

Incidence rate of chronic pain after 1.5–2 years of thoracotomy between paravertebral block versus epidural block: a cohort study

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ABSTRACT

Paravertebral block and epidural block are frequently employed for post-thoracotomy pain relief. It is not clear which postoperative analgesia method is effective for the chronic pain after the postoperative long term progress. Our hypothesis was that paravertebral block would be more effective than epidural block for chronic pain 1.5–2 years after thoracotomy. A cohort study investigating postoperative pain was performed in lung cancer patients undergoing thoracotomy between the ages of 20–80 year-old, employed for another randomized controlled trial. In previously study, the patients were randomly allocated into either the epidural block or paravertebral block group ($n = 36/\text{group}$). Patients in each group received the respective block placement with continuous 0.2% ropivacaine infusion at 5 ml/h. The patients completed a telephone observational survey using the EQ-5D-5L at 1.5–2 years. Forty-eight patients, 23 in the epidural block group and 25 in the paravertebral block group, were included in the final analysis. Quality of life scores at 1.5–2 postoperative years was similar in both groups. Mean scores \pm standard deviation and 95% confidence interval were 0.899 ± 0.081 (0.705–0.938) in the epidural block group and 0.905 ± 0.079 (0.713–0.938) in the paravertebral block group, respectively, $p = 0.81$. The incidence rate of chronic postsurgical pain was eight patients; four in the epidural block group (17.4%) and four in the paravertebral block group (16.0%). There was no difference in incidence rate of long-term chronic postsurgical pain at 1.5–2 years after thoracotomy between the both groups. Our result will be used for further study protocols.

Keywords: chronic pain, paravertebral, epidural, thoracotomy

Abbreviations:

Epi: epidural block

PVB: paravertebral block

CPSP: chronic postsurgical pain

NRS: Numeric Rating Scale

RCT: randomised controlled trial

QALY: Quality-Adjusted Life Year

SD: standard deviations

Received: June 29, 2021; accepted: December 28, 2021

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INTRODUCTION

Thoracotomy incisions are thought to be one of the most painful surgical incisions, as they involve a large amount of trauma on pain-sensitive structures.^{1,2} Epidural block (Epi), systemic opioids, or nerve blocks are employed for postoperative care.^{1–3} Epi is considered the gold standard for post-thoracotomy pain relief.⁴ Recently, paravertebral block (PVB) has gained popularity for post thoracotomy pain relief because of less side effects.^{3,5–8}

Chronic postsurgical pain (CPSP) is defined as pain lasting at least three months after surgery. Kehlet et al. found that CPSP occurs in 10–50% of surgical patients and is categorized as severe in 2–10% of those patients, interfering with daily activities.⁹ In a study on postoperative pain, Bendixen et al. compared pain associated with video-assisted thoracoscopic surgery with pain associated with open thoracotomy. Pain rated of 3 or higher on the Numeric Rating Scale (NRS) was significantly less at 52 weeks after video-assisted thoracoscopic surgery. However, patients with pain rated 7 or greater on the NRS did not significantly differ between the two groups.¹⁰ Differences in postoperative analgesia may be related to the development of CPSP. Previous studies comparing these two modes of analgesia have found the two blocks equivalent in terms of acute pain management; however, PVB was not associated with hypotension or urinary retention. Compared with Epi, PVB has the potential to completely block painful nerve signals from reaching the spinal cord.^{11,12} This total blockade of nerve signals could remove the stimulus, called central sensitization, which underpins the formation of chronic pain pathways. Therefore, PVB could be uniquely effective in preventing long-term pain.¹³

A Cochrane review recommended that a high-quality randomised controlled trial (RCT) comparing the incidence of chronic pain between Epi and PVB be performed.¹⁴ In a future large study, we plan to evaluate the incidence of CPSP and postoperative analgesia quality of life after a one-year period. Specific aim of our current study was to assess the feasibility of conducting a larger trial and enhance the likelihood of its success by developing the necessary structure and processes that a large trial would need. Fortunately, the authors had the opportunity to evaluate postoperative acute pain in an RCT, so they had the opportunity to use that patient group to make a long-term comparison. Therefore, this patient group was classified into the chronic pain group and the non-chronic pain group, and a cohort study which examined both incidence of chronic pain after long-term postoperative course and whether the postoperative analgesia method was related was planned.

METHODS

Design and patients

This study received institutional review board approval from the Japanese Red Cross Nagoya Daiichi Hospital (Nagoya, Japan, IRB-2019-273) and was registered with the University Hospital Medical Information Network (Study ID: UMIN000010187).¹⁵ An RCT evaluating acute pain was performed, comparing PVB and Epi for thoracotomy. The patients were approached 1.5–2 years later to participate in long-term postoperative chronic pain and quality of life surveys. Details of the anaesthetic management and perioperative treatment plan were previously published.¹⁵ A simplified overview of the anaesthetic management is as follows. Patients scheduled for elective single-side lung lobectomy with antero- or vertical-axillary incision were between the ages of 20–80 years old and had an American Society of Anaesthesiologists physical status of I–II. Eighty patients were

allocated randomly to receive either Epi or PVB. General anesthesia was immediately induced in group PVB, while an epidural catheter was inserted before anesthesia induction in group Epi. Epidural catheter did not use during surgery intervention. General anesthesia was induced with fentanyl (2 µg/kg) and propofol (1.5–2.5 mg/kg). Remifentanyl (0.25–0.40 µg/kg/min) and rocuronium (0.6–0.8 mg/kg) were used to facilitate tracheal intubation. A 20-gauge radial artery cannula was used for blood pressure monitoring and blood sampling. No fentanyl was administered after the induction of general anesthesia, which was maintained using air, oxygen, remifentanyl (0.25–0.50 µg/kg/min), and sevoflurane (1.0–1.5%). In group PVB, the catheter was inserted into the operative field by the surgeon after surgery intervention. A continuous infusion of 0.2% ropivacaine at 5 mL/h was used for both groups. Pain was defined as pain of the surgical skin incision. Exclusion criteria were patients with recurrent lung cancer and patients we were not able to connect with.

In previous our RCT, 50 mg of indomethacin was administered in suppository form to the patients immediately after surgery. Additional analgesic drugs, such as flurbiprofen axetil, pentazocine, loxoprofen sodium hydrate, and the antiemetic metoclopramide were administered on patient demand. Eighteen hours after the surgery interbention, 400 mg of celecoxib was administered, followed by 200 mg twice daily thereafter.

Evaluation of outcomes

The Quality-Adjusted Life Year (QALY) rating provided by the EQ-5D-5L¹⁶ survey was used as a primary outcome measure at 1.5–2 postoperative years. This is a validated quality of life assessment tool. We used the Japanese sentences¹⁷ of EQ-5D-5L approved by Euro QoL, the developer. (Table 1 and Supplementary Table 1) The EQ-5D-5L was developed to improve the measurement sensitivity and reduce the ceiling effect of the EQ-5D-3L, which was developed for the purpose of quantitatively evaluating the health-related quality of life, and to be applicable to a wider range of subjects. EQ-5D-5L is a “preference-based measure” mainly used to calculate QALY. It is available in more than 130 languages and is used worldwide. NRS was employed for pain score, and NRS evaluates the patient’s pain intensity on a scale of 0 to 10. Patients who rated pain as 4 or higher on the NRS were considered to have CPSP in this study. Previous studies were conducted from March 2013 to October 2014. A telephone survey was conducted between March and April 2015 for this group of patients.

Table 1 EQ-5D-5L (English version)

1. MOBILITY	I have no problems in walking about. I have slight problems in walking about. I have moderate problems in walking about. I have severe problems in walking about. I am unable to walk about.
2. SELF-CARE	I have no problems washing or dressing myself. I have slight problems washing or dressing myself. I have moderate problems washing or dressing myself. I have severe problems washing or dressing myself. I am unable to wash or dress myself.
3. USUAL ACTIVITIES (eg, work, study, housework, family or leisure activities)	I have no problems doing my usual activities. I have slight problems doing my usual activities. I have moderate problems doing my usual activities. I have severe problems doing my usual activities. I am unable to do my usual activities.

4. PAIN / DISCOMFORT	I have no pain or discomfort. I have slight pain or discomfort. I have moderate pain or discomfort. I have severe pain or discomfort. I have extreme pain or discomfort.
5. ANXIETY/DEPRESSION	I am not anxious or depressed. I am slightly anxious or depressed. I am moderately anxious or depressed. I am severely anxious or depressed. I am extremely anxious or depressed.

Statistical analysis

Previous RCT was designed to have 80% power to detect a significant difference of 0.7 standard deviations (SD) between treatment groups via the visual analogue scale at rest 2 h after surgery, according to a preliminary examination.¹⁷ We used Fisher's exact test to compare chronic pain rates. A student's t-test was used to analyse health-related quality of life. A Pearson Chi-square test was also used where appropriate. $P < 0.05$ was deemed statistically significant. All data were analysed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between March 2015 and December 2016, we attempted to survey 72 patients by telephone. From the original acute pain study conducted two years prior, 10 patients in the Epi group and six patients in the PVB group had died. Three patients in the Epi group and five patients in the PVB group were unreachable. Thus, 48 patients were included in the final analysis, 23 patients in the Epi group and 25 patients in the PVB group (Figure 1). Perioperative demographics

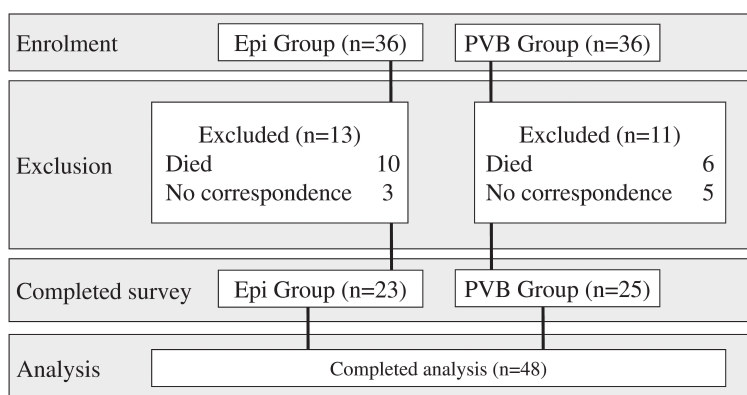


Fig. 1 Participant flow diagram

Of the 72 patients we attempted to survey, seven patients in the Epi group and nine patients in the PVB group had already died, and there was no correspondence from four patients in the Epi group and four patients in the PVB group. Data from 48 patients, 23 patients in the Epi group and 25 patients in the PVB group, were included in the final analysis. Epi, epidural block; PVB, paravertebral block. No correspondence means that we couldn't make contact with the patients because they would not take the phone call or had moved.

and surgical characteristics, including duration of anaesthesia, surgery, and hospitalization, were comparable in both groups.¹⁵

Quality of life scores rated using the EQ-5D-5L survey tool at 1.5–2 postoperative years were similar for both groups; mean scores \pm SD (95% CI), 0.899 ± 0.081 (0.705–0.938) in the Epi group and 0.905 ± 0.079 (0.713–0.938) in the PVB group, respectively, $p = 0.81$. All 48

Table 2 Demographics and surgical characteristics by chronic pain onset or not

	NRS < 4 (n=40)	NRS \geq 4 (n=8)	<i>P</i> value
Age (years)	66.5 \pm 10.0	65.9 \pm 10.8	0.817
Height (cm)	163.1 \pm 9.2	159.5 \pm 7.6	0.338
Body weight (kg)	60.2 \pm 11.4	57.0 \pm 15.2	0.526
Male : Female (number of cases)	36 : 4	6 : 2	0.241
Surgery			
Upper lobe/middle/lower (number of cases)	25/4/11	5/0/3	—
Duration of anaesthesia (min)	244.1 \pm 49.3	254.9 \pm 58.6	0.649
Operation time (min)	178.0 \pm 54.1	190.13 \pm 59.8	0.604
Hospitalization after surgery (day)	14.0 \pm 22.3	12.6 \pm 9.3	0.741
Postoperative days (day)	672.7 \pm 117.4	680.0 \pm 148.3	0.604
Epi Group/PVB Group (n=)	21/19	4/4	0.8972

NRS: Numerical Rating Scale

Epi: epidural block

PVB: paravertebral block

Data are mean \pm SD (n=48).

Statistical significance of differences between the two groups was assessed using two-tailed t-test and Pearson Chi-square test.

Table 3 Demographics and surgical characteristics by regional anesthesia method

	Epi (n=23)	PVB (n=25)	<i>P</i> value
Age (years)	66.7 \pm 9.4	67.1 \pm 9.7	0.881
Height (cm)	160.9 \pm 8.1	165.0 \pm 8.6	0.100
Body weight (kg)	56.3 \pm 9.1	64.1 \pm 12.5	0.016*
Male : Female (number of cases)	19 : 4	23 : 2	0.407
Surgery			
Upper lobe/middle/lower (number of cases)	13/8/2	17/6/2	—
Duration of anaesthesia (min)	247.3 \pm 63.1	249.2 \pm 48.1	0.907
Operation time (min)	174.7 \pm 64.0	181.9 \pm 46.4	0.665
Hospitalization after surgery (day)	11.0 \pm 2.7	10.3 \pm 3.4	0.471
Postoperative days (day)	670.9 \pm 175.5	670.1 \pm 159.3	0.987

Epi: epidural block

PVB: paravertebral block

Data are mean \pm SD (n=48).

Statistical significance of differences between the two groups was assessed using two-tailed t-test and Pearson Chi-square test.

*; $p < 0.05$

patients were divided into chronic pain with NRS scores ≥ 4 and non-chronic pain with NRS scores < 4 , as shown in Table 2. The incidence of CPSP, defined as NRS scores ≥ 4 , was eight patients, four in the Epi group (17.4%) and four in the PVB group (16.0%). There was no significant difference between the two groups, $p = 0.89$. All 48 patients were divided into Epi group and PVB group, as shown in Table 3. There was no significant difference between both groups except for body weight.

DISCUSSION

CPSP is pain that persists for at least three months after surgery, as suggested by Macrae et al.¹⁸ and revised by Werner et al.¹⁹ Multiple mechanisms are involved in the generation of CPSP: surgical neuropathy, abnormal neuronal firing, changes in dorsal root ganglion or spinal cord function, abnormalities in descending pain control pathways, and higher order functions such as limbic system function, cognitive behavior, and genetic predisposition. Postoperative pharmacologic pain management and behavioral therapy have been discussed to reduce CPSP.^{20,21} Unfortunately, it has been difficult to obtain the opportunity to manage postoperative pain after patients leave our hospital. This study provided us the opportunity to compare pure effects for long-term CPSP after thoracotomy in the PVB group with that in the Epi group. Because CPSP involves complex factors, evaluation of CPSP only using the presence or absence of pain and major pain and NRS pain scores are insufficient. In the current study, we compared PVB group and Epi group EQ-5D-5L and NRS scores at 1.5–2 years after thoracotomy. Our results show the following findings. First, there was no difference between the PVB and Epi groups in terms of Quality-Adjusted Life Year ratings and incidence of long-term pain. Second, as many as about 16% of patients rated pain with NRS scores of 4 or greater 1.5 to 2 years after thoracotomy. Third, cancer death should be considered in the chronic pain assessment when planning coming RCTs.

Epi has been shown to reduce the incidence of CPSP at six to 12 months after thoracotomy.²² However, few reports have evaluated long-term thoracotomy chronic pain for longer than one year. In addition, PVB has the potential to completely block painful nerve signals from reaching the spinal cord.^{11,12} When pain becomes intractable, signs such as immobilization and disuse appear, resulting in a decrease in activities of daily living. Assessment of quality of life is important because goals after CPSP include improvement of the patient's functional recovery and quality of life. Our study results indicated that both quality of life scores and the incidence of chronic pain in the PVB group were not significantly different from those in the Epi group, and the long-term results regarding CPSP after thoracotomy were equivalent in both groups. Our study cannot verify whether both analgesic techniques are effective in preventing outbreaks of CPSP because we did not evaluate CPSP at three months. However, reports of incidence rate of CPSP in the PVB group after prolonged periods of time are rare and may point to the need for future large-scale studies.

A wide range of incidence rates ranging from about 10% to 80% have been reported for CPSP in thoracotomy due to variable assessment methods.²³ The incidence was assessed in this study using the NRS score of 4 or greater to define moderate or greater pain. The incidence was not significantly different between the two groups and was considered to be the incidence of prior reports and degree of identification. CPSP is a complex disease state in which surgery-related factors such as the type and degree of invasiveness and patient-related factors such as psychophysiologic factors and individual differences are related, and it is necessary to evaluate not only the presence and intensity of pain but also its multiple facets. Identifying additional

measures that should be incorporated into future large-scale studies should be considered. In addition, the three-year survival rate of lung cancer in Japan is around 80%, 60%, and 30% in stage I, stage II, and stage III, respectively.²⁴ In planning for any future studies, a high dropout rate should be anticipated for this patient population. Considering both the high lung cancer mortality rate and not being able to connect with patients, 30–40% dropout rates will need to be expected for future larger prospective studies.

This study has some limitations that should be addressed. First, the chronic pain evaluation method was imprecise. Various factors are involved in the pathogenesis of CPSP, and simple subjective evaluations^{25–28} such as the presence or absence of pain, NRS, and visual analogue scale score, do not adequately assess CPSP. If objective assessment method linked to pain could be found, it would lead to a unified assessment method; however, no such tool exists.²⁹ Although there various methods can be used to evaluate quality of life, such as the SF-6D, Health Utilities Index, and EQ-5D, we decided to use the EQ-5D in this study because the Japanese translation is readily available and it can accurately survey patients. Lastly, pain was managed in hospital wards and outpatient settings by the thoracic surgeon. Thus, it was difficult to determine successive changes in pain and the association between oral drugs and CPSP. Previous studies were conducted from March 2013 to October 2014. A telephone survey was conducted between March and April 2015 for this group of patients. Thus, the postoperative period for evaluation varied from 1.5 to 2 years postoperatively. Unification of postoperative days will provide more accurate results for future large studies. We believe these limitations will help plan future large-scale research for success.

In conclusion, there was no difference in the incidence of long-term CPSP and mean EQ-5D-5L scores at 1.5–2 years after thoracotomy between the PVB and Epi groups. The results of this study can be used to assess the feasibility of future large-scale trials and provide the information needed for large-scale trials, including the number of dropouts considering tumor prognosis. Further large-scale studies will need to be conducted to explore the relationship between CPSP prevention and incidence and postoperative analgesia methods such as PVB and Epi.

ACKNOWLEDGEMENTS

We thank all anaesthesiology medical staff members of the Japanese Red Cross Nagoya Daiichi Hospital. The authors also thank Christine Burr (Scientific Writer, Department of Anaesthesiology and Perioperative Medicine/Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA) for her editorial assistance with the manuscript.

MEETING PRESENTATION

Part of this manuscript was presented in the 63rd annual meeting of the Society of Japanese Anesthesiologists at Kobe, 2016, Japan.

CONFLICT OF INTEREST AND SOURCE OF FUNDING

This research did not receive any specific grant funding from agencies in the public, commercial, or non-for-profit sectors.

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APPENDIX

Supplementary Table 1 EQ-5D-5L (Japanese version)

A) 移動の程度	1 歩き回るのに問題はない 2 歩き回るのに少し問題がある 3 歩き回るのに中程度の問題がある 4 歩き回るのにかなり問題がある 5 歩き回ることができない
B) 身の回りの管理	1 自分で身体を洗ったり着替えをするのに問題はない 2 自分で身体を洗ったり着替えをするのに少し問題がある 3 自分で身体を洗ったり着替えをするのに中程度の問題がある 4 自分で身体を洗ったり着替えをするのにかなり問題がある 5 自分で身体を洗ったり着替えをすることができない
C) ふだんの活動	1 ふだんの活動を行うのに問題はない 2 ふだんの活動を行うのに少し問題がある 3 ふだんの活動を行うのに中程度の問題がある 4 ふだんの活動を行うのにかなり問題がある 5 ふだんの活動を行うことができない
D) 痛み／不快感	1 痛みや不快感はない 2 少し痛みや不快感がある 3 中程度の痛みや不快感がある 4 かなりの痛みや不快感がある 5 極度の痛みや不快感がある
F) 不安／ふさぎ込み	1 不安でもふさぎ込んでもいない 2 少し不安あるいはふさぎ込んでいる 3 中程度に不安あるいはふさぎ込んでいる 4 かなり不安あるいはふさぎ込んでいる 5 極度に不安あるいはふさぎ込んでいる