



Post mastectomy Chronic Pain in Breast Cancer Survivors: An Update on Definition, Pathogenesis, Risk Factors, Treatment and Prevention

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Abstract

A large number of women are surviving breast cancer today as a result of earlier detection and advancement in treatments. The diagnosis of breast cancer and subsequent treatment results in substantial medical and psychosocial sequelae for survivors, because of which they face physical, social, emotional and functional disabilities. Chronic pain following surgery for breast cancer is one such important survivorship issue which affects over 20%-60% of women after mastectomy.

Introduction

Although there is no standard definition of Post Mastectomy Chronic Pain (PMCP), 'International Association for study of pain' (IASP) defines it as chronic pain in the anterior aspect of thorax, axilla, and /or upper half of the arm, beginning after mastectomy or quadrantectomy and persisting for more than 3 months after the surgery [1-3]. It is typically neuropathic in character and is described as burning sensations, dysesthesia or paroxysms of lancinating, shock like pain [4].

The concept of PMCP has been constantly evolving. Persistent pain after mastectomy was first reported during the 1970s by Wood "et al". [5], who characterized it as a dull, burning and aching sensation in the anterior chest, arm and axilla, exacerbated by movement of the shoulder girdle. Foley and colleagues coined the term Post Mastectomy Pain Syndrome (PMPS) to describe a distinct syndrome of pain and sensory abnormalities following mastectomy [6]. Damage to intercostobrachial nerve was implicated as the most common cause of this syndrome [4,6]. Jung "et al". [4]. Classified post mastectomy neuropathic pain into four categories: 1. Phantom breast pain; 2) Intercostobrachial neuralgia due to damage to Intercostobrachial Nerve (ICBN) presenting as pain and sensory changes localized to the axilla, medial upper arm, and/or anterior chest wall ; 3) Neuroma pain in the region of scar on the breast, chest and or arm, provoked by percussion; 4) other nerve injury pain resulting from damage to medial or lateral pectoral, long thoracic, or thoracodorsal nerves [4]. Vilholm "et al". [7]. Defined PMCP as a pain located in the area of the surgery or the ipsilateral arm, present at least 4 days per week and with an average intensity of at least 3 on a numeric rating scale from 0-10.

More recently some authors have used the term 'Persistent post mastectomy pain' (PPMP) to describe the persistent levels of breast pain in the first 6 months following surgery. This persistent pain is proposed to be multifactorial in origin with injury to nerves, persistent inflammatory response and inter-individual variability in pain perception all playing an important role [8-10].

Etiopathogenesis

This has been an area of intense research in the last two decades. Though the exact pathogenesis of PMPS remains unclear, many etiological theories have been postulated.

Injury to intercostobrachial nerve (ICBN)

Intercostobrachial neuralgia due to sectioning of ICBN has been reported to be the most common cause of PMCP in the literature [4,11,12]. ICBN is a sensory nerve that passes through the muscles of the thoracic wall, being mainly responsible for the sensitivity of the shoulder and proximal portion of the arm. In the axilla it is in close relation to the axillary lymph nodes and hence commonly damaged during Axillary Lymph Node Dissection (ALND). Patients are left with an area of numbness on the upper arm, but only a minority of these will be painful. Preservation of

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the ICBN was reported to be associated with preservation of the skin sensitivity and a lower incidence of pain [12,13]. However Ivanovo reported that though the sensitivity was preserved when ICBN was saved during axillary surgery, the incidence of pain was not reduced. Another nerve at risk of damage during axillary dissection is the medial cutaneous nerve of the arm which arises from medial cord of the brachial plexus. It can be harmed during section of the tributaries of the axillary vein, leaving patient with sensory loss on the lower medial skin of the upper arm [4].

Other nerves vulnerable to damage during breast cancer surgery are medial and lateral pectoral nerves, long thoracic nerve to serratus anterior and thoracodorsal nerve to latissimus dorsi. Though these are primarily motor nerves, even they have sensory nervi nervorum and vasorum and may contribute to chronic pain [4].

Surgical scar neuroma pain

Chest wall or surgical scar pain is more likely to be the result of extensive surgical removal of the breast tissue rather than ALND. The sensory nerves (medial and lateral cutaneous branches of the ventral ramus of the third through sixth intercostal nerves) that innervate the skin of the chest wall pass through the substance of the breast and are cut or damaged in the course of breast tissue resection. Recovery from mastectomy is marked by numbness in the affected area in most patients, although some will experience unpleasant or frankly painful paresthesia [14]. In most cases regeneration of disrupted nerves leads to return of at least some sensations. However in some patients aberrant connections between regenerating nerves and uninjured nerves may result in chronic paresthesia and pain. Formation of neuromas at the cut ends of sensory nerves may also lead to pain and hypersensitivity in the area of surgical scar.

Role of psycho-emotional factors

Psycho-emotional factors have also been shown to play an important part in the development of PMCP [9,15]. Chronic pain syndromes are thought to arise from a physical injury that causes damage to the sensory nerves. However there is an inconsistent relationship between the degree of trauma and the subsequent incidence of chronic postoperative pain syndromes. Studies have shown that severe and chronic pain in many patients results in remodeling of parts of the brain that deal with processing of painful stimuli. Limbic system of the brain becomes hyper sensitized to painful stimuli, resulting in a sort of feedback loop between injured sensory nerves and the emotional pain centres of the brain [16]. Additionally neural pain receptor networks within the spinal cord are also thought to play a role in perpetuation of painful sensations from the operative site [17,18]. For these reasons many psychotropic drugs and neurotropic drugs, including antidepressants can reduce the severity of chronic pain syndromes.

Clinical Presentation

A wide variation (20%-55%) is reported in the incidence of PMCP in different reports, which is probably because of differences in the definition of pain, prospective or retrospective collection of data and the different measures used to assess pain [1,2,7,8]. Belfer "et al". [19]. Reported a prevalence of 47% when a pain score of $\geq 1/10$ is taken as the criteria. But when clinically significant score of $\geq 3/10$ is taken as the criteria, the rate reduced to 34.3%. With a similar criteria, Vilholm "et al". [7]. Reported a rate of PMCP of 23.9%. There is evidence that the incidence of PMCP decreases over time [20,21]. Iven "et al" [22]. Found that incidence diminished from 31% at 1-2

years following breast cancer surgery to 20% after more than 4 years following surgery. The most common location of pain is reported in the axilla and arm (20%-60%), followed by pain in the area of the scar (23-49%) [4]. Pain at more than one location is also reported by many patients [7,23] Vilholm "et al". [7] reported that pain was located in the axilla/arm in 80.8%, area of the scar 55.8% and multiple sites in 75% patients in a population of 258 patients. Belfer "et al". [19]. Reported most common location of pain in the breast, followed by axilla, and less commonly in the side of arm. What is noteworthy is that most of the patients (73%) underwent SLNB in their study population. Though the rate of Phantom breast pain in studies quoted by Jung "et al". [4] was 13-44%, most of the other studies have reported much lower rates [4,23,24]. Pain is usually described as burning sensations or tenderness with paroxysms of lancinating shock like pain. It is also described by some patients as dysesthesia with different degrees of discomfort. Pain may begin weeks or months after treatment; however it is considered PMCP if only it persists for more than 3 months. As for pain severity, it varies from mild to severe and is intermittent or continuous with periods of worsening and improvement [5,9,23,25]. Pain may get aggravated by any type of pressure over the arm or chest wall, movement of the shoulder girdle or elevation of the limb. These movements can trigger pain when performing simple actions such as dressing oneself. Patient may experience some relief on rest or massage. Patients may experience this chronic pain after other surgical procedures on the breast, even in the absence of neoplastic diseases, such as breast reduction and augmentation [26]. However since it is more commonly associated with radical mastectomy and axillary lymphadenectomy, it is routinely called as PMCP.

Assessment of Patient with PMCP

Since it is impractical to use detailed neurological testing to classify patients into categories of neuroma pain or intercostobrachial neuralgia or other nerve injury pain, it is a routine practice to assess these patients on the basis of pain qualities using questionnaire based assessments such as Short form McGill Pain Questionnaire, Brief pain inventory or Pain qualities assessment scale, Breast Cancer Pain Questionnaire (BCPQ), Neuropathic Pain Symptom Inventory (NPSI) etc. [8,27-29]. These scales allow discrimination and quantification of clinically relevant dimensions of neuropathic pain syndromes, which correlate with possible underlying pathophysiological mechanisms. Such an assessment provides a better treatment approach towards management of PMCP. As regards severity, the intensity of chronic pain is usually assessed using a 0-10 rating scale of average intensity of pain, consistent with consensus guidelines for the assessment of pain intensity in chronic pain clinical trials [28].

Risk Factors

PMCP is a multifactorial condition and a lot of factors have been evaluated for their potential role in the causation of this pain. Risk factors for the development of PMCP can be related to the patient herself or her treatment. These include demographic, psychosocial, as well surgery and adjuvant therapies related factors. However there is little consensus in the literature about the role of various risk factors in the causation of PMCP.

Demographic Factors

Age: A higher rate of PMCP have been reported in younger women in many studies, which can be explained to the fact that younger patients have more aggressive disease and receive more radical surgical and adjuvant treatments [9,15,20,30]. They may

also have lower sensitive threshold due to higher levels of anxiety, compared to older women.

Body mass index: A higher BMI is associated with more difficult surgical dissection and hence more chances of nerve damage. An elevated BMI was considered a risk factor by Wallace “et al”. [25], Smith “et al”. [20], however many other authors have not found any such correlation [15,20].

Kernofsky Performance Scale: Preoperative status of the patients has also been found to be significant in causing PMCP. Miaskowski “et al”. [9]. Reported that women with multiple comorbidities and lower activity status are more prone to have chronic pain.

Psychosocial Factors

Psychosocial factors including anxiety, depression, sleep disturbance and catastrophizing about pain have proven to be important risk factors for the development of many types of persistent pain. Preoperative anxiety regarding surgery and outcome can lead to increase perception of pain and same is true for depression as well [9,19]. However Poleschuk “et al”. [15] did not find any correlation with preoperative emotional functioning [15].

Pre-operative Breast pain: Almost 1/5th of patients of carcinoma breast present with complains of pain in breast. Breast pain is associated predominantly with benign breast conditions and hence overlooked in malignancy. Few researchers have evaluated its association with development of PMCP and found contradictory results. Kudel “et al”. [31]. Found preoperative pain to be a significant factor [9,31]. While Poleschuk “et al”. [15] found no association.

Surgery Related Factors

Type of surgery: There is inconsistency in the reported literature about the association of PMCP with type of surgery. Radical mastectomy is reported as a major risk factor for PMCP when compared with more conservative techniques [7,15]. However Tasmuth “et al”. [32] and Beyaz “et al”. [23]. Reported that breast conservation is associated with more risk of pain [1]. Vilholm “et al”. [7]. Reported that previous history of breast surgery posed increased risk of PPMP in women. The logical explanation to this finding could be increased scarring and hence increased entrapment of nerve endings.

Axillary lymph node dissection (ALND) vs. Sentinel lymph node biopsy (SLNB): Evaluation of axilla by sentinel lymph node biopsy has been reported to have lower incidence of PMCP compared to axillary dissection. SLNB is a targeted sampling of few nodes. ALND leads to more extensive damage to tissues in the axilla including nerves, hence increasing the risk of postoperative neuropathic pain [9,33-35].

Complications: Seroma is the most common complication post breast surgery. Other commonly encountered complications include infection of surgical site, necrosis of skin or collection of blood in the subcutaneous plane. Blunt “et al”. [47] reported hematoma to be a risk factor for chronic pain. However Belfer “et al”. [19] did not find any association of pain with post-surgical complications.

Acute post operative pain: greater severity of postoperative pain and greater consumption of analgesics is associated with an increased rate of persistent postoperative pain [9,15,37,38]. Tasmuth “et al”. [1]. Observed that women complaining of moderate to severe immediate post operative pain and requiring medication may act as

good predictor of PMCP [39].

Adjuvant Radiotherapy and Chemotherapy

Literature is again inconsistent about the role of adjuvant chemotherapy and radiotherapy as a risk factor of PMCP. Radiotherapy has been identified as a risk factor in many studies [9,15,40]. While many others found no association [7,19]. Radiation can cause PMCP by damaging Brachial plexus lying in the field of radiation. In addition to that, radiotherapy stimulates persistent inflammation and local fibrosis which could result in a strong adherence of scar to the deeper muscular layer, and possible nervous entrapment. This can lead to a continuous trigger of nerve excitation, sustaining a painful syndrome. Many chemotherapeutic drugs are neurotoxic and may cause nerve damage. Some specific chemotherapeutic drugs causing neurotoxicity are Vinca alkaloids, Cisplatin, Taxanes, etc. [8]. Performed a well-designed study with predefined chemotherapy regime and subgroups, but found no significant results.

Post Mastectomy Chronic Pain and Quality of Life

Chronic pain following breast cancer surgery is associated with decreased health-related quality of life and is a source of additional psychosocial distress in women who are already confronting the multiple stresses of cancer. [9,15,32,41]. For a cancer patient, the appearance of pain may represent a continuous memory of both the treatment and the disease; furthermore, it may be viewed as a sign of incumbent disease and lead to a fear of worsening or recurring cancer. Alkan “et al”. [42] studied rate of Post-Traumatic Stress Disorder (PTSD) in 614 breast cancer survivors attending OPD and found that PTSD was present in 75% patients with PMCP.

Hence, breast cancer patients who feel pain even without progressive or recurrent disease suffer considerable psychosocial distress and adjust badly in terms of the quality of life. According to Gulluoglu “et al”. [43] mood was found to be the most affected life function. Langford “et al”. [40] reported that pain interfered with every day activities such as ability to carry things, drive a car, mood, enjoyment of life and sleep etc. [10]. Caffo “et al”. [44]. Performed a retrospective study on 529 patients. He concluded that pain is frequent sequelae of breast cancer surgery and regardless of the type of treatment, seems to distress almost one-third of the patients and have a negative effect on their long term quality of life.

Treatment

Currently, there are a wide variety of approaches to treat chronic pain, including medications, physical therapy, and interventional procedures. However the requirement of medication in patients with PMCP is generally low [7,21]. Patients can be prescribed a range of drugs such as; Anti-inflammatory agents (ibuprofen, naproxen, and other NSAIDS); low dose of antidepressant medications such as Amitriptyline, venlafaxine and topical anesthetics, such as lidocaine patches and opioidsetc [45-48]. Narcotics are relatively effective against established chronic neuropathic pains and the risk of dependency is high. Topical counterirritants such as capsaicin and mentholated creams are effective in some cases [49]. Role of gabapentin in relieving PMCP has also been reported [50]. Scar neuromas can often be diagnosed and simultaneously treated by injection of local anesthetics and corticosteroids into the painful site. Various types of nerve blocks have been reported to be successful in alleviation of chronic pain [51]. Reported a case

series of 8 patients who were successfully treated with serratus plane block for treatment of PMCP. The serratus plane block appears to be mediated through blockade of the lateral cutaneous branches of the intercostal nerves [52,53]. Wisotzky "et al". [54]. Described series of 3 cases in which ultrasound-guided intercostobrachialperineural injection was used for intercostobrachial neuralgia successfully. CT guided block of Stellate ganglion block has also been described as an effective treatment modality. For patients with very refractory pain syndromes, interventions such as epidural injections of anesthetics or corticosteroids or implantable spinal cord stimulators have been described, though the use of these options for PMCP has hardly ever been reported. Autologous fat graft has been reported as an effective complementary approach to relieve patients of PMCP. Fat grafting could lead to scar remodelling, inducing release of fibrotic tissue with nerve liberation and loose connective tissue regeneration, leading to increased scar softness. Fat grafting is also hypothesized to induce analgesia by inhibition of inflammation [55].

Prevention

Various strategies for prevention of development of PMCP have been evaluated with variable rates of success.

Minimize extent of dissection

Since the primary cause of PMCP is injury to the nerves during surgical dissection, minimizing extent of resection, both of the breast tissue as well as the axilla, should lower the rates of PMCP. Studies have shown lower rates of pain in patients who undergo SLNB compared to ALND and less after BCS than mastectomy or reconstruction [56].

Preservation of ICBN

Most accepted hypothesis of PMCP in women is ICBN nerve injury during axillary dissection. Hence preservation of the nerve should reduce the risk of PMCP. However the results following preservation of ICBN have been inconsistent. Abdullah "et al". [58] randomly assigned patients to ICBN preservation or section, but noted that the nerve was only preserved in 65% of those assigned to the preservation group. Pain and sensory changes were greater when the nerve was sectioned. By 3 months pain was no longer significant though the sensory deficits remained. However some patients with no sensory loss had developed pain [57].

Perioperative pain control

Poorly controlled postoperative pain is strongly associated with the development of chronic pain [58]. Reported that Topical morphine controlled acute post mastectomy pain in a dose-dependent manner and reduced the incidence and severity of chronic post mastectomy pain syndrome [48]. Amr "et al". [59]. Reported reduction in incidence of chronic pain by perioperative administration of Venlafaxine and gabapentin for inducing pre-emptive analgesia in patients undergoing surgery for breast cancer [58].

Conclusion

PMCP affects nearly half the number of patients who undergo surgery for breast cancer and adversely affects their functioning. The etiopathogenesis, risk factors, natural history and effective treatments still remain areas of active research as there is little consensus in the existing literature about these issues. Prospective studies on larger populations of breast cancer survivors are required to address the existing lacunae in knowledge.

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