

흉강절제술 후 통증모델에서 수술 전 늑간신경차단의 효과

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Effect of the Preoperative Intercostal Nerve Block in a Rat Model of Postthoracotomy Pain

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Background: Chronic pain after thoracotomy has been recently reproduced in a rat model that allows investigating the effect of potentially beneficial drugs that might reduce the incidence of allodynia or alleviate pain. Local anesthetics produce antinociception in normal animals and alleviate mechanical allodynia in animals with nerve injury although their mechanisms of action may differ in these situations. Our purpose of this study was to test whether the preoperative intercostal nerve block of bupivacaine could prevent the development of allodynia in a rat model of chronic postthoracotomy pain.

Methods: All male Sprague-Dawley rats were anesthetized and the right 4th and 5th ribs were exposed surgically. The pleura were opened between the ribs to which a retractor was placed and was opened 10 mm in width. Retraction was maintained for one hour. Total 1 mg of 0.5% bupivacaine was injected at the intercostal nerves before (n = 17) or after (n = 16) surgery. A control group (n = 25) that underwent rib retraction did not receive any drug. Rats were tested for mechanical allodynia using calibrated von Frey filaments applied around the incision site during the three weeks following surgery.

Results: The incidence of development of mechanical allodynia in the group that received intercostal injection with bupivacaine before surgery was significantly lower than that in the control group ($P < 0.05$).

Conclusions: Preoperative intercostal nerves block around the surgical incision before thoracotomy may decrease the incidence of postthoracotomy pain syndrome. (Korean J Pain 2008; 21: 106-111)

Key Words: allodynia, bupivacaine, preoperative intercostal nerve block.

INTRODUCTION

Chronic pain after thoracotomy was first reported in 1944 by a United States army surgeon who noted "chronic

intercostal pain" in men who underwent a thoracotomy because of a chest trauma during the Second World War.¹⁾ Chronic postthoracotomy pain (CPTP) is defined as "pain that recurs or persists along a thoracotomy incision at least two months following the surgical procedure".²⁾ CPTP is

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typically described as a continuous dysesthesia with burning and aching sensations in the general area of the surgical incision and affects up to 55% of patients followed for more than one year, representing one of the most commonly reported complications after thoracic surgery.³⁾

No preoperative risk factors have been identified in patients who developed pain after thoracotomy⁴⁾ while a number of intra- and postoperative variables have been found to play a role in the etiology and management of the CPTP.⁵⁾ Chest wall resection and pleurectomy seem to increase the likelihood of chronic pain when compared to pulmonary resection alone.⁶⁾ In contrast, the muscle-sparing thoracotomy approach⁷⁾ and the use of video-assisted thoracoscopic surgery⁸⁾ may decrease the incidence of chronic pain and disability when compared to conventional thoracotomy although the difference disappears one year after the procedure. Likewise, the combined use of intra- and postoperative epidural analgesia was found to exert a dramatic effect in decreasing the incidence of pain at the 6th month.⁹⁾ A significant number of patients do not seek help for CPTP and even when identified, drug treatment is often inadequate.⁸⁾

The etiology of CPTP has not been clearly determined even though clinical and animal research studies suggest that the functional impairment and the anatomical damage of the intercostal nerves are the leading factors in the development of this pain syndrome. Rogers et al.⁹⁾ have shown that rib retraction alone causes about 50% conduction block in the intercostal nerves on both sides of the retractor in almost every patient who underwent thoracotomy. Buvanendran et al.¹⁰⁾ have recently developed a postthoracotomy pain model where 50% of the animals developed allodynia and showed extensive axon loss in the intercostal nerves of the retracted ribs.

There are plenty of reports that local anesthetics injected close to the nerve or systemically in order to treat chronic neuropathic pain conditions in humans decreased the intensity of pain.¹¹⁻¹³⁾ However, the reports that the nerve block with local anesthetics can decrease the incidence in itself of development of neuropathic pain are very rare. This author hypothesized that preoperative intercostal nerves block with bupivacaine may decrease the incidence of the development of mechanical allodynia in a rat model

of postthoracotomy pain.

MATERIALS AND METHODS

1. Animal Preparation

This study was performed under a protocol approved by the Animal Care Committee of our institution. Male Sprague-Dawley rats (weight, 280–340 g) were housed individually in a temperature-controlled ($21 \pm 1^\circ\text{C}$) vivarium and allowed to acclimatize for 7 d in a 12 h/12 h light/dark cycle.

2. Surgical Procedures

1) Postthoracotomy pain model: All the animals were briefly anesthetized with sevoflurane (1–2% in oxygen) before receiving intraperitoneal xylazine (1.5 mg/kg) and ketamine (4 mg/kg). Animals were then intubated (16-gauge, 51 mm long Teflon intravenous catheter) and connected to a ventilator (Harvard ventilator model 683, USA) during the whole surgical procedure. A 3 cm incision was made in the skin of the right lateral chest wall between the right 4th and 5th ribs. The deep and superficial muscles covering the ribs were retracted to expose the intercostal muscle. A 1.5 cm incision was made in the intercostal muscle and pleura above the 5th rib. The blunt tines of a small self-retaining retractor (Goldstein retractor-1.8 cm spread, Germany) were coated with lubricant (Surgilube[®]) and placed between the 4th and 5th ribs. The retractor was opened 10 mm in width and was kept open for 60 min, as Buvanendran et al.¹⁰⁾ described previously. After the retraction period, the retractor was removed. Both the 4th and 5th ribs were approximated and ligated tightly using 3-0 chromic gut sutures. Air was aspirated from the pleural cavity with a 5 ml syringe attached to the tubing to restore normal intrapleural pressure. The superficial muscles covering the ribs were then apposed with 3-0 chromic gut sutures and the skin was closed with 3-0 nylon sutures. The animals were allowed to recover by themselves and the endotracheal catheter was removed when spontaneous breathing was reestablished.

2) Intercostal nerve block: The deep and superficial muscles covering the ribs were retracted to expose the intercostal muscle under general anesthesia. After confirming

the 3rd to 6th ribs, 0.05 ml of 0.5% bupivacaine (total 0.2 ml, 1 mg) was injected into the intercostal muscles just below the thoracic 3rd to 6th ribs relatively.

3. Experimental Protocol

The study was divided into two parts. The first part included the control group that underwent rib retraction (n = 25) to which intercostal nerve block was not performed. The second part comprised the two groups that underwent rib retraction to which intercostals nerve block was performed. The second part was performed by intercostal injection of bupivacaine either 10 min before placing the retractor (n = 17, preoperative group), or just after removing the retractor (n = 16, postoperative group). Behavioral testing had been always performed between 9 and 12 AM and was measured at the following time points: 1 d before and 1st, 3rd, 6th, 9th, 12th, 15th, 18th, and 21st d after surgery. For testing, rats were placed in individual semi-open plastic boxes, which allowed access to their chest wall, and were allowed to explore and groom until they settled. A series of calibrated von Frey filaments (Ugo-basile, Italy) with bending forces ranging from 0.4 to 15.0 g were applied perpendicularly to the dorsal skin surface (T3 to T6 dermatome) of the chest wall around the incision site with enough force to bend the filament for 6 sec. Escape behavior or scratching of the dorsal right upper back skin by the hindpaw within 6 sec of the application of a filament was considered positive response.¹⁰⁾ In the absence of a response, the filament of next greater force was applied. In the presence of a response, the filament of next lower force was applied. The tactile stimulus producing a 50% likelihood of withdrawal was determined using the up-down method, as previously described.¹⁴⁾ Each trial was repeated twice at approximately 2-min intervals, and the mean value was used as the withdrawal threshold. The rats that did not respond to even the highest force filament were assigned a value of 15.1 g while the rats that respond to even the lowest filament were assigned a value of 0.3 g. Mechanical allodynia was considered in the withdrawal threshold that was equal to or less than 4 g, a value that has been adopted in other rat models of neuropathic pain.¹⁴⁾

4. Statistical Analysis

Data are presented as mean \pm SE. Behavioral analysis comparisons until the 21st d after thoracotomy were performed by using the Kruskal-Wallis one way analysis of variance on ranks followed by Dunn's test. The comparisons of incidence at the 21st d after thoracotomy among the groups were performed by using the Fisher's exact test. $P < 0.05$ was considered as statistically significant.

RESULTS

Twelve (48%) out of the 25 rats in the control group, 1 (5.9%) out of the 17 rats in the preoperative group, and 2 (12.5%) out of the 16 rats in the postoperative group developed mechanical allodynia at the 21st d after thoracotomy (Fig. 1). The incidence of development of mechanical allodynia measured at the 21st d after thoracotomy in the preoperative group was significantly lower than the control group ($P < 0.05$). The values of withdrawal threshold measured at the 21st d after thoracotomy in the control, preoperative, and postoperative groups were 8.3 ± 7.3 , 14.0 ± 3.7 , and 12.8 ± 5.1 , respectively (Fig. 2).

The withdrawal thresholds measured from the 15th to the 21st d in the preoperative group were significantly higher than that of the control group ($P < 0.05$) (Fig. 3).

DISCUSSION

This study showed that preoperative intercostal nerves block with bupivacaine reduced the incidence of the development of mechanical allodynia in an animal model of postthoracotomy pain.

Thoracotomy is one of the most painful surgical procedures known, with multiple sources of nociception, including the surgical incision, disruption of ribs and intercostal nerves, pleural inflammation, pulmonary parenchymal damage, and the presence of post operative intercostal drains. A significant proportion of patients undergoing thoracotomy suffer from chronic pain.

The incidence of CPTP is reported to be 44–67%^{15,16)} and the pain is severe in 25% of these patients.¹⁷⁾

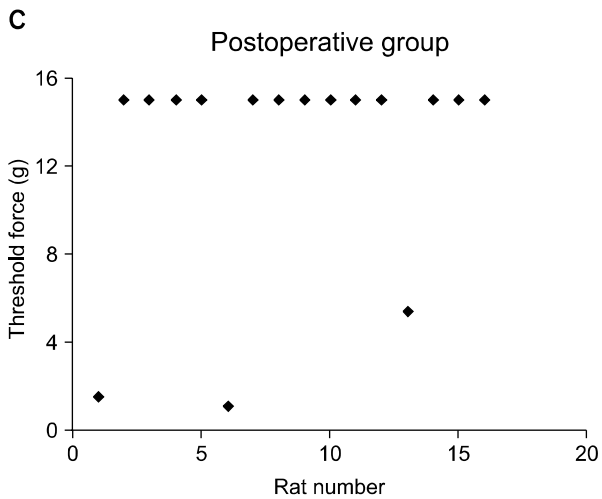
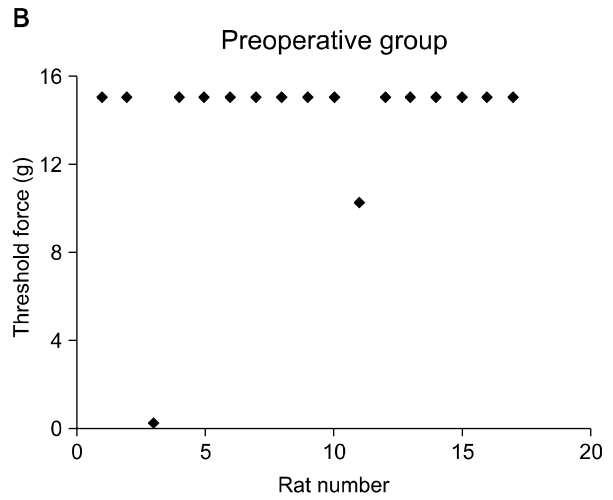
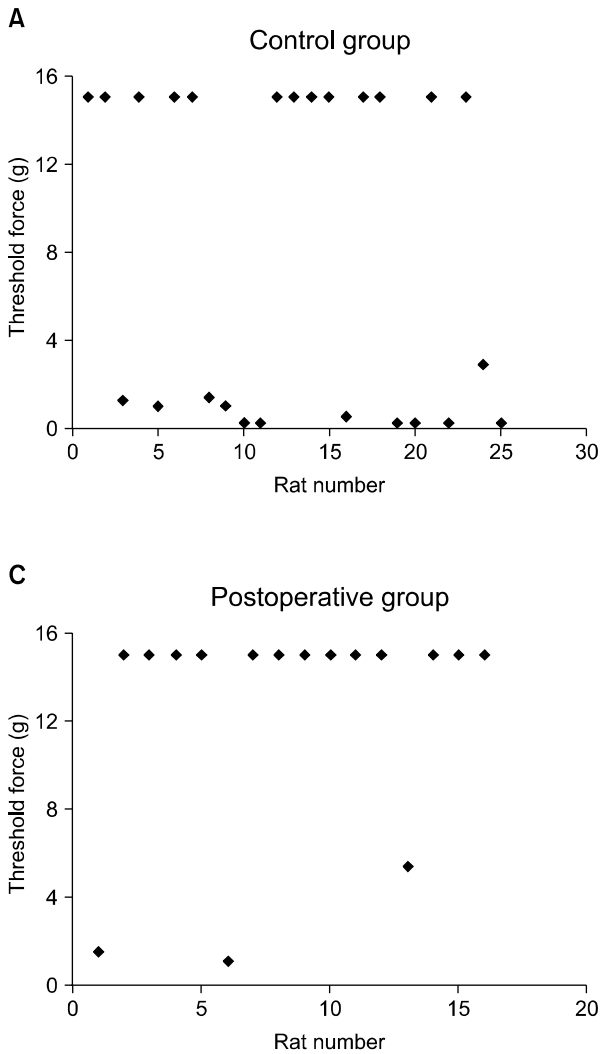


Fig. 1. Scattered distribution of withdrawal threshold (in grams) measured at the 21st d after thoracotomy. Each data point is the mean \pm SE, (A) Control group, 12 out of 25 rats (48%) developed allodynia, (B) Preoperative group, 1 out of 17 rats (5.9%) developed allodynia, (C) Postoperative group, 2 out of 16 rats (12.5%) developed allodynia.

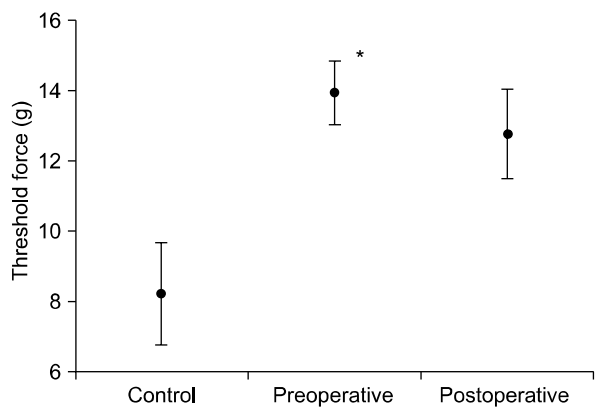


Fig. 2. The mean \pm SE of withdrawal threshold (in grams) measured at 21th d after thoracotomy.

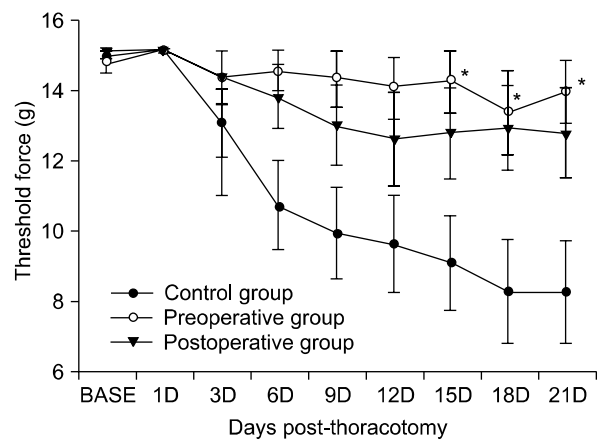


Fig. 3. Comparison of withdrawal threshold until 21d after thoracotomy. Each data point is the mean \pm SE, * $P < 0,05$ compared with control group by Kruskal-Wallis one way analysis of variance on ranks and Dunn's test.

The characteristics of CPTP are mechanical and thermal allodynia and the typical pain is described as a continuous dysesthesia with burning and aching sensations in the general area of the thoracotomy incision. Because the site of the pain is usually along the distribution of the peri-incisional intercostal nerves, they have been implicated in this neuropathic pain syndrome.^{16,18)}

The known main cause of CPTP is the application of the rib retractor for a long time which, in turn, induces intercostal nerve injury. Such nerve injury can be a result of pressure on the nerve transmitted from the retractor tines (causing direct axonal compressional injury or ischemic injury) or the stretching of the intercostal nerve at both edges of the retractor as a result of the displacement of the tissue containing the nerve.⁹⁾ Buvanendran et al.¹⁰⁾ reported that allodynia in this rib-retraction model is associated with the loss of nearly all myelinated fibers at the 14th d after surgery. Another clinical study has shown that rib retraction alone consistently caused total conduction block in the intercostal nerves on both sides of the retractor.¹⁹⁾

Highly effective postthoracotomy pain relief has been demonstrated using such a multifaceted approach, and the intercostal block appears to be the most important component for postthoracotomy pain relief.²⁰⁾ Moiniche et al.²¹⁾ reported whether analgesic agents are given preoperatively or postoperatively, it does not seem to be important. However, an early pain relief is considered better and has been associated with a lower incidence of CPTP,^{22,23)} which is consistent with the theory of the pathophysiology of chronic pain. For this reason, we suggested that preoperative intercostal nerves block with bupivacaine may reduce the incidence of the development of mechanical allodynia in an animal model of postthoracotomy pain.

This postthoracotomy model is the best one among other neuropathic pain models because the surgical procedure for making this model and the incidence (about 50%) of postthoracotomy pain are very similar to that observed in humans.

In this study, 48% of rats in the control group developed mechanical allodynia which is roughly similar to the incidence of allodynia in the study of Buvanendran et al.¹⁰⁾ However, the incidence (5.9%) of mechanical allodynia in

the preoperative group was significantly lower than that in the control group.

We suggest two mechanisms for these results. First is preemptive analgesia performed before placing of rib retractor and second is neuroprotective effect of bupivacaine in nervous system.

The proposed mechanism of the preemptive effect is that the administration of analgesia before a nociceptive stimulus reduces the degree of sensitization produced in the nervous system by the stimulus and thereby reduces the risk of a CPTP.²⁴⁾ There is a possibility that the preoperative intercostal nerve block might prevent the peripheral and central sensitization produced in the nervous system by the stimulus.

Local anesthetics do not only block voltage-dependent sodium channels but also inhibit calcium or potassium channels, and consequently have a neuroprotective action against ischemic insult in the central nervous system.^{25,26)} Unlike other local anesthetics, bupivacaine blocks potassium conduction strongly. Bupivacaine reduces the depolarization of hippocampal neurons resulting from glucose deficiency and hypoxia, and re-provides glucose and oxygen, leading to the recovery of normal membrane potential.²⁵⁾

Another neuroprotective action of bupivacaine is that, by blocking neuronal calcium channels, it prevents the entry of calcium in injured and perilesional cells. In this manner, it reduces the ischemic lesion of the gray matter, the primary element of the secondary lesion. Even if these neuroprotective mechanisms of bupivacaine have been approved in the central nervous system, there is a possibility that these mechanisms might affect the peripheral nervous system in a similar manner.

We suggest that these neuroprotective effects of bupivacaine might decrease the degree of ischemic injury in the intercostal nerve by the rib retractor and the incidence of development of mechanical allodynia.

In conclusion, intercostal nerves block before thoracotomy may decrease the incidence of CPTP. However, more animals and histological assessment of intercostal nerves are necessary to clarify this result.

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