

## Simultaneous Administration of Pregabalin and Loxoprofen Provides Superior Acute Pain Relief after Thoracic Surgery

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### Abstract

**Introduction:** Administering nonsteroidal anti-inflammatory drugs (NSAIDs) alone are not always sufficient for acute postoperative intercostal pain relief after thoracic surgery. We evaluated the efficacy of combined administration of pregabalin and loxoprofen compared to continuous ropivacaine epidural infusion.

**Methods:** From April to October 2011, 40 patients underwent thoracic surgeries at our institution. Postoperatively, continuous epidural analgesia with 0.2% ropivacaine hydrochloride was administered to 20 patients (Epidural group), and one pregabalin 75 mg capsule and one loxoprofen 60 mg tablet were administered orally twice a day to the other 20 patients (Pregabalin group). The total numbers of additional analgesics required from the day of surgery to postoperative day 2 were statistically compared between the groups. There were three additional pro re nata (p.r.n.) analgesics offered: loxoprofen 60 mg tablet, diclofenac sodium 25 mg suppository, and pentazocine 15 mg intramuscular injection. Retrospectively, the total number of p.r.n. administration was counted based on the medical records' documentations.

**Results:** The mean number of p.r.n. analgesics administered was significantly lower in the pregabalin group ( $2.4 \pm 1.8$  vs.  $1.2 \pm 1.4$  times;  $p = 0.034$ ).

**Conclusion:** Pregabalin can significantly augment the analgesic effect of NSAIDs for acute postoperative pain after thoracic surgery.

**Key words :** Pregabalin; Postoperative pain; Thoracic surgery, Analgesia

### Introduction

Severe acute postoperative intercostal pain is one of the serious clinical problems associated with thoracic surgery, even after the development of video-assisted thoracic surgery (VATS)<sup>1,2)</sup>. However, administration of nonsteroidal anti-inflammatory drugs (NSAID) alone is not sufficient to control such pains. It has been the generally recommended pain measure to combine continuous epidural analgesia and NSAIDs administration for such pain<sup>1,3,4)</sup>. However

anesthesiologists sometimes elect not to place epidural catheters to cut the anesthesia induction time, especially during non-elective surgeries<sup>3)</sup>. In such cases, we often perform an intercostal nerve block intraoperatively by injecting local anesthetics<sup>1)</sup>. As compared to continuous epidural infusion though, the duration of this nerve block lasts only a few hours at most, and then additional analgesics, such as NSAIDs, are often required postoperatively<sup>1,3)</sup>. Some adjuvant analgesic agents to augment the effect of NSAIDs are therefore often desired.

Pregabalin is a new class of oral analgesic recently

introduced and has been in application for various types of pain, mainly for post-herpetic neuralgia<sup>5-8)</sup>. Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system, which exhibits potent anticonvulsant, analgesic and anxiolytic activity<sup>9)</sup>. Although limited evidence supports its analgesic efficacy for acute postoperative pain, it theoretically may reduce such pain<sup>5-9)</sup> and reinforce the effect of NSAIDs. Therefore, we investigated the analgesic effects of combined administration of pregabalin and a NSAID after thoracic surgeries, as opposed to analgesia achieved by continuous epidural infusion.

### Subjects and Methods

From April to October 2011, 40 patients (30 males and 10 females, mean age: 46.0 years) underwent thoracic surgeries at our institution (Table 1). The underlying conditions were 21 pneumothorax patients, 11 lung cancer, and 8 other conditions such as metastatic lung tumors, neurilemmoma, and thymoma. Partial lung resection was performed in 22 patients, lobectomy in 11, and resection of mediastinal tumors in 7 patients. Thirty six patients received VATS and 4 had open thoracotomy. Three small ports were employed in most of the VATS but a 4-8 cm length access port and two

small ports were used for lobectomy cases. Combination of general anesthesia and epidural analgesia has been the common anesthesia technique for elective thoracic cases at our institution. But the epidural catheter placement will sometimes be skipped or aborted by anesthesiologists' discretion, especially in non-elective cases to cut induction time or when they have difficulties placing the catheter. Of course, however, anesthesiologists did not intentionally select patients in whom epidural catheter placement was skipped or aborted. The main reasons were merely because anesthesiologists could not keep to their initial plans due to an unexpected tight schedule of the operating room on a day. Eventually, general anesthesia with epidural was provided to 20 patients, and the remaining 20 received general anesthesia and intercostal nerve blocks via ropivacaine hydrochloride sub-pleural injection performed by surgeons intraoperatively. A total of 20 mL of 0.75% ropivacaine hydrochloride was injected into a few intercostal levels where the port placements and thoracotomies were done. Postoperatively, the 20 patients with epidural catheters were continuously injected with 0.2% ropivacaine hydrochloride at 2-4 mL/hr through the catheter using a regional analgesia infuser system (Baxter INFUSOR Multirate; Baxter International Inc, U.S.A.)<sup>10)</sup> Of note, patient-controlled analgesia is not implemented in our institution. These

Table 1 Patient Characteristics

Variable	Pregabalin	Epidural
Patients, No.	20	20
Gender, No.		
Male	15	15
Female	5	5
Age, mean (range), y	46.8 (16-78)	45.2 (17-78)
Diagnosis, No.		
Lung cancer	5	6
Pneumothorax	10	11
Other	5	3
Surgical approach, No.		
VATS	17	19
Open	3	1
Surgical procedure, No.		
Lobectomy	5	6
Wedge resection	11	11
Other	4	3

**Table 2 The total numbers of patients using additional analgesics**

Variable	Pregabalin	Epidural	<i>p</i> Value
Loxoprofen tablet, No.	8	17	0.0090
Diclofenac sodium suppository, No.	6	5	0.72
Pentazocine injection, No.	3	1	0.60
None, No.	8	3	0.157

20 patients with epidural infusions were defined as the “Epidural group”, whereas the remaining 20 patients without epidurals were administered one pregabalin 75 mg capsule and one loxoprofen 60 mg tablet twice a day orally starting three hours after surgery. The 20 patients who received intercostal nerve blocks followed by enteral administration of pregabalin and loxoprofen were classified as the “Pregabalin group”. The characteristics of the two groups are shown in Table 1. Every patient had a 28Fr chest drainage tube placed intraoperatively which was then removed during the postoperative course.

We looked up the number of times that patients had required additional analgesics from the day of the operation to postoperative day 2 (POD2). If patients complained of postoperative pain, nurses independently assessed their conditions and administered additional analgesics without any restrictions, choosing from the following options: oral administration of loxoprofen 60 mg, rectal administration of diclofenac sodium 25 mg, or intramuscular injection of pentazocine 15 mg. In both groups, basically, some four hours interval was required to the next administration of additional analgesia. These data were retrospectively collected from the clinical records documented by nurses, and the number of times was statistically compared between the two groups. Incidentally, the investigation duration was unified to 3 days, from the day of surgery to POD2. This was because we assumed the removal of chest tubes on POD2 in some cases might contribute to decreased pain level.

The data were statistically analyzed using the StatMateIII software program (ATMS Inc, Tokyo, Japan). The number of times that patients required additional administration of analgesics was compared between the two groups by Welch’s *t*-test. A *p* value < 0.05 was considered to be statistically significant.

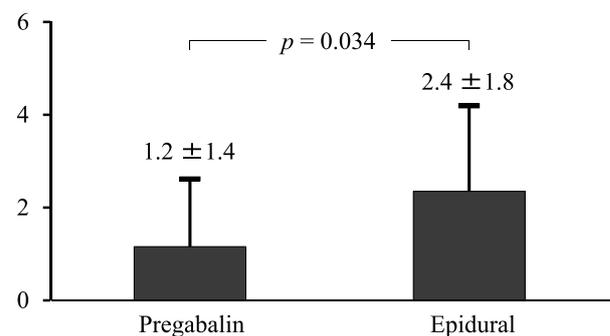
The study protocol was informed to all patients involved. Before each operation, written consent

was obtained from all patients giving us permission to include their information in our study, with an understanding that their privacy would be protected.

## Results

There were no significant differences between the two groups in terms of age, gender, and surgical procedures. In both groups, there were no morbidities or mortalities. No analgesic-induced complications occurred in either group.

The mean number of times of additional analgesics were used from the day of the operation until POD2 were  $1.2 \pm 1.4$  in the Pregabalin group and  $2.4 \pm 1.8$  in the Epidural group; which was significantly lower in the Pregabalin group ( $p = 0.034$ ; Fig.1). The breakdowns of the use by different subgroups are shown in Table 2. No significant difference was found between the two groups in terms of the number of patients who did not require any additional analgesics (Yates’s chi-squared test,  $p = 0.157$ ).



**Figure 1.** The mean number of times additional analgesics were used from the day of the operation to POD2. POD = postoperative day

## Discussion

Even with the introduction of VATS, severe postoperative pain due to intercostal nerve injuries is still a

serious clinical issue after thoracic surgeries<sup>1,2)</sup>. Various analgesics, including opioids have been applied for such pain. However, adverse effects such as somnolence, nausea and vomiting are relatively common in opioid analgesics<sup>7)</sup>, and appetite loss associated with the nausea would adversely affect the prompt recovery<sup>4)</sup>. NSAIDs, on the other hand, often fail to achieve satisfactory pain relief if used alone<sup>2,3,5)</sup>. Continuous epidural infusion with a small amount of opioid analgesics plus administration of NSAIDs is currently recommended for postoperative analgesia<sup>4)</sup>. This recommendation means that NSAIDs somewhat require adjuvant or augmentation in their analgesic potency.

Pregabalin is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system, and it has been reported to block pain transmission through peripheral nerves<sup>8,9)</sup>. There are other nonopioid analgesics that work via the central nervous system; some antidepressants such as gabapentin have been known to have an analgesic effect<sup>11)</sup>, although the mechanism of action has not been clearly elucidated. Regarding gabapentin, it is mainly applied not for acute pain, but for chronic pain after conditions such as a stroke<sup>11,12)</sup>. However, such antidepressants almost always induce drowsiness and dizziness<sup>11,12)</sup>. Pregabalin, which also works via the central nervous system, has similar side effects<sup>7)</sup>. Nonetheless, according to our limited study, no side effects were noted following the administration of 150 mg of pregabalin a day. Of course, but this may have been because the dose was too small to induce side effects. In general, pregabalin is used at dose range of 300 mg to 600 mg a day, initially starting from 150 mg<sup>7,13)</sup>. The side effects may be dependent on the dose<sup>7)</sup>. If the dose used for analgesia is increased, then such adverse effects may occur, and patients should be carefully monitored.

Our present study suggests that pregabalin can dramatically improve the analgesic effects of loxoprofen, although the mechanism of the synergy between pregabalin and loxoprofen still remains unclear. While it has been reported that pregabalin alone is not completely efficacious for acute postoperative pain<sup>14)</sup>, our combined administration of pregabalin and loxoprofen is a reasonable solution to complement for their weakness. Further investigations are warranted to evaluate this synergy, since our study is non-randomized with small number of patients.

Nevertheless, the decreased complaints of pain issues were clinically meaningful. Our method appears to be able to not only substitute for epidural infusions in those who had difficulty placing catheters, but may also help providing much superior analgesia in patients even with working epidural infusion. Moreover, this method is simple and easy to manage. We believe this treatment combination can be considered as a way to provide effective analgesia in the acute postoperative phase. As we did not investigate the long-term effectiveness of pregabalin and loxoprofen use or the optimum dosing of the agents, further investigations are needed to examine these issues.

In conclusion, the combined administration of pregabalin and loxoprofen can effectively treat acute postoperative pain after thoracic surgery. It is important to try proactively to treat such severe pain in a multimodal approach employing various types of analgesics, including, but not limited to this method.

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