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Original Research Article

Effect of propofol and sevoflurane on perioperative and postoperative outcomes in lung cancer patients after thoracoscopic surgery

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Abstract

Purpose: *To investigate the effects of propofol and sevoflurane on intraoperative and postoperative outcomes of lung cancer patients after thoracoscopic surgery.*
Methods: *Lung cancer patients (n = 265) aged 51 – 73 years (mean age = 62 ± 11 years) who underwent thoracoscopic surgery under propofol or sevoflurane anesthesia were recruited over a 2-year period for this study. Data on perioperative pulmonary function, inflammatory responses, awakening time, postoperative pain and adverse reactions, pre- and postoperative cognitive functions, as well as duration of hospital stay were retrospectively analyzed.*
Results: *Perioperative pulmonary function was poor in patients who were operated under sevoflurane, relative to those who were operated under propofol ($p < 0.05$). After sternal closure (just before one-lung ventilation), levels of serum of interleukin 6 (IL-6), matrix metalloproteinase 9 (MMP-9), and S100β protein were reported to be higher in patients of sevoflurane group than those in propofol group, but interleukin 10 (IL-10) level was markedly reduced in sevoflurane group, relative to propofol group ($p < 0.05$). Awakening times and visual analog scale score of patients 24 h after thoracoscopic surgery of patients in sevoflurane group were significantly higher than those in propofol group ($p < 0.05$).*
Conclusion: *These results indicate that propofol is more effective than sevoflurane in the protection of pulmonary and cognitive functions of patients after thoracoscopic surgery. Thus, intravenous propofol anesthesia is recommended for thoracoscopic surgery for lung cancer.*

Keywords: *Cognitive function, Lung cancer, Propofol, Sevoflurane, Thoracoscopic surgery*

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INTRODUCTION

Lung cancer is a common malignant tumor among Chinese [1,2]. The disease is managed by thoracoscopic surgery and adjuvant therapies [3]. Lung cancer patients often miss timely treatment due to its insidious nature [4]. Thoracoscopic surgery causes trauma and triggers inflammatory response which adversely affects the living standard of patients after surgery. The surgical procedure also causes injury to other organs/tissues [5]. Proper use of narcotics is often advised during thoracoscopic surgery, since narcotic drugs inhibit the accumulation and release of neutrophils responsible for perioperative inflammation [6].

Propofol is a fast-acting drug with rapid action time, and low adverse actions. It is generally used in systematic anesthesia during thoracoscopic surgery [6]. Propofol has been reported to mitigate postoperative cognitive dysfunction [7]. Sevoflurane is an effective anesthetic in children and elderly patients [9]. Postoperative cognitive dysfunction (POCD) is a serious complication which accompanies major surgeries [9,10]. Studies on laparoscopic radical hysterectomy and lung cancer resection have demonstrated the effectiveness of propofol over sevoflurane in mitigating POCD [4,8,11]. Similarly, studies involving major cardiac surgeries and laparoscopic cholecystectomy have revealed the safety and effectiveness of sevoflurane in ameliorating POCD [9,13,14]. The actions of propofol and sevoflurane on intraoperative and post-surgical outcomes vary, but not much is known about their effect on cognitive function after thoracoscopic surgery [12].

This study investigated their actions on perioperative and postoperative outcomes in lung cancer patients after thoracoscopic surgery.

METHODS

Materials

Midazolam was product of Pfizer Inc. (USA), fentanyl was obtained from Taylor Pharmaceuticals (USA), and multifunctional monitor was bought from GE Healthcare (USA). Propofol was purchased from Fresenius Kabi AG (Germany). Sevoflurane was product of Abbott Healthcare Pvt. Ltd. (USA). Paracetamol was obtained from Bristol-Myers Squibb Pharmaceuticals Ltd (UK), while blood gas analyzer was obtained from Radiometer Medical Group (Denmark).

General information on patients

Lung cancer patients (n = 265) aged 51 – 73 years (mean age = 62 ± 11 years) who underwent thoracoscopic surgery under propofol or sevoflurane anesthesia at the Ninth People's Hospital of Suzhou, Suzhou, China were recruited over a 2-year period for this study. The inclusion criteria were: (1) patients diagnosed of lung cancer; (2) patients undergoing thoracoscopic surgery; and (3) patients who scored I or II in the American Society of Anesthesiologists (ASA) scoring system.

Patients with MMSE score < 24 before induction of anesthesia were excluded from the study. The study protocol was approved by the Human Ethics Committee of the Ninth People's Hospital of Suzhou (approval no. NPHSCLPB111547) and carried out in adherence to the laws of China, the Helsinki Declaration (2008) [15] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [16]. Written informed consent was obtained from patients and their family members. Being a retrospective study, documentation in the Chinese clinical trial registry was waived by the institute.

Study design

The patients were assigned to 2 groups: propofol (n = 149) and sevoflurane (n = 116) groups. The operative patients received 0.1 mg midazolam/kg body weight (bwt) half an hour before induction of anesthesia, followed by intravenous injection of fentanyl (3 µg/kg bwt). Physiological parameters of patients were monitored using multifunctional monitor. Patients in propofol group received 6 mg/kg bwt/h intravenous injection of propofol, while those in sevoflurane group were exposed to 8 % sevoflurane via inhalation. After 5 min of ventilation, tracheal intubation was performed. Patients heart beat and blood pressure were maintained with anesthesia machine so as not to exceed 20 % of baseline value. On completion of surgery, the patients received paracetamol infusion for 3 days (100 mL infusions/day). Pulmonary function and inflammatory response parameters were determined before induction of anesthesia, after sternal closure (just before one-lung ventilation), and 24 h after surgery.

Determination of pulmonary function

Arterial blood was drawn from patients and analyzed. Arterial blood gas was measured with a blood gas analyzer. Arterial/central line insertion procedure was performed during surgery where appropriate. Alveolar-arterial oxygen partial pressure difference (A-aDO2), respiratory index (RI), and intra-pulmonary shunt fraction (Qs/Qt) were calculated from fraction of inspired oxygen (FiO_2), partial pressure of oxygen (PaO_2), that of carbon dioxide ($PaCO_2$), venous oxygen content (CvO_2), and arterial oxygen content (CaO_2) as shown in Eqs 1, 2 and 3 [17].

$$A\text{-}aDO_2 = (FiO_2(713–5)/4(PaCO_2–PaO_2)\} \ldots (1)$$

$$RI = A – (aDO_2/PaO_2) \ldots\ldots (2)$$

$$Qs/Qt = \{(CcO_2\text{-}CaO_2)/(CcO_2\text{-}CvO_2)\} \text{--------} (2)$$

Determination of levels of inflammatory mediators

The protein levels of inflammatory mediators were determined in patients serum using their respective enzyme-linked immunosorbent assay (ELISA) kits [19].

Assessment of cognitive function

Mini-mental state examination (MMSE) was performed before induction of anesthesia, and 24 h after thoracoscopic surgery. A total of 11 questions covering a total of five areas of cognitive function (temporal orientation, spatial orientation, attention, calculation, recall, and language) were used for MMSE.

The highest score was 30, and scores < 24 were considered as indicative of cognitive impairment, while scores of 27 to 30 were considered normal. Scores of 21 to 26 were taken as indicative of mild condition of cognitive impairment. Scores ranging from 10 to 20 indicated moderate condition of cognitive impairment, while scores from ≤ 9 indicated severe condition of cognitive impairment [10].

Determination of awakening time

Extubation time, eye-opening time, and response time of patients were recorded and analyzed at the end of thoracoscopic surgery. Extubation time was the time it took a patient to open his/her mouth for removal of endotracheal tube (ETT) at the end of anesthesia.

Eye-opening time was the time it took a patient to open his/her eye, while response time was the time taken to respond to external stimulus [4].

Evaluation of postoperative pain

Visual analog scale (VAS) was used to measure postoperative pain 24 h after thoracoscopic surgery (after patients regained consciousness). The score ranged from 0 to 10 (a score of 0 indicated no of pain, while a score 10 indicated maximum possible pain). Fentanyl injection (50 µg/kg bwt) was intravenously administered in the event that VAS score was ≥ 3.

Measurement of adverse reactions

Data on low blood pressure, bradycardia, nausea, and vomiting from the time when a patient was anesthetized to 24 h after thoracoscopic surgery were recorded and analyzed.

Assessment of duration of hospital stay

Duration of hospital stay was defined as the period from admission for thoracoscopic surgery to discharge.

Statistical analysis

Power analysis was performed using an online calculator, assuming α = 0.05 with a power (β) of 80 % and 95 % confidence interval (CI). Qualitative data are expressed as relative frequency (percentage), while quantitative data are shown in the form of mean ± standard deviation (SD). Qualitative data were compared using Student's *t*-test and quantitative data were compared using Fisher exact test. SPSS version 25.0 was used for statistical analysis. Values of $p < 0.05$ were considered significant.

RESULTS

Perioperative profile of patients

Significant differences were not reported for in clinical and demographic conditions, perioperative parameters, and surgical pathological characteristics between the two anesthesia groups before thoracoscopic surgery (Table 1).

Effect of anesthesia on patients' pulmonary function

Significant differences were not reported in A-aDO2, RI, and Qs/Qt between the both groups of patients before the induction of anesthesia ($p > 0.05$ for all). However, after sternal closure (just before one-lung ventilation), A-aDO2, RI, and Qs/Qt were significantly elevated in both groups, relative to the values before the induction of anesthesia ($p < 0.05$ for all). The values of these parameters 24 h after thoracoscopic surgery were not significantly different from those before induction of anesthesia ($p > 0.05$). Moreover, after sternal closure (just before one-lung ventilation), A-aDO2, RI, and Qs/Qt were reported higher in sevoflurane group as compared those in propofol group ($p < 0.05$ for all).

Effect of anesthesia on inflammatory responses of patients

Before induction, there were no significant differences in the serum levels of inflammatory mediators in patients between the two groups ($p > 0.05$ for all).

Table 1: Clinical and demographic characteristics of patients **(**n, %*)*

Variable		Group		*P*-value
		Propofol (n = 149)	***Sevoflurane (n = 116)***	
Age (years)		67.15 ± 15.14	63.42 ± 17.11	0.061
Sex	Male	105 (70)	75 (65)	0.354
	Female	44 (30)	41(35)	
Ethnicity	Han Chinese	136 (91)	106 (91)	0.916
	Mongolian	12 (8)	8 (7)	
	Tibetan	2 (1)	2 (2)	
Body mass index (kg/m^2)		24.15 ± 2.11	23.65 ± 1.98	0.051
American Society of Anesthesiologists score	I	85 (57)	73 (63)	0.378
	II	64 (43)	43 (37)	
Ejection fraction		0.62 ± 0.07	0.60 ± 0.11	0.073
Mini-mental state examination score before anesthesia		26.12 ± 1.45	25.89 ± 1.24	0.174
Operation time (min)		245.15 ± 35.12	251.42 ± 30.41	0.128
Intraoperative complications		7 (5)	6 (5)	0.998
Surgical pathology	Non-small-cell lung cancer	72 (48)	57 (49)	0.985
	Squamous cell	32 (21)	22 (19)	
	Adenocarcinoma	21 (14)	18 (16)	
	Undifferentiated	13 (9)	11 (9)	
	Small-cell lung cancer	11 (8)	8 (7)	

However, after induction of anesthesia, and 24 h after thoracoscopic surgery, serum levels of IL-6, MMP-9, and S100*β* protein were increased in both groups, but serum level of IL-10 was decreased ($p < 0.05$ for all). Moreover, after sternal closure (just before one-lung ventilation), serum levels of IL-6, MMP-9, and S100*β* were reported higher in sevoflurane group than in propofol group, but IL-10 level was markedly reduced in sevoflurane group, relative to propofol group ($p < 0.05$).

Effect of anesthesia on awakening time

As shown in Figure 1, extubation time, eye-opening time, and response time of patients in sevoflurane group were reported higher than those in propofol group ($p < 0.05$).

Effect of anesthesia on postoperative pain

Visual analog scale (VAS) score of patients in sevoflurane group 24 h after thoracoscopic surgery was reported higher than that of propofol group ($p < 0.05$). After surgery, patients in propofol group received lower amount of paracetamol infusion and fentanyl injection, relative to those in sevoflurane group ($p < 0.05$). However, at the time of discharge, significant difference was nor reported in postoperative pain of patients between the two groups ($p > 0.05$; Table 2).

Effect of anesthesia on the occurrence of adverse reactions

There were fewer adverse reactions in the propofol group, relative to sevoflurane group ($p < 0.05$). Low blood pressure and nausea occurred more frequently in sevoflurane group of patients than in propofol group, while patients in propofol group experienced bradycardia ($p < 0.05$ for all; Table 3).

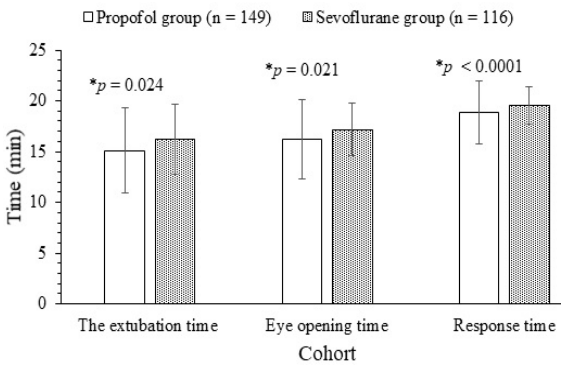

Figure 1: Comparison of awakening time after operation. *p < 0.05 with respect to sevoflurane group

Table 2: Comparison of VAS scores between the two groups (n, %)

VAS score	Group *Propofol (n = 149)*	*Sevoflurane (n = 116)*	*P*-value
0	0 (0)	0 (0)	
1	1 (1)	0 (0)	
2	5 (3)	4 (3)	
3	12 (8)	11 (9)	
4	18 (12)	17 (15)	
5	11 (7)	8 (7)	
6	25 (17)	13 (11)	< 0.0001
7	34 (23)	27 (23)	
8	24 (16)	19 (16)	
9	12 (8)	10 (9)	
10	7 (5)	7 (6)	
Mean ± SD	6.25 ± 2.07	6.27 ± 2.16	

Table 3: Adverse reactions of operative patients (n, %)

Adverse reaction	Group Propofol (n = 149)	Sevoflurane (n = 116)	*P*-value
Low blood pressure	5 (3)	11 (9)*	0.014
Bradycardia	5 (3)**	1 (1)	0.045
Nausea	4 (3)	16 (14)*	0.001
Vomiting	2 (1)	5 (4)	0.083
Total adverse reactions	16 (11)	33 (28)	< 0.0001

*P < 0.05, relative to propofol group; **p < 0.05, relative to sevoflurane group

Effect of anesthesia on cognitive function

Mini-mental state examination (MMSE) score of patients in propofol group was reported higher than that in sevoflurane group 24 h after thoracoscopic surgery (p < 0.05). The MMSE values of both anesthesia groups were increased 24 h after thoracoscopic surgery, when compared to the values before induction of anesthesia (p < 0.05). In addition, 24 h after thoracoscopic surgery, 4 patients in propofol group and 11 patients in sevoflurane group developed mild condition of cognitive impairment. Moreover, there were no cases of moderate or severe cognitive impairment. The results are shown in Figure 2.

Effect of anesthesia on duration of hospital stay

Significant difference in the duration of stay in hospital was not reported between patients of the two anesthesia groups (p > 0.05).

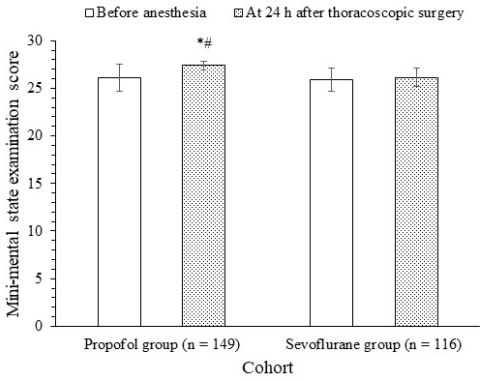

Figure 2: Comparison of MMSE scores. *P < 0.05, relative to sevoflurane group; *#p < 0.05, relative to value before induction of anesthesia

DISCUSSION

Postoperative cognitive dysfunction (POCD), a serious complication accompanying major surgeries in elderly patients, related to decline in memory and executive functions) and may last 1 year after surgery [9,10].

Thoracoscopic surgery is a procedure used frequently to treat early-stage lung cancers. The actions of propofol and sevoflurane on perioperative and after operation outcomes differ, but little or nothing is known about their effects on cognitive function after thoracoscopic surgery [12]. Sevoflurane causes neurodegeneration characterized by aggregation of β-amyloid protein, changes in exploratory and anxiety-like behavior in patients, and activation of specific kinases that lead to phosphorylation of tau and spatial memory deficits. Propofol is a short-acting anesthetic drug. Propofol-induced hypnotic effect through GABA receptor. This study investigated the actions of propofol and sevoflurane on perioperative and after operation outcomes in lung cancer patients after thoracoscopic surgery.

The results revealed significantly poor perioperative pulmonary function in patients who received sevoflurane, relative to those who received propofol, and they are in agreement with reports in previous studies [4,11,17]. Thoracoscopic surgery impairs pulmonary function [4,20,21]. Sevoflurane causes lung edema and aggravates hypoxia via reduction in lung elasticity [17]. In this study, perioperative inflammatory response was markedly higher in sevoflurane group than in propofol group. These results are in agreement with reports in previous studies, and indicate that propofol may protect pulmonary function more effectively during thoracoscopic surgery than sevoflurane [4,8,11,17].

Thoracoscopic surgery has been reported to cause pulmonary edema [17]. It is likely that propofol inhibits inflammatory response during thoracoscopic surgery [25]. Studies have shown that sevoflurane significantly upregulated the expression of proinflammatory cytokines after inhalation [17]. In this study, awaking time, of patients in sevoflurane group were significantly higher than those in propofol group. There were fewer adverse reactions and markedly reduced postoperative pain in propofol group, relative to sevoflurane group. These results suggest that propofol may be relatively safer than sevoflurane during thoracoscopic surgery. This finding is in agreement with reports in a previous study [4].

The results obtained in this study showed that intravenous propofol markedly improved cognitive function in patients, and are consistent with findings in previous studies [11,12]. However, these results are not in agreement with those obtained in studies involving major cardiac surgeries and laparoscopic cholecystectomy [13]. The observed inconsistency may be due to differences in operational setting [12]. Thoracoscopic surgery decreases the ratio of ventilatory capacity to blood flow, which causes hypoxemia and postoperative cognitive impairments [26]. MMSE score is a simple, effective, and reliable method for evaluation of postoperative cognitive function [4]. The effectiveness of propofol over sevoflurane in the protection of cognitive function of patients after thoracoscopic surgery may be due to the fact that sevoflurane inhibits synaptic transmission for a longer period than propofol [27,28].

Limitations of the study

The likely limitations of this study are: (1) small sample size/population; (2) short follow-up period; (3) failure to account for the influence of experience of surgeons on the occurrence of cognitive dysfunction in patients during surgery; (4) failure to perform multivariate analysis for an independent predictor of POCD; (5) failure to account for the possible effects of midazolam and fentanyl used during surgery on postoperative cognitive function; (6) failure to include other surgical parameters that could affect POCD; and (7) non-inclusion of a normal control group.

CONCLUSION

The results of this study indicate that propofol is more effective than sevoflurane in the protection of pulmonary and cognitive functions of patients after thoracoscopic surgery. Thus, intravenous propofol anesthesia is recommended for thoracoscopic surgery for lung cancer.

DECLARATIONS

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Conflict of interest

No conflict of interest or any other competing interest is associated with this study.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The authors read and approved the manuscript for publication. Ying Zhou contributed to conceptualization, data curation, formal analysis, investigation, methodology of the study. Ting Xu contributed to project administration, resources, software, supervision, validation, visualization of the study, draft and edited the manuscript for intellectual content. The authors agree to be accountable for all aspects of work, including its integrity and accuracy.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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