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REVIEW

Identification, Evaluation, and Management of Post-breast Surgery Pain Syndrome

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Abstract

Purpose of Review The purpose of this review is to provide a practical framework for the diagnosis and treatment of post-breast surgery pain syndrome.

Recent Findings There has been increasing evidence that nerve blocks, regional anesthetic blocks, and surgeries including fat grafting and targeted muscle reinnervation may be effective in treating post-breast surgery pain syndrome.

Summary Post-breast surgery pain syndrome is identified as clinically affecting the upper extremity and chest wall on the post-surgical side. There are several treatment options including topicals, oral medications, therapeutic interventions, and surgeries which may be discussed and explored with affected patients.

Keywords Post-breast surgery pain · Post-breast surgery pain syndrome · Post-mastectomy pain syndrome · Post-mastectomy pain · Breast surgery pain

Introduction

Surgery remains a cornerstone of treatment for localized breast cancer. While the majority of patients undergoing surgery recover without issue, it is not uncommon for some patients to develop chronic pain. There are myriad sources of pain including musculoskeletal sources, lymphedema, infection, seromas, and radiation complications to list a few. The most common cause of postoperative neuropathic pain however remains post-breast surgery pain syndrome (PBSPS).

PBSPS was first termed as post-mastectomy pain syndrome (PMPS) which was coined by Dr. Iris Granek in 1984 [1] and was formally defined by the International Association for the Study of Pain in 1986 [2]. More recently, the term PBSPS has come into favor over PMPS as it more accurately describes pain that occurs following any type of surgery and not just mastectomies. For the purposes of this review, we use the terms PBSPS and PMPS interchangeably.

While there is no standardized definition for PBSPS, experts generally agree that it is a neuropathic pain syndrome involving the ipsilateral chest wall and upper extremity. While definitions vary regarding the intensity, frequency, and duration of pain, most generally agree that pain should be present for a minimum of 3–12 months following surgery.

PBSPS is unfortunately not an uncommon problem with estimates of incidence ranging from 12–60% [3]. Hopefully with advanced surgical techniques and new research obviating the need for axillary dissection, these cases could become less common. Until then, however, any clinician managing pain can expect to see PBSPS at some point. We write this narrative review to discuss the evaluation and comprehensive treatment of PBSPS when such a time arises.

Types of Pain and Identification of PBSPS

PBSPS is most often characterized as a neuropathic syndrome caused by direct damage to nerves in the surgical areas including graft harvest sites. Damaged nerves will

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typically include intercostal nerves 2–6 along with their cutaneous branches and the intercostobrachial nerve. While other nerves including the pectoral, thoracodorsal, and long thoracic nerves may become damaged, these do not cause neuropathic pain as they are primarily motor nerves. Rather, when purely motor nerves are damaged, it may result in myofascial pain and muscle spasms most often in the pectoralis muscles. Pain from muscle spasms is increasingly being acknowledged as part of PBSPS although it is not neuropathic and responds better to other treatments such as botulinum toxin.

Neuropathic pain on the other hand is defined as pain caused by a demonstrable lesion or disease of the somatosensory nervous system [4]. While localized neuromas causing PBSPS have been described and on occasion imaged, this is traditionally not required for identification, and history including ipsilateral breast surgery with pain occurring in expected anatomic distributions will suffice. When the type of pain at play is still in doubt, questionnaires such as painDetect [5] may be useful in differentiating the presence of neuropathic pain. Lastly, it should be recognized that nociplastic pain (commonly known as centrally sensitized pain) has been increasingly recognized in breast cancer survivors [6, 7]. This type of pain may be the predominant type or occur concurrently with neuropathic PBSPS pain. Algorithms for recognizing nociplastic pain in breast cancer survivors have been proposed and may be useful as the approach to treatment may differ depending on the predominant pain type [6].

Evaluation

History

A comprehensive approach to pain characterization is critical in the recognition of PBSPS. When gathering information at the initial patient encounter, it is often beneficial to use a checklist to ensure all potentially relevant data points are captured. Such a checklist should include information on when the pain started, if there was a particular inciting event, provoking factors, quality of pain, location of pain, radiation of pain, severity (preferably captured as worst, best, and current in the past week), and different aspects of time including if the pain is overall getting better or worse, how frequent are episodes, how long are episodes, and if it is worse during any time of the day. Discussion of all forms of palliation attempted should also occur as this will inform the treatment plan. While many of these pain characteristics will vary from person to person, in general, the location of pain should always involve the ipsilateral chest wall and upper extremity following peripheral nerve distribution patterns. It is also non-negotiable that the onset of pain should be following breast surgery. It should be noted that pain from PBSPS is usually present as a pain that starts immediately after surgery and either never fully goes away or becomes worse in some way. If the patient notes that they had complete resolution of pain following surgery for a defined period and then the pain came back, different etiologies should be considered such as infection, seroma, or complications from radiation treatment.

Physical Exam

The physical exam should be equally comprehensive with a point made to rule out common confounders. At a minimum, strength, sensation, and deep tendon reflexes for myotomes and dermatomes covering nerve roots, C5-T1 should be performed. Particular attention should be paid to the ipsilateral thoracodorsal, long thoracic, pectoral, intercostobrachial, and intercostal nerves. These may help to tease out underlying radiculopathies, plexopathies, and/or mononeuropathies which may masquerade as PBSPS. Range of motion in all planes and special testing for shoulder impingement syndrome can assess for adhesive capsulitis which may be more common in the breast cancer population as well as subacromial impingement. Special attention should be paid to the presence of shoulder asymmetries, upper crossed posture, kyphosis, and scapular dyskinesia which may hint at neuropathies of motor nerves and myofascial pain. Finally, an examination of the involved breast and chest wall should occur. A meticulous examination of the skin should be conducted to identify potential issues such as scar adherence, fibrosis, scar tenderness, seromas, signs of infection, and the possibility of malignant disease recurrence. Palpation and light stroking may illicit allodynia or hyperalgesia and the presence of a more centralized process. Finally, pain from true PBSPS will often be reproduced with direct palpation, typically along scar lines. At times, a Tinel's sign may be elicited from these tender areas traveling in the distribution of the involved intercostal nerves and/or the intercostobrachial nerve. Schepelmann's sign [8] may also be performed and indicate an intercostal neuropathy.

Differential Diagnosis

There are several etiologies of chronic pain following treatment for breast cancer. While it is beyond the scope of this review to discuss the identification and treatment of these in detail, we have written about them previously and common etiologies of pain can be found in Table 1.

Table 1 Etiologies of chronic pain following treatment for breast cancer

Neuropathic sources of pain
-Phantom breast pain
-Pectoralis minor syndrome/neurogenic thoracic outlet syndrome
-Cervical radiculopathy
Musculoskeletal sources of pain
-Scapulothoracic bursitis
-Shoulder impingement syndrome
-Glenohumeral joint adhesive capsulitis
-Myofascial pain
-Lymphedema

EMG/NCS

Although not routinely performed, nerve conduction studies can have a role in the evaluation of PBSPS and should be considered on a case-by-case basis. Hojan and colleagues found a significant decrease in amplitudes in sensory nerve conduction studies following stimulation of ulnar and lateral antebrachial cutaneous nerves in women after mastectomy with postoperative radiation therapy in comparison to a control group of healthy women, significant decreases in the amplitude and conduction velocity in sensory fibers of the median and medial antebrachial cutaneous nerves in women after mastectomy without radiation therapy in comparison to the control group [9]. In addition, a significant increase was also found in the distal latency parameter in motor fibers of the median nerve on the surgically treated side in women after mastectomy without radiation therapy in comparison to the control group. Perhaps more importantly, electrodiagnostic studies may have more value in ruling out other causes of nerve-mediated pain including radiculopathy, brachial plexopathy, and polyneuropathy when suspected.

Imaging

MR Neurograms

Magnetic resonance neurography (MRN) augments selective multiplanar visualization of peripheral nerves and pathology by incorporating a combination of two-dimensional, three-dimensional, and diffusion imaging pulse sequences [10]. On MRN, pathological nerves may exhibit nerve and/or fascicular caliber changes, irregular contour, intra- or perineural tumor or scarring, abnormal enhancement, and signal discontinuity or alterations. Chalian et al. demonstrated that MRN can provide an accurate diagnosis of intercostal neuralgia and identify candidates who will most likely benefit from perineural injections and/or neurectomy [11]. PBSPS remains a clinical diagnosis; however, MRN may prove useful when considering neurectomy or when initial treatments have failed.

Ultrasound

Ultrasound is helpful in visualizing nerves commonly injured from mastectomy, including the intercostobrachial nerve [12]. Traumatic neuromas are hyperplastic proliferations of neuronal and connective tissue that may be visualized under ultrasound [13]. Ultrasound may be used for the assessment of traumatic neuromas in breast cancer patients after mastectomy, as they are often located near the surgical scar and characterized by an oval shape, circumscribed margin, parallel orientation, and hypoechogenicity [14]. Ultrasound-guided core needle biopsy is the standard of care to distinguish neuromas from breast cancer recurrence, in patients with a history of breast cancer [13, 15]. Light tapping (Tinel sign) or palpation with the ultrasound transducer over the neuroma may reproduce neuropathic pain along the affected nerve and has been referred to as the "ultrasound trigger sign" [16, 17].

Prevention and Natural Course

Preoperative pain is a significant predictive risk factor for PBSPS. Approaches to prevent PBSPS have included perioperative systemic analgesics and intraoperative/perioperative nerve blocks. A recent systemic review analyzing pain management in oncological surgery recommended a combination of paracetamol and conventional NSAIDs or COX-2-selective inhibitors (if no contraindications) administered preoperatively or intra-operatively and continued into the postoperative period for pain control [18]. Preoperative gabapentin is recommended and has been shown to reduce postoperative pain and opioid consumption; however, caution must be exercised as high doses may induce side effects such as dizziness, blurred vision, or sedation [18, 19]. Pregabalin has also been shown to decrease pain scores and morphine consumption in the PACU setting and appears to have similar efficacy to gabapentin [19]. In a study comparing venlafaxine and gabapentin, venlafaxine showed equipotent effects in reducing analgesic requirements and reduced the incidence of developing PBSPS after 6 months [20]. In the intraoperative setting, thoracic paravertebral blocks (TVPB) can be effective in decreasing the incidence and intensity of chronic pain following breast surgery [21]. Alternatively, PECS block, PECS II block, and serratus plane blocks may be considered and have been shown to have similar efficacy compared to TVPB [22]. Other regional plane blocks with promising results in the prevention of postoperative pain include erector spinae plane blocks, thoracic nerve blocks,

paravertebral blocks, pectoserratus plane blocks, and stellate ganglion blocks [23–27].

Longitudinal studies following the natural course of post-breast surgery pain are limited and difficult to interpret given the lack of a consensus definition. However, one retrospective analysis of 511 breast cancer survivors followed patients for 6 years and found that both pain presence and intensity decreased over time which can be of some solace to patients when providing education [28].

Treatment

Topicals

Lidocaine For patients with PBSPS, Aboelnour and Abouelnaga found a significant reduction in visual analog scale and pain DETECT questionnaire results for lidocaine iontophoresis compared to lidocaine 5% patch treatment [29]. Paladini and colleagues found that treatment with lidocaine plaster, a topically acting hydrogel plaster containing 5% lidocaine, in patients with chronic post-surgical neuropathic pain led to a clinically relevant pain reduction when compared to placebo [30].

Arnica In patients who underwent mastectomy and immediate breast reconstruction, one study showed that the use of combined homeopathic treatments of *Arnica montana* and *Bellis perennis* significantly reduced the time to drain removal when compared to placebo [31].

Menthol Fallon and colleagues found that topical 1% menthol cream applied twice daily for 4–6 weeks provided effective analgesia for chronic neuropathic pain in post-mastectomy patients [32].

CBD/THC Weiss et al. surveyed 257 breast cancer patients, of which 46% reported using topical formulations of cannabis, 54% using cannabis after completion of treatment, and 78% using it for joint and muscle aches, discomfort, stiffness, or nerve pain [33].

Ketamine Topical ketamine may be effective in patients with chronic regional pain syndrome by reducing pain measures, tactile allodynia, and visual analog scale (VAS) pain score [34]. It has also been effective in postherpetic neuralgia, but evidence for topical ketamine in the treatment of neuropathic cancer pain is not as strong as the other routes of administration (oral/intravenous).

Capsaicin Watson et al. showed that treatment with topical 0.025% capsaicin over 4 weeks in 14 patients with PBSPS led to improvement in 12 (86%), with 8 (57%) deemed to have good or excellent responses [35]. In a randomized parallel trial, topical 0.075% capsaicin cream treatment over 6 weeks in 13 patients was found to be more effective than placebo, with statistically significant differences found in the VAS for jabbing pain, category pain severity scales, and overall pain relief scales [36]. Dini et al. studied topical 0.025% capsaicin over 2 months in 19 patients, with 11 (57.9%) having a reduction of pain which was never worse than mild at the end of treatment [37].

Pharmacologic

Many patients may benefit from analgesics such as acetaminophen and NSAIDs for first-line therapy; however, here, we will discuss typical medications for the treatment of neuropathic pain.

Gabapentinoids/Antiepiletepics The anticonvulsants gabapentin and pregabalin exert their effects on the voltage-gated calcium channels reducing the excitability of neurons. A meta-analysis of the use of gabapentin after breast cancer surgery showed it was able to reduce acute and chronic postoperative pain, total morphine consumption, and the occurrence of nausea [38]. Levetiracetam is not seen to have any benefit in reducing pain in PBSPS [39].

Tricyclic Antidepressants (TCA's) TCAs exert their effects through the inhibition of serotonin and norepinephrine reuptake. They also block histamine, adrenaline, acetylcholine, and sodium channels contributing to its broad side effect profile. TCAs are able to exert pain relief independent of their anti-depressant effects at lower doses [40]. In a randomized control trial of 15 patients, amitriptyline in doses ranging from 25 to 150 mg daily or in two divided doses was effective in managing the neuropathic pain in PBSPS [41].

Serotonin Norepinephrine Reuptake Inhibitors (SNRI's) SNRIs exert their effects by blocking the reuptake of serotonin and norepinephrine thus facilitating descending inhibition. One study showed perioperative duloxetine may reduce postoperative analgesic requirements and incidence of chronic pain at 3- and 6-month follow-up after radical mastectomy [42]. Venlafaxine in doses ranging from 150 to 225 mg daily has been seen to decrease average pain intensity [43].

Opioids Opioids are often utilized perioperatively to manage post-surgical pain, but there is limited data to support long-term use especially for neuropathic pain. A systemic review of opioid prescribing after breast cancer surgery revealed conflicting recommendations on opioid prescriptions and variability in adjunctive treatment recommendations [44]. However, there is a unanimous agreement on the

importance of an opioid-sparing approach in the treatment of chronic pain after breast surgery [44]. If long-term opioids are to be used, clinicians should comply with Centers for Disease Control guidelines on opioid use and may consider the World Health Organization pharmacologic guidelines for the treatment of chronic pain in cancer [45, 46•].

Interventions

Trigger Point Injections Khoury et al. demonstrated a 91.2% success rate in significant or complete relief of PBSPS with 91 trigger point injections (2 mL of 1:1 mixture of 0.5% bupivacaine and 4 mg/mL dexamethasone) in 52 patients [47••]. Trigger point tenderness was along the inframammary fold, and the injections were intended for the perineural space where T4 or T5 cutaneous nerve branches exit the chest wall and enter the breast and subcutaneous tissue. It should be noted that while termed "trigger point injections," these were not typical trigger point injections given for myofascial pain syndrome. Regarding myofascial pain syndrome, Vas and Pai showed ultrasound-guided dry needling in 20 patients with PBSPS-deactivated trigger points and led to reduced pain, disability, and opioid use [48].

Nerve Blocks The intercostobrachial nerve (ICBN) branches off from the lateral cutaneous branch of the second intercostal nerve and supplies sensation to the medial upper arm, axilla, and lateral chest wall. ICBN blockade can provide pain relief to the medial upper arm, axilla, and lateral chest wall for weeks to months [49].

The serratus anterior plane block targets the long thoracic nerve, thoracodorsal nerve, and the lateral cutaneous branches of the intercostal nerves of T2-T9 and provides analgesia to the anterolateral chest wall for up to several months [49]. The superficial serratus plane block target is the fascial space between the most anterior surface of the serratus anterior muscle and the posterior aspect of the latissimus dorsi at the level of the fifth rib on the mid-axillary line [50]. The deep serratus plane block is between the serratus anterior muscle and external intercostal muscle at the level of the fifth rib at the mid-axillary line, separating the serratus anterior muscle off the rib [50, 51]. Prior radiation/axillary lymph node dissections may cause scarring of the plane between the latissimus dorsi and serratus anterior muscles, making adequate separation of the superior serratus plane difficult, in which case, a deep serratus plane block may be more efficacious [50, 52].

The thoracic paravertebral spinal nerve block delivers anesthetic adjacent to the intervertebral foramina into the thoracic paravertebral space, where the spinal nerves exit, targeting the dorsal rami, ventral rami, and sympathetic chain. As the paravertebral space is continuous with the intercostal space, the anesthetic can spread to the intercostal nerves, resulting in somatic and sympathetic nerve blockage that extends laterally and medially to the intercostal space [49].

The PECS I and II nerve blocks can provide pain relief to the anterior upper chest wall. The PECS I block is an interfascial plane block technique, where the anesthetic mixture is deposited between the pectoralis major and minor muscles, targeting the medial and lateral pectoral nerves [53]. The PECS II block is an interfascial plane block technique, where the anesthetic mixture is given between the pectoralis minor and the serratus anterior at the third and fourth ribs, targeting the lateral branch of the intercostal nerve [53].

The erector spinae plane block relieves pain at the anterior, posterior, and lateral thoracic and abdominal walls, through a paraspinal fascial plane nerve block of the dorsal and ventral rami of the thoracic spinal nerves and sympathetic nerve fibers [49, 54].

Yang et al. retrospectively reviewed 350 ultrasound-guided peripheral nerve blocks (chosen based on the anatomic location of the painful area with the corresponding peripheral sensory innervation) performed on 169 patients with PBSPS, and found a significant reduction of pain intensity (56%), with a mean pain relief duration of 45 days, with a median of 84 days [53]. Fujii and colleagues found that the PECS 2 block decreased the rate of moderate or severe chronic pain 6 months after mastectomy, compared to the superficial serratus plane block in 80 patients [55].

Ablation Cryoneurolysis refers to the application of exceptionally low temperatures (approximately − 70 °C using nitrous oxide) to reversibly ablate peripheral nerves, resulting in prolonged pain relief [56]. Ilfeld et al. studied preoperative ultrasound-guided percutaneous cryoneurolysis of the ipsilateral T2 to T5 intercostal nerves, compared to sham, in 60 patients undergoing mastectomy, and found markedly improved analgesia at the 3-, 6-, and 12-month follow-up without complications [57]. Nezami et al. found that percutaneous CT-guided cryoneurolysis of the ICBN in 14 patients with PBSPS was technically safe and feasible and led to a significant decrease in postmastectomy pain for up to 6 months [58]. Fam et al. evaluated pulsed radiofrequency and transforaminal epidural steroid injection on the T2 and T3 dorsal root ganglions for intercostobrachial neuralgia post-mastectomy and found significant pain reductions in the visual analog scale for up to 6 months [59]. Abbas and Revad compared thermal radiofrequency (RF) versus super voltage pulsed RF applied to the stellate ganglion for PBSPS in 80 patients and found significant differences in post-mastectomy pain intensity, functional improvement, and less rescue analgesia, in favor of the thermal RF group [60].

Surgery

Neuromas are a potential source of neuropathic pain after breast cancer surgery. The nerves contained within neuromas have lower excitatory potential and may lead to allodynia and hyperalgesia. In cases of intractable pain not responsive to pharmacologic management, surgical exploration for neuroma identification and excision may be considered [61]. Additionally, a number of other surgical interventions may be considered to manage pain including autologous fat grafting, targeted muscle reinnervation, regenerative peripheral nerve interface, and dermatosensory peripheral nerve interfaces [62]. In autologous fat grafting, adipose tissue is harvested from the abdominal region and then injected into painful areas of scar tissue [22]. Fat grafting has historically been used to treat chronic neuropathic pain of varying etiologies [63], and several studies have shown improved pain in PBSPS after fat grafting [64–66]. However, a more recent study with 35 participants evaluating autologous fat grafting in PBSPS showed no statistically significant change in average or maximum pain when compared to sham surgery [67]. Targeted muscle reinnervation and regenerative peripheral nerve interfaces have been used for the treatment of neurogenic pain after amputation [68]. A recent case–control study showed that patients who underwent targeted muscle reinnervation after breast surgery were found to have a reduction in pain severity, pain behaviors, and less interference of pain in daily living [69]. Regenerative peripheral nerve interfaces involve the implantation of residual peripheral nerve or an individual nerve fascicle into an autologous free skeletal muscle graft [70]. They may be beneficial in preventing the formation of neuromas and alleviating neuropathic pain [71], but further studies are required in their application for PBSPS.

Other

Integrative There have been increasing studies showing the value of integrative therapies for chronic pain following treatment for breast cancer. These encompass various interventions including mindfulness-based stress reduction, hypnosis, acupuncture, music therapy, and several others. Many of these interventions may work by mitigating psychosocial factors such as catastrophizing, insomnia, and anxiety which are known to increase the risk of PBSPS [72]. Furthermore, integrative therapies are recognized by the American Society of Clinical Oncology and have Grade C–level evidence for the management of pain.

Physical Therapy Many institutions frequently incorporate physical therapy following breast cancer surgery, and a recent review has found it to be beneficial in improving the quality of life and pain severity for PBSPS [73]. Physical therapists utilize a number of techniques including therapeutic exercise, manual therapies like myofascial release, compression therapy, decongestive therapy, and neuromuscular taping. In their review which included 18 trials, Kannan and colleagues demonstrated that physical therapy interventions including six exercise trials and two myofascial trials significantly improved pain severity compared to control groups.

Conclusion

PBSPS is a common neuropathic pain syndrome which can occur following breast surgery. While there is no strict consensus definition, the pain should have onset after surgery involving the ipsilateral chest wall and upper extremity from damage to the involved sensory nerves. PBSPS is primarily identified clinically based on a comprehensive history and physical exam although additional testing including electrodiagnostics and imaging may be useful in ruling out other conditions. Myriad treatments are available and should be pursued based on collaborative decision-making from the patient and provider.

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Declarations

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- • Of importance
- •• Of major importance

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