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Review Article

Current treatment options for post-thoracotomy pain syndrome: a review

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ABSTRACT

Thoracotomy is one of the most painful surgical procedures known. Chronic pain in the postoperative period after thoracotomy is a common complication. Post-thoracotomy pain syndrome (PTPS) is a chronic pain with neuropathic and non-neuropathic components, continuing after 2 months of thoracotomy, causing disability by affecting the daily activities and functions of patients. Patients generally describe neuropathic symptoms such as hyperalgesia, allodynia, hypoesthesia at the site of the incision or related dermatomes. Etiology includes preoperative, intraoperative and postoperative factors. Although the mechanism of PTPS formation is not clear yet, the most common cause is the intercostal nerve injury. PTPS treatment is complex because of the neuropathic component of the pain. The risk of PTPS formation can be reduced by controlling early pain before the onset of the disease. When pain occurs, medical treatments are implemented and also minimally invasive interventional procedures could be performed if necessary.

Key Words: Thoracotomy, Chronic pain, Neuropathic pain

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Introduction

Postoperative pain is an acute pain associated with surgical trauma accompanied by inflammatory processes and diminishes in severity by tissue healing. Thoracotomy is one of the most painful surgical procedures known [1]. Multiple muscle layers in the thorax, bones, joints, neurovascular structures, fascia and parietal pleura are pain-sensitive structures. Nociceptive stimuli generated during surgery are transmitted to the upper centers via afferents originating from these structures. Post-thoracotomy pain syndrome (PTPS) is defined as the pain that recurs or persists along a thoracotomy incision at least two months following the surgical procedure by 'The International Association for The Study of Pain' (IASP) [2,3]. The chronic post-thoracotomy pain was first reported in 1944, during World War II, as 'chronic intercostal pain' in US troops who underwent thoracotomy for thoracic trauma [4].

Although the pathogenesis of PTPS has not yet been fully elucidated, it is known that it is a complex pain of neuropathic and nociceptive components. The neuropathic component in PTPS causes difficulties in the management of the pain [5]. Most patients describe neuropathic pain, with 82-90% of patients reporting that the pain is caused by an incision scar, and the pain may be localized or radicular [6,7]. Neuropathic pain is defined as a pain that develops secondary to the damage or dysfunction of the somatosensory system. Symptomatology in neuropathic pain is generally in the form of hypoesthesia, hyperesthesia, allodynia, paresthesia, dysesthesia, burning, and electrical shock like pain [8,9]. It is thought that the neuropathic component of the pain is probably due to the iatrogenic nerve damage during the surgery [10].

Post-thoracotomy pain generally has a mild or moderate course and tends to disappear over time. Treatment is generally conservative because it does not cause disability and limitations in daily life activities in the vast majority of patients. Only 5% of patients develop severe pain and disability-related difficulties in daily living activities [1,4,5,11]. One study reported that 27% of patients described chronic pain at 6 months post-thoracotomy and 8.2% had pain at a level that limited their daily activities [12]. Approximately half of the patients describe persistent thoracotomy pain between the first and second years after surgery and 30% between the fourth and fifth years [5, 13].

Prevalence

Chronic pain is one of the most common health problems and it is known that approximately 22.5% of chronic pain is secondary to surgical procedures [12]. Although the prevalence of PTPS after thoracic surgery ranged from 14% to 83% [14], the incidence of PTPS neuropathic pain ranged from 35 to 83% and neuropathic pain is associated with more severe chronic pain [15, 16].

Pathophysiology

PTPS etiopathogenesis is not fully understood yet. Surgical trauma-related nociceptive somatic afferent stimuli are transmitted through the intercostal nerves to the ipsilateral dorsal horn of the spinal cord and then transmitted to the somatosensory and limbic system via the anterolateral contralateral routes. Visceral afferent stimulants that occur after bronchial and pleural injury are transmitted through the nervus phrenicus and nervus vagus. Mediators released from damaged tissue decrease pain threshold by increasing the activity of nociceptors (primary sensitization). Due to the secretion of substance P, the calcitonin gene-related peptide, and the glutamate secondary to the continuation of the perioperative nociceptive stimulation, NMDA receptors are activated. As a result, the dorsal horn and upper pain centers become hypersensitive. Nociceptive stimuli reaching the central nervous system (CNS) initiate functional changes, and after these changes, the central nervous system becomes more susceptible to stimuli (central sensitization). The activation of these pain cascades leads to chronic pain and neuropathic pain [17,18].

Etiology

Costochondral and costovertebral joint injuries, muscle and pleural injuries that occur during costal retraction are thought to play a role in etiology [19,20]. Pain may also occur due to pulmonary parenchymal damage and irritation of the tubes used for drainage [21]. Although the mechanism of PTPS formation has not been fully elucidated, intercostal nerve injuries, especially during surgery, have been reported as the most common cause of PTPS formation [5,22,23]. As a result of the use of the costal retractor, the blockage may occur in 50% to 100% of the signal conduction of the intercostal nerve in the segments close to the incision field [24]. Allodynia, hyperalgesia, and accompanying drowsiness throughout the intercostal nerve innervation area suggest intercostal nerve injury [4, 25].

Risk Factors

1. Preoperative Factors: Young age, female gender, genetic predisposition, and psychosocial factors have been reported to be the risk factors for the development of chronic pain [6]. The presence, duration, and severity of preoperative pain are also the risk factors for PTPS development [26].
2. Surgical Factors: The type of operation was associated with the risk of PTPS development. The incidence of PTPS has been reported to be between 40-80% after thoracotomy and between 20-40% after video-assisted thoracic surgery (VATS) [22]. In addition to the intraoperative application, postoperative epidural analgesia has been reported to reduce the risk for PTPS development [27]. The severity of the pain was determined to be related to the location and length of the thoracic incision. In some publications, anterolateral thoracotomy and median sternotomy have been reported to cause less pain intensity than posterolateral thoracotomy. In order to prevent the development of PTPS, muscle sparing surgery was not found superior to posterolateral incisions [21, 28].
3. Postoperative Factors: Severe acute postoperative pain and inadequate early control of pain are among the most important risk factors for the development of PTPS. Therefore, it is necessary to control the pain immediately in the postoperative period [20, 27]. Although there are many treatment options for postoperative pain control, it has been reported that the use of high-dose analgesics in the first week of surgery, especially the use of oral morphine equivalents, may be a risk factor for the development of PTPS [29, 30]. Radiotherapy, chemotherapy, tumor recurrence, and prolonged hospitalization can be considered as postoperative risk factors [6, 30, 31].

Complications

The decrease in respiratory capacity in the early post-thoracotomy period creates a predisposition to deterioration in the respiratory functions, hypoxemia, atelectasis and pulmonary infections. Impairment of mental status, social status, and emotional functions, decreased patient satisfaction, chronic persistent pain, and limitation of daily activities may be seen in the long term. These complications are particularly more common in elderly, smokers, patients with cardiovascular disease, and patients with obesity. These complications lead to increased mortality, morbidity, hospital stay and cost [19,32,33]. The ipsilateral shoulder pain developed after thoracotomy can be seen due to serratus anterior and latissimus dorsi incisions. If pain control and rehabilitation are insufficient, the frozen shoulder may develop in these patients [25].

Treatment

Meticulous postoperative pain control in addition to the evaluation of primary disease and concurrent clinical conditions such as depression, anxiety, and sleep disorders are critically important. Regulation of postoperative rehabilitation, including methods of coughing, breathing exercises, and ambulation are effective in preventing complications [34]. Interventional procedures can be performed where medical treatments are inadequate.

Preemptive Analgesia: This method is the control of pain through the prevention of central sensitization that occurs secondary to nociceptive stimuli associated with surgical trauma, before the beginning of the stimulus. For this purpose, local anesthetics, opioids, non-steroid anti-inflammatory drugs (NSAID) can be used preoperatively. This method has been shown to prevent PTPS development in addition to providing pain control in the acute phase [4, 35].

A. Medical Treatments

1. Tricyclic Antidepressants: Tricyclic antidepressants are thought to produce analgesic effects by providing central blockade of monoamine reuptake. Amitriptyline and nortriptyline are used. Their efficacy in neuropathic pain has been demonstrated in many randomized controlled trials. Analgesic effects are independent of antidepressant effects. Advantages include being single dose daily, low cost, and relief of depression in neuropathic pain. The most important disadvantage is anticholinergic side effects. They can cause sedation, dry mouth, constipation, urinary retention, and orthostatic hypotension. They should be used with great caution due to cardiotoxic side effects especially in patients with ischemic heart disease and ventricular dysfunction. Tricyclic antidepressants are among the first-line treatments in neuropathic pain treatment guidelines [36-39].
2. Anticonvulsants: These drugs bind to the alpha 2-delta subunit of voltage-dependent calcium chan-

nels, and reduce the release of neurotransmitters such as glutamate, noradrenaline, and substance P. The effects, side effects and patient tolerance profiles of pregabalin and gabapentin have similar properties. Dizziness, somnolence, peripheral edema, and dry mouth may develop after the use of this group of drugs [36,40]. Because pregabalin has linear pharmacokinetics, dose adjustment is easier, analgesic effects occur faster than gabapentin, and there are also positive effects on common anxiety disorder and sleeping [37,41,42]. It has been reported that the use of gabapentin in the treatment of PTPS is effective and reliable in reducing neuropathic pain and can be used because of the low side effects and high patient compliance [43,44]. Pregabalin therapy has been reported to be an effective and reliable method for reducing chronic post-thoracotomy pain [34]. These drugs are among the first-line treatments in neuropathic pain treatment guidelines [39].

3. Selective Serotonin Noradrenaline Reuptake Inhibitors: Duloxetine and venlafaxine were found effective in the treatment of peripheral neuropathic pain. They are also effective in the treatment of depression and generalized anxiety disorder. The most common side effect of duloxetine is nausea. Apart from this, there are also gastrointestinal side effects, such as dry mouth and constipation. Tolerance to these side effects can be improved by appropriate dose titration in patients with nausea [36]. Venlafaxine should be used with caution in patients with cardiac problems as it may cause hypertension and impaired cardiac conduction. It should be kept in mind that withdrawal symptoms may occur when venlafaxine is discontinued. These drugs are among the first-line treatments in neuropathic pain treatment guidelines [38, 39].

4. Topical lidocaine: 5% lidocaine patch was found to be effective in localized peripheral neuropathic pain cases where allodynia was predominant [36].

5. Opioids: Opioids bind to opioid receptors (μ, κ, δ), which are common in the brain, spinal cord and peripheral tissues. In meta-analyses they have been shown to be the most potent pain relievers in neuropathic pain [45]. Opioids have adverse effects on postoperative recovery due to side effects such as sedation, nausea, and constipation. The induction of opioid-induced respiratory failure may further deepen pulmonary complications, and opioids may also increase existing pain due to opioid-induced hyperalgesia side effects. Although the use of opioids in acute pain, postoperative pain, and cancer-related pain are common, the use of this group of drugs in the long-term treatment of pain is controversial due to the tolerance to analgesic effects, addiction, drug abuse, and side effects such as high dose-mortality. Due to these side effects and disadvantages, opioids are among the second- or third-line medical treatments in the final guidelines [17, 39, 46, 47].

6. Tramadol: It is a weak μ-opioid agonist and also provides analgesia by inhibiting serotonin and noradrenaline reuptake. Tramadol is used more commonly because of less constipation, sedation, dizziness, and lower risk of addiction than other opioids. It is among the second-line treatments in neuropathic pain treatment guidelines. However, it can be used as a first-line treatment in acute exacerbations of pain [36, 39, 47, 48].

7. NSAIDs: Since there is no evidence that these drugs have an effect on neuropathic pain, they are not commonly used in PTPS treatment [49]. However, when used to provide preemptive analgesia, they reduce peripheral sensitization by reducing the release of inflammatory mediators [17]. It has been reported that combined thoracic epidural analgesia with preemptive intravenous dexketoprofen administration reduces and prevents chronic post-thoracotomy pain formation [50].

B. Interventional Methods

1. Intercostal Nerve Blockage: The intercostal nerve block prevents the neural impulses from the motor and sensory fibers of the intercostal nerve from transmitting to the spinal cord and higher centers as an impediment to ipsilateral transmission. With this method, spinal nerves between T1 and T11 can be effectively blocked and the pain can be controlled. It can be used in acute and chronic painful situations for thorax and upper abdomen [51]. The systemic dissemination of the local anesthetic agent is particularly disadvantageous, especially at multiple level injections, because the applied zone is rich in the vasculature. Especially neurolytic blockade can be used to control chronic post-thoracotomy pain effectively [21]. Complications include local anes-

thetic toxicity, pneumothorax, bleeding, infections, and hypotension [52].

2. Thoracic Paravertebral Block: The local anesthetic is injected near the intervertebral foramen of the spinal nerves near the thoracic vertebrae. Ipsilateral sympathetic and somatic nerve blockage is achieved in dermatomes below and above the thoracic level after injection. It is used in acute and chronic chest pain of unilateral origin. Contraindications include allergies to local anesthetics, infections at the injection site, and edema. Complications of the thoracic paravertebral block can be listed as vascular and pleural injury, pneumothorax, and hypotension [53].
3. Spinal Cord Stimulation: Large diameter afferent fibers in the spinal cord are stimulated to inhibit chronic pain. It is based on the principle of electrical stimulation of the posterior column and dorsal roots with electrodes placed in the posterior epidural space. It is an effective and reliable method of neuromodulation that can be used for the symptoms of drug-resistant neuropathic pain [54,55].
4. Dorsal Root Ganglion Pulse Radiofrequency Application: Dorsal root ganglion pulse radiofrequency application inhibits excitatory C fiber response by providing a repetitive, burst-like stimulus to A-delta fibers in neuropathic pain treatment, resulting in decreased evoked synaptic activity. There is less risk of damaging the tissues than other radiofrequency methods; therefore, it is the more preferred method [56].
5. Interpleural Block: Local anesthetics are injected into the parietal and visceral pleura and attempt to block ipsilateral somatic nerve blockage at multiple thoracic dermatomal levels. After the bilateral spread of local anesthetic material, sympathetic chain and splanchnic nerve blockage develop, resulting in decreased pain. Although it is reported to be effective in unilateral surgery and non-surgical acute and chronic chest pain, it is not widely used due to the difficulty of application and the risk of lung parenchyma damage. Contraindications include infection in the treatment area, allergy to local anesthetics; and complications of this type of block include local anesthetic toxicity, phrenic nerve palsy, pneumothorax and infections [52,57,58].
6. Thoracic Sympathetic Block: This method is used in the diagnosis and treatment of chronic thoracic pain syndromes such as neuropathic pain, chest wall pain, and thoracic visceral pain [59].
7. Thoracic Epidural Anesthesia: This method used in the early postoperative pain control and have been reported in numerous studies to reduce the risk of development PTPS [21, 60, 61].

C. Other Methods

1. Transcutaneous Electrical Nerve Stimulation: This method was found to be effective in early post-thoracotomy pain [62]. There are conflicting results for the use in neuropathic pain [63].
2. Botulinum Toxin Application: This is a neurotoxin obtained from Clostridium botulinum. PTPS usually produces peri-incisional focal pain. Therefore, low-dose toxin administration is suitable to control the symptoms, and there are minimal risks due to low dose requirements [64].
3. Acupuncture: It is a widely used treatment for pain and other diseases in traditional Chinese medicine. It has been reported that postoperative pain and opioid use are significantly reduced using acupuncture [65]. Acupuncture has also been found to be effective in the treatment of chronic pain [66].

As a conclusion PTPS remains a poorly understood complication of thoracotomy which reduces the quality of life and leads to functional and psychosocial limatations from mild to severe. The neuropathic component of the pain makes treatment more difficult and patients may require more than one form of therapy to control pain and reduce disability. Patient should be evaluated before operation carefully and pain control should be provided perioperatively. Further well designed study are required to investigate the etiopathogenesis of PTPS and alternative treatment options.

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