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Review Article

Time to revisit the enigma of mastalgia management

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ABSTRACT

Mastalgia (breast pain) also known as mastodynia, is one of the most common causes of breast issues for which a female visits a medical practitioner. It is divided into cyclical mastalgia, which is associated with menstruation, or can be noncyclical mastalgia which can present premenopausal or postmenopausal. The incidence of breast cancer associated with mastalgia is extremely low and reassurance plays a major role in the treatment of patients. Hormonal changes have been associated with the pathogenesis of cyclical mastalgia. Outdated treatment modalities are still being followed even though newer and more effective treatment options have been established. Objective assessment of breast pain should be done with the visual analog scale. Non-pharmacological therapy should be encouraged in every patient of mastalgia such as counseling and reassurance, sports bra, yoga, and relaxation therapy. Tamoxifen and ormeloxifene are now the drug of choice in severe mastalgia and care should be taken to counsel the patients about use and common and detrimental side effects. The available treatment modalities and their directions to use are discussed in this review.

Keywords: Mastalgia, Mastodynia, Breast pain, Management of mastalgia

INTRODUCTION

Mastalgia (breast pain) also known as mastodynia, is one of the most common causes of breast symptoms for which a female visits a medical practitioner. It's a debilitating condition for some women and also affects men. Its pathophysiology and treatment options are still inadequately defined which requires a revisit. As breast awareness is spreading, more women are seeking medical care for breast symptoms. It can be diffusely present or localized to a quadrant, and either can be unilateral or can present as bilateral breast pain. it is divided into cyclical mastalgia, which is associated with menstruation, or can be noncyclical mastalgia which can present premenopausal or postmenopausal.[1] It is paramount to exclude the extramammary chest pain before working up the patient for breast disease, especially in females where the breast pain can be the symptom of underlying malignancy.[2] However, the association of breast cancer with breast pain is open for debate. Two third of the cases present with cyclical mastalgia.[3] Mastalgia has been associated with various psychiatric illnesses such as anxiety, depression, and neurosis. It has also shown an association with chronic myalgia, fibromyalgia syndrome, and irritable bowel syndrome.[4] The association of breast pain with ovarian hormonal activity, prolactin hyperresponsiveness to Thyrotropin-releasing hormone (TRH), and abnormal fatty acid metabolism are all studied well but the presence of breast pain even after menopause and non-cyclical mastalgia contradicts the available literature and allows establishing uniform aetiopathogenesis.[5] The mainstay of the treatment is reassurance, breast support, and physical therapy, second line therapy includes the use of tamoxifen and ormeloxifene. Previously used outdated treatments such

as vitamin E, evening primrose oil and have shown no benefit as compared to placebo in trials.[2]

REVIEW

Etiology

The breast has been one of the most extensively studied organs and yet some pathophysiology, histological, and contributing factors of mastalgia are still left to uncover.

Anatomy

The breast is a modified sweat gland with its structure divided into various lobes and lobules and at the microscopic end of this, some glands and acini produce and eject milk in response to the hormones. Ducts connect the glands and lobules and also deliver milk during lactation. Blockade of these ducts was also considered to be a cause of mastalgia which can be due to polyp, epithelial debris, and ductal cell overgrowth.[6]

Histopathology

In one study, 39 patients with cyclical breast pain underwent breast biopsy, and every one of them had microscopic features of fibrocystic changes. These findings were also present in patients without breast pain. Therefore, the correlation is loose and yet to be established.[7] There was a long-term link between mastalgia and fibrocystic disease. However, this association has been found conflicting as detailed pathological examination in patients with breast disease including mastalgia and other causes have shown fibrocystic histology, which highlights that fibrocystic change is a normal variant of breast microstructure and if only present with atypia or proliferative changes have association with breast cancer.[8] Fibrocystic disease of the breast is a term used to describe breast pain associated with nodularity and breast tenderness with microscopic features of florid epithelial hyperplasia and cystic changes due to expansion of terminal duct lobular unit (TDLU).[9]

Hormone association

There are three theories, that try to explore the etiology of mastalgia, ovarian stimulation via increased estrogen. Decrease progesterone, increased thyrotropin-induced prolactin secretion.[2] By understanding these theories different treatment options have been developed to manage the patients of mastalgia. Some of them have shown good results in controlled trials. Although body hormone assessment in patients and control do not show any major variations the 1 and 2 theories have less weight.[10] Cyclical mastalgia has a clinical presentation of being present in the luteal phase and pain usually occurs one to two weeks before menses.[11] This category has been found to have an association with thyrotropin-releasing hormone and hyperprolactinemia.[12] A novel study was performed by Ramakrishna et al in 2003, which tried to understand the potential role of inflammatory cytokines and interleukins in breast pain but failed to correlate any pathological basis.[13]

Water and electrolytes

Retention of water in breast tissue which was previously postulated as a causative agent for breast pain, is now not considered as one of the etiologies as described by the Cardiff mastalgia clinic.[3]

PSYCHOLOGICAL ASSOCIATION

Psychological stress, anxiety, and depression can be considered as an etiological factor or a symptom complex following breast pain. As the mean age group affected by mastalgia is 42 years, these women go through severe mental distress, as they consider breast pain associated with breast cancer.[14] Sir Astley Cooper wrote “A woman seeking advice for breast pain usually had a nervous and irritable temperament’’.[2] Hence, it is now considered that mastalgia is just like irritable bowel syndrome, dyspepsia a stress-based disorder whose psychological background is not yet fully understood.[4]

CLINICAL EVALUATION AND ASSESSMENT

A detailed history and necessary examination of bilateral breast usually gives a diagnosis. History should be taken properly to elicit the site of pain, severity, any association with strenuous activity, any history of trauma, nipple discharge, fever, or palpable lump. History should be taken to know about any substance abuse, use of contraceptives, hormone therapy, or pregnancy. Physical Examination should be done in a usual breast examination format and care should be taken to examine the spine, chest wall, lung, heart, and shoulders, pathology of which may mimic Mastalgia.[2] Patients coming with breast pain usually asked to undergo an ultrasonographic examination of the breast if age is less than 40 and a mammography if more than 40 years old. Reassurance plays a very important role in the management of such cases as ruling out breast cancer effectively relieves some patients from their symptoms .[14]

In a study conducted by Arslan et al. It was shown that in females with mastalgia who undergo ultrasonography of the breast, 42.3% have normal findings, 37.1 % have a cyst, 9.9% duct dilatation, and 6.4% have fibroadenoma. In the same study females who underwent mammography, 51.6% had BI-RADS 2 i.e. normal study and none of the patients had BI-RADS 5 or 6. Pathological examination was also done in these patients (4.9% of the total presenting patients) 32.3% of them showed fibrocystic disease.[14] In a study by Joyce et al in 2014, there is an extremely low incidence of breast cancer, with mastalgia as the only complaint. Only 1.2% of these patients developed breast cancer predominantly after 35 years of age. This study proposes that, given the

low incidence of breast cancer in cases of mastalgia, there is no role of initial imaging in these patients, as the only symptom at presentation is pain. In some cases, there is a need to complete the triple assessment, therefore biopsy and imaging become a must.[3,15]

OBJECTIVE ASSESSMENT

Daily pain charting and Visual Analog Scale (VAS) are being used to assess the patient's pain, its occurrence, association with cycle, and severity. VAS of more than equal to 3 has been universally defined as significant pain to require therapy.[16] A new pain chart recording has been devised which allows the recording of menstrual experience separately, record pain in each breast separately, and numerical value is given to pain score each day, through these various numerical objective calculations can be made (Figure 1).[17]

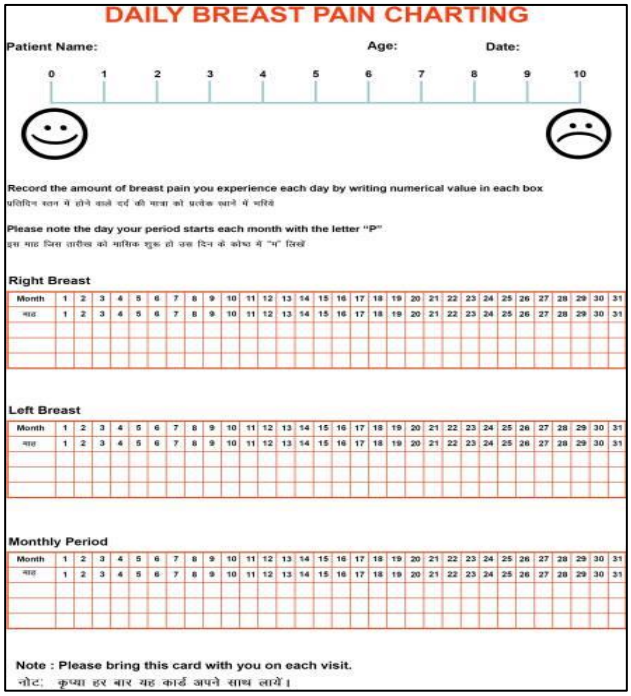

Figure 1: Daily breast pain assessment chart.[17] (source-new breast pain chart for objective record of mastalgia).

MASTALGIA MANAGEMENT

Counseling and reassurance

A good clinical evaluation becomes important as understanding the patient's condition and reassuring her that breast pain is a common symptom not usually associated with breast cancer.[15] A triple assessment can be done to reassure the patient if clinically there is no significant finding.[13] After ruling out organic causes with physical tests and appropriate radiological testing, psychological variables like worry, stress, and depression should be considered. Given that mastalgia affects quality of life, a psychiatrist ought to be consulted.[18]

Importance of brassiere

Properly fitted soft supportive bra or sports bra use is universally advised for patients with breast pain.[3] A study comparing the use of danazol versus a supportive bra showed that the use of a supportive bra provides better pain relief in more patients with no side effects.[19] Supportive bra alleviates symptoms by decreasing tension on Cooper's ligament.[20] Use of heat and cold therapy, and acupuncture, have also been implemented in the treatment of mastalgia.[2]

Relaxation therapy

Relaxation therapy has been used in some patients with pain, tension headache, and irritable bowel syndrome with widespread use in depression and anxiety disorders. Patients were made to listen to recorded audiocassettes concentrating on progressive muscle relaxation and cue-cue controlled relaxation. Relaxation therapy patients with cyclical mastalgia have shown that it can be used as an alternative to medical therapy as 61% of patients showed complete and substantial improvement.[21]

Yoga therapy

Yoga/yogik kriyas have been used in patients with anxiety and as an adjunct to pain management. The psychological association of cyclical mastalgia makes yoga an appropriate therapy to manage the symptoms with no side effects. Detailed proper controlled trials are yet to be performed. It is seen that women suffering from mastalgia have their prana (energy) localized in the breast over a long period and present as pain. Pain is an involuntary sensation in our nervous system that can cause hormonal imbalance (estrogen, progesterone, prolactin). The practice of yoga helps control this imbalance through meditation and postures.[22]

Topical analgesics

Topical NSAIDs have been shown to significantly reduce pain in patients with mastalgia. In a study by Colak et al, pain was significantly decreased in both patients of cyclical and noncyclical mastalgia with no systemic side effects assessed with the use of VAS for pain assessment.[23]

Dietary modifications

Reduced total fat intake, reduction of caffeine(methylxanthine) data is available which suggests the efficacy and contradicts any role greater than placebo. Reduction of total fat to less than 20% and eliminating caffeine from daily diet is difficult. The absence of satisfactory evidence makes it difficult to implement these strategies in routine patients.[2]

HORMONAL AND MEDICAL THERAPY

With the association of mastalgia with low progesterone, topical and systemic progesterone has been studied as a treatment option, and no significant improvement was noted as compared to placebo in one trial.[23] In the other trial oral progesterone lynestrenol, promegestone given during the luteal phase of the menstrual cycle markedly improved breast symptoms in approximately 80% of the patients with benign breast disease. The use of hormonal therapy has been limited to two to six months of use because of anticipated side effects. Topical use of progesterone has shown no improvement in symptoms.[24]

TAMOXIFEN

It is the drug of choice presently given in the Western population for mastalgia.[20] A selective estrogen receptor modulator (SERM) is used for the treatment of breast cancer and its prevention. Has been used in patients with breast pain in a study conducted by Fetiman et al 71 % underwent remission as compared to 38% in the placebo group. Keeping in mind the side effects of tamoxifen in premenopausal group females such as hot flushes, vaginal discharge, and menorrhagia and on long-term endometrial hyperplasia and endometrial carcinoma.[25] 10 mg daily is preferred as a drug of choice in Western practice.[20] Patients should be counseled about the drug and its side effects and they should be counseled that the medicine is not being prescribed for cancer therapy.

CENTCHROMAN

Also known as ormeloxifene (SAHELI, "once a week pill" in Indian national family welfare program) 30mg once daily dose improved the symptoms in 89.7% of the patients of mastalgia in a study conducted in All India Institute of Medical Science which was assessed by VAS ≤3. There was a 1.67 greater chance of significant pain relief as compared to Danazol, with a longer carrying effect, It is cost-effective, devoid of steroidal side effects as compared to tamoxifen with no effect on ovulation. With 2 rupees per tablet and a safer pharmacological profile, it can be used as a drug of choice but larger multicentric randomized trials are required for wider acceptance.[20]

DANAZOL

A derivative of 17-α-ethinyl testosterone, Danazol is the only drug licensed by the food and drug administration to treat mastalgia, that stops the secretion of gonadotropin, inhibits luteinizing hormone spike, and prevents the production of ovarian steroids. Breast discomfort and tenderness are reduced by danazol in controlled research studies. Use of danazol during the luteal phase i.e., low dose (mean total dose of 800 mg per month) luteal phase administration of danazol relieves the patient of breast pain with fewer side effects.[26] The initial dose of danazol can be 50-100 mg per day with a maintenance dose of 50 mg twice daily or 100 mg once daily or alternative days for three to six months.[20] Similarly, Gestrinone, a synthetic analog of testosterone originally produced as a contraceptive provides a reduction in breast pain in a multicentric double-blind trial with a dose of 2.5 mg per week but is of limited use because of androgenic side effects. The use of these drugs is contraindicated in pregnancy due to possible teratogenic side effects.[2]

BROMOCRIPTINE

The hormonal profile of mastalgia showed an increase in thyrotropin-induced prolactin secretion. Bromocriptine is a dopamine agonist that inhibits the release of prolactin from the anterior pituitary.[27] It markedly reduces breast pain but with 29% of females withdrawing from a study due to side effects such as nausea, vomiting, heaviness, and fatigue. With clinical improvement in 47-88% of patients. A dose of 1.25-2.5 mg twice a day showed good results.[5]

GOSERELIN

Gonadotropin-releasing hormone agonist- showed promising results by significantly reducing breast pain in 100% of the patients with recurrent mastalgia and in 56% of patients who showed less than desired effect on danazol, bromocriptine, and tamoxifen. Because of side effects and less known studies, its use is preserved for patients who are refractory to other medical management.[28]

VITAMIN D

Patients of non-cyclical mastalgia have shown less response towards hormonal therapy and patients with mild to moderate deficiency of vitamin D have shown improvement in mastalgia symptoms. Duration of treatment and baseline vitamin D levels are yet to be established.[29]

OTHER DRUGS AND SUPPLEMENTS

Vitamin E which was previously considered as one of the treatment modalities for mastalgia, is now shown to predispose to hemorrhagic brain stroke, on chronic usage. Its efficacy is no better than a placebo.[30]

Oil of evening primrose

Evening primrose (EPO) (gamma-linolenic acid) deficiency was seen in some patients of mastalgia. In a meta-analysis of the efficacy of evening primrose oil for the treatment of mastalgia, it was concluded that its effect is similar to a placebo.[31]

CONCLUSION

Mastalgia (breast pain) is the most common breast-related reason, a female patient visits medical care.

Proper history and examination are required to counsel the patient and provide reassurance. Care should be taken to rule out any breast lump, or nipple discharge. The possibility of breast cancer should be ruled out and unnecessary tests should be avoided. Initial nonpharmacological therapies play an important role in the management of mastalgia-reassurance, properly fitted bra, relaxation therapy, and yoga therapy can be considered. Patients not responding to non-pharmacological therapy and having a VAS of more than 3 can be considered for medical management. The role of primrose oil, and vitamin E are outdated and prescription depends on practitioner discretion. Tamoxifen, and centchroman, are preferred as a drug of choice, and danazol, bromocriptine, and goserelin can be used in refractory cases. More detailed research is required for a better understanding of breast pain and its etiological factors.

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