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Original Article

Comparison of remifentanil with sevoflurane and remifentanil with propofol on perioperative inflammatory response and pulmonary function in patients with lung cancer

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Abstract: Objective: The aim of this study was to compare effects of the combination of remifentanil with sevoflurane and remifentanil with propofol on perioperative inflammatory response and pulmonary function in patients with lung cancer. Methods: This study enrolled 382 patients diagnosed with lung cancer. Patients were divided into a sevoflurane group (n=190) and propofol group (n=192). Ejection fraction (EF) and one-lung ventilation time (OLV-T) were recorded for all patients. Alveolar-arterial oxygen difference (A-aDO_2), intrapulmonary shunt (Qs/Qt), and respiratory index (RI) were also calculated. This study measured serum levels of malondialdehyde (MDA) and matrix metalloproteinase-9 (MMP-9). Results: A-aDO_2 in the sevoflurane group was significantly higher than the propofol group ($P < 0.05$) at initiation of one-lung ventilation (T1), completion of one-lung ventilation (T2), and chest closure (T3). RI in the sevoflurane group was significantly higher than the propofol group at T2 and T3 ($P < 0.05$). Qs/Qt in the sevoflurane group was significantly higher than the propofol group at T1, T2, and T3 ($P < 0.05$). MMP-9 and MDA levels at T3 were significantly higher in the sevoflurane group than the propofol group ($P< 0.05$). Conclusion: Combination of propofol-remifentanil is more effective than combination of sevoflurane-remifentanil in reducing perioperative inflammatory response and protection of pulmonary function in patients with lung cancer and may be more suitable for anesthetic management during lung resection.

Keywords: Sevoflurane, propofol, inflammatory response, pulmonary function

Introduction

Lung cancer most commonly originates in the epithelium of bronchial mucosa and is the most common primary malignant lung tumor [1]. According to Brahmer et al. [2], in 2015, 1.8 million new patients were diagnosed with lung cancer, worldwide, of which one third were men. Herbst et al. [3] demonstrated that incidence of lung cancer is higher in developed countries, including the United Kingdom and United States. Furthermore, mortality from lung cancer is as high as 60% [4]. According to Garon et al. [5], 800,000 people died of lung cancer in 2015, with mortality rates increasing. Current treatment for lung cancer mainly includes surgical resection which may induce ischemia-reperfusion (IR) injury due to the effects of anesthetic agents, significantly impacting patient prognosis [6]. Therefore, clinical research on anesthetic agents during lung resection has become an important topic.

Narcotic agents enable protection at the cellular level by inhibiting inflammatory response as well as ameliorating IR-induced lung injury during the intraoperative period. Current clinical research regarding anesthetic agents during lung resection has been mainly focused on remifentanil [7-9]. However, Liang et al. [10] pointed out that the effects of sevoflurane in combination with remifentanil were superior to that of conventional anesthetic agents. Przybyowski et al. [11] also suggested that propofol combined with remifentanil was optimal for lung resection. At present, there are no studies supporting the superiority of any specific anesthetic agent during lung surgery.

Therefore, this study compared administration of either sevoflurane or propofol in combination with remifentanil for anesthetic management of patients undergoing lung resection for cancer. This study compared the effects of two different anesthetic regimens on perioperative

Table 1. Clinical data comparison for the two groups of patients [n (%)]

	Sevoflurane group (n=190)	Propofol group (n=192)		P
Age			t=0.36	0.718
	47.24 ± 8.03	46.92 ± 9.21		
Gender			χ^2=0.01	0.942
Male	126 (66.3)	128 (66.7)		
Female	64 (33.7)	64 (33.3)		
Marital status			χ^2=0.63	0.429
Married	172 (90.5)	169 (88.0)		
Unmarried	18 (9.5)	23 (12.0)		
Body weight (KG)			t=1.10	0.274
	73.62 ± 15.62	75.33 ± 14.36		
Pathological staging			χ^2=0.88	0.349
I~II	69 (36.3)	61 (31.8)		
III~IV	121 (63.7)	131 (68.2)		
Excision site			χ^2=0.37	0.542
Left lung	94 (49.5)	89 (46.4)		
Right lung	96 (50.5)	103 (53.6)		
OLV-T (min)			t=0.89	0.372
	124.34 ± 16.53	122.86 ± 15.86		
EF			t=1.15	0.252
	0.65 ± 0.08	0.64 ± 0.09		

inflammatory response and pulmonary function with an aim of providing future guidance in the treatment of lung cancer.

Materials and methods

Patient information

This study retrospectively analyzed 382 patients with lung cancer, received into the Department of Respiration and Department of Oncology, from March 2014 to June 2017. There were 254 men and 128 women, aged 40-65 years, with a mean age of 46.34 ± 10.28 years. Inclusion criteria were: (1) Diagnosis of lung cancer by biopsy in the pathology department; (2) Lung resection performed following diagnosis; (3) Availability of complete medical records; and (4) Ages between 40-65 years old. Exclusion criteria were: (1) Impaired cardiac or pulmonary function noted during preoperative assessment; (2) Presence of other cancers; (3) Presence of hematological disease; (4) Presence of immunological diseases; (5) Disability; (6) Pregnancy; (7) Lack of fitness for surgery; and (8) Local or distant metastasis upon postoperative histopathological examination. This study was approved by the Ethics Committee and all patients provided informed consent.

Methods

All patients underwent lung resection by the Chief Physician of the Department of Respiration in strict accordance with 2012 Operative Guidelines for Non-Tissue Resection [12]. A total of 382 patients underwent lung resection. Inhalational anesthesia with 6-8% sevoflurane in combination with 4-6 μg/kg of remifentanil was administered in 190 patients (sevoflurane group) while intravenous anesthesia with 6-10 mg/kg propofol in combination with 4-6 μg/kg remifentanil was administered in 192 patients (propofol group). Double lumen endobronchial tubes were inserted after induction of anesthesia and mechanical ventilation was controlled using the S/5Avance type of anesthesia workstation (Datex-Ohmeda). Parameters of mechanical ventilation were set in strict accordance with a previous report [13].

Ejection fraction (EF) and one-lung ventilation time (OLV-T) of the two groups were recorded. All patients had 2 mL of blood drawn from the radial artery at the following time points: (1) Prior to induction of anesthesia; (2) At commencement of one-lung ventilation (T1); (3) At completion of one-lung ventilation (T2); and (4) After chest closure (T3) and at 24 hours postoperatively.

Collected blood was divided into two samples. One sample was for blood gas analysis to record the alveolar-arterial oxygen difference (A-aDO_2), intrapulmonary shunt (Qs/Qt), and respiratory index (RI) while the other sample was for determination of serum malondialdehyde (MDA) and matrix metalloproteinase-9 (MMP-9) levels.

Statistical methods

Data were analyzed using SPSS 22.0 statistical software. Measured data including EF, OLV-T, A-aDO_2, Qs/Qt, RI, MDA, and MMP-9 are expressed as X ± S. Comparison between groups

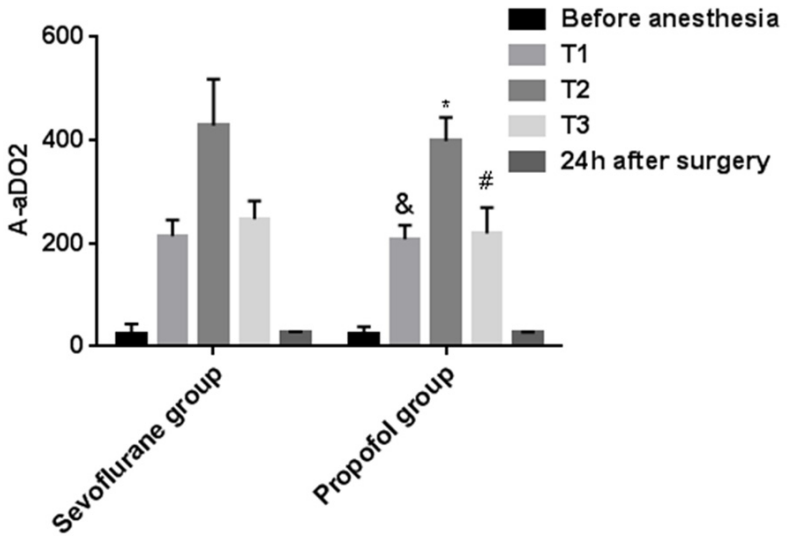

Figure 1. A-aDO$_2$ in the two groups of patients. In the sevoflurane group, A-aDO$_2$ before anesthesia, at T1, T2, T3, and 24 hours after surgery was 24.72 ± 1.82, 213.64 ± 31.52, 428.64 ± 45.19, 246.92 ± 35.18, and 26.15 ± 2.63, respectively, while that in the propofol group was 23.64 ± 1.64, 208.34 ± 26.73, 398.94 ± 45.29, 219.19 ± 32.08, and 25.86 ± 1.96, respectively. *Represents comparison of A-aDO$_2$ between the two groups at T1, P < 0.05. #Represents comparison of A-aDO$_2$ between the two groups at T2, P < 0.05. &Represents comparison of A-aDO$_2$ between the two groups at T3, P < 0.05.

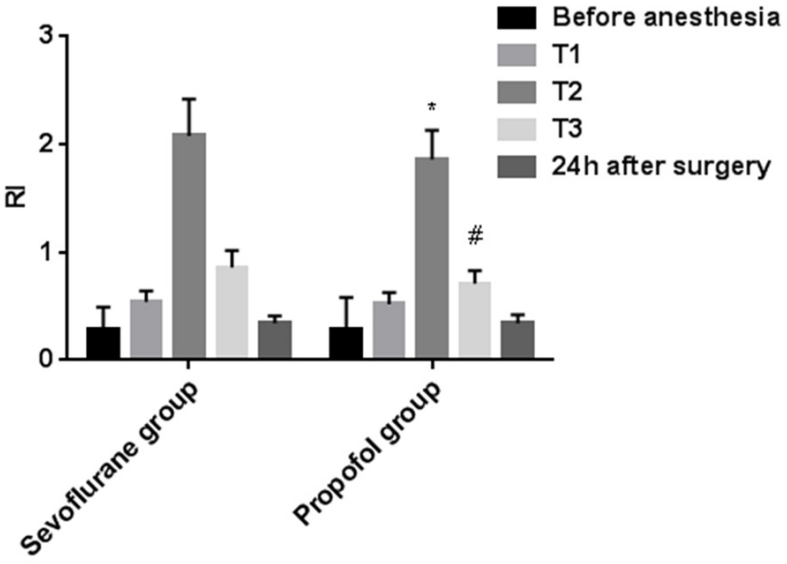

Figure 2. RI in the two groups of patients. In the sevoflurane group, RI before anesthesia, at T1, T2, T3, and 24 hours after surgery was 0.29 ± 0.05, 0.54 ± 0.10, 2.08 ± 0.34, 0.86 ± 0.16, and 0.34 ± 0.07, respectively, while that in the propofol group was 0.28 ± 0.04, 0.52 ± 0.11, 1.86 ± 0.27, 0.71 ± 0.12, and 0.34 ± 0.08, respectively. *Represents comparison of RI between the two groups at T2, P < 0.05. #Represents comparison of RI between two groups at T3, P < 0.05.

was performed using t-tests. Differences between other data including gender, marital status, pathological staging, and clinical data were examined using Chi-square test for categorical variables. Differences between the two groups at various time points were determined using one-way analysis of variance (ANOVA), while *P* values < 0.05 were considered statistically significant.

Results

Comparison of clinical data

Baseline clinical data including age, gender, marital status, body weight, pathological stage, site of resection, OLV-T, and EF between the two groups were recorded and compared. As shown in **Table 1**, no significant differences were found between the sevoflurane group and propofol group in baseline characteristics, demonstrating that the two groups were comparable.

Arterial blood gas analysis

A-aDO$_2$ before induction of anesthesia and at T1, T2, T3, and 24 hours postoperatively were 24.72 ± 1.82, 213.64 ± 31.52, 428.64 ± 45.19, 246.92 ± 35.18, and 26.15 ± 2.63, respectively, in the sevoflurane group and 23.64 ± 1.64, 208.34 ± 26.73, 398.94 ± 45.29, 219.19 ± 32.08, and 25.86 ± 1.96, respectively, in the propofol group. There were no significant differences in A-aDO$_2$ between groups before induction of anesthesia and at 24 hours postoperatively (P > 0.05). A-aDO$_2$ in the sevoflurane group was significantly higher than the propofol group (P < 0.05) at T1, T2, and T3 (**Figure 1**).

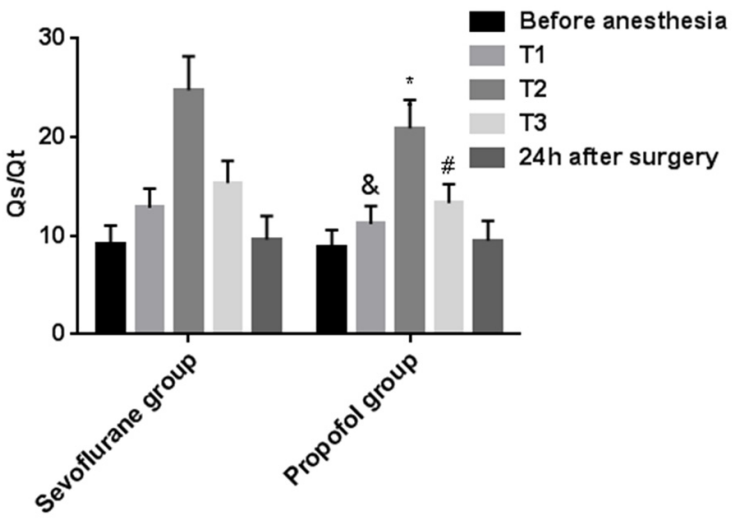

Figure 3. Qs/Qt in the two groups of patients. In the sevoflurane group, Qs/Qt before anesthesia, at T1, T2, T3, and 24 hours after surgery was 9.18 ± 1.86, 12.83 ± 19.96, 24.76 ± 3.46, 15.34 ± 2.26, and 9.60 ± 2.42, respectively, while that in the propofol group was 8.86 ± 1.72, 11.19 ± 1.82, 20.92 ± 2.86, 13.32 ± 1.92, and 9.52 ± 2.01, respectively. *Represents comparison of Qs/Qt between the two groups at T1, P < 0.05. #Represents comparison of Qs/Qt between the two groups at T2, P < 0.05 and &represents comparison of Qs/Qt between the two groups at T3.

Table 2. MMP-9 test results (ng/mL) for the two groups

	Sevoflurane group	Propofol group	t	P
Before anesthesia	101.82 ± 14.62	102.62 ± 13.71	0.55	0.582
T3	186.62 ± 19.31	163.24 ± 13.29	13.80	< 0.001
24 h after surgery	113.64 ± 14.26	112.27 ± 14.56	0.93	0.354

Table 3. MDA test results for both groups (nmol/mL)

	Sevoflurane group	Propofol group	t	P
Before anesthesia	6.82 ± 1.34	6.73 ± 1.27	0.67	0.501
T3	11.24 ± 1.62	8.92 ± 1.36	15.17	< 0.001
24 h after surgery	7.52 ± 1.34	7.47 ± 1.08	0.40	0.688

RI before induction of anesthesia and at T1, T2, T3, and 24 hours postoperatively was 0.29 ± 0.05, 0.54 ± 0.10, 2.08 ± 0.34, 0.86 ± 0.16, and 0.34 ± 0.07, respectively, in the sevoflurane group and 0.28 ± 0.04, 0.52 ± 0.11, 1.86 ± 0.27, 0.71 ± 0.12, and 0.34 ± 0.08, respectively, in the propofol group. There were no significant differences in RI between the two groups before induction of anesthesia, at T1, and 24 hours postoperatively (P > 0.05). RI in the sevoflurane group was significantly higher than the propofol group at T2 and T3 (P < 0.05) (**Figure 2**).

Qs/Qt before induction of anesthesia and at T1, T2, T3, and 24 hours postoperatively was 9.18 ± 1.86, 12.83 ± 19.96, 24.76 ± 3.46, 15.34 ± 2.26, and 9.60 ± 2.42, respectively, in the sevoflurane group and 8.86 ± 1.72, 11.19 ± 1.82, 20.92 ± 2.86, 13.32 ± 1.92, and 9.52 ± 2.01, respectively, in the propofol group. There were no significant differences in Qs/Qt between the two groups before induction of anesthesia and at 24 hours postoperatively (P > 0.05). Qs/Qt in the sevoflurane group was significantly higher than the propofol group (P < 0.05) at T1, T2, and T3 (**Figure 3**).

Comparison of inflammatory factors between the two groups

MMP-9 levels before induction of anesthesia and at 24 hours postoperatively were (101.82 ± 14.62) ng/mL and (113.64 ± 14.26) ng/mL, respectively, in the sevoflurane group. MMP-9 levels were (102.62 ± 13.71) ng/mL and (112.27 ± 14.56) ng/mL, respectively, in the propofol group. Differences were not significantly different (P > 0.005). MMP-9 level in the sevoflurane group at T3 was (186.62 ± 19.31) ng/mL, significantly higher than that in the propofol group (163.24 ± 13.29) ng/mL, (P < 0.001) (**Table 2**). There were no significant differences in MDA levels between the two groups before induction of anesthesia and at 24 hours postoperatively (P > 0.05). At T3, MDA level in the sevoflurane group was (11.24 ± 1.62) nmol/mL, significantly higher than that in the propofol group (8.92 ± 1.36) nmol/mL, (P < 0.001) (**Table 3**).

Discussion

Protection of organ function is an important part of anesthesiology [13]. With increasing incidence and mortality of lung cancer in recent years, advances had been made regarding techniques of one-lung ventilation (OLV) [14]. OLV enables effective ventilation and prevents cross infection and spread of pathogens from one lung to the other. For patients undergoing

pneumonectomy, OLV effectively prevents expansion of the affected lung, reduces significant lung injury, and greatly improves operative success [15, 16]. However, OLV inevitably induces some unfavorable effects, including OLV related IR injury and oxidative stress [17]. In recent years, there has been increasing focus on amelioration of lung injuries induced by OLV during lung resection for cancer, with propofol and sevoflurane emerging as preferred anesthetic agents. Wang et al. [18] revealed that propofol has anti-inflammatory and cell-protective effects. Buse et al. [19] suggested that sevoflurane may reduce perioperative injury by promoting immunometabolism. At present, there are no studies comparing the effects of propofol and sevoflurane in combination with remifentanil on perioperative inflammatory response and lung function in patients undergoing resection for lung cancer. This study aimed to investigate which of these agents may be more suitable in this setting, providing future clinical guidance.

This study showed that perioperative serum MMP-9 levels were lower with the propofol-remifentanil combination. Moreover, MDA levels were lower with more favorable A-aDO_2, RI, and Qs/Qt in this group of patients, suggesting that the propofol-remifentanil combination was superior to sevoflurane-remifentanil for lung resection in patients with cancer. Intraoperative A-aDO_2 and RI are sensitive indicators of pulmonary diffusion function, effectively reflecting the extent of lung injury [20], with higher values suggesting greater severity [21]. In this study, there were no significant differences between the groups in both indices before induction of anesthesia and at 24 hours postoperatively, suggesting that both drugs may be used as anesthetic agents for lung resection. However, at T1, T2, and T3, both indices were significantly lower with propofol compared to sevoflurane. This may be due to aggravation of lung tissue edema or reduced surfactant activity induced by sevoflurane. Zhumadilov et al. [22] suggested that inhalation anesthesia may affect the permeability of the biofilm to water and electrolytes. It has been speculated that inhalational anesthesia with sevoflurane may cause reversible accumulation of alveolar fluid, reduce the clearance rate of lung water, and aggravate perioperative pulmonary edema, thus inhibiting the diffusion of oxygen. As surfactant activity is reduced, there is a fall in lung compliance, possibly leading to an increase in A-aDO_2 and inducing RI. An important indicator for prevention of hypoxia, Qs/Qt has a strong correlation with hypoxic pulmonary vasoconstriction (HPV) [23]. However, inhalational anesthesia with sevoflurane inhibits HPV in the dependent lung and aggravates the potential risk of hypoxia during OLV. Intravenous anesthesia with propofol may be more favorable by preserving HPV besides avoiding negative effects of partial pressure of the inhalational agent. A highly sensitive marker of inflammation, MMP-9 acts on the pulmonary capillary basement membrane, inducing infiltration of inflammatory factors and promoting formation of pulmonary edema with an increase in vascular permeability [24]. In this present study, MMP-9 levels in the sevoflurane group were significantly higher than the propofol group, suggesting that inflammatory reaction in the lungs was more severe with sevoflurane. Sevoflurane-induced inflammatory reaction may be due to the release of inflammatory mediators and promotion of gene expression of inflammatory factors. Moreover, it worsens lung injury and pulmonary function, consistent with a previous report by Kalafatovic et al. [25]. Recently, free radical-induced injuries have been found to be closely associated with anesthesia. MDA, an indicator of the extent of free radical-induced injuries, was significantly higher in the sevoflurane group than the propofol group. This result suggests that pulmonary lipid peroxidation is more intense during sevoflurane anesthesia with exacerbation of free radical-induced pulmonary capillary endothelial cell injuries leading to pulmonary edema and an increase in degree of lung injury.

This present study compared the perioperative inflammatory response and lung function of patients undergoing lung resection for cancer with a sevoflurane-remifentanil or propofol-remifentanil combination. This study was limited by experimental conditions, including a small sample size. This study aimed to carry out a longer period of follow up of patients taking part in the study and improve the design for future studies, hopefully producing more robust results.

In conclusion, the propofol-remifentanil combination is more effective than sevoflurane-remifentanil in reducing perioperative inflammatory response and protecting pulmonary function in patients with lung cancer. This combination

may be more suitable for anesthetic management of these patients during lung resection.

Disclosure of conflict of interest

None.

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