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An Overview on Post-Mastectomy Pain and its prevention

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Abstract

An unpleasant sensory and emotional experience associated with possible or actual tissue damage, or defined in terms of such damage, is called pain. Postoperative pain falls into two categories: acute pain and persistent pain. Persistent pain lasting more than three months is a characteristic of post-mastectomy pain syndrome, or PMPS. Either a primary lesion or a neural system malfunction causes it. It is thought to be a neuropathic illness that arises after breast cancer surgery. It could be caused by an intercostobrachial nerve (ICBN) lesion, phantom breast discomfort, neuromas, or lesions of other nerves. Unlike other painful syndromes, PMPS typically causes shooting, scorching, numbing, or pressure-sensitive pain in the axillary, medial upper arm, and/or front or lateral region of the thorax. Patients undergoing breast cancer surgery need to be closely watched by a multidisciplinary team both before and after the procedure. This approach can diagnose post-mastectomy pain syndrome early, identify patients who have risk factors, reduce or eliminate risk factors as much as possible, and provide the right treatment to improve the quality of life for this specific patient population.

Keywords: Post Mastectomy, Pain, Opioid, Nerve block

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1. Introduction

The most frequent invasive malignancy in women worldwide is breast cancer. 16% of all female cancers and 22.9% of invasive cancers in women are breast cancers. Globally, breast cancer claimed 458,503 lives in 2008, accounting for 13.7% of all cancer-related deaths in women and 6.0% of all cancer-related fatalities in men and women combined [1]. Treatment for this cancer is contingent upon the stage at which it manifests. Surgical resection, comprising various mastectomy variants with or without reconstruction such as modified radical mastectomy, skin-sparing mastectomy, simple mastectomy, etc., is principal treatment for approximately 37–40% of women with breast cancer. Numerous issues can occur following surgical treatments [2]. Acute discomfort following surgery is a common side effect of breast cancer surgery. Twenty percent of postoperative patients in a population-based research conducted in Norway had moderate-to-severe pain in the surgical site [3]. According to Katz et al.'s research, 54% of patients who underwent breast cancer surgery reported having clinically relevant pain, which characterized as having a worst pain intensity of five or more on a 0–10 numerical rating scale [4].

Twenty to sixty-eight percent of women who have had mastectomy surgery experience post mastectomy pain syndrome (PMPS), a common postoperative complication [5-6]. Anterior thorax, axilla, and/or medial upper arm pain that persists longer than three months following a mastectomy is known as post-mastectomy pain syndrome. Typically, people describe it as pulling, burning, and stabbing around surgical side. This illness is categorized as a neuropathic disorder that develops after breast cancer surgery [7]. After breast cancer surgery, opioids, various oral analgesics, and regional analgesia frequently utilized to alleviate acute pain. Combining localized blocks with general anesthetic to limit postoperative nausea and vomiting and decrease incidence of pain following a mastectomy can be an effective way to manage pain associated with breast surgery [8]. It can also lessen need for opioids. Thoracic epidural and thoracic paravertebral block (TPVB) are two most often utilized regional block procedures; nonetheless, they have potential to cause consequences, including but not limited to inadvertent dural puncture, epidural abscess, hematoma, spinal cord injury, and pneumothorax [9]. Newer blocks and alternate methods with lower inherent risks have developed to address these problems. Thoracic paravertebral blocks replaced in clinical practice by "paravertebral by-proxy" [10].

2. Definition and clinical presentation of PMPS

The most often used definition of PMPS is chronic pain that persists after the usual healing period has passed and all other possible reasons, such as infection or recurrence, have been ruled out. According to Couceiro et al. [11], pain that lasts longer than three months is classified as PMPS, whereas Vilholm et al. [12] PMPS is characterized as neuropathic pain that lasts longer than six months following surgery and has an intensity greater than four on a 10-point numerical scale. Often, the axilla, shoulder, arm, chest wall, or breast area are where the pain is felt. A common description of PMPS is that it is a type of typical neuropathic pain that is characterized by sensations of burning, unpleasant cold, electrical shock, stinging, numbness, tingling, stabbing, pulling, or pins & needles [13]. Pressure can result in severe, painful discomfort that is brought on by pressure.

In a series by Kakati et al., pain was detected in the medial upper arm (25.6%), axilla (32.6%), and anterior chest wall (41.8%) in 120 patients [6]. Movement, straining, overhead activity, and cold exposure are some of the conditions that aggravate PMPS. Kakati et al. [6] used the European Organization for Research and Treatment of Cancer's QOL questionnaire (QLQ) and the Brief Pain Inventory (BPI) questionnaire (EORTC-QLQ 30) to prospectively monitor 120 women after mastectomy in order to ascertain the prevalence and intensity of PMPS and its impact on Indian patients' Quality of Life (QOL). After six months, they discovered that 35.8% of patients had PMPS, and roughly 49% of patients described their pain as dull aching. Of the patients, about 56% experienced mild-to-moderate discomfort, which they were trying to control and accept as an unavoidable part of their care [6].

2.1. Pathophysiology

The specific pathophysiology remains to be ascertained. PMPS is now thought to be most likely caused by intercostobrachial nerve neuralgia, while other theories have been proposed. The intercostobrachial nerve, the cutaneous lateral branch of the second intercostal nerve, leaves the body through the serratus anterior muscle and innervates the axilla and internal portion of upper arm. [14-15]. Intercostobrachial nerve may sustain varying degrees of damage during axillary dissection due to frank transection (neurotmesis) or stretching or compression during retraction (neuropraxia, axonotmesis). Intraoperative or postoperative indirect nerve damage is a potential. A hematoma, a seroma, or surgical scarring might result in stretch and compression injuries, as well as by improper arm posture during surgery that can stress and compress nerve [16]. Ectopic neural activity that originates at the dorsal root ganglion and the site of nerve lesion follows injury, boosting sense of pain's sensitivity to chemical or mechanical stimulation. Other nerves linked to PMPS include thoracodorsal, medial and lateral pectoral, long thoracic, and intercostal nerves [17].

2.2. Etiology

Development of PMPS, persistent post mastectomy syndrome, has linked to a number of risk factors [7].

2.2.1. Risk factors

- ***Age***

Younger age groups have been found to be riskier. Though a number of theories have been put forth, the cause of this association is unclear. These include variations in the status of estrogen receptors, a greater histological tumor grade in younger patients needing adjuvant chemotherapy, and older patients having less pain receptor sensitivity [18].

- ***Sociodemographic Factors, Race/Ethnicity***

Data indicate that sociodemographic traits and race/ethnicity have an impact on likelihood of acquiring PMPS. Eversley et al.[19] found PMPS was more common and intense in minority groups, including Latinas and African American women. Several reasons are offered, such as fact that patients belonging to ethnic minorities frequently are diagnosed at a later stage of illness, requiring more complex surgical operations as well as harsher adjuvant and neoadjuvant therapies (such radiation and chemotherapy).

- ***Psychosocial Factors***

Several important studies show that a number of psychological factors contribute significantly to increased PMPS sensitivity. In Miaskowski et al.'s study, there was a noteworthy correlation observed b/w preoperative anxiety and depression and the eventual development of moderate-to-severe PMPS [20] longitudinal research of 410 cancer survivors. In a three year cross-sectional cohort research, Belfer et al. [21] observed 611 patients and found that anxiety and sleep disturbance independently linked to PMPS. 970 participants included in a study by Meretoja et al. [22] \found correlations between anxiety and depression and later PPMP. After looking at potential connection between PMPS and clinical and psychological factors, Ghadimi et al. [23] came to conclusion that loneliness might be a major risk factor.

- ***BMI***

Numerous epidemiological research have indicated a possible correlation between PMPS and body mass index (BMI). They found that there may be a positive correlation between PMPS risk and BMI [24].

- ***Preoperative Pain***

Preoperative pain at the surgery location has found to raise the chance of post-prostatin muscle soreness. It has proposed that central sensitization and/or pain sensitivity may increase a patient's susceptibility to chronic pain following surgery, albeit precise mechanisms underlying this may not be known. More over half of participants in Roth et al.'s study [24] reported having some degree of preoperative pain. They concluded that pain after operation might not always be connected to chronic pain after breast reconstruction.

- ***Type of Surgery***

The type of surgery has related to the incidence of PMPS. It has found that more invasive breast operations such as radical mastectomy, modified radical mastectomy, skinsparing mastectomy, simple mastectomy, etc., and axillary lymph node dissection are more likely to cause damage to sensory nerves in advanced cancers than breast conservation procedures and sentinel lymph node biopsy [25]. Alves Nogueira Fabro et al. found that patients who underwent axillary lymph node dissection—removal of more than 15 lymph nodes—had a markedly higher chance of developing PMPS [26].

- ***Surgical Department Patient Turnover***

The prevalence of PMPS is considerably higher in patients receiving care at low-volume hospitals facilities that execute less than 100 different types of mastectomy procedures each year than in surgical units that perform more than 100 mastectomies annually. High turnover enhances experience and helps surgical teams hone their skills, according to Tasmuth et al. [27]. In order to ensure that the dissection is performed with greater care, lower the chance of nerve damage occurring during the process, and avoid problems like hematoma, seroma, and dense scarring that could potentially result in stretch or compression of the nerves, the more experienced teams often use safer patient positioning and more precise surgical techniques.

- ***Postoperative Factors***

The occurrence of intense postoperative pain has been repeatedly related to the development of PMPS as a key risk factor. Increased postoperative pain was linked to increased chances of PMPS at four and nine months, according to research by Bruce et al. [28] involving 362 postmastectomy patients. Higher levels of postoperative pain were found to increase the risk of moderate-to-severe PMPS after a year by Andersen et al. [29].

- ***Chemotherapy***

The use of systemic medications in the treatment of breast cancer has increased. Examples of these medications include taxanes, platinum agents, vinca alkaloids, and aromatase inhibitors (AIs) used as hormonal therapy. The terms "persistent pain in breast cancer treated with hormone therapy" (PPBCHT) and "persistent pain in breast cancer treated with chemotherapy" (PPBCC) have been linked to the potential onset of PMPS in a number of studies [30].

- ***Radiation Therapy***

When neoadjuvant or adjuvant radiation therapy is administered over the chest wall and/or axilla as part of multimodality breast cancer treatment, it has been reported that PMPS risk is significantly increased. This has to do with tissue fibrosis, which entraps nerves and limits shoulder joint mobility. Moreover, lymphedema and skin responses may increase degree of discomfort [31]. Adjuvant radiation was connected to a greater risk of PMPS, per Gartner et al. [32].

*2.3. **Current approaches to the prevention of post mastectomy pain***

Patients with strong risk factors for PMPS need to identified, and proper efforts need to made for its prevention through use of multimodal care involving psychotherapy, proper surgical technique, physiotherapy, and peripherally targeted or centrally acting pharmacotherapy. When undergoing breast surgery, care should be given to minimize damage to surrounding fascia, pectoralis major, and pectoralis minor. If axillary exploration is necessary, caution should take to prevent harm to intercostobrachial nerve [33].

2.3.1. Perioperative systemic analgesics

In order to lessen acute discomfort and may be prevent development of chronic pain, perioperative systemic analgesics are widely utilized in prevention of persistent postmastectomy pain. A summary of pharmacological compounds that are frequently used to treat postmastectomy pain may be seen in Table 1. NSAIDs and paracetamol are two of these medications that are commonly used for opioid sparing and proactive analgesia. They can have drawbacks, such as increased bleeding while using NSAIDs, and they might not be sufficient for treating extreme pain. Even though they linked to drowsiness, peripheral edema, and somnolence, gabapentin and pregabalin are thought to be beneficial for treating both acute and chronic pain. Preemptive analgesia involves use of intravenous dexamethasone, despite possibility that it could affect postoperative glucose management. Systemic opioids are beneficial when used in titrated doses, they should be closely monitored due to possibility of respiratory depression, drowsiness, and gastrointestinal adverse effects. Selective noradrenaline reuptake inhibitors and tricyclic antidepressants used for their analgesic benefits, albeit caution should be taken regarding their adverse effects, include tachycardia, hypertension, and anticholinergic effects [34]. Analgesic efficacy of gabapentin and venlafaxine for pain associated with cancerous mastectomy examined in a prospective research.

When compared to gabapentin and placebo group, venlafaxine was found to have a lower incidence, severity, and requirement for analgesics six months after surgery. However, control groups had a higher frequency of burning pain than gabapentin group did [35]. An antagonist of NMDA receptors is memantine. According to Morel et al., at three months, patients on memantine had significantly reduced levels of rescue analgesia, improved emotional states, and postmastectomy pain severity when compared to the placebo group [36]. Nefopam is a non-opioid, non-steroidal benzoxazocine analgesic that works by preventing serotonin, norepinephrine, and dopamine from being reabsorbed. It also affects glutamatergic pathway's calcium and sodium channels, which lessens activation of N-methyl-D-aspartate (NMDA) receptors. According to Na et al. [37], prophylactic nefopam decreased acute postoperative pain and need for rescue analgesic medications, which in turn led to a three-month decrease in incidence of PMPS. The International Association for Study of Pain (IASP), procedural-specific postoperative pain management (PROSPECT), preferred reporting items for systematic reviews, and meta-analysis guidance all emphasize how important it is to tailor pharmacotherapy to each patient's needs while accounting for potential drawbacks and restrictions of each medication [38].

- ***Breast innervation***

The anterior and lateral cutaneous branches of the second to sixth intercostal nerves supply sensory and sympathetic efferent fibers that innervate the breast. The innervation of the breast is equally contributed to by the anterior and lateral branches. Additional cutaneous branches from the 3rd to 5th nerves are supplied to the nipple and areola by the 4th intercostal nerve. During surgery, skin incisions or tension on these sensory nerves may cause temporary dysaesthesias or sensory loss [39]. The lateral pectoral nerve supplies the deep surface of the pectoralis major, which is located beneath the breast. The ventral rami of the fifth through seventh cervical nerves are the source of this nerve. Before puncturing the clavipectoral fascia to reach the pectoralis major, it sends a ramus to the medial pectoral nerve in front of the axillary artery to provide pectoralis minor fibers. The first thoracic and eighth cervical nerves give rise to the medial pectoral nerve. It transmits branches to the pectoralis minor and major and forms a loop with the lateral pectoral nerve [40].The thoracodorsal nerve innervates the latissimus dorsi muscle around the breast by passing inferomedially from the posterior cord of the brachial plexus on the ventral aspect of the subscapularis muscle. The serratus anterior muscle is innervated by long thoracic nerve, which originates from the fifth and seventh cervical nerves and descends down mid axillary line. The inner upper arm's skin supplied by intercostal-brachial nerve, which is a lateral cutaneous branch of second or third intercostal nerves [41].

2.3.2. Perioperative Regional analgesia

Prior research has demonstrated that the postsurgical comorbidity is influenced by the analgesic method selected. Regional analgesics are generally useful in reducing the incidence of chronic pain following mastectomy.

➢ ***Pectoral nerve (Pecs) block I and II***

A new method for blocking the pectoral nerves, intercostal nerves 3–6, intercostobrachial nerves, and the long thoracic nerve is the pectoral nerve (Pecs) block I and II. Analgesia for a range of anterior thoracic wall operations, most notably breast surgery, can be achieved using these blocks. Targeting the lateral pectoral nerves, the Pecs I block was initially defined by Blanco et al. (2011) as a high volume interfascial block between the pectoralis major and pectoralis minor muscles.[42] A second iteration of the Pecs block known as the modified Pecs block, or Pecs II block, was described by Blanco et al. in 2012. In order to block intercostal nerves 3 to 6, intercostobrachial, and the long thoracic nerves—all of which are essential for axillary node dissection—the Pecs II targets the same interfacial plane as the Pecs I. It also targets the interfacial plane between the pectoralis minor muscle and the serratus anterior muscle [43].
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➢ ***Erector spinae block (ESB)***

The erector spinae block (ESB) is another technique used in regional anesthetic for thoracic neuroblockade [44]. Fascial plane between the erector spinae muscle and spinal transverse process is identified by the ESB using ultrasound guidance. Next, medical professional injects a local anesthetic into fascial plane under ultrasound guidance [45].

➢ ***Serratus anterior plane block (SAPB)***

The lateral cutaneous branches of thoracic intercostal nerves, which originate from thoracic spinal nerves' anterior rami and run in a neurovascular bundle just below each rib, are focus of the SAPB. The lateral cutaneous branches of the thoracic intercostal nerve innervate the lateral thorax's musculature at the midaxillary line via passing through the serratus anterior, internal, and external intercostal muscles [46]. As a result, the two possible areas mentioned above are traversed by these intercostal nerve branches. Insertion of a local anesthetic into these planes will cause paresthesia in T2 through T9 dermatomes of anterolateral thorax, spreading along the lateral chest wall. [47].

➢ ***Pecto-intercostal fascia plane block (PIFP)***

PIFP block intended for analgesia of parasternal regions of chest wall and sternum. It targets anterior cutaneous branches of second through sixth intercostal nerves. Between pectoralis major and external intercostal muscle/membrane, at fascial layer, is where PIFP block applies local anesthetic. It is therefore not utilized alone as a regional approach in mastectomy procedures; rather, it used in conjunction with another technique such as Pecs I & II since it blocks anterior cutaneous branches prior to intercostal nerve piercing pectoralis major [48].

➢ ***Thoracic PVB***

The triangle-shaped region between the skull and rib cage is known as the paravertebral space. The paravertebral space is defined by the ribs inferiorly and superiorly, the vertebrae medially, the costotransverse ligament posteriorly, and the parietal pleura anterolaterally. The dorsal and ventral branches of the vertebral root split in this anatomical area subsequent to its emergence from the intervertebral foramen [49]. Adipose tissue, intercostal vessels, anterior and posterior ramus of the spinal (intercostal) nerves, sympathetic chain, and rami communicants are therefore the contents of this area. The rami communicants facilitate communication between the sympathetic chain and the intercostal nerves [50]. In the paravertebral region, local anesthetic (LA) extends medially into the epidural space and laterally into the intercostal space over a number of levels. Consequently, ipsilateral blockage of the somatic and sympathetic nerves in the thoracic area occurs [51]. In breast surgery, thoracic PVB (TPVB), which has strong evidence in the literature, is utilized to reduce postoperative discomfort and opiate use.

TPVB is a helpful perioperative analgesic that also has the ability to cause surgical anesthesia. [52]. Single-injection TPVB requires less work and less time to complete than multiple-injection TPVB or paravertebral catheters. It should be noted that more LA infiltration to the axilla (i.e., T1 nerve distribution) would be required because TPVB is unable to regularly provide analgesia to the area [53]. Acute pain was successfully reduced right after surgery, according to a prospective trial that examined the impact of a single shot PVB at the T3 level before surgery [54]. Further research revealed that PVB decreased postsurgical pain for a full year following surgery in both resting and movement settings as compared to saline-treated controls [55]. Two most common regional block procedures are thoracic epidural and thoracic paravertebral block (TPVB); they can result in complications such as pneumothorax, accidental dural puncture, hematoma, epidural abscess, and spinal cord injury [56].

➢ ***Paravertebral byproxy***

There have been reports of several methods involving injections outside thoracic paravertebral region. Without actually inserting block needle into paravertebral space, retrolaminar 1, intercostal/paraspinal 2, erector spinae plane 3, and midpoint transverse process to pleura (MTP 4) blocks can all accomplish blocking of thoracic nerve roots in this region (Fig. 1). Recently, these variations of the PVB have referred to as the "paraspinal blocks" collectively 5. From an anatomical perspective, these indirect methods of achieving a PVB can be understood as achieving a the paravertebral spread by the proxy, without actually inserting needle tip in the paravertebral space, but rather in close proximity to pleura, if definition of a PVB reflects blockade of nerve roots in paravertebral space. Thoracic paravertebral blocks (TPVBs) replaced in clinical practice a few years ago with inter-transverse paravertebral blocks (ITP). ITP blocks include multiple-injection the costotransverse block (MICB), the costotransverse foramen block (CTFB), mid-point transverse process to pleura (MTP) block, and sub transverse process inter-ligamentary (STIL) block [57]. A relatively recent endpoint for the thoracic paravertebral block is mid the transverse process to the pleura block. The pleura and transverse process separated by use of the local anesthetic [10].

Table (1): Pharmacotherapy agents used in management of PMPS.

Drugs	Dose	Disease consideratio ns	Limitations	PROSPECT recommendatio ns	IASP guidelin es
Paracetamol	1 g q.i.s./p.r.n.	Pre-emptive analgesia; opioid sparing	Inadequate for severe pain	B	NA
NSAIDs	Drug dependent	Pre-emptive analgesia; opioid sparing	Inadequate for severe pain; increases bleeding	A	NA
Gabapentin/pregab alin	900–3600 mg t.d.s.; 300–600 mg b.i.d.	Useful in both acute and chronic pain	Somnolence, sedation, peripheral oedema, dizziness	A	NA
Intravenous dexamethasone	8 mg one hour before surgery	Used in preemptive analgesia	Impairs postoperative sugar control	B	NA
Systemic opioids	Titrated to effect	Multiple administratio n, forms part of ERAS pathway	Respiratory depression, sedation, nausea, vomiting, constipation, tolerance	B	NA
Tricyclic antidepressants	Amitriptyli ne 25–150 mg b.i.d.	Poorly tolerated; useful in depression and anxiety	Anticholiner gic effects	NA	First line
Selective noradrenaline reuptake inhibitors	Venlafaxin e 150–225 mg q.d.	Fewer anticholinerg ic effects; useful in depression and anxiety	Tachycardia, hypertension, sexual dysfunction	NA	First line
Gabapentin/pregab alin	900–3600 mg t.i.d. 300–600 mg b.i.d.	Used in both acute and chronic pain	Somnolence, sedation, dizziness	NA	First line
Capsaicin	8% one to four patches 30– 60 minutes	Used for chronic neuropathic symptoms	Skin sensitivity	NA	Second line

PROSPECT: Procedural-specific postoperative pain management, PMPS: post-mastectomy pain syndrome; IASP: International Association for the Study of Pain; NSAIDs: non-steroidal anti-inflammatory drugs; ERAS: enhanced recovery after surgery, NA: no action, A: first line, B: second line.

3. Conclusions

Patients undergoing breast cancer surgery need to be closely watched by a multidisciplinary team both before and after the procedure. This approach can diagnose post mastectomy pain syndrome early, identify patients who have risk factors, reduce or eliminate risk factors as much as possible, and provide the right treatment to improve the quality of life for this specific patient population.

References

[1] M.E. Effiong, I.S. Afolabi, S.N. Chinedu. (2023). Influence of age and education on breast cancer awareness and knowledge among women in South Western Nigeria. African Journal of Reproductive Health/La Revue Africaine de la Santé Reproductive. 27(3): 87-107.

[2] A. Chatterjee, B. Pyfer, B. Czerniecki, K. Rosenkranz, J. Tchou, C. Fisher. (2015). Early postoperative outcomes in lumpectomy versus simple mastectomy. journal of Surgical Research. 198(1): 143-148.

[3] A. Johansen, L. Romundstad, C.S. Nielsen, H. Schirmer, A. Stubhaug. (2012). Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. PAIN®. 153(7): 1390-1396.

[4] A. Katz, E.A. Strom, T.A. Buchholz, H.D. Thames, C.D. Smith, A. Jhingran, G. Hortobagyi, A.U. Buzdar, R. Theriault, S.E. Singletary. (2000). Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. Journal of clinical oncology. 18(15): 2817-2827.

[5] L. Macdonald, J. Bruce, N.W. Scott, W.C.S. Smith, W. Chambers. (2005). Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. British journal of cancer. 92(2): 225-230.

[6] B. Kakati, N. Nair, A. Chatterjee. (2023). Post mastectomy pain syndrome at an Indian tertiary cancer centre and its impact on quality of life. Indian Journal of Cancer. 60(2): 275-281.

[7] I.M. Larsson, J. Ahm Sørensen, C. Bille. (2017). The Post-mastectomy Pain Syndrome—A Systematic Review of the Treatment Modalities. The Breast Journal. 23(3): 338-343.

[8] J. Ingrande, J.B. Brodsky, H.J. Lemmens. (2009). Regional anesthesia and obesity. Current Opinion in Anesthesiology. 22(5): 683-686.

[9] M. Eason, R. Wyatt. (1979). Paravertebral thoracic block-a reappraisal. Anaesthesia. 34(7): 638-642.

[10] I. Costache, L. De Neumann, C. Ramnanan, S. Goodwin, A. Pawa, F. Abdallah, C. McCartney. (2017). The mid-point transverse process to pleura (MTP) block: a new end-point for thoracic paravertebral block. Anaesthesia. 72(10): 1230-1236.

[11] T.C. de Menezes Couceiro, M.M. Valenca, M.C.F. Raposo, F.A. de Orange, M.M. Amorim. (2014). Prevalence of post-mastectomy pain syndrome and associated risk factors: a cross-sectional cohort study. Pain management nursing. 15(4): 731-737.

[12] O.J. Vilholm, S. Cold, L.a. Rasmussen, S.H. Sindrup. (2008). The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. British journal of cancer. 99(4): 604-610.

[13] G. Kokosis, K. Chopra, H. Darrach, A.L. Dellon, E.H. Williams. (2019). Re-visiting post-breast surgery pain syndrome: risk factors, peripheral nerve associations and clinical implications. Gland Surgery. 8(4): 407.

[14] D. Waltho, G. Rockwell. (2016). Post–breast surgery pain syndrome: establishing a consensus for the definition of post-mastectomy pain syndrome to provide a standardized clinical and research approach—a review of the literature and discussion. Canadian journal of surgery. 59(5): 342.

[15] A. Capuco, I. Urits, V. Orhurhu, R. Chun, B. Shukla, M. Burke, R.J. Kaye, A.J. Garcia, A.D. Kaye, O. Viswanath. (2020). A comprehensive review of the diagnosis, treatment, and management of postmastectomy pain syndrome. Current pain and headache reports. 24: 1-12.

[16] A.G. Chappell, J. Bai, S. Yuksel, M.F. Ellis. (2020). Post-mastectomy pain syndrome: defining perioperative etiologies to guide new methods of prevention for plastic surgeons. World Journal of Plastic Surgery. 9(3): 247.

[17] M. Beederman, J. Bank. (2021). Post-breast surgery pain syndrome: shifting a surgical paradigm. Plastic and Reconstructive Surgery–Global Open. 9(7): e3720.

[18] M. Calapai, E. Esposito, L. Puzzo, D.A. Vecchio, R. Blandino, G. Bova, D. Quattrone, C. Mannucci, I. Ammendolia, C. Mondello. (2021). Post-mastectomy pain: an updated overview on risk factors, predictors, and markers. Life. 11(10): 1026.

[19] R. Eversley, D. Estrin, S. Dibble, L. Wardlaw In *Post-treatment symptoms among ethnic minority breast cancer survivors*, Oncology nursing forum, 2005; Oncology Nursing Society: 2005; p 250.

[20] C. Miaskowski, B. Cooper, S.M. Paul, C. West, D. Langford, J.D. Levine, G. Abrams, D. Hamolsky, L. Dunn, M. Dodd. (2012). Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. The journal of pain. 13(12): 1172-1187.

[21] I. Belfer, K.L. Schreiber, J.R. Shaffer, H. Shnol, K. Blaney, A. Morando, D. Englert, C. Greco, A. Brufsky, G. Ahrendt. (2013). Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. The journal of pain. 14(10): 1185-1195.

[22] T.J. Meretoja, K.G. Andersen, J. Bruce, L. Haasio, R. Sipilä, N.W. Scott, S. Ripatti, H. Kehlet, E. Kalso. (2017). Clinical prediction model and tool for assessing risk of persistent pain after breast cancer surgery. Journal of clinical oncology. 35(15): 1660-1667.

[23] D. J. Ghadimi, M.A. Looha, M.E. Akbari, A. Akbari. (2023). Predictors of postoperative pain six months after breast surgery. Scientific Reports. 13(1): 8302.

[24] R.S. Roth, J. Qi, J.B. Hamill, H.M. Kim, T.N. Ballard, A.L. Pusic, E.G. Wilkins. (2018). Is chronic postsurgical pain surgery-induced? A study of persistent postoperative pain following breast reconstruction. The Breast. 37: 119-125.

[25] S. Pereira, F. Fontes, T. Sonin, T. Dias, M. Fragoso, J. Castro-Lopes, N. Lunet. (2017). Neuropathic pain after breast cancer treatment: characterization and risk factors. Journal of pain and symptom management. 54(6): 877-888.

[26] E.A.N. Fabro, A. Bergmann, B.d.A. e Silva, A.C.P. Ribeiro, K. de Souza Abrahão, M.G.d.C.L. Ferreira, R. de Almeida Dias, L.C.S. Thuler. (2012). Post-mastectomy pain syndrome: incidence and risks. The Breast. 21(3): 321-325.

[27] T. Tasmuth, C. Blomqvist, E. Kalso. (1999). Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units. European Journal of Surgical Oncology (EJSO). 25(1): 38-43.

[28] J. Bruce, A.J. Thornton, R. Powell, M. Johnston, M. Wells, S.D. Heys, A.M. Thompson, W.C. Smith, W.A. Chambers, N.W. Scott. (2014). Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. PAIN®. 155(2): 232-243.

[29] K.G. Andersen, H.M. Duriaud, H.E. Jensen, N. Kroman, H. Kehlet. (2015). Predictive factors for the development of persistent pain after breast cancer surgery. Pain. 156(12): 2413-2422.

[30] S.A. Salati, L. Alsulaim, M.H. Alharbi, N.H. Alharbi, T.M. Alsenaid, S.A. Alaodah, A.S. Alsuhaibani, K.A. Albaqami. (2023). Postmastectomy pain syndrome: A narrative review. Cureus. 15(10).

[31] F. Fekrmandi, T. Panzarella, R. Dinniwell, J. Helou, W. Levin. (2020). Predictive factors for persistent and late radiation complications in breast cancer survivors. Clinical and Translational Oncology. 22(3): 360-369.

[32] R. Gärtner, M.-B. Jensen, J. Nielsen, M. Ewertz, N. Kroman, H. Kehlet. (2009). Prevalence of and factors associated with persistent pain following breast cancer surgery. Jama. 302(18): 1985-1992.

[33] S.S. Yuksel, A.G. Chappell, B.T. Jackson, A.B. Wescott, M.F. Ellis. (2022). Post mastectomy pain syndrome: a systematic review of prevention modalities. JPRAS open. 31: 32-49.

[34] P.Y. Tan, S.P. Anand, D.X.H. Chan. (2022). Post-mastectomy pain syndrome: a timely review of its predisposing factors and current approaches to treatment. Proceedings of Singapore Healthcare. 31: 20101058211006419.

[35] Y.M. Amr, A.A.A.-M. Yousef. (2010). Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. The Clinical journal of pain. 26(5): 381-385.

[36] V. Morel, D. Joly, C. Villatte, C. Dubray, X. Durando, L. Daulhac, C. Coudert, D. Roux, B. Pereira, G. Pickering. (2016). Memantine before mastectomy prevents post-surgery pain: a randomized, blinded clinical trial in surgical patients. Plos one. 11(4): e0152741.

[37] H.-S. Na, A.-Y. Oh, B.-W. Koo, D.-J. Lim, J.-H. Ryu, J.-W. Han. (2016). Preventive analgesic efficacy of nefopam in acute and chronic pain after breast cancer surgery: a prospective, double-blind, and randomized trial. Medicine. 95(20): e3705.

[38] A. Jacobs, A. Lemoine, G. Joshi, M. Van de Velde, F. Bonnet, P.W.G. collaborators#, E. Pogatzki-Zahn, S. Schug, H. Kehlet, N. Rawal. (2020). PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 75(5): 664-673.

[39] B.P. Bengtson. (2009). Sensory nerves in the lower pole of the breast encountered in breast (augmentation) surgery. Plastic and Reconstructive Surgery. 123(1): 32e-33e.

[40] P.M. Prendergast. (2013). Anatomy of the Breast. Cosmetic Surgery: Art and Techniques. 47-55.

[41] J.E. Skandalakis, Embryology and anatomy of the breast. In *Breast Augmentation: Principles and Practice*, Springer: 2009; pp 3-24.

[42] R. Blanco. (2011). The'pecs block': a novel technique for providing analgesia after breast surgery. Anaesthesia. 66(9).

[43] R. Blanco, M. Fajardo, T.P. Maldonado. (2012). Ultrasound description of Pecs II (modified Pecs I): a novel approach to breast surgery. Revista espanola de anestesiologia y reanimacion. 59(9): 470-475.

[44] E. Powell, D. Cook, A. Pearce, P. Davies, G. Bowler, B. Naidu, F. Gao, U. Investigators, L. Strachan, J. Nelson. (2011). A prospective, multicentre, observational cohort study of analgesia and outcome after pneumonectomy. British journal of anaesthesia. 106(3): 364-370.

[45] M. Forero, S.D. Adhikary, H. Lopez, C. Tsui, K.J. Chin. (2016). The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Regional Anesthesia & Pain Medicine. 41(5): 621-627.

[46] J. Mayes, E. Davison, P. Panahi, D. Patten, F. Eljelani, J. Womack, M. Varma. (2016). An anatomical evaluation of the serratus anterior plane block. Anaesthesia. 71(9): 1064-1069.

[47] R. Blanco, T. Parras, J. McDonnell, A. Prats-Galino. (2013). Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia. 68(11): 1107-1113.

[48] P.A. de la Torre, P.D. García, S.L. Álvarez, F.J.G. Miguel, M.F. Pérez. (2014). A novel ultrasound-guided block: a promising alternative for breast analgesia. Aesthetic Surgery Journal. 34(1): 198-200.

[49] A. Sirohi. (2020). Functional Anatomy of Thorax. Clinical Thoracic Anesthesia. 33-45.

[50] J.A. Gosling, P.F. Harris, J.R. Humpherson, I. Whitmore, P.L. Willan. (2016). Human Anatomy, Color Atlas and Textbook E-Book: Human Anatomy, Color Atlas and Textbook E-Book. Elsevier Health Sciences: pp.

[51] A.S. Sabouri, L. Crawford, S.K. Bick, A. Nozari, T.A. Anderson. (2018). Is a retrolaminar approach

to the thoracic paravertebral space possible?: a human cadaveric study. Regional Anesthesia & Pain Medicine. 43(8): 864-868.

[52] R.P. Parikh, T.M. Myckatyn. (2018). Paravertebral blocks and enhanced recovery after surgery protocols in breast reconstructive surgery: patient selection and perspectives. Journal of Pain Research. 1567-1581.

[53] C. Lee, F.M. Ferrante. (2017). Complications of Thoracic Wall Regional Anesthesia and Analgesia. Complications of Regional Anesthesia: Principles of Safe Practice in Local and Regional Anesthesia. 199-218.

[54] P.M. Kairaluoma, M.S. Bachmann, A.K. Korpinen, P.H. Rosenberg, P.J. Pere. (2004). Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy. Anesthesia & Analgesia. 99(6): 1837-1843.

[55] P.M. Kairaluoma, M.S. Bachmann, P.H. Rosenberg, P.J. Pere. (2006). Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesthesia & Analgesia. 103(3): 703-708.

[56] M.J. Dayer, V.K. Bharambe. (2021). A cadaveric study of thoracic paravertebral spaces from the point of view of paravertebral block. Sahel Medical Journal. 24(2): 80-89.

[57] R.M. Sethuraman, Costotransverse block versus costotransverse foramen block: Long way to clarity on the difference in anatomy and techniques. In Medknow: 2023; Vol. 18, pp 3-5.