graph 4. Association of thyroid function abnormalities with mastalgia.



Clinical response of mastalgia to GLA **[***Graph 5***]**
All patients of mastalgia (excluding those with inflammatory or malignant breast disease) presenting to the Breast Clinic OPD were prescribed Gamma linolenic acid (GLA) 120mg twice daily, orally for 3 months.

Clinically significant mastalgia was defined according to the research definition of mastalgia as breast pain of an intensity of 4 or more on a visual analogue scale and lasting for at least 7 days in a month [3].

Pain scores of the patients were recorded on a Wong Baker faces pain scale at induction (Visit 1) and at two subsequent visits, at 6 weeks (Visit 2) and at 10 weeks (Visit 3) after induction into the study.

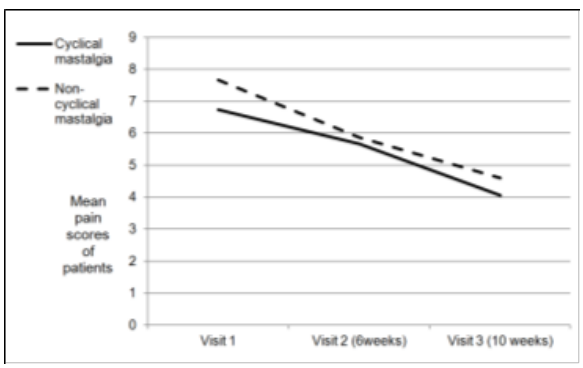
At visit 1, mean pain scores in patients of cyclical mastalgia were 6.73 whereas those in patients of non- cyclical mastalgia were 7.66. This difference was not statistically significant (p= 0.05134).

In patients of cyclical mastalgia, mean pain scores showed significant reduction at Visit 2 (6.73 v/s 5.67; p= 0.03261) as well as at Visit 3 (6.73 v/s 4.06; p= 0.000003136) when compared to pain scores at initial visit.

In patients of non- cyclical mastalgia, mean pain scores showed significant reduction at Visit 2 (7.66 v/s 5.86; p= 0.003436) as well as at Visit 3 (7.66 v/s 4.6; p= <0.0000001) when compared to pain scores at initial visit.

There was no significant difference in mean pain scores between the cyclical and non- cyclical mastalgia group at Visit 2 (5.67 v/s 5.86; p= 0.6969) or at Visit 3 (4.06 v/s 4.6; p= 0.3246).

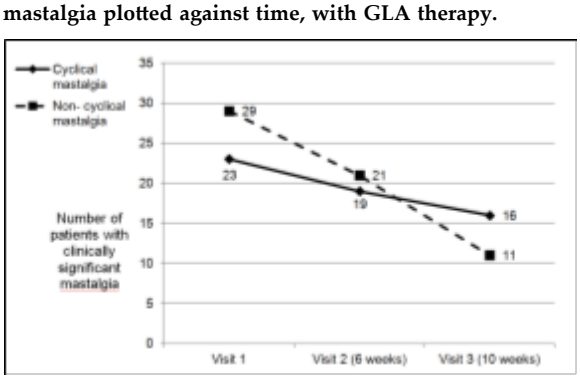
Graph 5. Mean pain scores plotted over time in response to GLA therapy.



Impact of mastalgia treatment on quality of life **[***Graph 6***]**
In the cyclical mastalgia group, 23 (76.66%) out of 30 women had a clinically significant level of mastalgia which interfered with daily activity. After 6 weeks of receiving treatment, the number of women with a significant level of mastalgia had dropped down to 19 (63.33%) [p = 0.2783], which further dropped down to 16 (53.33%) [p = 0.03313] after 10 weeks of receiving treatment.

In the non- cyclical mastalgia group, 29 (96.66%) out of 30 women had a clinically significant level of mastalgia which interfered with daily activity. After 6 weeks of receiving treatment, the number of women with a significant level of mastalgia had decreased to 21 (70%) [p = 0.006490], which further dropped down to 11 (36.66%) [p = 0.000000405] after 10 weeks of receiving treatment.

Graph 6. Number of women with clinically significant mastalgia plotted against time, with GLA therapy.



Discussion
The research definition of mastalgia is breast pain with an intensity of 4 or more and a duration of at least 7 days in a month [3]. In a large cohort of 2400 women enrolled in a health maintenance organization in the United States during a 10-year period, pain was the most common breast symptom, prompting medical evaluation and accounting for 47% of breast-related visit [8]. Mastalgia is commonly divided into two types; cyclical and non- cyclical [9]. Cyclical mastalgia is the commonest, with the pain, which is commonly bilateral, starting characteristically 3 to 4 days before menstruation and subsiding within a few days of the onset of menses. The exact mechanisms of this condition are not fully understood, though it is suspected to be tied to fluctuating hormone levels and altered sensitivity of the breast tissue to hormones, the most important being estrogen, progesterone and prolactin [10]. The rise of circulating estrogen in the body a few days prior to the menstrual cycle leading to excess water retention in the breast tissue, with subsequent pain and tenderness is one of the postulated mechanisms of cyclical mastalgia [11].

Cyclical breast pain (cyclical mastalgia) is frequently associated with fibrocystic breast disease, a benign condition of **breast** tissue affecting an estimated 58% to 89% of women [12, 13].

Non cyclical mastalgia is the cause of pain in a quarter of the women presenting with breast pain, but unlike cyclical mastalgia, shows no temporal relationship to the menstrual cycle [14]. Non cyclical mastalgia is also called as trigger zone pain and is site specific, and may be unilateral as well as bilateral [15]. Some degree of non-cyclical breast tenderness can normally be present due to hormonal changes in puberty (both in girls and boys), in **menopause** and during **pregnancy.** Other causes of non-cyclical breast pain are alcoholism with liver damage (likely due to abnormal steroid metabolism), mastitis and certain medications such as digitalis, methyldopa, spironolactone, chlorpromazine and oxymethalone [16].

In our study sample, cyclical and non- cyclical mastalgia were equally distributed. Both, cyclical as well as non- cyclical mastalgia were most common in women in their 4th decade of life, essentially confirming that mastalgia is an entity predominantly affecting pre- menopausal women. Cyclical mastalgia was more strongly associated with a higher BMI, giving credence to the theory that alteration in the composition of membrane lipids may play a role in the pathogenesis of cyclical mastalgia, thus paving the way for newer, non- hormonal agents in its management. The association of mastalgia with an underlying inflammatory cause is also supported in part by approximately 20% of the patients in both groups having an elevated ESR.

Non- cyclical mastalgia correlated more strongly with the presence of a neutrophilic leucocytosis, suggesting certain inflammatory lesions as an underlying cause of the pain. This also points to a key difference to be taken into consideration while adopting management strategies for non- cyclical mastalgia. Since it may be associated more frequently with an underlying inflammatory component, strategies to identify the cause of the inflammation and anti- inflammatory agents may play a role in its management.

Ader DN et al. observed that 30% of premenstrual women suffered from cyclical mastalgia which lasted for more than 5 days a month, and this was of sufficient severity to interfere with sexual, physical, social and work-related activities [3].

Although reassurance is sufficient in a majority of women, approximately 15% require pain-relieving therapy. Mechanical breast support; a low-fat, high-carbohydrate diet; and topical non- steroidal anti- inflammatory agents are reason-

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able first-line treatments. Hormonal agents, such as bromocriptine, tamoxifen and danazol, have all demonstrated efficacy in the treatment of mastalgia but their use is limited by side effects.

Gamma-linolenic acid (GLA) has recently been found to be beneficial in the management of breast pain [4]. Gamma-linolenic acid or GLA (γ-Linolenic acid) is a fatty acid found primarily in vegetable oils such as rapeseed canola oil, soy beans, walnuts, flax seed (linseed oil), perilla, chia, and hemp seed [17]. GLA is a precursor of unsaturated fatty acids which are important in membrane structures, as second messengers in their own right and as precursors of eicosanoids. From GLA, the body forms dihomo-γ-linolenic acid (DGLA). This is one of the body's three sources of eicosanoids (along with arachidonic acid (AA) and eicosaprostanoic acid (EPA). GLA is the precursor of the prostaglandin PGH_1, which in turn forms PGE_1 and thromboxane $\mathbf{A}_1$ ($TXA_{1)}$. Both $PGE1_1$ and TXA_1 are anti-inflammatory agents [18, 19]. Alongwith its anti- inflammatory properties, GLA also has important non- eicosanoid mechanisms of actions such as modification of cell membrane composition and of the functions of lipid-associated receptors and changes in the inositol cycle [20]. Being a non- hormonal agent, GLA has no reported serious side- effects [21].

In our study, we used the Wong Baker faces pain scale to gauge the intensity of mastalgia experienced by the women. It shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". The patient must choose the face that best describes how they are feeling [5-7].

GLA administration is part of the standard management protocol at our institute for patients with mastalgia (excluding those with inflammatory and malignant lesions of the breast).

When we analysed the pain scores of these women over a period of 10 weeks, there was a significant reduction in the pain levels after initiation of GLA therapy in patients with cyclical as well as non- cyclical mastalgia.

In fact, a significant number of women who initially had a level of mastalgia which interfered with their daily activities, reported the mastalgia to have decreased to a level that did not impact their daily functioning after GLA therapy, thus demonstrating the improvement in the quality of life that GLA produces in women suffering from mastalgia.

Conclusion

Mastalgia is a widespread entity adversely affecting the quality of life of women, and requiring definitive rather than solely supportive management. Therapy with oral Gamma- linolenic acid (GLA) significantly decreases mastalgia and improves quality of life without any harmful side- effects.

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