



Effects of Inhalation versus Total Intravenous Anesthesia on Postoperative Pulmonary Complications after Anatomic Pulmonary Resection

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Background: No consensus exists regarding whether volatile anesthetics are superior to intravenous anesthetics for reducing postoperative pulmonary complications (PPCs) in patients undergoing general anesthesia for surgery. Studies of this issue focused on anatomic pulmonary resection are lacking. This study compared the effects of total intravenous anesthesia (TIVA) versus volatile anesthesia on PPCs after anatomic pulmonary resection in patients with lung cancer.

Methods: This retrospective study examined the medical records of patients with lung cancer who underwent lung resection at our center between January 2018 and October 2020. The primary outcome was the incidence of PPCs, which included prolonged air leak, pneumonia, acute respiratory distress syndrome, empyema, atelectasis requiring bronchofiberscopy (BFS), acute lung injury (ALI), bronchopleural fistula (BPF), pulmonary embolism, and pulmonary edema. Propensity score matching (PSM) was used to balance the 2 groups. In total, 579 anatomic pulmonary resection cases were included in the final analysis.

Results: The analysis showed no statistically significant difference between the volatile anesthesia and TIVA groups in terms of PPCs, except for prolonged air leak. Neither of the groups showed atelectasis requiring BFS, ALI, BPF, pulmonary embolism, or pulmonary edema after PSM. However, the length of hospitalization, intensive care unit stay, and duration of chest tube indwelling were shorter in the TIVA group.

Conclusion: Volatile anesthetics showed no superiority compared to TIVA in terms of PPCs after anatomical pulmonary resection in patients with lung cancer. Considering the advantages of each anesthetic modality, appropriate anesthetic modalities should be used in patients with different risk factors and situations.

Keywords: Anesthesia, Propofol, Lung neoplasms, Lobectomy, Segmentectomy, Pneumonia

Introduction

Postoperative pulmonary complications (PPCs) refer to a composite of adverse pulmonary outcomes after surgery. The global incidence of PPCs has been reported to be as high as 23% [1]. Patients who develop PPCs are expected to have a higher mortality and morbidity rate. In addition, PPCs significantly prolong the length of hospital stay, resulting in increased health care costs. Since thoracic surgery is a known risk factor for PPCs [2], evaluating factors

that may prevent PPCs after thoracic surgery has been a concern for thoracic surgeons.

Lung resection surgery is usually performed under general anesthesia with either volatile or intravenous anesthetics, with sevoflurane and propofol being the most commonly used anesthetics. However, there is still no consensus regarding the comparative results of the effects of these 2 anesthetic modalities on PPCs or inflammation. Thus, the selection of anesthetic regimens depends on the hospital's policy or anesthesiologist's preference.



Our institution changed the anesthetic modality from volatile to propofol-based total intravenous anesthesia (TIVA) for lung resection surgery between September 2018 and December 2018. The main reason for this change was the fact that TIVA decreased the risk of postoperative nausea and vomiting (PONV), had a smaller effect on hypoxic pulmonary vasoconstriction (HPV), and had better survival rates after cancer surgery than volatile anesthesia [1-6]. A previous study reported that the incidence of pulmonary complications was higher after cardiac surgery using TIVA, but this finding was questionable for lung surgery [6], underscoring the need for validation to determine whether this anesthetic modality should be used. Additionally, meta-analyses or studies comparing the effects of the 2 modalities have been conducted with patients undergoing thoracic surgery, lung resection, or other cancer surgery [7-9], but no studies have investigated outcomes confined to the operative extent of segmentectomy and above. The objective of the present study was to determine which anesthetic modality is better for reducing PPCs after anatomic pulmonary resection in patients with lung cancer.

Methods

This study was approved by the Institutional Review Board of Pusan National University Hospital (IRB approv-

al no., 2110-015-108). The requirement for informed consent was waived because the analysis was retrospectively performed based on electronic patient records.

Inclusion of patients

Electronic medical records of patients diagnosed with lung cancer who underwent pulmonary resection (wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy) between January 2018 and October 2020 were analyzed. Records from September 2018 to December 2018 were excluded because our institution used both anesthetic regimens in the transition period, making it difficult to divide the patients into 2 clear groups. Data from patients who underwent pulmonary wedge resection were excluded (Fig. 1). Further, the following data were excluded from the analysis because they had the same values in both groups: intraoperative conversion to open resection, atelectasis requiring bronchofiberscopy (BFS), acute lung injury (ALI), bronchopleural fistula (BPF), pulmonary embolism, pulmonary edema, and delirium tremens. The missing data and rates were different for each variable and were considered before the analysis.

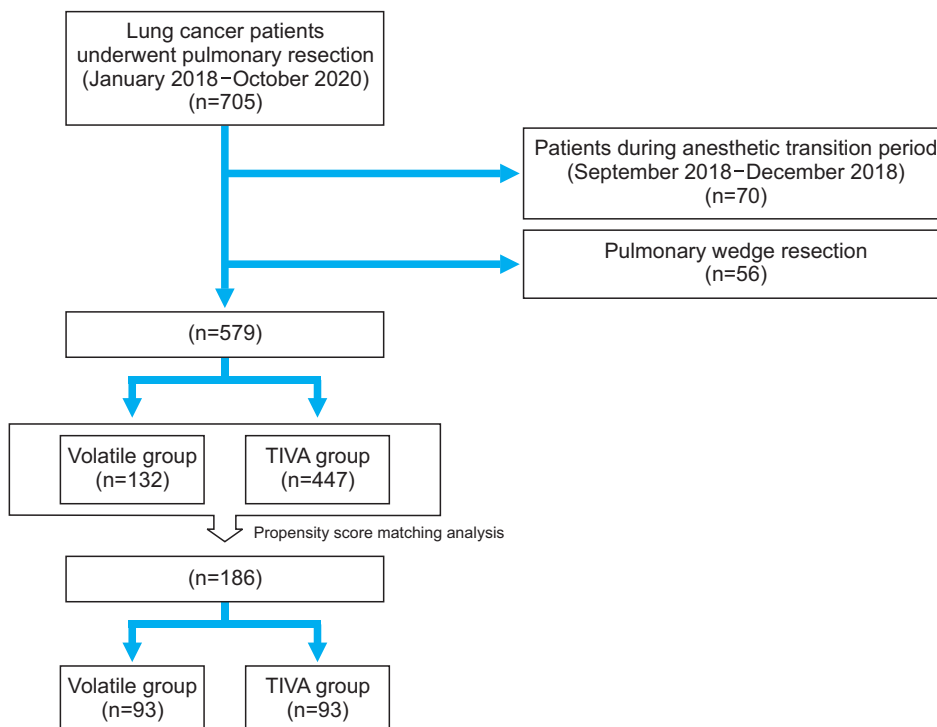


Fig. 1. Flow chart of the study.

Anesthetic protocol for video-assisted thoracoscopic surgery lung resection

Patients were divided into 2 groups: the volatile anesthesia group, which received inhalation agents between January 2018 and August 2018, and the TIVA group, which received propofol between January 2019 and October 2020. Either desflurane or sevoflurane was administered to the patients in the volatile anesthesia group, and continuous propofol infusion using a target-controlled infusion system based on the Schnider model was administered to the TIVA group during surgery. In the volatile anesthesia group, 1.5 mg of 1% propofol per kilogram of body weight was administered intravenously to induce general anesthesia in the early period. Intravenous remifentanyl was administered by continuous infusion to both groups. The other anesthetic protocol was identically performed except for the use of different anesthetic agents. Hemodynamic monitoring (electrocardiography, pulse oximetry, noninvasive blood pressure and invasive arterial pressure measurements) and bispectral index (Medtronic, Minneapolis, MN, USA) monitoring were routinely performed, and in some patients in both groups, epidural anesthesia was administered before anesthesia induction.

Measurements for comparative analysis

Preoperative data such as age, sex, smoking history, preoperative forced expiratory volume in 1 second, preoperative diffusing capacity of the lungs for carbon monoxide, whether the patient received preoperative or postoperative pulmonary rehabilitation therapy, preoperative comorbidities (hypertension, diabetes, history of pulmonary tuberculosis, cardiovascular disease, and cerebrovascular disease), body mass index, clinical stage and whether the patient received neoadjuvant therapy were collected. Intraoperative data such as the approach modality, operative extent of the lung (segmentectomy, lobectomy, bilobectomy, and pneumonectomy), operation time, and estimated blood loss were collected. Short-term postoperative data such as pathologic stage, duration of intensive care unit (ICU) stay, degree of pain, PPCs (prolonged air leak, atelectasis requiring BFS, pneumonia, ALI, acute respiratory distress syndrome [ARDS], BPF, pulmonary embolism, and pulmonary edema), postoperative events (acute myocardial infarction [AMI], new central neurologic event, delirium tremens, gastrointestinal trouble, empyema, new renal failure, reintubation, and tracheostomy), duration of chest tube indwelling, duration of hospitalization, and mortality within

30 days postoperatively were collected.

Primary endpoint of this study

The incidence of PPCs compared between the volatile and TIVA groups was the primary outcome. PPCs comprised prolonged air leak, pneumonia, ARDS, empyema, atelectasis requiring BFS, ALI, BPF, pulmonary embolism, and pulmonary edema after lung resection surgery.

Statistical analysis

In the comparison of the volatile anesthesia and TIVA groups, the independent t-test or Wilcoxon rank-sum test was used for continuous variables and the chi-square test or Fisher exact test was used for categorical variables. To balance covariates between the 2 groups, the propensity score matching (PSM) method was used with a standardized mean difference (SMD) of less than 0.25. R software ver. 4.0.1 (R Development Core Team, Vienna, Austria) was used for all statistical analyses. A p-value of <0.05 was considered to indicate statistical significance.

Results

Inclusion of patients and patient characteristics

The medical records of 705 patients diagnosed with lung cancer who underwent pulmonary resection (wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy) between January 2018 and October 2020 were analyzed. The 70 patients treated between September 2018 and December 2018 were excluded. Pulmonary wedge resection (n=56) was set as the exclusion criterion before the analysis (Fig. 1).

The final study included 579 patients, with 132 in the volatile anesthesia group and 447 in the TIVA group. The baseline characteristics of the volatile anesthesia and TIVA groups after PSM are compared in Table 1. A total of 93 patients in each group were included in the PSM analysis. The covariates were well-balanced, with SMD values <0.25 [10].

Comparison of PPCs between the volatile anesthesia and TIVA groups after anatomic pulmonary resection in patients with lung cancer

The results of the PSM analysis of PPCs after surgery are shown in Table 2. Prolonged air leak showed a significant difference between the 2 groups (11% versus 2%, p=0.021).

Table 1. Baseline characteristics after propensity score matching

Characteristic	Total (n=186)	Volatile anesthesia group (n=93)	TIVA group (n=93)	p-value	SMD
Age (yr)	66.98±8.17	66.74±7.56	67.23±8.77	0.687	0.059
Sex				0.755	0.069
Male	125 (67.2)	61 (65.6)	64 (68.8)		
Female	61 (32.8)	32 (34.4)	29 (31.2)		
Smoking history	95 (51.1)	46 (49.5)	49 (52.7)	0.742	0.115
Preoperative FEV1 (%)	84.82±14.81	85.03±14.79	84.61±14.90	0.847	0.028
Preoperative DLCO (%)	81.55±15.99	80.85±16.22	82.25±15.82	0.553	0.087
Preoperative pulmonary rehabilitation	62 (33.3)	31 (33.3)	31 (33.3)	1.000	<0.001
Chronic obstructive pulmonary disease	11 (5.9)	6 (6.5)	5 (5.4)	1.000	0.046
Pulmonary tuberculosis	14 (7.5)	7 (7.5)	7 (7.5)	1.000	<0.001
Cardiovascular disease				0.935	0.075
None	166 (89.2)	82 (88.2)	84 (90.3)		
Angina pectoris	7 (3.8)	4 (4.3)	3 (3.2)		
Myocardial infarction	11 (5.9)	6 (6.5)	5 (5.4)		
Arrhythmia	2 (1.1)	1 (1.1)	1 (1.1)		
Neurologic event				0.859	0.106
None	176 (94.6)	87 (93.5)	89 (95.7)		
Stroke	8 (4.3)	5 (5.4)	3 (3.2)		
Intracerebral hemorrhage	2 (1.1)	1 (1.1)	1 (1.1)		
Body mass index (kg/m ²)	24.27±3.37	24.19±3.42	24.36±3.33	0.724	0.052
Type of disease				0.444	0.17
Primary lung cancer	179 (96.2)	88 (94.6)	91 (97.8)		
Double primary lung cancer	7 (3.8)	5 (5.4)	2 (2.2)		
Pathologic stage				0.983	0.178
IA1	17 (9.1)	9 (9.7)	8 (8.6)		
IA2	40 (21.5)	21 (22.6)	19 (20.4)		
IA3	30 (16.1)	16 (17.2)	14 (15.1)		
IB	45 (24.2)	21 (22.6)	24 (25.8)		
IIA	16 (8.6)	9 (9.7)	7 (7.5)		
IIB	12 (6.5)	6 (6.5)	6 (6.5)		
IIIA	23 (12.4)	10 (10.8)	13 (14.0)		
IIIB	3 (1.6)	1 (1.1)	2 (2.2)		
IIIC	0	0	0		
Neoadjuvant therapy	1 (0.5)	0	1 (1.1)	1.000	0.147
Operative extent				0.894	0.088
Segmentectomy	26 (14.0)	12 (12.9)	14 (15.1)		
Lobectomy	155 (83.3)	78 (83.9)	77 (82.8)		
Bilobectomy	5 (2.7)	3 (3.2)	2 (2.2)		
Pneumonectomy	0	0	0		
Approach modality				0.814	0.069
Video-assisted thoracoscopic surgery	166 (89.2)	82 (88.2)	84 (90.3)		
Open	20 (10.8)	11 (11.8)	9 (9.7)		
Operative time (hr)	3.24±1.26	3.25±1.10	3.24±1.42	0.952	0.009
Estimated blood loss (mL)				0.818	0.178
0–50	23 (12.4)	12 (12.9)	11 (11.8)		
50–200	121 (65.1)	58 (62.4)	63 (67.7)		
200–1,000	41 (22.0)	22 (23.7)	19 (20.4)		
>1,000	1 (0.5)	1 (1.1)	0		

Values are presented as mean±standard deviation or number (%).

TIVA, total intravenous anesthesia; SMD, standardized mean difference; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide.

Table 2. Comparison of postoperative pulmonary complications and other clinical outcomes of anatomic pulmonary resection in patients with lung cancer after propensity score matching

Variable	Total (n=178)	Volatile anesthesia group (n=89)	TIVA group (n=89)	p-value
Prolonged air leak	13 (7.0)	11 (11.8)	2 (2.2)	0.021
Pneumonia	3 (1.6)	1 (1.1)	2 (2.2)	1.000
Acute respiratory distress syndrome	1 (0.5)	1 (1.1)	0	1.000
Reintubation	2 (1.1)	1 (1.1)	1 (1.1)	1.000
Tracheostomy	0	0	0	-
Empyema	1 (0.5)	1 (1.1)	0	1.000
Pain Visual Analog Scale on POD 1	5.35±1.71	5.51±1.79	5.20±1.63	0.231
Gastrointestinal trouble	0	0	0	-
New renal failure	1 (0.5)	1 (1.1)	0	1.000
Acute myocardial infarction	0	0	0	-
New central neurologic event	1 (0.5)	1 (1.1)	0	-
Length of hospitalization after operation (day)	6.00 (3.00–38.00)	8.00 (4.00–37.00)	5.00 (3.00–38.00)	<0.001
Length of ICU stay after operation (day)	1.00 (0.00–11.00)	1.00 (1.00–2.00)	1.00 (0.00–11.00)	<0.001
Chest tube indwelling duration (day)	3.00 (0.00–20.00)	4.00 (1.00–20.00)	2.00 (1.00–14.00)	<0.001
Mortality by POD 30	0	0	0	-

Values are presented as number (%), mean±standard deviation, or median (range). TIVA, total intravenous anesthesia; POD, postoperative day; ICU, intensive care unit.

Except for prolonged air leak, no significant difference in PPCs was identified (pneumonia: 1% versus 2%, $p=1.000$; ARDS: 1% versus 0%, $p=1.000$; reintubation: 1% versus 1%, $p=1.000$; and empyema: 1% versus 0%, $p=0.001$). Tracheostomy was not performed in either group. Other important postoperative complications such as gastrointestinal trouble, new renal failure, AMI, or new central neurologic events did not show significant differences. The pain Visual Analog Scale on postoperative day 1 also did not show a significant difference (5.51 versus 5.20, $p=0.231$). However, the duration of ICU stay and hospitalization showed significant differences ($p<0.05$) between the 2 groups after PSM: the ICU stay and hospitalization were shorter in the TIVA group. The duration of chest tube indwelling was also significantly shorter in the TIVA group ($p<0.001$).

Discussion

PPCs are an assortment of clinical outcomes following surgery, which included prolonged air leak, pneumonia, ARDS, empyema, atelectasis requiring BFS, ALI, BPF, pulmonary embolism, and pulmonary edema in this study. Although the incidence of PPCs varies across populations and depending on how studies define PPCs, it is estimated to be up to 23% [11]. The 30-day mortality has been shown to be significantly higher in patients with PPCs (14%–30% versus 0.2%–3%), with an increase in both morbidity and health care costs [2]. Since thoracic surgery itself is a

non-modifiable risk factor, thoracic surgeons, especially those who perform lung resection surgery, recognize the importance of prevention and management of PPCs. For this reason, selecting an optimal anesthetic modality to minimize PPCs during thoracic surgery has become an emerging issue.

Therefore, trials to investigate better anesthetic regimens to reduce PPCs during general anesthesia have been conducted with various designs. TIVA is beneficial for lowering the risk of PONV when compared to volatile anesthesia [4]. In addition, TIVA has little effect on HPV, which is a protective reflex to maintain oxygenation during 1-lung ventilation (OLV) [5]. Furthermore, favorable postoperative survival rates are one of the reasons our center chose TIVA as an anesthetic modality [3,6]. In contrast, sevoflurane reduced the incidence of minor PPCs in patients after head and neck cancer surgery [9]. An interesting systematic review reported that propofol had a significant adverse effect on postoperative cognitive function in elderly patients with lung cancer when compared to sevoflurane [12], and impaired cognitive function has been reported as a non-modifiable risk factor for PPCs [2]. Furthermore, the oxygen index, which represents intraoperative pulmonary function, within 30 minutes after initiation of OLV, was lower in the inhalation group. The incidence of pulmonary complications, such as esophagectomy and pulmonary lobectomy, was higher in the TIVA group in patients undergoing thoracic surgery requiring OLV [7]. The incidence of pul-

monary complications was higher after cardiac surgery using TIVA, but it remains unclear whether this is also the case after lung surgery [6]. A systematic review and meta-analysis suggested that volatile anesthetics are beneficial in reducing the mortality rate and have fewer pulmonary complications than TIVA in cardiac surgery, but there was no significant difference in noncardiac surgery [13]. Because of the current inconsistencies in the literature, further studies are required to examine the impact of anesthetic regimens on PPCs in specific operations. Therefore, we retrospectively analyzed the data of patients with lung cancer who underwent surgery confined to anatomic pulmonary resection at a single institution to select optimal anesthetic agents during surgery.

The results of our study revealed that no single anesthetic agent was superior to other agents in reducing PPCs following anatomic pulmonary resection. Conversely, a rat experiment demonstrated that volatile agents exerted a protective effect against lung injury by slowing the inflammatory response [14]. The contrasting result could be attributed to the fact that we focused on single cancer surgery with a confined operative extent, which has not been conducted before. In addition, pulmonary complications are affected not only by inflammatory effects on the lungs, but also by numerous other factors that need to be considered. Experimental studies have reported that volatile agents exert a myocardial protective effect during surgery through the regulation of mitochondrial permeability transition pores and signaling pathways of myocardial cells, but this effect has yet to be revealed in clinical studies [15,16]. If future clinical studies support the myocardial protective effect of volatile agents, induction with volatile agents rather than intravenous agents might be advantageous for patients at a high risk of postoperative cardiac complications.

In our study, the lengths of hospitalization and ICU stay were shorter and the incidence of prolonged air leak was significantly lower in the TIVA group than in the volatile anesthesia group. A previous meta-analysis showed a contrasting result that volatile agents significantly reduced the length of hospital stay, but there was no reduction in the length of ICU stay in noncardiac surgery [13]. The decrease in the incidence of prolonged air leak might have been caused not by anesthetic differences, but by changes in postoperative management. The 2 thoracic surgeons who were enrolled in this study had already gone through learning curves as independent surgeons before the change of anesthetic modality; therefore, surgeon-related technical factors are unlikely to have a substantial effect during the

time period of this study. The shorter duration of chest tube indwelling, length of hospitalization after the operation, and ICU stay in the TIVA group are thought to have resulted from the lower incidence of prolonged air leak.

Our study has several limitations. There were patients with and without epidural anesthesia in both groups, and they were not clearly separated before the analysis. Therefore, the anti-inflammatory effect of epidural anesthesia has not been adequately considered [17]. In addition, the initial use of propofol in the volatile anesthesia group could have influenced the results. A comparison between groups with TIVA versus volatile induction/maintenance anesthesia could yield more accurate results in future studies. Finally, this study had a small sample size. Nevertheless, we believe that our study is clinically significant because it provides meaningful data on the effect of inhalation anesthesia versus TIVA on PPCs after anatomic pulmonary resection in patients with lung cancer.

In summary, there were no statistically significant differences between the volatile anesthesia and TIVA groups in terms of PPCs after anatomic pulmonary resection in patients with lung cancer. Both modalities of anesthesia have respective advantages in various aspects, making it necessary to use appropriate anesthetic modalities in patients with different risk factors and in different situations. In the future, there is a need for multidisciplinary studies, conducted in consultation with anesthesiologists, regarding the application of both anesthetic modalities in general anesthesia to achieve better outcomes for patients with lung resection.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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