Original Article

Risk factors for discontinuing intravenous patient-controlled analgesia after thoracic surgery

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Abstract:

PURPOSE: This study examined the risk factors of experiencing side effects from using intravenous patient-controlled analgesia (IV PCA) following lung and esophageal surgery.

METHODS: Our study included adult patients who underwent lung or esophageal surgery and received IV PCA for postoperative acute pain control between 2020 and 2022. We collected information on side effects from IV PCA use, the decision to discontinue PCA, and the PCA regimen from the daily reports of the acute pain management team and verified the accuracy using electronic records from ward nurses. The primary outcome was the risk factor associated with discontinuing IV PCA due to its side effects.

RESULTS: Out of the 1796 patients in our study, 1795 used PCA containing opioids; 196 patients stopped IV PCA due to unbearable side effects. Being female (adjusted odds ratio [aOR]: 2.65, 95% confidence interval [CI]: 1.70, 4.13) was linked to a higher chance of stopping PCA use. Having hypertension (aOR: 0.46, 95% CI: 0.26, 0.81) and being classified as the American Society of Anesthesiologists class 3 or higher (aOR: 0.48, 95% CI: 0.23, 0.86) were associated with a lower chance of discontinuing PCA use.

CONCLUSION: Our study determined the risk factors to stop using IV PCA due to side effects following lung or esophageal surgery. These results emphasize the need for personalized pain management plans that take into account the patient's characteristics and the type of surgery performed.

Keywords:

Analgesia, esophageal cancer surgery, opioid, side effects, thoracic surgery

Thoracic surgery encompasses diseases in the regions of the lung, esophagus, foregut, mediastinum, chest wall, pleura, and pleural space.[1] As lung cancer is the second-most prevalent cancer regardless of sex in the United States, approximately 530,000 general thoracic surgery cases are performed yearly in the United States, with the most common procedure performed being video-assisted thoracoscopic surgery (VATS) lobectomy.[2] The pain accompanying thoracic surgery is very severe in intensity and duration;[3] therefore, postoperative analgesia is clinically important to alleviate acute pain, prevent deterioration into chronic pain, and promote better recovery outcomes.

Since 1976, patient-controlled analgesia (PCA) devices have evolved to safely and effectively administer a titrated bolus of analgesics, ensure appropriate lockout interval times between doses, and control the background infusion rate. While intravenous (IV) PCA has the same side effects as IV opioids, such as nausea, vomiting, pruritus, and sedation, PCA offers a better analgesic effect with superior patient satisfaction[4] while avoiding excessive opioid administration. IV PCA devices allow postoperative patients in wards to immediately administer analgesics by

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simply pressing a button. This offers a convenient delivery of postoperative analgesia, which is essential after thoracic surgery. However, it is necessary to evaluate the risk factors of developing side effects when using IV PCA after thoracic surgery to ensure adequate monitoring and provision of proper analgesia. This study compared patients who underwent thoracic surgery and were using IV PCA and those who were not due to its side effects. We also investigated the characteristics of patients at high risk of discontinuing IV PCA usage for the optimal management of postoperative pain after thoracic surgery.

Methods

We adhered to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology.[5] The Institutional Review Board (IRB) approved this retrospective cohort study in a single tertiary academic hospital (IRB approval number: B-2304-825-108; approval date: April 07, 2023). Due to its retrospective cohort design, the IRB exempted this study from the requirement of obtaining informed consent from patients.

Data source and study population

This study employed BESTCare[6] for electronic health records and used the ICD-10 codes for comorbidities. The study included adult patients (18 years or older) who were admitted to our hospital between January 1, 2020, and December 31, 2022, and received postoperative PCA following thoracic surgery. Patients excluded were those who received anesthesia other than general, those who used PCA through routes other than IV, those who underwent thoracic surgeries other than lung or esophageal surgery, those who continued receiving remifentanil after exiting the operating room, and those who were discharged within 2 days after surgery. Multiple surgeries on one patient performed on the same date were treated as one sample. Patients lacking any medical information or who expired in the hospital were excluded as well.

Study endpoints

The primary endpoint was to identify the risk factors related to discontinuation of postoperative IV PCA following lung or esophageal surgery due to its side effects. Our hospital launched an acute pain management team involving an attending anesthesiologist and a registered nurse from the department of anesthesiology and pain medicine in 2020; this team conducted daily rounds to assess patients receiving PCA to evaluate pain relief, side effects, and continuity of PCA usage. They also monitored the number of refills, interventions to control side effects, and patient satisfaction with overall PCA use. Ward nurses also confirmed the PCA regimen and recorded the starting and ending date of use.

Study parameters

Using the electronic health record system, we collected data on the patients' demographic and medical information, such as age, sex, American Society of Anesthesiologists (ASA) physical status, smoking status, alcohol consumption status, preoperative usage of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or opioids, and comorbidities such as hypertension, diabetes, heart disease (coronary artery disease, arrhythmias, valvular heart disease, and heart failure), and brain disease (cerebrovascular disease). Moreover, we also gathered information such as the length of hospital stay after surgery, anesthetic method, in-hospital death, postoperative usage of remifentanil, and surgery type, including the use of video-assisted thoracoscopy; wedge resection, lobectomy, bilobectomy, segmentectomy, and pneumonectomy were categorized as lung surgery, while any surgery involving the esophagus were categorized as esophageal surgery. Then, we gathered information regarding the postoperative PCA settings (background infusion rate, bolus dose, and interval between doses), device and drug used, and the duration of PCA use (refill and discontinuation) from PCA assessment records.

Statistical analysis

Continuous variables, such as age and postoperative length of stay, were presented as means with standard deviations (SDs). Categorical variables, such as sex and medical history, were reported as numbers with percentages. Patients were divided into either the PCA continuation group or the PCA discontinuation group depending on PCA usage. We used *t*-tests for continuous variables and Chi-square tests for categorical variables to compare the characteristics of each group. Both univariable and multivariable binary logistic regression were performed to analyze the PCA discontinuation group after thoracic surgery. The results of multivariable logistic regression analyses were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). For this study, we utilized IBM SPSS Statistics for Windows (version 27.0, IBM Corp., Armonk, NY, USA) and considered $P < 0.05$ as statistically significant.

Results

Study population

We collected 10,946 cases of patients who utilized postoperative PCA following thoracic surgery from January 1, 2020, to December 31, 2022. We removed 6948 duplicate records and 21 cases that did not undergo general anesthesia. We also excluded 57 cases that used epidural PCA instead of IV PCA, as well as 65 cases involving patients less than 18 years old. Furthermore, we eliminated 995 cases of patients who underwent thoracic surgery other than lung or esophagus surgery,

504 cases that received continuous IV remifentanil after surgery, and 556 cases that left the hospital within 2 days of surgery. We also discarded three cases that lacked the necessary medical information. Hence, a total of 1796 patients were included in the final analysis. Figure 1 shows a flowchart of the selection process, while Table 1 and Supplementary Table 1 present the clinical characteristics of the patients.

The mean age of the patients who had IV PCA following lung or esophageal surgery was 65.02 years (SD = 12.56), and most of them (66.8%) had ASA classification 2. The majority of patients (99.2%) underwent VATS instead of laparotomy, with lung surgery accounting for most cases (97.8%) in this study. The PCA device, drug, and settings were determined by a standardized regimen that considered factors such as the patient's weight, kidney and liver functions, type of surgery (VATS or not), and information about side effects or allergies. Supplementary Table 1 shows that opioid-containing PCA with background infusion and a 15-min lockout time were used for most patients.

Patient-controlled analgesia discontinuation

Table 2 shows that the PCA discontinuation group had more female patients (40.6% in the PCA continuation group vs. 70.4% in the PCA discontinuation group; $P < 0.001$) and a lower mean age (65.39 ± 12.40 vs. 62.05 ± 13.41, $P < 0.001$). The PCA continuation group had more patients with HTN (19.6% vs. 8.2%; $P < 0.001$), ASA class higher or equal to 3 (21.8% vs. 9.7%; $P < 0.001$), and who were smoking (48.8% vs. 25.5%; $P < 0.001$) or drinking alcohol (35.9% vs. 25.0%; $P = 0.002$) on admission. The percentage of patients who regularly used paracetamol (5.5% vs. 1.5%; $P = 0.017$) or opioids (5.9% vs. 1.5%; $P = 0.011$) before surgery was also higher in the PCA continuation group. In terms of PCA regimen, only one case had NSAID-only PCA [Supplementary Table 2].

Logistic regression

Tables 3 and 4 both show the results of univariable and multivariable logistic regression analyses for PCA discontinuation after thoracic surgery. Table 4 shows

Table 1: Baseline information of patients

Variable	Mean±SD or *n* (%)
Age (years)	65.02±12.56
Female sex	788/1796 (43.88)
LOS after surgery (days)	5.42 (3.82)
Medical history - *n*/total (*n*)	
DM	156/1796 (8.69)
HTN	330/1796 (18.37)
Heart disease	113/1796 (6.29)
Brain disease	155/1796 (8.63)
ASA physical status classification	
1	228/1796 (12.69)
2	1200/1796 (66.82)
≥3	368/1796 (20.49)
VATS	1782/1796 (99.22)
Type of surgery	
Lung	1757/1796 (97.83)
Esophagus	39/1796 (2.17)
Smoking	830/1796 (46.21)
Alcohol	624/1796 (34.74)
Preoperative drug usage	
NSAID	121/1796 (6.74)
Paracetamol	91/1796 (5.07)
Opioid	97/1796 (5.40)

LOS=Length of hospital stays, DM=Diabetes mellitus, HTN=Hypertension, ASA=American Society of Anesthesiologists, NSAID=Nonsteroidal anti-inflammatory drug, SD=Standard deviation, VATS=Video-assisted thoracoscopic surgery

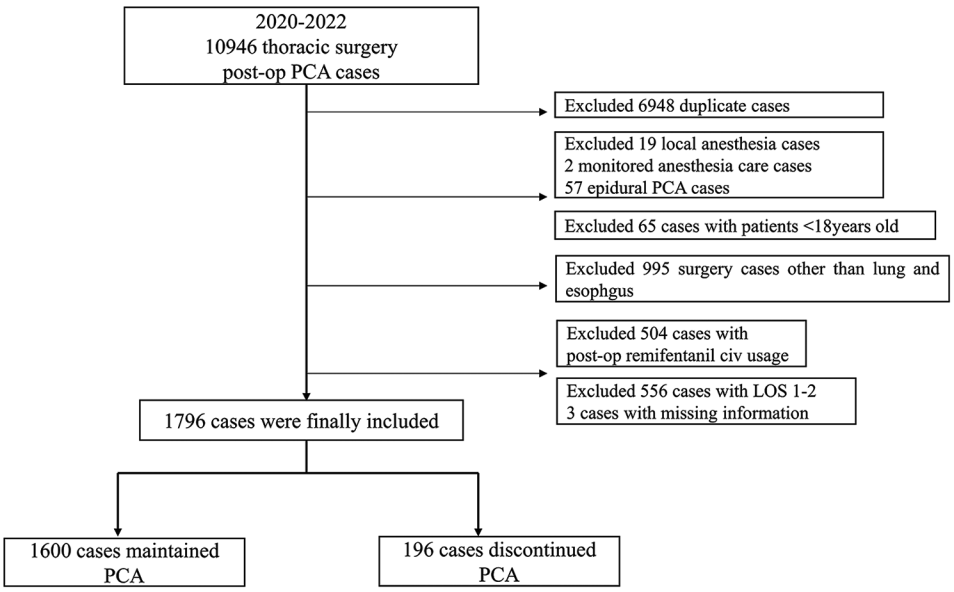

Figure 1: Flowchart of the patient selection process. PCA = Patient-controlled analgesia, LOS = Length of hospital stays

Table 2: Comparison of characteristics between the patient-controlled analgesia groups

Variable	PCA continuation (*n*=1600), *n* (%)	PCA discongon (*n*=196), *n* (%)	*P*
Age (SD)	65.39 (12.40)	62.05 (13.41)	<0.001
Sex (female)	650 (40.63)	138 (70.41)	<0.001
LOS after surgery (SD)	5.48 (3.90)	4.96 (3.07)	0.033
Medical history			
DM	148 (9.25)	8 (4.08)	0.015
HTN	314 (19.63)	16 (8.16)	<0.001
Heart disease	106 (6.63)	7 (3.57)	0.097
Brain disease	142 (8.88)	13 (6.63)	0.291
ASA physical status classification			
1	191 (11.94)	37 (18.88)	<0.001
2	1060 (66.25)	140 (71.43)	
≥4	349 (21.81)	19 (9.69)	
VATS	1586 (99.13)	196 (100.00)	0.189
Type of surgery			
Lung	1561 (97.56)	196 (100.00)	0.027
Esophagus	39 (2.44)	0	
Smoking	780 (48.75)	50 (25.51)	<0.001
Alcohol	575 (35.94)	49 (25.00)	0.002
Preoperative drug usage			
NSAID	107 (6.69)	14 (7.14)	0.810
Paracetamol	88 (5.50)	3 (1.53)	0.017
Opioid	94 (5.88)	3 (1.53)	0.011

LOS=Length of hospital stays, DM=Diabetes mellitus, HTN=Hypertension, ASA=American Society of Anesthesiologists, PCA=Patient-controlled analgesia, NSAID=Nonsteroidal anti-inflammatory drug, SD=Standard deviation, VATS=Video-assisted thoracoscopic surgery

Table 3: Univariable logistic regression analyses for discontinuation of patient-controlled analgesia after thoracic surgery

Variable	OR (95% CI)	*P*
Age (years)	0.98 (0.97–0.99)	<0.01
Female sex (vs. male sex)	3.48 (2.52–4.80)	<0.01
LOS after surgery (days)	0.96 (0.91–1.01)	0.08
Medical history		
DM	0.42 (0.20–0.86)	0.02
HTN	0.36 (0.22–0.62)	<0.01
Heart disease	0.52 (0.24–1.14)	0.10
Brain disease	0.73 (0.41–1.31)	0.29
ASA physical status classification		<0.01
1	1	
2	0.68 (0.46–1.01)	0.06
≥3	0.28 (0.16–0.50)	<0.01
VATS (vs. laparotomy)	199,642,476.0 (0.00)	1.00
Type of surgery		
Lung	1	
Esophagus	0.00 (0.00)	1.00
Smoking (vs. nonsmoking)	0.36 (0.26–0.50)	<0.01
Alcohol (vs. no alcohol drinking)	0.59 (0.42–0.83)	<0.01
Preoperative drug usage		
NSAID	1.07 (0.60–1.91)	0.81
Paracetamol	0.27 (0.08–0.85)	0.03
Opioid	0.25 (0.08–0.79)	0.02

OR=Odds ratio, LOS=Length of hospital stays, DM=Diabetes mellitus, HTN=Hypertension, ASA=American Society of Anesthesiologists, NSAID=Nonsteroidal anti-inflammatory drug, VATS=Video-assisted thoracoscopic surgery, CI=Confidence interval

that female patients were more likely to discontinue PCA after thoracic surgery (aOR: 2.65, 95% CI: 1.70, 4.13; $P < 0.01$). Hypertension was a meaningful predictor of PCA continuation (aOR 0.46, 95% CI: 0.26, 0.81; $P = 0.01$). Patients with ASA classification 3 or higher were highly likely to continue IV PCA compared to ASA classification 1 patients (aOR 0.48, 95% CI: 0.23, 0.86; $P = 0.02$).

Discussion

In this study, we investigated the factors that contribute to the cessation of IV PCA following lung or esophageal surgery. Our findings indicate that the female sex was the most significant factor linked to the discontinuation of IV PCA due to its side effects. In addition, hypertension and an ASA class of 3 or higher were associated with the continuation of IV PCA. Preoperative opioid medication, smoking history, and age did not impact the usage of IV PCA.

Our study found that female sex was significantly associated with the discontinuation of IV PCA. There has been continuous attention to the role of sex in pain perception, sensitivity, and analgesia. Several studies have shown a higher incidence of opioid-induced emesis and respiratory depression in women.[7] Experimentally induced pain resulted in greater pain sensitivity, enhanced pain facilitation, and reduced pain inhibition in female patients.[8] Ferentzi *et al*. found that males had significantly higher pain thresholds and tolerance levels than females; hence, female patients required more morphine[9] and had a higher probability of encountering

Table 4: Multivariable logistic regression analyses for discontinuation of patient-controlled analgesia after thoracic surgery

Variable	AOR (95% CI)	*P*
Age (years)	0.99 (0.98–1.00)	0.18
Female sex (vs. male sex)	2.65 (1.70–4.13)	<0.01
LOS after surgery (days)	1.01 (096–1.07)	0.64
Medical history		
DM	0.78 (0.36–1.71)	0.54
HTN	0.46 (0.26–0.81)	0.01
Heart disease	0.98 (0.42–2.29)	0.96
Brain disease	1.22 (0.64–2.33)	0.54
ASA physical status classification		0.04
1	1	
2	0.83 (0.54–1.28)	0.40
≥3	0.48 (0.23–0.86)	0.02
VATS (vs. laparotomy)	0.93 (0.00)	1.00
Type of surgery		
Lung	1	
Esophagus	0.00 (0.00)	1.00
Smoking (vs. nonsmoking)	0.81 (0.51–1.30)	0.38
Alcohol (vs. no alcohol drinking)	0.91 (0.62–1.34)	0.63
Preoperative drug usage		
NSAID	1.47 (0.79–2.72)	0.23
Paracetamol	0.45 (0.10–2.02)	0.30
Opioid	0.43 (0.10–1.88)	0.26

AOR=Adjusted odds ratio, LOS=Length of hospital stays, DM=Diabetes mellitus, HTN=Hypertension, ASA=American Society of Anesthesiologists, NSAID=Nonsteroidal anti-inflammatory drug, VATS=Video-assisted thoracoscopic surgery, CI=Confidence interval

side effects.[10] Similarly, Fillingim *et al*. found that women reported more significant morphine-related adverse effects than men when using IV morphine.[11] In response to experimental pain, men demonstrated higher magnitudes of both endogenous opioid release and mu-opioid receptor activation in the brain regions implicated in the suppression of sensory and affective qualities of pain, such as the anterior thalamus, ventral basal ganglia, and amygdala.[12] However, these results were not consistent across all studies. Chia *et al*. reported that men typically receive more morphine through PCA than females for postsurgical pain relief;[13] and male patients with cancer required higher doses of fentanyl patches than female patients with cancer.[14] Even though the mechanisms underlying the disparities in opioid requirements and pain sensitivity are not yet clear, it is necessary to tailor perioperative pain management approaches to the specific needs of male and female patients undergoing thoracic surgery.

Our study found that hypertensive patients with an ASA class of 3 or higher were associated with the continuation of PCA. When pain is present, a phenomenon called "hypertensive hypoalgesia" occurs. This is characterized by a decrease in pain sensitivity due to a homeostatic feedback loop that stabilizes blood pressure. Multiple studies have found that hypertension has a pain-killing effect in the presence of acute pain, which applies to postoperative acute pain in this study. Several studies proposed possible physiological mechanisms for this phenomenon, including enhanced activation of baroreceptor reflex arcs, dysregulation of central endogenous opioid and noradrenergic activity, and increased stimulation of descending pain modulation pathways.[15] In addition, long-term anti-inflammatory effects of angiotensin-converting enzyme inhibitors may cause less postoperative pain and require fewer analgesics from IV PCA.[16]

An ASA class 3 represents physical status with a significant disease that limits normal daily activities. Studies have shown that patients with ASA class 3 or above experience more intense acute postoperative pain[17] and slower resolution of pain.[18] However, there is still debate about whether a higher ASA class is associated with increased postoperative opioid use.[19,20] It is possible that the perception of pain or caution in taking higher doses of opioids in patients with higher ASA class may have prevented them from having side effects. Further analysis is needed to understand the underlying mechanisms of this observation.

Our study has several limitations. First, since most cases involved VATS and lung surgery, it is difficult to predict whether the results would be the same for thoracotomy and other thoracic surgeries beyond lung operations. Second, the PCA regimen consisted mostly of fentanyl and only differed by patient age and weight. Various patient factors that may have influenced pharmacokinetics, such as sex, body mass index, or fat mass, were not considered in the PCA regimen. This is important because fentanyl is highly lipophilic. Third, the study excluded patients who received continuous remifentanil after the operation; hence, we were not able to include patients who underwent complex surgeries that were expected to result in severe postoperative pain. While it is logical to exclude them, since additional remifentanil could interfere with the usage of IV PCA and its side effects, the need for adequate pain control in these patients should be studied in further research.

Conclusion

This study identified patient characteristics associated with the discontinuation of postoperative IV PCA after lung or esophageal surgery. The female sex is a significant risk factor for IV PCA discontinuation due to side effects, while hypertension and an ASA class 3 or higher have the opposite effect. These results should be taken into account when developing better PCA regimens, monitoring pain more closely, and providing patient-tailored prophylactic medication for expected side effects of IV PCA.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1: Baseline information of patients

Variable	*n* (%)
PCA type	
Opioid included	1795/1796 (99.94)
NSAID only	1/1796 (0.06)
PCA background infusion	1772/1796 (98.66)
PCA lockout time (min)	
10	15/1796 (0.84)
15	1780/1796 (99.11)
20	1/1796 (0.06)

PCA=Patient-controlled analgesia, NSAID=Nonsteroidal anti-inflammatory drug

Supplementary Table 2: Comparison of patient-controlled analgesia regimen between the patient-controlled analgesia groups

Variable	PCA continuation (*n*=1600), *n* (%)	PCA discontinuation (*n*=196), *n* (%)	*P*
PCA type			
Opioid included	1600 (100.00)	195 (99.49)	0.004
NSAID only	0	1 (0.51)	
Background infusion	1577 (98.56)	195 (99.49)	0.286
Lockout time (min)			
10	14 (0.88)	1 (0.51)	0.015
15	1586 (99.13)	194 (98.98)	
20	0	1 (0.51)	

PCA=Patient-controlled analgesia, NSAID=Nonsteroidal anti-inflammatory drug