Original Article

Risk factors of neuropathic pain after thoracic surgery

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Background: This study aimed to clarify the incidence and risk factors of neuropathic pain after thoracic surgery, focusing especially on patients who underwent complete video-assisted thoracoscopic surgery (VATS).

Methods: We retrospectively identified 185 patients who underwent thoracic surgery at our hospital over a 2-year period. Logistic regression analysis was used to analyze the association of various factors with postoperative neuropathic pain.

Results: Forty-eight (25.9%) patients developed postoperative neuropathic pain, and 9 (18.8%) of these patients reported persistent pain 1 year postoperatively. The median interval from surgical treatment to the onset of neuropathic pain was 7 days, and the duration was 50 days. Multivariate logistic regression analysis revealed a significant positive correlation between postoperative neuropathic pain and preoperative use of hypnotic medication [odds ratio (OR), 5.45; 95% confidence interval (CI); 2.52–12.17] and duration of surgery ≥2.5 hours (OR, 2.72; 95% CI, 1.27–6.09), and a significant negative association with the complete VATS approach (OR, 0.18; 95% CI, 0.073–0.42).

Conclusions: Preoperative use of hypnotic medication, the thoracotomy approach, and duration of surgery ≥2.5 hours are associated with increased risk of neuropathic pain after thoracic surgery. The complete VATS approach could decrease the incidence of postoperative neuropathic pain, regardless of the duration of surgery.

Keywords: Neuropathic pain; thoracic surgery; video-assisted thoracic surgery; thoracotomy

Submitted Dec 31, 2017. Accepted for publication Apr 24, 2018.
doi: 10.21037/jtd.2018.05.25
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.25

Introduction

Neuropathic pain after thoracic surgery, known as post-thoracotomy pain, is common and sometimes severe. The pain often becomes chronic and is associated with symptoms including burning, shooting, shocking, pressure-like, and aching sensations (1). Chronic pain can cause insomnia and loss of appetite and may incapacitate patients, making daily activities difficult or impossible (2). Although there are several mechanisms for the development of chronic pain after thoracotomy, intercostal nerve damage and subsequent dysfunction has long been implicated. Many methods of pain management have been tested, and video-assisted thoracoscopic surgery (VATS) is believed to result in less severe postoperative pain.

Our hospital began using complete VATS lobectomy without a mini-thoracotomy in 2002 (3). Since then, most patients requiring lobectomy at our hospital have undergone complete VATS. Complete VATS is a minimally invasive procedure, and patients are discharged from the hospital sooner compared with patients who undergo thoracotomy. However, some patients who often denied

pain during the initial hospitalization return complaining of postoperative pain. Furthermore, the pain these patients describe is characteristic of neuropathic pain. Neuropathic pain can occur even after complete VATS without a mini-thoracotomy.

Neuropathic pain after thoracic surgery has been investigated previously, although many questions remain unanswered, including the onset, duration, location, and patient characteristics that may increase the risk of postoperative neuropathic pain. It is also unclear as to whether the incidence of neuropathic pain after complete VATS is equal to the incidence of VATS with a mini-thoracotomy. The purpose of this study was to determine the timing and perioperative risk factors of neuropathic pain after thoracic surgery, as well as whether the complete VATS approach has a lower incidence of postoperative neuropathic pain.

Methods

Study design and patients

In this retrospective study, we identified all patients older than 18 years who underwent thoracotomy or VATS at the Toyama University Hospital (Toyama, Japan) between January 2010 and December 2011. Exclusion criteria were as follows: previous history of thoracic surgery, preoperative neuropathic pain, or if a median sternotomy was performed. These dates were chosen to include all available data from our clinical database at the onset of this study. This study was approved by the Ethics Committee of the University of Toyama with a waiver of informed consent due to its retrospective design (RIN 29-52).

Inclusion criteria for patients with neuropathic pain

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory system" (4). We made use of validated neuropathic pain screening tools such as the Leeds assessment of neuropathic symptoms and signs and the related self-completed version to ensure consistency and reduce missing data between assessments in the acute and follow-up periods (5,6). Chronic pain was defined as pain that persisted for more than three months after surgery.

Surgical approach

General anesthesia was performed using a single-lung ventilation technique with a double-lumen endotracheal tube. Patients were placed in a lateral decubitus position. The most common surgical approach in this study was complete VATS. In cases of partial resection, mediastinal tumor resection, pleural/chest wall resection, and decortication, we performed VATS with three 5-mm ports. For lobectomy and segmentectomy cases, we used an additional 5-mm port and a subxiphoid incision to remove the resected lobe or lung segment (3). Patients with locally advanced carcinoma or cases in which a complex segmentectomy or partial resection of a deep-seated lung tumor was required typically underwent VATS with a mini-thoracotomy or an open thoracotomy. Three surgeons and their staff performed the surgeries, and complicated surgeries were performed by the chief surgeon. A 24-French chest tube was inserted at the end of each procedure.

Pain management

Figure 1 showed pain management algorithm. Standard perioperative pain control was performed using epidural analgesia, intravenous fentanyl, or oral analgesics. Epidural analgesia was considered to be the standard pain management technique. Intravenous fentanyl was administered to patients with contraindications for epidural analgesia, such as prolonged coagulation time, or patients who declined epidural analgesia.

Thoracic epidural catheterization was usually performed prior to anesthesia induction at the T4-5, T5-6, or T6-7 intervertebral space with a loss-of-resistance technique. Catheter placement was confirmed with a test dose of 4 mL of 1% lidocaine. The epidural infusion was started in the operating room. The drug combination in the continuous infusions was 2.0 mg/mL ropivacaine and 2.5 μg/mL fentanyl. The infusion rate was adjusted to between 2 and 4 mL/h.

In patients who did not received an epidural, intravenous fentanyl was started in the operating room. The fentanyl infusion rate was adjusted to between 0.01 and 0.04 mg/h. Epidural analgesia or the intravenous fentanyl infusion was stopped on the day of chest tube removal. When a chest tube was unable to remove, epidural analgesia or the intravenous fentanyl infusion was stopped by the postoperative day 14 according to pain.

Oral analgesics mostly consisted of the non-steroidal anti-inflammatory drug loxoprofen 180 mg/day beginning on the first postoperative day. In patients with an estimated glomerular filtration rate (eGFR) less than 50 mL/min,

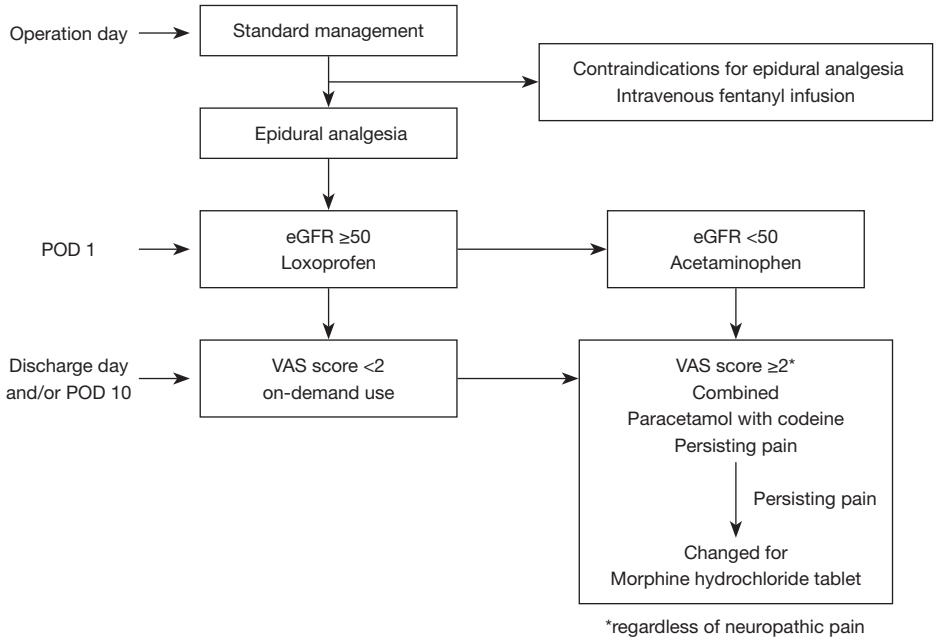

Figure 1 Postoperative pain management. POD, postoperative day; eGFR, estimated glomerular filtration rate; VAS, visual analog scale.

acetaminophen 1,200 mg/day was used in lieu of loxoprofen (7).

Pain was measured three times a day with the visual analog scale (VAS) during rest and coughing by floor nurses. The target level of pain control was a VAS score <2 during rest. When severe pain persisted beyond postoperative day 10 regardless of neuropathic pain, the patients were given oral opioids; the first choice was paracetamol with codeine, and the second choice was morphine hydrochloride tablet.

Variables and outcomes

The goal was to assess the perioperative risk factors of neuropathic pain after thoracic surgery. To do this, the following patient characteristics, surgical characteristics, and follow-up parameters were recorded: age, gender, smoking history, diabetes, body mass index (BMI), preoperative use of hypnotic medication, eGFR, diagnosis, diseased side, procedure type, surgical approach (complete VATS *vs.* thoracotomy), epidural analgesia, intraoperative blood loss, duration of surgery, chest tube duration, complications (prolonged air leak, defined as an air leak longer than 5 days, arrhythmia, pneumonia, delirium, acute respiratory distress syndrome, chylothorax), duration of postoperative hospitalization, postoperative acute pain requiring additional analgesics, number of analgesic doses used, postoperative neuropathic pain, and location and duration of postoperative neuropathic pain.

Statistical analysis

For the univariate analysis, differences between groups (i.e., patients who experienced neuropathic pain following surgery versus those who did not) were evaluated using a non-parametric Wilcoxon rank-sum test and either the χ^2 test or Fisher's exact test for categorical variables when necessary. Significance was defined as $P<0.05$.

Risk factors included in the multivariate analyses were selected on the basis of the univariate analyses, statistical independence, and clinical significance. Multivariate logistic regression was used to identify independent risk factors of neuropathic pain following thoracic surgery. A nominal logistic regression was initially performed with preoperative and intraoperative variables that were significant univariate predictors of the outcome being modeled. Due to the rarity of the outcome events being modeled, the variables identified in this step with a P value cutoff of 0.1 became candidates for the multivariate logistic regression models.

All reported P values are two-sided. The cutoff value for duration of surgery was set at 2.5 hours based on the results of a preliminary receiver operating characteristics analysis, which showed 153 minutes to be the optimal cutoff value with a C-index of 0.672. For intraoperative blood loss, 55 mL

Table 1 Patient backgrounds

Variable	Data
Age, median [range] {IQR}	68 [15–87] {57–76}
Gender, male/female	126/59 (68.1/31.9)
Smoking history, yes/no	98/87 (53.0/47.0)
BMI, median (range) [IQR]	22.3 (14.5–43.6) [19.9–24.8]
Preoperative use of hypnotic medication	53 (28.6)
eGFR (mL/min)	76.1±21.2
Diagnosis (%)	
Primary lung cancer	105 (56.8)
Metastatic lung tumor	21 (11.4)
Pneumothorax	13 (7.0)
Other lung disease	10 (5.4)
Mediastinal tumor	16 (8.6)
Empyema	6 (3.2)
Pleural/chest wall tumor	14 (7.6)
Malignant disease (%)	133 (71.9)
Diseased side, right/left	114/71 (61.6/38.4)
Procedure type (%)	
Partial resection	38 (20.5)
Segmentectomy	32 (17.3)
Lobectomy	79 (42.7)
Mediastinal tumor resection	16 (8.6)
Pleural/chest wall tumor resection	14 (7.6)
Thoracostomy	2 (1.1)
Decortication	4 (2.2)
Surgical approach, complete VATS/ thoracotomy	83/102 (44.9/55.1)
Epidural analgesia (%)	163 (88.1)
Intraoperative blood loss (mL), median [range] {IQR}	80 [1–2,800] {1–225}
Duration of surgery (min), median [range] {IQR}	148 [19–484] {94–214}
Chest tube duration (days), median [range] {IQR}	2 [0–62] {1–4}
Complications (%)	52 (28.1)
Prolonged air leak	22 (11.9)
Arrhythmia	17 (9.2)
Pneumonia	15 (8.1)
Delirium	5 (2.7)
ARDS	4 (2.2)
Chylothorax	4 (2.2)
Postoperative hospitalization (days), median [range] {IQR}	9 [2–152] [7–12]
Postoperative acute pain requiring additional analgesics (%)	98 (53.0)
Number of analgesic uses, median [range] {IQR}	2 [1–41] [1–4]
Postoperative neuropathic pain (%)	48 (25.9)

IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; VATS, video-assisted thoracoscopic surgery; ARDS, acute respiratory distress syndrome.

was also determined to be the cutoff value with a C-index of 0.744. All statistical analyses were performed with JMP software version 12.0 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 185 patients were enrolled in this study. The patient backgrounds are summarized in *Table 1*. Follow-up was completed in all patients within 12 months. Forty-eight (25.9%) patients developed postoperative neuropathic pain, and 9 (18.8%) of these patients reported pain that persisted one year postoperatively. The median interval from surgical treatment to neuropathic pain onset was 7 days, and the median duration of neuropathic pain was 50 days. All patients with neuropathic pain felt the pain along the anterior aspect of the surgical wound (including the nipple and epigastric region). No patients described neuropathic pain in other areas. Patients with postoperative neuropathic pain had significantly more severe acute postoperative pain that required additional analgesics [35 (72.9%) *vs.* 63 (46.0%); P=0.0014], higher frequency of analgesic use (4 *vs.*

1; P<0.0001), and longer postoperative hospitalization (11 *vs.* 8 days; P<0.0001).

Univariate analysis of risk factors of neuropathic pain

Table 2 showed the result of the univariate analysis of potential risk factors of postoperative neuropathic pain. The univariate analysis identified age (P=0.017), smoking history (P=0.0014), preoperative use of hypnotic medication (P<0.0001), primary lung cancer (P=0.0038), pneumothorax (P=0.023), malignant disease (P=0.016), partial resection (P=0.013), segmentectomy (P=0.047), complete VATS (P<0.0001), intraoperative blood loss (P<0.0001), duration of surgery ≥2.5 hours (P=0.0023), and chest tube duration (P=0.0003) as significant risk factors of postoperative neuropathic pain.

Multivariate analysis of risk factors of neuropathic pain

Multivariate logistic regression analysis was performed using four independent variables for which the P values were <0.10 by univariate analysis. There was a significant positive correlation between neuropathic pain after thoracic surgery and preoperative use of hypnotic medication [odds ratio (OR), 5.45; 95% confidence interval (CI), 2.52–12.17; P<0.0001] and duration of surgery ≥2.5 hours (OR, 2.72; 95% CI, 1.27–6.09; P=0.0102). There was a significant negative correlation between neuropathic pain after thoracic surgery and undergoing complete VATS (OR, 0.18; 95% CI, 0.073–0.42; P<0.0001) (*Table 3*).

Risk factor analysis of neuropathic pain following thoracic surgery in patients without epidural analgesia

Subgroup analysis was carried out for the patients who did not receive epidural analgesia (n=22). Age, intraoperative blood loss, and duration of surgery were identified as possible risk factors of neuropathic pain by the univariate analyses. Duration of surgery was significantly associated with age and intraoperative blood loss.

Risk factor analysis of neuropathic pain following thoracic surgery in patients with impaired renal function

Subgroup analysis was carried out for the patients with an eGFR <50 mL/min (n=17). Smoking history and preoperative use of hypnotic medication were identified as possible risk factors of neuropathic pain by the univariate analyses. Preoperative use of hypnotic medication was significantly associated with smoking history.

Risk factor analysis of neuropathic pain following thoracic surgery in patients who underwent the complete VATS approach

Subgroup analysis was carried out for the patients who underwent the complete VATS approach (n=83). Preoperative use of hypnotic medication and intraoperative blood loss were identified as possible risk factors of neuropathic pain by the univariate analyses. There was no significant difference in the duration of surgery between the group that underwent complete VATS and the groups that underwent mini-thoracotomy or thoracotomy (153 *vs.* 128 minutes; P=0.31). Multivariate analysis using these factors only identified preoperative use of hypnotic medication as an independent risk factor of postoperative neuropathic pain in patients who underwent complete VATS (OR, 5.98; 95% CI, 1.29–32.89; P=0.022) (*Table 4*).

Risk factor analysis of neuropathic pain following thoracic surgery in patients who underwent the thoracotomy approach

Subgroup analysis was carried out for the patients who underwent the thoracotomy or mini-thoracotomy approach (n=102). Preoperative use of hypnotic medication, intraoperative blood loss, and duration of surgery were identified as possible risk factors of neuropathic pain by the univariate analyses. Duration of surgery was significantly associated with intraoperative blood loss.

Multivariate analysis using these factors identified preoperative use of hypnotic medication (OR, 4.97; 95% CI, 1.99–13.11; P=0.0005) and duration of surgery ≥2.5 hours as independent risk factors of postoperative neuropathic pain (OR, 3.63; 95% CI, 1.48–9.47; P=0.0045) (*Table 5*).

Risk factor analysis of neuropathic pain following thoracic surgery in patients who underwent lung resections

Subgroup analysis was carried out for the patients who underwent lung resections (n=149). Smoking history, preoperative use of hypnotic medication, primary lung cancer, pneumothorax, partial resection, complete VATS, intraoperative blood loss, duration of surgery ≥2.5 hours, and chest tube duration were identified as possible risk factors of neuropathic pain by the univariate analyses. Duration of surgery was significantly associated with

Table 2 Univariate analysis of all study patients with postoperative neuropathic pain

Variable	Neuropathic pain		P value
	Yes (n=48)	No (n=137)	
Age (years), median	71	66	0.017
Males, n (%)	31 (64.6)	95 (69.3)	0.59
Smoking history, n (%)	35 (72.9)	63 (46.0)	0.0014
BMI	22.4	22.2	0.87
Preoperative use of hypnotic medication, n (%)	27 (56.3)	26 (19.0)	<0.0001
eGFR <50 (mL/min), n (%)	4 (8.3)	13 (9.5)	0.54
Diagnosis			
Primary lung cancer	36 (75.0)	69 (50.4)	0.0038
Metastatic lung tumor	4 (8.3)	17 (12.4)	0.59
Pneumothorax	0 (0)	13 (9.5)	0.023
Other lung disease	2 (4.2)	8 (5.8)	0.78
Mediastinal tumor	2 (4.2)	14 (10.2)	0.25
Empyema	2 (4.2)	4 (2.9)	0.65
Pleural/chest wall tumor	2 (4.2)	12 (8.8)	0.53
Malignant disease, n (%)	41 (85.4)	92 (67.2)	0.016
Right-sided disease, n (%)	28 (58.3)	86 (62.8)	0.61
Procedure type			
Partial resection	4 (8.3)	34 (24.8)	0.013
Segmentectomy	13 (27.1)	19 (13.9)	0.047
Lobectomy	26 (54.2)	53 (38.7)	0.089
Mediastinal tumor resection	2 (4.2)	14 (10.2)	0.25
Thoracostomy	2 (4.2)	0 (0)	0.066
Decortication	0 (0)	4 (2.9)	0.57
Pleural/chest wall tumor resection	2 (4.2)	12 (8.8)	0.53
Complete VATS, n (%)	9 (18.8)	74 (54.0)	<0.0001
Epidural analgesia, n (%)	46 (95.8)	117 (85.4)	0.069
Intraoperative blood loss (mL), median	193	50	<0.0001
Duration of surgery ≥2.5 hours, n (%)	33 (68.8)	58 (42.3)	0.0023
Chest tube duration (days), median	3	2	0.0003
Complications	18 (37.5)	18 (13.1)	0.097
Prolonged air leak	7 (14.6)	15 (10.9)	0.604
Arrhythmia	7 (14.6)	10 (7.3))	0.15
Pneumonia	3 (6.3)	12 (8.8)	0.76
Delirium	2 (4.2)	3 (2.2)	0.61
ARDS	1 (2.1)	3 (2.2)	0.702
Chylothorax	2 (4.2)	2 (1.5)	0.28

BMI, body mass index; eGFR, estimated glomerular filtration rate; VATS, video-assisted thoracoscopic surgery; ARDS, acute respiratory distress syndrome.

Table 3 Multivariate logistic regression analysis of all study patients with postoperative neuropathic pain

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	5.45	2.52–12.17	<0.0001
Complete VATS, n (%)	0.18	0.073–0.42	<0.0001
Duration of surgery ≥2.5 hours, n (%)	2.72	1.27–6.09	0.0102

OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

Table 4 Multivariate logistic regression analysis of the complete VATS subgroup

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	5.98	1.29–32.89	0.022
Intraoperative blood loss ≥55 mL	3.48	0.67–25.9	0.14

OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

Table 5 Multivariate logistic regression analysis of the thoracotomy subgroup

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	4.97	1.99–13.11	0.0005
Duration of surgery ≥2.5 hours	3.63	1.48–9.47	0.0045

OR, odds ratio; CI, confidence interval.

Table 6 Multivariate logistic regression analysis of lung resection subgroup

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	4.16	1.79–9.93	0.0009
Complete VATS, n (%)	0.22	0.070–0.58	0.0018
Duration of surgery ≥2.5 hours, n (%)	2.65	1.12–6.61	0.026

OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

intraoperative blood loss.

Multivariate analysis using these factors identified preoperative use of hypnotic medication (OR, 4.16; 95% CI, 1.79–9.93; P=0.0009) and duration of surgery ≥2.5 hours as independent risk factors of postoperative neuropathic pain (OR, 2.65; 95% CI, 1.12–6.61; P=0.026). There was a significant negative correlation between neuropathic pain after thoracic surgery and undergoing complete VATS (OR, 0.22; 95% CI, 0.070–0.58; P=0.0018) (*Table 6*).

Risk factor analysis of neuropathic pain following thoracic surgery in patients who underwent lung partial resection

Subgroup analysis was carried out for the patients who underwent lung partial resections (n=38). Age, preoperative use of hypnotic medication, primary lung cancer, intraoperative blood loss, and chest tube duration were identified as possible risk factors of neuropathic pain by the univariate analyses. Multivariate analysis using these factors identified just preoperative use of hypnotic medication (OR, 32.99; 95% CI, 2.29–948.35; P=0.011) (*Table 7*).

Risk factor analysis of neuropathic pain following thoracic surgery in patients who underwent lobectomy

Subgroup analysis was carried out for the patients who underwent lung partial resections (n=142). Preoperative use of hypnotic medication, right-sided disease, complete

Table 7 Multivariate logistic regression analysis of lung partial resection subgroup

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	32.9	2.29–948.35	0.011

OR, odds ratio; CI, confidence interval.

Table 8 Multivariate logistic regression analysis of lobectomy subgroup

Variable	OR	95% CI	P value
Preoperative use of hypnotic medication	4.20	1.43–13.24	0.0009
Complete VATS, n (%)	0.13	0.026–0.45	0.0008

OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery

VATS, intraoperative blood loss, and chest tube duration were identified as possible risk factors of neuropathic pain by the univariate analyses.

Multivariate analysis using these factors identified preoperative use of hypnotic medication (OR, 4.20; 95% CI, 1.43–13.24; P=0.0009) and complete VATS (OR, 0.13; 95% CI, 0.026–0.45; P=0.0008) (*Table 8*).

Discussion

Postoperative pain is associated with patient satisfaction with regard to both pain management and the overall hospital experience (8). Neuropathic pain following thoracic surgery is common, and it would behoove surgeons to better understand the potential risk factors of this potentially debilitating complication. Furthermore, neuropathic pain continues to occur despite increasing use of the less invasive VATS approach. This study sought to identify the perioperative risk factors of neuropathic pain after thoracic surgery, focusing especially on patients who underwent complete VATS. The results show that a quarter of patients experienced neuropathic pain after surgery; the median onset time was seven days, and the median duration of pain was 50 days. All of these patients felt the pain along the anterior aspect of the surgical wound and had significantly longer postoperative hospitalization than patients who did not experience neuropathic pain. The neuropathic pain persisted in about 20% of these patients one year after surgery. Our study found that risk factors of neuropathic pain after thoracic surgery include preoperative use of hypnotic medication, duration of surgery ≥2.5 hours, and undergoing the thoracotomy approach. In particular, preoperative use of hypnotic medication and long duration of surgery (≥2.5 hours) were risk factors in patients who did not receive epidural analgesia, patients with low renal function, and patients who underwent the complete VATS approach. The same tendencies were also denoted in patients underwent lung resection.

Postoperative neuropathic pain can result in prolonged hospitalization and increased healthcare cost. Most patients are treated with combinations of non-opioid analgesics. Opioids are key analgesic agents for treating moderate to severe pain after major surgery (9,10). Some patients develop longer term persistent opioid use. Long term use of opioid is associated with increased risks of injury and cardiac events (11,12). In particular, chronic neuropathic pain after thoracic surgery was an important determinant of prolonged opioid use (13). A better understanding of risk factors of neuropathic pain after thoracic surgery should greatly aid the decision making of both patients and clinicians.

Previous studies have investigated neuropathic pain after thoracic surgery (14,15). However, few studies have included the onset, duration, and location of postoperative neuropathic pain, and whether there is a significant difference in the incidence of neuropathic pain in patients who undergo the complete VATS approach. The incidence of neuropathic pain after thoracic surgery has been reported to be 80% at three months and 61% at one year after surgery (15); however, our results suggest a lower incidence of neuropathic pain compared with previous reports. We believe that complete VATS is less invasive than either an open thoracotomy or VATS with a mini-thoracotomy. On the other hand, a prospective randomized study did not demonstrate any significant difference in pain and post-thoracotomy syndrome between muscle-sparing thoracotomy and posterolateral thoracotomy (16). So that, analysis between mini-thoracotomy and thoracotomy

may not have much meaning. In all of the patients with neuropathic pain in this study, the pain manifested along the anterior aspect of the surgical wound. Most patients with chronic pain after thoracotomy also experienced almost same area of pain (15). This area is innervated by the anterior cutaneous branch of the intercostal nerves (2). In the present study, pain in areas innervated by other branches was not encountered; thus, these findings could help to distinguish neuropathic from non-neuropathic pain.

In this study, we found two additional risk factors of neuropathic pain after thoracic surgery: (I) preoperative use of hypnotic medication and (II) long duration of surgery (≥2.5 hours), apart from the surgical approach and pain management technique. Psychosocial condition is a well-established factor affecting the perception and effects of chronic neuropathic pain conditions, including the presence of anxiety and depression, a diagnosis of malignant disease, the lack of a social support network, and poor social status (17-19). Preoperative fear and anxiety have been shown to be correlated with acute postoperative pain and analgesic consumption, and risks of subsequent persistent postoperative pain (20-22). Hypnotic drugs may be used more frequently in patients with anxiety and depression; therefore, we investigated the association between neuropathic pain and preoperative use of hypnotic medication. As expected, the preoperative use of hypnotic medication was a significant risk factor of postoperative neuropathic pain, regardless of the surgical approach or pain management technique. Thus, preoperative use of hypnotic medication could be a very useful predictor of neuropathic pain after thoracic surgery.

Long duration of surgery (≥2.5 hours) is another reasonable risk factor of neuropathic pain. Thoracic surgery routinely crushes the intercostal nerves, particularly where the nerves are exposed along the caudal side of the rib (2). Intercostal nerve damage might increase proportionately with the duration of surgery. However, the duration of surgery showed no significant effect on the incidence of postoperative neuropathic pain in patients who underwent the complete VATS approach. Thus, the complete VATS approach could minimize intercostal nerve damage, regardless of the duration of surgery.

Limitations

This study has several limitations. First, the study population included only a limited number of consecutive cases at a single institution. Second, there may have been case selection bias regarding the surgical approach, as the choice between complete VATS or thoracotomy was based partly upon the surgeon's preference.

Postoperative neuropathic pain may be unavoidable for some high-risk patients after thoracic surgery. For most patients, however, prevention of postoperative neuropathic pain can yield a better postoperative experience, shorter hospitalization, and reduced healthcare cost. Pregabalin has become a validated drug for treating neuropathic pain in recent years (9,23). and a randomized controlled prospective study should be carried out to determine if pregabalin is useful in preventing neuropathic pain after thoracic surgery.

Conclusions

Preoperative use of hypnotic medication, the thoracotomy surgical approach, and duration of surgery ≥2.5 hours are significantly associated with neuropathic pain after thoracic surgery. The complete VATS approach could decrease the incidence of postoperative neuropathic pain, regardless of the duration of surgery.

Acknowledgements

We offer our sincere gratitude to Dr. Takehisa Asahi (Division of Anesthesiology, Joetsu General Hospital) for his valuable input in the preparation of this manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Ethics Committee of the University of Toyama with a waiver of informed consent due to its retrospective design (RIN 29-52).

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Cite this article as: Homma T, Doki Y, Yamamoto Y, Ojima T, Shimada Y, Kitamura N, Yoshimura N. Risk factors of neuropathic pain after thoracic surgery. J Thorac Dis 2018;10(5):2898-2907. doi: 10.21037/jtd.2018.05.25

