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RECENT ADVANCES IN THE MANAGEMENT FOR CANCER RELATED PAIN

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ABSTRACT

The incidence of breast cancer has stabilized over the past 10 years, while death rates have declined. Thus, many women are living with long-term effects of breast cancer, including pain syndromes relating to breast cancer. As our understanding of these types of pain syndromes improves, delivery of care to this population becomes paramount. In this review, we discuss advances in rehabilitation and interventional pain management to improve pain and symptom management. Appropriate use of physical therapy may significantly improve a patient's functional status, while fascial plane blocks can lead to pain relief which may last for months. Targeted therapies for pain relief may result in better quality of life for individuals suffering from breast cancer related pain.

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INTRODUCTION

Chronic pain following breast cancer treatment is commonly observed and often undertreated. There were an estimated 246,660 new cases of breast cancer in 2016, comprising 14.6% of all new cancer cases (Bethesda). The incidence of breast cancer has remained stable over the past 10 years, while rates of death have decreased roughly 1.9% per year between 2004 and 2013. Therefore, quality of life of breast cancer survivors is an important consideration, as there are many women living with the long-term effects of this disease (https://seer.cancer.gov/statfacts/html/breast.html). Breast cancer-related pain can be divided into three distinct categories: tumor-related pain, treatment-related pain and debility or pain unrelated to cancer, and can occur as acute, subacute or chronic pain. Tumor-related pain usually occurs during active treatment and in advanced disease stages. Treatment-related pain can present acutely and become chronic during treatments consisting of chemotherapy, radiation or hormonal therapy (Glare, 2016). Subacute breast cancer-related pain is most often associated with arm and shoulder pain following breast cancer surgery (Medline, 2012). However, surgical pain syndromes can vary in temporal presentations and may overlap with other treatment-related pain. Therefore, it may also be helpful to consider pain syndromes with an organ systems approach. The systems primarily affected in breast cancer-related pain include the musculoskeletal, neurologic, lymphatic and integumentary systems. Therapeutic options for breast cancer-related pain are predominantly in response to development of pain, although strategies attempting to prevent development of chronic pain are under active investigation. Physical therapy is underutilized, with one study suggesting up to 90% of patients would benefit from some form of physical therapy, while only 30% received it (Ewertz, 2011). Pharmacologic management of pain includes use of opioids, anti-epileptics, sodium channel blockers and antidepressants. Interventional therapies are widely varied and many are currently under investigation. However, it is often necessary to utilize multiple modalities of treatment to achieve adequate pain control of women with breast cancer-related pain.

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Advances in rehabilitation for breast cancer related pain

Exercise has been shown to reduce chronic cancer pain related to treatment (Cheville, 2008). Physical therapy is the use of physical methods such as exercise, stretching, massage and modalities to maximize function, improve quality of life and treat pathology. Physical therapy typically involves a stepwise progression of gentle range of motion and stretching exercises, followed by strengthening and conditioning exercise when acute symptoms subside. Therapy should also include postural/ergonomic training as well as a home exercise program for maintenance (Robb, 2006). As a treatment modality, physical therapy is grossly underutilized in the breast cancer population (Iyer, 2016). In the acute phase, mastectomy and axillary dissection results in local inflammation, tissue damage, nerve dysfunction and focal edema, all of which may lead to pain. Post-surgical pain can lead to learned disuse of the arm on the affected breast and protective posturing, which results in shortening of the muscles of the anterior chest wall, straining/stretching of the upper neck and back muscles and weakness of the rotator cuff muscles, potentiating poor biomechanics and painful pathology of the shoulder (Iyer, 2016 and Stubblefield, 2014 and Crosbie, 2010). Physical therapy has been shown to significantly decrease pain in breast cancer patients with common painful shoulder disorders (Torres Lacomba, 2010; McNeely, 2010; Cheville, 2007). Treatment is typically focused on the upper extremity; specifically maintaining shoulder range of motion (forward flexion, abduction, internal rotation and external rotation), rotator cuff and upper back strengthening, pectoral stretching, scapular stabilization, myofascial release/soft tissue mobilization, neuromuscular re-education and home exercise program (Itoi, 2013). Therapy with skin desensitization may also help to reduce post-operative hyperalgesia and neuromas (De Groef, 2015; Halbert, 2002; Lotze, 1999; Chan, 2007 and Oerlemans, 1999). Breast reconstruction with surgical implants following mastectomy may lead to pain and dysfunction due to surgical trauma, stretching secondary to tissue expander use, muscle spasms and fibrosis (Pachman, 2011). In breast cancer patients with painful post-mastectomy adhesions, radiation-induced fibrosis and axillary web syndrome, physical therapy with an emphasis on scar tissue mobilization may be beneficial (Vadivelu, 2008). Physical therapy addressing core strength is especially important in those who have undergone breast reconstruction with an autologous transverse rectus abdominis myocutaneous flap. Harvesting from the transverse rectus abdominis may result in a core weakness and a subsequent increase in the incidence of lower back pain, especially in those with pre-existing low back pain (Fourie, 2009; Petit, 1997). The use of aromatase inhibitors in post-menopausal women with hormone receptor positive breast cancer is now a routine because it significantly reduces the rate of cancer recurrence and decreases mortality. Unfortunately, myalgias and arthralgias are a common side effect of this medication class, leading to medication noncompliance (Dell, 2008 and Seber, 2016). This patient population seems to respond well to conservative treatment. Aerobic exercise, yoga and physical therapy have all been shown to significantly decrease pain in patients with aromatase-inhibitor induced arthralgias and myalgias (Seber, 2016; Coleman, 2008; Peppone, 2015 and Irwin, 2015). Lymphedema is commonly seen in breast cancer patients and over time it may contribute to both primary and secondary pain syndromes. Increased limb weight from lymphedema may result in subsequent abnormal biomechanics, leading to pathology, such as rotator cuff tendinopathy, shoulder impingement and adhesive capsulitis (Knols, 2005; Herrera, 2004). Conservative treatment of lymphedema in breast cancer patients involves complete decongestive lymphatic therapy with an 'intense phase' manual lymphatic drainage, compression dressings/gloves, physical therapy to maximize functional ability and restore lymphatic circulation and a 'self-management phase' (Ebaugh, 2011). A specialized physical therapist trained in the lymphedema management is critical to the 'intense phase' of treatment, which involves manual lymphatic drainage, compression dressings/gloves as well as active physical therapy to maximize functional ability and restore lymphatic circulation (Ebaugh, 2011). There are not universally accepted guidelines on when to initiate physical therapy; it is typically started shortly after the completion of breast cancer treatment. Of note, studies show that initiation of physical therapy early in the first week postoperatively (status post mastectomy or lymphadenectomy) is associated with an increased risk of wound drainage and seroma formation. Therefore, it is recommended to introduce physical therapy in a graded fashion; waiting until a few days to a week postoperatively to start low intensity exercises (i.e., PROM, AROM and light stretching exercises such as pendulums, wall climbs and pulley exercises), before advancing to more high-intensity resisted exercises (Korpan, 2011). The literature is not consistent with regard to the frequency and duration of physical therapy. Most treatment ranges from one- to three-times per week for a total of 1–3 months and will vary based on the individual needs of the patient (De Groef, 2015). Compliance with physical therapy is often the mainstay of treatment for a long-term return to painless range of motion and strength in patients who are affected by chronic pain relating to breast cancer. Physical therapy should be considered as first line or adjuvant treatment for many painful pathologies in breast cancer. Most importantly, specialized therapies for specific sequelae (rotator cuff tendinopathy, shoulder impingement syndrome, adhesive capsulitis, myofascial pain syndrome, scapular dyskinesias, lymphedema) of post mastectomy pain syndrome are available and need to be considered for our breast cancer survivors. More high-quality studies are needed to further elucidate the timing, duration, frequency and exercises for physical therapy in breast cancer.

Advances in interventional procedures for breast cancer related pain

Interventional options for management of pain are often a key component of a multimodal treatment plan, allowing the patients to fully participate in rehabilitation activities that are integral to a return to normal function. Unfortunately, there are limited high-quality studies assessing interventions for chronic pain after treatment for breast cancer. In fact, a recent systematic review found only seven high-quality studies assessing three targets: paravertebral blockade, stellate ganglion blockade and intercostal neural blockade (Beurskens, 2007). However, there are exciting new interventional options being currently investigated on a preliminary basis. Initially described by Blanco, the Pecs block and modified Pecs block, also known as the Pecs block type II, are two novel approaches to pain management for breast cancer. The anatomic target of these ultrasound-guided blocks is the interfacial plane between the pectoralis major muscle and the pectoralis minor muscle (Wijayasinghe, 2014). The modified Pecs block has an additional step of anesthetizing the space between the

pectoralis minor muscle and the serratus anterior muscle (Blanco, 2011). Blanco's initial report of 50 patients undergoing surgery for breast cancer who received the Pecs block found that these women had minimal analgesic requirements in the post-surgical period (Wijayasinghe, 2014). A subsequent randomized controlled trial by Bashandy and Abbas found that pain scores were significantly lower in the post-operative period in women who underwent Pecs block type II prior to modified radical mastectomy for breast cancer. Additionally, analgesic usage was lower, and patients had shorter post-anesthesia care unit stays and overall hospitalization time (Blanco, 2012). A pilot study by Wijayasinghe *et al*. investigating the use of the Pecs block in eight patients with chronic pain after surgery for breast cancer demonstrated pain relief and reduced sleep interference for 7 days after the procedure, far beyond the expected duration of relief from local anesthetic alone (Wijayasinghe, 2014). These two approaches would be appropriate for women experiencing acute pain relating to breast cancer surgery, and chronic pain in the breast region post-surgery and possibly post-radiation therapy. Potential complications of these methods, and the methods discussed below, include bleeding, infection and damage to surrounding structures by the needle.

The serratus plane is another potential target for interventional management of pain related to breast cancer. There are two potential fascial planes surrounding the serratus anterior muscle on the chest wall, one superficial and one deep to the muscle. Injecting a local anesthetic into either plane under ultrasound guidance results in anesthesia of the hemithorax, likely secondary to targeting the intercostal nerves, although it is possible that the intercostobrachial nerve branches lie within this plane (Bashandy, 2015). A recent case series found that utilization of the serratus plane block in conjunction with a Pecs block was effective in providing intra-operative and post-operative analgesia during surgery for breast reconstruction (Wijayasinghe, 2017). A recent retrospective study examined eight women who underwent this block with a local anesthetic and steroid, as treatment for chronic anterior chest wall pain relating to treatment for breast cancer. All women experienced initial pain relief after the block, and the duration of pain relief was variable, ranging from 2 to 3 days to 12 weeks, although some women still had pain relief at the time of the study's publication (Blanco, 2013). Further support for the use of the serratus anterior block as a treatment for chronic pain relating to treatment for breast cancer can be seen in a case report by Takimoto *et al*. utilizing a series of serratus plane blocks for a woman with chronic pain after surgery for breast cancer. Repeating these blocks allowed the woman to participate more readily in other modalities such as physical therapy and over time she improved to the point of no longer requiring interventional treatment (Khemka, 2016). The intercostobrachial nerve is an additional anatomic target for interventional treatments for pain related to breast cancer. The intercostobrachial nerve, which arises from the lateral cutaneous branch of the second intercostal nerve, is very vulnerable to damage during surgery for breast cancer, which can result in neuropathic pain. A pilot study conducted by Wijayasinghe *et al*. demonstrated that the second intercostal space was able to be consistently identified under ultrasound (Zocca, 2016). Since the intercostobrachial nerve reliably passes through this space, this allowed a target for an ultrasound-guided block of the intercostobrachial nerve. All of the six patients with chronic pain relating to treatment for breast cancer who underwent intercostobrachial nerve block had significantly reduced pain scores post-procedure, with one patient reporting pain relief at 3 months post-injection, despite only being treated with a local anesthetic (Wijayasinghe, 2016). Further investigation into this technique would be beneficial, including consideration of whether the addition of steroid might prolong the analgesic effects of this procedure. Exploring all surgical options for the management of chronic pain relating to breast cancer is outside the scope of this review article; however, it is worth noting that Caviggioli *et al*. have had success with autologous fat grafting in painful mastectomy scars (Takimoto, 2016). A more recent study by Maione *et al*. found similar improvement in pain scores with autologous fat grafting for women suffering from chronic pain after breast conservative surgery and radiotherapy, an increasingly popular method of surgical treatment for breast cancer (Caviggioli, 2011). Interventional management options for chronic pain relating to breast cancer are important because they often facilitate participation in rehabilitation treatments that are instrumental in allowing a return to function. They also often allow for a decrease in medication usage, which is often associated with undesirable side effects. These novel techniques may soon become common place in the treatment of the post mastectomy pain syndrome continuum.

Conclusion

Pain relating to breast cancer is a constellation of pain symptoms with numerous potential targets for treatment. Understanding the pathophysiology of the various etiologies may allow the pain practitioner to better direct a pain treatment plan for each individual patient. It is clear from our review that pain treatment begins at the start of the treatment for breast cancer, whether surgical or medical. Each breast cancer treatment chosen for a patient may lead to specific pain symptoms that should be diagnosed and treated. We advise that physical therapy and rehabilitation are the mainstay of treatment of these pain symptoms, while interventions may be used to alleviate pain symptoms during therapy. Perhaps, further investigation is needed for pain symptoms that are chronic and not improving with conventional treatments mentioned above. Consideration for neuromodulation of neuropathic pain symptoms and regenerative medicine for musculoskeletal pain will be the next frontier for our patients. Regardless of the advances, it is clear that because of the complexity of breast cancer related pain, unique paradigms should be developed for each patient.

Future perspective

Clearly much work is still to be done to improve the treatment of pain relating to breast cancer. We feel that in the future treatments will be tailored to anatomic targets that are unique to a specific patient, taking into account the type of tumor and therapies the patient was subjected to. We also feel that there are exciting options in the areas of neuromodulation, both spinal cord stimulation and peripheral field stimulation. Other future considerations will include prolonging duration of pain relief from the blocks discussed above, including options such as radiofrequency ablation or chemoablation of certain targets.

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