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Post Mastectomy Pain is no Longer Nightmare

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Abstract

Background: PMPS nowadays is common due to advances in both; diagnosis and treatment of cancer breast. Choosing proper treatments can improve the patients' quality of life. Cancer breast is common and quite important disease and female in our family must be aware of it. Improvement of the diagnosis and treatment PMPS lead to increased patients satisfaction and decrease fear of cancer breast.

Objective: Discuss different methods for management of PMPS with less side effects, adequate analgesia, improvement of quality of life, and better patient satisfaction in the future.

Methods: Treatment approaches include both pharmacological interventions and non-pharmacological strategies. However, current treatments of the PMPS are near-optimal and prevention much better than treatment.

Conclusion: Continuous perioperative thoracic epidural Fentanyl–bupivacaine infusion was much better in pain relief, less sedating effect and shorter duration of hospital and ICU stay than continuous perioperative entanyl intravenous infusion in patients undergoing major upper gastrointestinal cancer surgery.

Keywords: PMPS; Cancer breast; Postoperative pain; VAS scale

Introduction

Cancer breast is the most common cancer in women and second most common cancer overall. It is the fifth most common cause of death from cancer in women according to International Agency of Research On Cancer and WHO. There are more than 1.7 million new cases diagnosed worldwide. This represents about 12% of all new cancer cases and 25% of all cancers in women [1]. The risk of breast cancer doubles each decade until menopause, after menopause the risk increase slows. Survival rates for breast cancer vary worldwide, but in general rates have improved. In most countries, the five-year survival rate of early stage breast cancers is 80–90 per cent, falling to 24 per cent for breast cancers diagnosed at a more advanced stage [2]. There are several factors which increase a woman's risk for the breast cancer; such as hyperprolactinemia due to neuroleptics and other dopamine antagonists. Breast cancer subtypes mostly are hormone-related. The natural history of the disease differs between those diagnosed before and after the menopause, which may be due to different kinds of tumors and possibly different effects of nutritional factors on hormones depending on menopausal status. Also, patients with Parkinson's disease have lower rates of malignancies specially breast cancer [3].

Variations observed in rates of incidence and mortality because to breast cancer, are due to a number of factors like age, race, socio-economic status, life style, reproductive history and finally family history [4]. As a consequence of advancements in both diagnosis and treatments, the survival rate patients have increased. So, population susceptible to develop pain as a complication is expected to increase [5]. It has been estimated that about 70 percent of new breast cancer cases would be seen by 2020 in developing nations [6]. But although adequate treatment, many patients experience severe pain either from disease progression or from treatment related side effects (like surgery or radiotherapy). And this under managed pain affects negatively physical and psychosocial patients' lives [6]. Pain arising in advanced stage of breast cancer can cause emotional suffering and affects quality of life of patients [6]. As per the estimates of the International Association for the Study of Pain (IASP) the prevalence of pain in breast cancer ranges from 40-89 percent [7].

Breast cancer causes pain due to multiple causes. It may be due to cancer itself, release of inflammatory mediators, and distant spread to other tissues like bones or neuronal tissue or due to different modalities of treatment as chemotherapy which causes degeneration of sensory neurons and lead to neuropathic pain [8]. And radiotherapy induce pain as a result of changes which occur at micro vascular level and nerve compression The main causes for surgery induced pain are neuroma formation and intercostobrachial nerves damage [9]. Finally Estrogen deficiency caused by aromatase inhibitors leads to arthralgia's [10].

When we mention different modalities of treatment, we must know that surgery is the keystone in the treatment of solid neoplastic tumours in general including breast cancer. Paradoxically, there is high risk of metastatic spread the perioperative period represents in cancer patients [11]. This is due to depression of antitumoral cellular immunity and depression occur in the postoperative period is linked to the metabolic and hormonal changes caused by the "stress reaction" to surgery [12].'By any reasonable code, freedom from pain should be a basic human right, limited only by our knowledge to achieve it' Ronald Melzack [13]. It is the basic duty of all healthcare professionals

to relieve pain, and the most important indication for treating pain after surgery is humanitarian. As pain is a nightmare for most patients and influences their overall experience [14]. Usually adequate analgesia is achieved by following the WHO's step analgesic ladder. As the cancer progresses, the pain experienced by the patient increases. This necessitates the administration adjuvant analgesics with opioids to control this severe pain. Unfortunately, analgesics affect immunity and tumor development by direct interfering with cellular mechanisms (e.g., cell apoptosis) or indirect interacting with the sympatho-adrenal systems [15].

Persistent pain after mastectomy is common and about 20-50 percent women are complaining of persistent neuropathic pain after mastectomy [16]. More common among young patients, those undergoing radiotherapy and axillary lymph node dissection [17]. There is a strong evidence that; suppression of the immune system in the perioperative period increase postoperative complications which includes bad wound healing infections leading to sepsis, multiple organ failure and death [18]. Also the development of residual malignant cells and the formation of new metastases are accelerated by immune suppression [19]. Other concerns of the anaesthesiologists are prevention of post-operative pain and suppression of the surgical stress response. Stress responses to surgical trauma and postoperative pain elicit diffuse changes in the hormonal secretion of cortisol and prolactin [20]. So this review aimed to summarize the different perioperative methods to prevent post mastectomy pain because Aggressive perioperative pain prevention can yield both short-term and long-term benefits as unrelieved pain affects patient recovery, prolongs hospital stays, increases hospital morbidity, and adds to the burden of growing health-care costs [21].

Post mastectomy pain syndrome (PMPS)

PMPS first by reported by Wood in late 1970, and then Folly et al described PMPS as pain and sensory disorders following mastectomy.

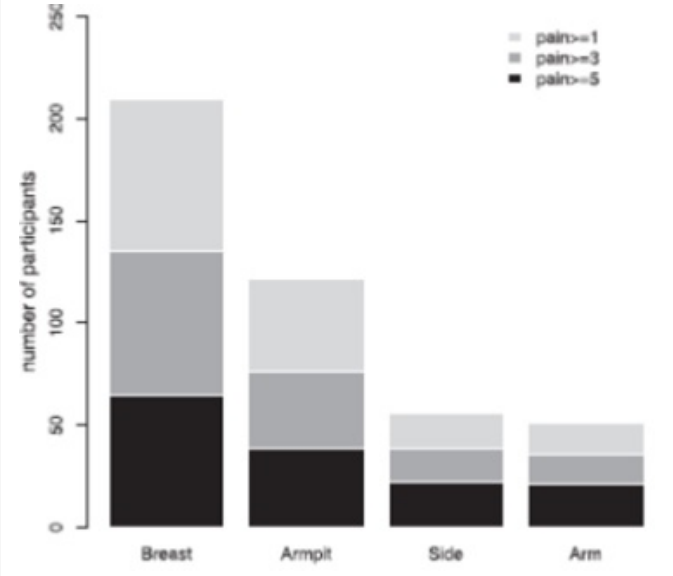

Figure 1: location of PMPS [29].

Post-mastectomy pain syndrome is described as a chronic neuropathic pain which caused by damage of the multiple nerves, and occurred after all types of breast cancer surgery (radical mastectomy, modified radical mastectomy, and lumpectomy associated with axillary lymph node dissection) [22]. It represents about 25%-60% of patients suffer from chronic pain after breast cancer-related surgery (Figure 1) [23]. Damage to the intercostobracial nerve is the most common cause of PMPS. Unfortunately, the risk of damage to the intercostobrachial nerve during breast conserving surgery is equivalent to that which occurs during complete mastectomy. This is due to a wide variation in the size, location and branching of the intercostobrachial [24]. Pain features (neuropathic) are burning like sensation, paroxysmal lancinating pain, shock-like, and pinprick pain [25]. The pain decrease everyday activities, social function and causes heavy economic burden for the healthcare system [26].

Several factors make PMPS persistent, like adjuvant therapy, psychosocial status, preoperative breast pain, type of surgery and type of analgesia. Being a problem of such important, should increase attention to PMPS [27]. The pain is perceived mainly in the axilla, medial upper arm, breast, and chest wall after more than three months of surgery to eliminate all other causes of pain such as infection [28, 29].

VAS score was used as pain score, If it was less than 3=mild pain, (3-5)=moderate and more than 5=sever

Many mechanisms explain PMPS such as; tissue injury, nerve damage related to surgery, and neuroma pain. Different types of sensory disturbances (e.g., numbness) are sequelae to surgical intervention and an important part of the pain characteristics [30]. PMPS can be related to the patient or the surgery itself. Among patient-related factors, the younger age was proved to be a high risk for the development of PMPS, and these findings are consistent with previous literature [31]. Many explanations have been proposed, including

(1) These age group were subjected to more aggressive use of adjuvant therapies

(2) Pain perception decrease with age

(3) Negative estrogen receptor status

(4) Greater surgical invasion in axillary dissection. For axillary clearance is more difficult because of plenty fatty tissue, the researchers consider high BMI as a risk factor for PMPS, but no evidence prove this finding [32].

Consequences of undermanaged PMPS

PMPS is a form of neuropathic pain caused by surgical trauma and is associated with an inflammatory reaction that has many consequences involving multiple organ systems, including local and systemic effects [33].

Sympatho-adrenal and metabolic stress responses

Surgical trauma leads to a cascade of endocrine and metabolic effects and release of inflammatory mediators and pro-inflammatory cytokines including interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF). It also decreases in anti-inflammatory cytokines such as IL-10 [33]. The clinical consequences of these changes include immune suppression, hypothermia, and thromboembolic complications among others. In addition to an inflammatory response, acute postoperative pain can also induce endocrine metabolic changes. These changes

induce a catabolic response with clinical consequences including loss of muscle mass, impaired wound healing and ileus [34].

Cardiovascular system

Post mastectomy pain causes a global sympathetic response capable of increasing heart rate, peripheral vascular resistance, blood pressure, and subsequently cardiac output. This sympathetic cascade can increase the oxygen demand of the myocardium and potentiate myocardial ischemia, especially in patients with pre-existing coronary artery disease [35].

Respiratory system

Pain from surgery to the chest or abdomen often results in splinting of the muscles of the diaphragm and chest wall [35]. This leads to decreased lung vital capacity, forced expiratory volume and functional residual capacity.

Musculoskeletal system

Immobility due to PMPS causes venous stasis and increases the risk of deep vein thrombosis. Also, vasoconstriction because of pain can lead to muscle wasting which can be debilitating. This leads to prolonged stay in the hospital and rehabilitation facilities [35].

Psychological effects

Anxiety, depression, fear, sleeplessness, and fatigue are increased due to poor pain control. In turn, sleep deprivation can decrease the effectiveness of pain therapy. Strong evidence suggests that depression and anxiety modulate activity in the dorsal horn, through the descending pathways and change pain perception [36].

Chronic pain

Untreated acute post mastectomy pain can be changed to chronic pain and this was proved by multiple studies [36]. Up regulation of peripheral nociception and increased nerve excitability due to prolonged exposure to noxious stimuli are the possible mechanisms. Noxious stimuli sensitize the nervous system response to subsequent stimuli. This is known as "windup" or "central sensitization" and is further illustrated in Figure 2 [37].

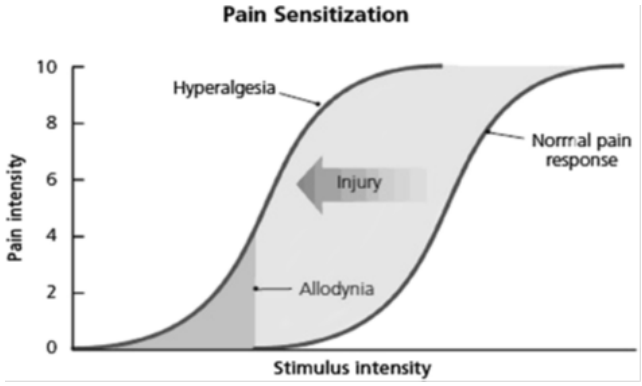

Figure 2: Noxious stimuli can sensitize the nervous system response to subsequent stimuli [37].

Method

We aimed to illustrate different methods to prevent or control PMPS which is defined as mentioned above. Studies reporting on PMPS or analgesia for cancer breast surgeries were identified by electronic searches of different databases. The terms used in the search strategy were "PMPS" and "cancer breast surgeries". No language restriction was applied (Figure 3).

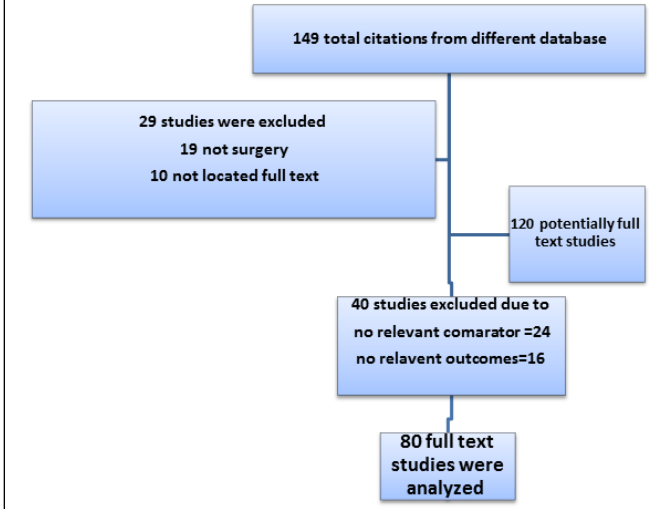

Figure 3: Flow diagram of the included studies.

Discussion

According to a previous review, the literature was inconsistent in defining chronic pain after mastectomy [38]. To improve comparability between studies in the future, Jung et al suggested a time frame definition of chronic neuropathic syndrome classification based on the etiology.

The authors suggested that neuropathic pain syndromes due to breast surgery are considered chronic after 3 months and that shorter time frames should raise a consideration of pain associated with tumour recurrence. In Jung et al. review, there were approximately 21 studies with follow-up periods from (1-96) months which revealed the following.

- Phantom breast pain prevalence is (3-44) per cent
- Intercostobrachial neuralgia (ICN) 16-39 percent for all breast cancer surgery
- Neuroma pain prevalence is (23-49) percent [39].

There were many trials (randomized, doubled-blinded, placebo-controlled) done to investigate the best neuropathic pain treatment algorithm. Many trials were included studying a lot of neuropathic conditions. The most studied oral medications were; anti-depressants, anticonvulsants, opioids, NMDA antagonists, mexilitine, topical lidocaine, cannabinoids, topical capsaicin, and glycine antagonist. We here mention the most effective methods for controlling PMPS that were published in last few years.

One prospective randomized controlled clinical study was done in South Egypt Cancer Institute, titled (Analgesic efficacy of pregabalin in acute postmastectomy pain: placebo controlled dose ranging study) that published in Journal of Clinical Anesthesia, 2016. The conclusions was a single preoperative oral dose of pregabalin 150 mg is an optimal dose for reducing postoperative pain and morphine consumption in patients undergoing MRM [40].

Another important method is paravertebral block, as proved by study by Brian M. et.al. That published in 2015 and concluded that "Adding a multiple-day, continuous Ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block may result in a decreased incidence of pain and pain-related physical and emotional dysfunction for 1 year after mastectomy [41].

Also, Pecs block (pectoral nerves block) which is an easy and reliable block inspired by the infra clavicular block approach and the intercostal abdominis plane blocks. Its technique as following, the pectoralis muscles are located under the clavicle then the space between the two muscles is dissected to reach the lateral pectoral and the medial pectoral nerves. The main indications are breast expanders and subpectoral prosthesis because the distension of these muscles is very painful [42]. A second version of the Pecs block was described, called "modified Pecs block" or Pecs block type II. This novel approach aims to block at least the pectoral nerves, the intercostobrachial, intercostals III-IV-V-VI and the long thoracic nerve (Figure 4). These nerves must be blocked to provide complete analgesia during breast surgery [43].

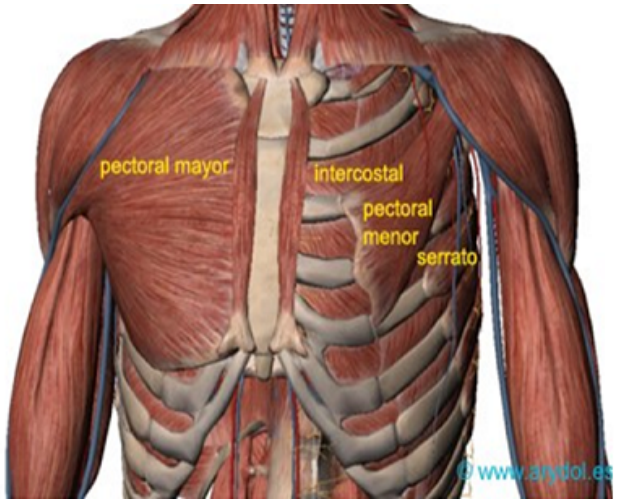

Figure 4: Anatomy of pectoral muscle.

In a study published 2012 in Elsevier Doyma "modified Pecs's block" or Pecs block type II was described. Using Ultrasound images that were very conclusive as the contrast was taken up by the axilla and reaches the thoracodorsal nerve area, passing above the serratus muscle and hence, the long thoracic nerve was anesthetized with the clinical usefulness. This approach aims to block the axilla that is vital for axillary evacuation and the intercostal nerves, necessary for wide local excisions of the tumor. Two needle approaches used to perform the Pecs II block or "modified Pecs's block" instead of one (Figure 5) [44].We must know that, Thoracic epidural and paravertebral blocks became the gold standard techniques to achieve this goal, but not every anesthesiologist is comfortable performing these procedures [45].

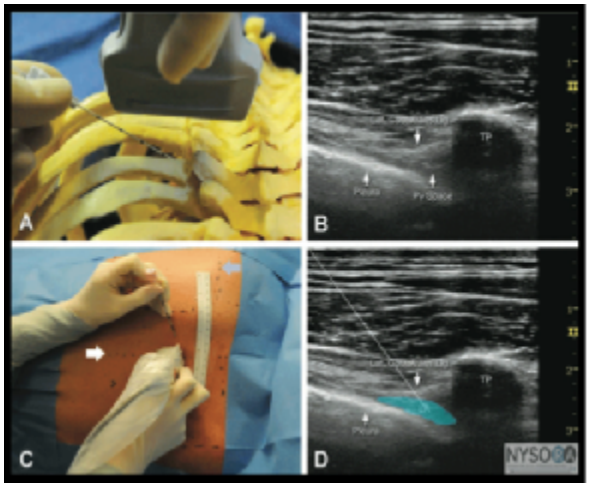

Figure 5: U/S guided Thoracic epidural and paravertebral blocks [43].

Other interventional method "interscalene brachial plexus block" which was proved by Kaya M et al, 2013 who evaluated the effects of interscalene brachial plexus block on postoperative pain relief and morphine consumption after modified radical mastectomy (MRM). Sixty ASA I-III patients scheduled for elective unilateral MRM under general anaesthesia were included. Pain intensity was assessed with the visual analogue scale (VAS). Other parameters as morphine consumption, side effects of opioid, antiemetic requirement, and complications associated with interscalene block were recorded. VAS scores were significantly lower in interventional group, except in the first postoperative 24 h ($p<0.007$). The patients without block consumed more morphine [group 1, 5 (0-40) mg; group 2, 22 (6-48) mg; $p=0.001$] [46]. Until now paravertebral blocks and thoracic epidurals are the most effective and the gold standard pain treatment for breast cancer surgery. However, we questioned the effectiveness based on the fact that the brachial plexus nerves are the main component of this painful surgery and we described for the first time the use of pectoral nerve blocks with this indication [47].

We cannot ignore role of non-pharmacological methods of pain relief as preoperative explanation, education, Physical therapy techniques, relaxation therapy, hypnosis, splinting of wounds and transcutaneous electrical nerve stimulation (TENS) [48]. One of the best reviews that illustrated in detail effectiveness of postoperative physical therapy for upper-limb impairments after breast cancer treatment published in 2015 with the following recommendations.

1) First week post-op: low-intensity program involving elbow/wrist.

2) 7-10 days post-op: gradually increase intensity passive mobilization (manual stretching, active exercises and increase muscle strength).

3) No recommendations can be made on length of time, content and intensity.

4) Multifactorial therapy consisting of manual stretching and active exercises effectively treated impaired shoulder ROM [48]. And sure the pharmacological methods of pain relief according to the 'analgesic

ladder' introduced for treatment of cancer pain by the World Health Organization (WHO). It is formed of three steps according to intensity of pain. The first step involves the use of non-opioid +/- adjuncts (e.g. paracetamol, aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). If pain is still uncontrolled, in addition to step 1 medication weak opioids (e.g. codeine, tramadol) can be added [49].

In moderate to severe pain or pain increasing in spite of step 2 treatment, stronger opioids are considered in addition. All these involve the concept known as multimodal analgesia. It is important to include the analgesic ladder in individual patient analgesic plan along with the adjunctive therapies. The analgesics act at different sites. Drugs that act at the site of injury and decrease pain associated with inflammatory reaction (e.g. NSAIDs), other drugs may alter nerve conduction (e.g. local anesthetics), some may modify transmission in the dorsal horn (e.g. opioids and antidepressants) while group of drugs may affect the central component and the emotional aspects of pain (e.g. opioids and antidepressants) [50]. Fourth step was added to WHO analgesic ladder which was interventional pain management such as stellate ganglion block (radiofrequency thermal neuro modulation) or local anesthetic injection of stellate ganglion block). Intervention pain management was advised to be done early before tumor spread or patient became deteriorated. Opioid use could be associated with an increased incidence of opioid-related adverse drug events, including over sedation and respiratory depression. Further study are needed because opioid-related adverse drug events have been associated with an increase in overall cost, length of stay, and even decreased survival during in-hospital resuscitation [51].

It is frequently not possible to administer sufficient opioids alone, due to coexisting medical conditions, patient tolerance, allergies, or efforts to reduce total opioid use. In such cases, a multimodal approach to intravenous pain management must be employed. This may include the use of opioids, NSAIDS, and other adjuvant as needed to optimize patient pain control in the immediate postoperative period as a bridge until the patient can be transitioned to less potent oral medications [52]. And finally Minimizing damage to nerves during surgery Improved screening methods detect breast cancer at earlier stages. Earlier detection means smaller tumour sizes, which has made breast-conserving surgical treatments possible and widely used. These currently account for up to 40 per cent of breast cancer surgery [53].

Breast conserving techniques include lumpectomy, conservative breast surgery, wide local excision, partial mastectomy, segmentectomy, or tylectomy. Such approaches include reducing the number of axillary dissections required. Combining reduced surgical trauma with nerve preservation techniques may reduce the risk of sensory deficits and the occurrence of ICN [54-55]. In this regard, the increased use of less invasive staging techniques such as sentinel lymph node biopsy has helped to reduce the number of patients undergoing axillary dissection and the resulting trauma to intercostobrachial nerves [56].

Conclusion

PMPS nowadays is frequency due to advances in diagnosis and treatment of breast cancer. Choosing proper treatments can improve the patients' quality of life. Cancer breast is common and important disease to female in our family and all female must be aware of it, Improvement of the diagnosis and treatment of patients with breast cancer lead to increased incidence rate of PMPS. Treatment approaches include both pharmacological interventions and non-pharmacological strategies. However, current treatments of the PMPS are near-optimal and prevention much better than treatment. Further investigations are required to achieve the appropriate developments in diagnosis and screening of breast cancer, and evaluation and treatment of PMPS that will provide less side effects, adequate analgesia, and finally, improved quality of life, and patient satisfaction in the future.

Conflict of Interests

The authors have no conflicts of interest to disclose.

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