

Surgical Strategy and Treatment for the Prevalence of the Post-Thoracotomy Pain Syndrome

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Short Communication

The various types of pain evoked after thoracic surgery are wound pain, pulmonary apex pain due to the drain, pain caused by intercostal nerve damage, visceral pain due to manipulation of the pleura/bronchi during surgery. As the dominant nerve differs among painful areas, the innervation regions requiring analgesia are extensive, causing difficulty in pain control. These pains are treated by the thoracic epidural anesthesia, the administration of anti-inflammatory analgesics such as non-steroidal anti-inflammatory drugs, gabapentin (anti-epileptic drug) as a central nerve system drug, or tranquilizers. When nociceptive input into the central nerve system with acute, intense postoperative pain is sustained, a change to chronic pain such as post-thoracotomy pain syndrome (PTPS) can occur [1]. PTPS is defined by the International Association for the Study of Pain as neuropathic pain with dysesthesia that is burning and stabbing, and persists for at least two months following the surgical procedure. Its incidence is 80% at 3 months, 75% at 6 months, and 61% at 1 year after surgery; the incidence of severe pain is 3-5%. PTPS interferes with daily life in 50% of patients [2]. The incidence of PTPS is similar between thoracoscopic surgery and thoracotomy [3-5], and the causes of PTPS include rib fracture, intercostal nerve injury due to compression by the rib retractor, and rib hyperextension. An anxious personality of patients was also reported to tend to be positively correlated with the incidence of PTPS [6]. In thoracic surgery, there are differences in the incision size among surgical techniques and surgical invasiveness to the chest wall among approaches to the thoracic cavity, such as posterolateral thoracotomy, axillary thoracotomy, median sternotomy, a median incision, a small incision, and conventional video-assisted thoracic surgery (c-VATS) with only a trocar used in VATS. It is self-evident that the intensity and the fear of postoperative pain also differs among patients. When postoperative wound pain is compared between c-VATS using only the trocar and thoracotomy involving rib resection with a large wound, the degree of surgical invasiveness to the chest wall is often inconsistent with the pain intensity, which supports the above individual differences. Even when thoracotomy is performed after the intercostal bundle is treated as minimally as possible, or even when c-VATS is performed, some patients occasionally develop marked symptoms of neuropathic pain such as burning, shooting, and tingling sensations and hypesthesia in the area from the precordial region at the intercostal thoracotomy level to the upper abdominal region. Their stress is marked when these symptoms develop. Actually, in patients with PTPS, sensory abnormalities such as allodynia (pain induced by normally innocuous, weak stimuli) and hypesthesia sometimes persist around the thoracotomy wound or the anterior axillary line area or upper abdominal area at the thoracotomy intercostal level for a long period after surgery. Since no drugs have been developed to alleviate

these symptoms, pain causing discomfort whenever clothes come into contact with the area around the wound may reduce patients' activities of daily living and delay their return to society.

With the advent of pregabalin, an antineuropathic pain drug, the treatment for PTPS used by thoracic surgeons have been changing and improving [7,8]. This mechanism of action of neuropathic pain differs from that of general inflammation-associated pain. The latest definition of neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [9,10]. Pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but does not bind to GABA receptors, and does not inhibit GABA reuptake for metabolism. This drug neither blocks the sodium channel nor activates opioid receptors. The main mechanism of pregabalin is its binding to the $\alpha 2\delta$ subunit of the voltage-gated calcium channel with high affinity. Pregabalin, based on the characteristics of its pharmacokinetics, is also considered to infrequently induce interactions with other drugs and can be used as the other multimodal analgesia. The degree of anxiety about pain and pain threshold differ among individuals. In particular, in patients with mental disorders as complications, pain control at the outpatient clinic is sometimes difficult. Pregabalin, which binds to the $\alpha 2\delta$ subunit of the voltage-gated calcium channel, was reported to reduce the excessive release of excitatory neurotransmitters by hyper-excited neurons involved in the development of anxiety symptoms, and suggested to have early-onset effects on both somatic and psychological symptoms of anxiety about pain [11]. The antidepressant medicine, duloxetine (serotonin-norepinephrine reuptake inhibitor) which facilitates the descending analgesic circuits by increasing the concentration of serotonin and noradrenalin was also reported to be effective to the patients with neuropathic pain combination treatment of pregabalin [12,13]. Additionally, cathepsin S, cysteine protease of the papain family is likely to play an important role in the maintenance and chronicity of neuropathic pain [14] and is expected as a promising therapeutic agent.

Previous studies have suggested the involvement of the activity of the anterior cingulate gyrus in the mechanism of the change from acute to chronic pain [15,16] and, therefore, individual differences in pain might be associated with changes in the activity of this gyrus after surgery [15,16]. At present, for pain, symptomatic therapy according to its intensity is mainly performed. Concerning pregabalin administration methods, its preoperative administration has been reported to reduce postoperative pain [17,18]. Therefore, preoperative pregabalin administration is expected to also have adequate inhibitory effects on postoperative wound pain in patients in whom intercostal thoracotomy is planned and those with a low pain threshold and

psychological disorders represented by depression as complications in the thoracic surgery.

In recent years, thoracic operations have become less invasive. Among the less invasive operative procedures, robot-assisted surgery and single-port VATS (SPVATS) for lung cancer are recent topics [19,20]. SPVATS is thoracoscopic surgery performed using a small thoracotomy wound (3-5 cm). This surgical procedure, which does not require a rib retractor and can be performed avoiding contact between surgical instruments and the intercostal nerve, may be the least invasive surgery for patients. Though SPVATS can only be performed by skilled surgeons because of limitations in forceps manipulation and difficulty in performing delicate procedures, it has rapidly been spreading among some countries, such as in Europe and a part of Asia. Recently, we have mastered an SPVATS procedure that does not impose stress on the intercostal bundle, showed surgical results in patients with early lung cancer, and performed detailed evaluation of this procedure in terms of postoperative pain [21]. Comparison between the SPVATS and multi-port VATS groups showed no significant difference in the blood loss, operative time, postoperative hospital stay, drainage period, or the total number of dissected lymph nodes between the two groups but a definite decrease in the incidence of neuropathic pain for SPVATS [22]. At present, the least invasive operative procedure to chest wall in the thoracic surgery field may be SPVAT that is paid close attention to the intercostal nerve injury. Even if PTPS occurs after operation, pregabalin or serotonin-norepinephrine reuptake inhibitor administration is therapeutic consideration. Moreover, the trial of preoperative pregabalin administration is planned for the patients who will perform open thoracotomy at our institute. Naturally, it is also important that thoracic surgeons actively ask patients about symptoms associated with neuropathic pain and perform the appropriate pain or mental stress assessments. Although further investigations will be still needed, SPVATS, a less invasive surgical procedure and early medications such as pregabalin or duloxetine administration may be a promising treatment for reducing the prevalence of PTPS on various thoracic diseases.

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