

Comparison of the effects of intravenous and inhalational anesthesia on postoperative pulmonary complications after oral and maxillofacial surgery with free flap reconstruction: a double-blind, randomized, controlled trial

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Abstract

Background: The effects of intravenous and inhalation anesthesia on intraoperative and postoperative pulmonary inflammatory responses have been reported in many studies. The differences in clinical postoperative pulmonary complications (PPCs) have been also studied in cardiac and lung resection surgery. However, there are few relevant reports and the findings remain controversial. Clinical evidence for the effects of these two anesthetics on PPCs in other types of surgery is still missing. The main goal of the current study was to assess the impact of sevoflurane and propofol on the incidence of PPCs in patients undergoing oral and maxillofacial surgery.

Methods: In this double-blind, randomized, controlled trial, we randomly assigned 220 adults at intermediate-to-high risk of pulmonary complications after oral and maxillofacial cancer surgery with radial forearm or fibular flap reconstruction to either propofol or sevoflurane as a general anesthetic. The occurrence of pulmonary complications according to the Clavien-Dindo score was defined as the primary (within 7 days after surgery) outcome.

Results: The two intervention groups had similar characteristics at baseline. The PPCs incidence during 7 days after surgery was 32.4% and 18.2% in the propofol and sevoflurane groups, respectively (adjusted relative risk, 0.44; 95% confidence interval CI, 0.22 to 0.91; $P = 0.027$). The corresponding incidence of PPCs in patients who underwent tracheotomy at the end of surgery in the two groups was 44.8% and 24.5% (adjusted relative risk, 0.39; 95% CI, 0.17 to 0.91; $P = 0.030$). In addition, the Clavien-Dindo classification showed significant differences between groups in minor complications (grade I and II) but not in major complications (grade III to V). Intergroup difference in the time to occurrence of the first PPC after surgery was significant ($P = 0.021$). There was no difference in postoperative hospital stay between the two groups.

Conclusions: Compared with intravenous anesthesia, the administration of sevoflurane reduces the incidence of minor PPCs (grade I to II) in moderate- and high-risk patients who have undergone tracheotomy after oral and maxillofacial cancer surgery with radial forearm or fibular flap reconstruction.

Introduction

Postoperative pulmonary complications (PPCs) are important factors affecting the prognosis of patients. PPCs prolong hospitalization time and increase hospitalization expenses; severe PPCs increase the mortality of patients. Oral and maxillofacial surgery is considered a risk factor for PPCs.¹ The radial forearm, fibula, and anterolateral thigh flaps are usually used for soft tissue and/or bone tissue repair after tumor resection. Perforator-based free flaps have been increasingly used in the repair and reconstruction in head and neck surgery. Previous studies have shown that the incidence of PPCs after free flap surgery is 18.8% to 44.8%,^{1,2,3} while that of PPCs in patients undergoing head and neck surgery with tracheotomy is up to 47%.⁴ It is a key point for anesthesiologists to prevent and reduce the occurrence of PPCs.

Propofol and sevoflurane are commonly anesthetics, both of which can effectively maintain general anesthesia. The choice for anesthesia maintenance is mostly based on the anesthesiologists' preference and hospital practice. The incremental value of anesthetics, such as their anti-inflammatory effects, have also been studied.^{5, 6}

At present, the effect of intravenous or inhalation anesthesia on PPCs after different operations is controversial. A meta-analysis showed that volatile anesthetics were associated with fewer PPCs compared to those associated with total intravenous anesthesia (TIVA) in patients who underwent cardiac surgical procedures ($P = 0.038$).⁷ Current research indicates that compared to propofol, sevoflurane for anesthesia maintenance is more conducive for reducing the incidence of PPCs after lung resection surgery (LRS).^{8, 9} Furthermore, a logistic regression model showed that the type of anesthesia (inhalational versus intravenous) used was more closely associated with PPCs after LRS. (OR, 2.94; 95% CI, 1.23–7.04).¹⁰ However, conflicting data exist about LRS.^{11,12} With regard to non-cardiothoracic surgery, clinical evidence from high-quality randomized clinical trials (RCTs) is lacking; therefore, further research is needed.

The present study was designed to compare the incidence of PPCs in intermediate- and high-risk patients who received propofol or sevoflurane during oral and maxillofacial cancer surgery. We hypothesized that compared to propofol, sevoflurane could decrease the incidence of PPCs after free

flap surgery.

Methods

Trial design

This single-center study was conducted by the Department of Anesthesiology, Peking University Hospital of Stomatology in Beijing, China. Ethics approval was received from the Biomedical Ethics Committee of Peking University Hospital of Stomatology (Number: PKUSSIRB-201734029) in December 2017. The trial is registered with the Chinese Clinical Trial Registry (Number: ChiCTR1800015347). This was a prospective trial with two parallel arms to test the hypothesis of whether maintenance of anesthesia with sevoflurane leads to fewer PPCs within 7 days compared to maintenance of anesthesia with propofol.

Randomization and blinding

Randomization was performed by an independent statistician, and random numbers generated by SAS 8.0 software were used to assign participants randomly (1:1) to either intravenous propofol or inhalational sevoflurane for maintenance of anesthesia. The codes were kept in sealed envelopes. Before surgery, these envelopes were provided to the attending anesthesiologist by a researcher not involved in patient care. Patients and surgeons did not know about the grouping during surgery and follow-up. In addition, the physicians who conducted follow-up examinations after surgery were blinded to the group allocation.

Patients

The study population comprised 220 patients between March 26, 2018, and March 25, 2019. Written informed consent was obtained before randomization from each patient. Patients with oral and maxillofacial cancer surgery were eligible for participation in the study if they were 19 to 79 years of age, were scheduled to undergo oral and maxillofacial cancer resection and free flap (fibula or forearm) reconstruction surgery with an expected duration of at least 4 h, and had a preoperative pulmonary complication risk index (Canet score) of 26 points or more. The Canet score is a risk score for pulmonary complications, with a score of 26-44 representing moderate risk and that of 45 or greater representing high risk. ¹³

Patients were ineligible if they refused to participate in the clinical trial or had a body mass index of 35 or higher, severe chest wall malformation, acute phase of chronic obstructive pulmonary disease (AECOPD), uncontrolled asthma (Asthma Control Test \leq 18), ¹⁴ pulmonary artery stenosis, pulmonary hypertension and congestive heart failure, complex heart deformities, severe liver (Child-Pugh grade C) or kidney dysfunction (requirement of renal replacement therapy), or a history of mental illness.

Intervention

All patients were managed according to the same anesthesia protocol. Routine hemodynamic monitoring (continuous 5-lead electrocardiogram, pulse oximetry, and noninvasive blood pressure), as well as the bispectral index (BIS) (Covidien, USA), was performed and cannulation of the dorsalis pedis for monitoring of invasive arterial pressure was completed immediately after anesthesia induction.

Anesthesia induction was carried out in both groups with 0.1 mg/kg penehyclidine hydrochloride, 0.05 mg/kg midazolam, 0.3 μ g/kg sufentanil, 2 mg/kg propofol, and 0.6 mg/kg rocuronium. The parameters were volume-controlled ventilation, tidal volume (Vt) of 8 ml/kg (ideal weight), and fraction of inspiration O₂ (FiO₂) of 0.4–0.5; the respiratory rate was adjusted to maintain an end-tidal carbon dioxide concentration (ETCO₂) between 35 and 45 mmHg.

In the propofol group, anesthesia was maintained by propofol as a target-controlled infusion (2 to 6 μ g/ml), while in the sevoflurane group, sevoflurane was applied with end-tidal concentrations of 2 to 5%. Analgesia was administered by applying target-controlled infusion of remifentanil up to 6 ng/ml and or boluses of sufentanil 0.2 to 0.5 μ g/kg in accordance with patient needs. Muscle relaxation was achieved by intermittent injection of rocuronium bromide. The depth of anesthesia was to maintain a BIS between 40 and 60. In patients who underwent surgery for more than 4 h, cefuroxime sodium 1.5 g was used 30 min before surgery and for the fourth hour during surgery. At the end of surgery, whether the prophylactic tracheotomy is needed according to patient's range of tumor resection, repair method and neck mobility. All patients with endotracheal intubation or tracheotomy returned to the post-anesthesia care unit (PACU) after they showed spontaneous respiration.

Postoperative data

Postoperative patients who underwent tracheotomy (decannulation on the fifth day) or endotracheal intubation (extubation the next morning) were observed for a night in the PACU. Low-flow supplemental oxygen and dexmedetomidine sedation (the dose of 1 µg/kg was pumped for 10 min, and then maintained at 0.3 µg/kg/h until the total dose reached 200 µg) were routinely provided. All patients were treated with intravenous patient-controlled analgesia (PCA) (48 h). The target was to maintain a Visual Analogue Scale (VAS) score of 3 or less.¹⁵ A nonsteroidal anti-inflammatory drug (flurbiprofen axetil) was administered when considered necessary, and without contraindications. If there were no special circumstances, patients returned to the ward the next morning.

Patients in the ward inhaled hydrocortisone up to discharge (4 mg hydrocortisone + 100 ml normal saline, tid) and a vibrating sputum clearance device (TC Johnson) was used until the sixth day after surgery. Patients with forearm flaps were treated with cefuroxime sodium (1.5 g bid) until the fifth day after surgery. Cefuroxime sodium (1.5 g bid) and ornidazole (0.5 g bid) were used up to 6 days for patients with fibula flaps after surgery.

Outcomes

Primary outcome

The primary outcome was the difference in the occurrence of PPCs within the first 7 days after surgery between the two groups (tracheotomy and non-tracheotomy patients)

Secondary outcomes

1. The difference in the occurrence of PPCs between two groups of tracheotomy patients within the first 7 days after surgery
2. The difference in the incidence of PPCs between two groups of non-tracheotomy patients within the first 7 days after surgery
3. Main types and grading of PPCs
4. The time to onset of PPCs (from the end of surgery to the first diagnosis of PPCs)
5. The incidence of postoperative extrapulmonary complications, length of stay (LOS) in

the hospital after surgery, and 30-day mortality.

Patient follow-up and outcome assessment

Patients were followed up once a day until postoperative day 7. PPCs were defined as previously described: pulmonary infection, pleural effusion, atelectasis, pneumothorax, bronchospasm, pulmonary edema, pulmonary embolism, respiratory failure, and acute respiratory distress syndrome (ARDS).^{16,17} They were classified according to diagnostic criteria (Additional file 1) and assessed using the Clavien-Dindo classification, whereby grade 0 indicated no complication and grade V indicated death. PPCs of grade II or higher were used to calculate the incidence of PPCs (Additional file 2). The diagnosis of a PPC was made by the attending medical team (anesthesia, ICU, or respiratory medicine team). The physician who diagnosed PPCs considered physical examination results, conventional monitoring findings, laboratory results, X-ray findings, and others. All radiologic diagnoses were based on reports of attending radiologists not involved in the present study. Furthermore, surgical complications (vascular crisis or hematoma), extrapulmonary complications, hospital stay, and mortality at 30 days were also recorded. Cardiologic complications were defined as atrial fibrillation, cardiac failure, myocardial ischemia, and cardiac arrest. Hypotension was defined as systolic blood pressure < 90 mmHg or a decrease of more than 30% from baseline. Hematoma or vascular crisis were defined as the need for urgent surgical re-exploration due to clinical evidence of vascular flap compromise or hematoma. Postoperative delirium (POD) was assessed with the confusion assessment method for the intensive care unit (CAM-ICU).¹⁸

Statistical analysis

The sample size was calculated based on previous studies. The incidence of PPCs after a free flap surgery in the propofol group was 26%, compared to 54% in the sevoflurane group.² Considering that clinical research mostly involves studies with a small sample, the power is increased as much as possible to increase the credibility of the results. Therefore, in this study, 95% power was considered. In order to detect differences, it was necessary to include 90 patients per group with an alpha risk of 2.5% and a beta risk of 5% in a two-tailed comparison. The ratio of the two groups was 1:1.

Considering a dropout rate of about 20%, 110 pairs were enrolled.

Categorical variables were analyzed using the chi-squared test, continuity correction chi-squared test, or Fisher exact test based on sample size or frequency. The independent t-test was used for normally distributed continuous variables, and Mann-Whitney U test was used for non-parametric continuous variables. The relative risk and the 95% confidence interval of the differences were calculated for the primary outcome. Univariate logistic regression analysis was used to determine relevant baseline covariates associated with the primary outcome. If P values were less than 0.10 and were clinically relevant, then adjusted analyses were performed using a multivariate logistic regression model. Furthermore, the time to occurrence of the PPCs was compared using the Kaplan-Meier estimator, and the differences between groups were tested by the log-rank test. All analyses were performed using SPSS version 21.0. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

Results

Study population

From March 26, 2018, to March 25, 2019, a total of 220 patients were recruited into the study. Eleven patients in the sevoflurane group and eight in the propofol group were excluded because of protocol violations. Thus, a total of 201 patients were included in the intention-to-treat analysis and were followed up for 7 days after surgery (Fig 1). Baseline characteristics were similar between the two groups (Table 1).

Intraoperative data

Intraoperative characteristics were comparable (Table 2). In particular, there was no difference between limb ischemia time as well as the duration of surgery and anesthesia. Approximately 52 (52.5%) of patients in the sevoflurane group and 52 (51.0%) of those in the propofol group underwent repair of the defect with a fibula flap. Fifty-three patients (53.5%) in the sevoflurane group and 58 (56.9%) in the propofol group underwent tracheotomy at the end of surgery. However, the total dosage of sufentanil and remifentanil during the operation was lower in the sevoflurane group than in the propofol group. ($p < 0.001$). In addition, the urine volume in the propofol group was significantly

higher than that in the sevoflurane group. ($p < 0.001$)

OUTCOMES

Primary Outcome

Pulmonary complications occurred within the first 7 days after surgery in 18 patients (18.2%) in the sevoflurane group and 33 patients (32.4%) in the propofol group (adjusted relative risk, 0.44; 95% CI, 0.22 to 0.91; $P = 0.027$) (Table 3).

Secondary Outcomes

More tracheotomy patients experienced pulmonary complications in the propofol group (44.8%) than in the sevoflurane group (24.5%) (adjusted relative risk, 0.39; 95% CI, 0.17 to 0.91; $P = 0.030$).

However, among non-tracheotomy patients, there was no significant difference in PPCs between the two groups. In addition, the Clavien-Dindo classification showed significant differences between groups in minor complications (grade I and II) but not in major complications (grade III to V). The proportion of patients who required postoperative ventilatory assistance for acute respiratory failure was similar in the sevoflurane and propofol groups (3 of 99 patients [3.0%] vs. 5 of 102 [4.9%]). Kaplan-Meier analysis of PPCs occurring within 7 days after surgery showed a statistically significant difference between the sevoflurane and propofol groups (Fig. 2, $P = 0.021$). No differences were found for hospital stay, extrapulmonary complications, and 30-day mortality (Table 3).

Discussion

Oral and maxillofacial cancer surgery comprises a resection phase and a reconstruction phase. The duration of surgery is generally longer than 4 h. Because adequate perfusion is required for the vascular anastomosis of the flap, a large amount of intravenous fluid is often used to maintain systemic blood pressure on account of microvascular surgeons' belief against the use of vasopressors,¹⁹ and acquisition of forearm or tibial flaps may result in ischemia-reperfusion injury (IRI) in distant organs (lungs).^{20, 21} Furthermore, some patients require prophylactic tracheotomy at the end of surgery. These factors induce lung damage, inflammation, and stress protein expression. It is becoming clear that anesthetic agents exert pharmacologic effects beyond sedation and anesthesia. The immunomodulatory properties of anesthetic agents have been evaluated in vitro and

in laboratory animal models but they have not been fully investigated in humans.^{5,6} Previous research has demonstrated a distinct difference in the effects of intravenous and inhalation anesthesia on the immune response.⁶ A few RCTs involving patients who underwent LRS showed that sevoflurane decreased the incidence of PPCs based on the reduction in the pulmonary inflammatory response.^{5,6} Studies also have shown that the systemic or local inflammatory response is closely related to the development of lung injury.^{22,23} A meta-analysis showed that the release of alveolar TNF- α , IL-6, and IL-8 significantly decreased during volatile anesthetic administration compared to that during propofol-based intravenous anesthesia in LRS.²⁴ Nevertheless, conflicting data from other types of surgery exist.²⁵ The present prospective study was the first to compare the effects of the two anesthetics on PPCs after extrathoracic surgery.

This trial suggested that sevoflurane for maintenance anesthesia, in comparison with propofol, significantly reduced the incidence of PPCs in patients after oral and maxillofacial cancer surgery with radial forearm or fibular flap reconstructions. This finding was in line with that obtained in studies by Conno et al. and Gala et al.^{8,9} We found that more tracheotomy patients experienced pulmonary complications in the propofol group (44.8%) than in the sevoflurane group (24.5%). However, we failed to detect the difference in the incidence of PPCs between the two groups of non-tracheotomy patients, which may be the fact that the low incidence of PPCs could not be effectively compared. This study further confirmed that tracheotomy was an independent predictor for PPCs (13.3% vs 35.1%, the incidence of PPCs in non-tracheotomy patients versus that in tracheotomy patients).²⁶ In addition, except for prophylactic tracheotomy at the end of surgery, emergency tracheotomy was not performed in any patient after surgery. In our study, we found a significant difference in grade I and II PPCs, but no difference in grade III and IV PPCs between the sevoflurane and propofol groups according to the Clavien-Dindo classification of PPCs. One explanation for it may be that sevoflurane had a certain anti-inflammatory effect but could not prevent the occurrence of severe disease. Another explanation for our finding may be the incidence of complications of grade III or higher was

too low to be comparable. The lack of differences in the need for ventilation and hospital stays between the two groups could also validate this result. Most of the PPCs recorded in our study were included as minor complications following the Clavien-Dindo classification.²⁷

Although we excluded patients with a low risk of PPCs and a larger proportion of patients underwent tracheotomy, the observed rate of PPCs in our study was slightly lower than that in the previous study.^{2,3,28} This finding may be associated with the improvement in operation time, intravascular volume management, blood loss and transfusion (no patient underwent blood transfusion in this study), etc, which appear to have an important impact on the risk of PPCs during major surgery.^{2,29}

Thirty-three of the 201 patients in our study had postoperative pneumonia (POP), which is inconsistent with previous reports. Pulmonary edema or respiratory failure were the main types of PPCs in previous studies.^{3,28} Most of our patients were male (70.7% vs. 69.6%, respectively), of advanced age (mean age: 59 years vs 61 years), required a prolonged operation (340 min vs 327 min), and underwent tracheotomy (53.5% vs 56.9%), which could have been responsible for the high incidence of POP.^{30,31} In addition, the time between surgery and the appearance of the first PPCs was 3 (2 to 4) days, which was in agreement with the results of previous large retrospective studies.³²

Our results showed a significant difference in intraoperative opioid consumption between the two groups, and it could be argued that the lower opioid consumption in the sevoflurane group is caused by the analgesic effect of sevoflurane,^{33,34} and intraoperative opioid savings are thought to play a role in lower rates of PPCs development.³⁵ However, the multivariate analysis in this study showed that intraoperative opioid dosage did not affect PPCs, which may be correlated with the overall dose being a low dose, requiring further large-sample studies.³⁶ In addition, the amount of urine was significantly greater in the propofol group, but there is no evidence showing that the amount of urine is associated with PPCs.

The limitations of this study are as follows: (1) For experimental consistency, all flaps in this study were fibula and forearm, and other types of flaps, such as thigh flap and iliac bone flap, were not

used. Since the first two flaps had limb IRI caused by a tourniquet, their use might have influenced the incidence of PPCs. (2) We did not detect inflammatory markers of bronchoalveolar lavage fluid (BALF) and blood samples during the intraoperative and postoperative periods, which is helpful for exploring the relationship between biomarkers and postoperative clinical outcomes. (3) The definition of PPCs is complex and no standard definition of PPCs exists. We used PPCs of grade II or higher in the Clavien-Dindo classification as a composite reference standard, and the definition of PPCs was based on radiologic evidence and the subjectivity of the treating physician. Underestimation or overestimation of the actual incidence of PPCs could not be avoided; therefore, further research should be performed considering the above-mentioned factors.

Conclusion

Our study provides evidence that administration of sevoflurane rather than propofol reduces the incidence of minor PPCs (grade I to II) in moderate- and high-risk patients who have undergone tracheotomy after oral and maxillofacial cancer surgery with radial forearm or fibular flap reconstruction. For non-tracheotomy patients with PPCs or patients had major PPCs (grade III to V), a larger sample size may be required to detect the difference.

Abbreviations

PPCs: Postoperative pulmonary complications; TIVA: Total intravenous anaesthesia; LRS: Lung resection surgery; CI: Confidence interval; RCTs: Randomized controlled trials; AECOPD: Acute phase of chronic obstructive pulmonary disease; BIS: Bispectral index; Vt: Volume tidal; FiO₂: Fraction of inspiration O₂; ETCO₂: End-tidal carbon dioxide concentration; PACU: Post-anesthesia care unit; PCA: Patient-controlled analgesia; VAS: Visual analogue scale; ARDS: Acute respiratory distress syndrome; POD: Post-operative delirium; IRI: limb ischemia-reperfusion injury; POP: Postoperative pneumonia; BALF: Bronchoalveolar lavage fluid; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; ASA: American society of anesthesiologists.

Declarations

Acknowledgements

Not applicable

Authors contributions

DZ designed the study, conducted follow-up examinations, analyzed the data, and wrote the manuscript. XZ designed the study, modified the article, and approved the version to be submitted. LKW designed the study and conducted follow-up examinations. XDY administered anesthesia to the patients, collected the data, revised the article, and approved the version to be submitted. YL and XZ administered anesthesia to the patients and collected the data. All authors read and approved the manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author on a reasonable request.

Ethics approval and consent to participate

Ethical approval was received from the Biomedical Ethics Committee of Peking University Hospital of Stomatology (Number: PKUSSIRB-201734029) in December 2017. Written informed consent was obtained from each patient before randomization.

Consent for publications

Not applicable

Competing interests

The authors declare that they have no conflict of interest.

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Tables

Table 1. Baseline characteristics of patients in the sevoflurane and propofol groups

Characteristic	Sevoflurane (n = 99)	Propofol (n = 102)	P value
Age (y r), median (IQR)	59(55-64)	61(55-67)	0.067
BMI (kg·m ⁻²), median (IQR)	22.8(21.2-24.5)	22.7(20.2-24.6)	0.884
Sex: male, n (%)	71(70.7%)	71(69.6%)	0.865
Canet points, n (%)			0.730
26-44	96(97.0%)	98(96.1%)	
≥45	3 (3.0%)	4(3.9%)	
ASA, n (%)	28(28.3%)	30(29.4%)	0.984
I-II-III-IV	/67(67.7%)/4(4.0%)/0(0%)	/68(66.7%)/4(3.9%)/0(0%)	
Coexisting condition, n (%)			
Current smoking	39(39.4%)	39(38.2%)	0.886
Any alcohol intake	37(37.4%)	27(26.5%)	0.097
Hypertension.	30(30.3%)	39(38.2%)	0.236
Diabetes mellitus	14(14.1%)	22(21.6%)	0.170
Respiratory disease	4(4.0%)	6(5.9%)	0.783

BMI = body mass index; IQR = interquartile range; ASA = American Society of Anesthesiologists;
 Canet points: pulmonary complications risk points; 26-44 points: moderate risk; ≥ 45 points: high risk.

Table 2 Intraoperative procedures in the sevoflurane and propofol groups

Variable	Sevoflurane (N = 99)	Propofol (N = 102)	P value
Type of flap, n (%)			0.827
forearm	47(47.5%)	50(49.0%)	
fibula	52(52.5%)	52(51.0%)	
Cervical lymph node dissection, n (%)			0.344
unilateral	64(64.6%)	68(66.7%)	
bilateral	20(20.2%)	25(24.5%)	
no	15(15.2%)	9(8.8%)	
Crystalloid (ml), median (IQR)	17001700-2200	22001700-2200	0.346
Colloid (ml), median (IQR)	5000-500	5000-500	0.340
Duration of anesthesia (min), median (IQR)	375295-445	360300-420	0.721
Duration of surgery (min), median (IQR)	340264-405	327260-400	0.673
Duration of limb ischemia time (min), median (IQR)	5445-65	5140-64	0.155
Blood loss (ml), median (IQR)	300200-400	300200-300	0.065
Urine output (ml), median (IQR)	500350-650	700500-912	<0.001
Sufentanil dosage (μg)	39.5 \pm 17.6	47.6 \pm 17.4	<0.001
Remifentanil dosage (mg)	1.6 \pm 0.4	2.3 \pm 0.7	<0.001
Sufentanil dosage in PCA(μg)	65.5 \pm 11.4	64.3 \pm 10.6	0.725
Postoperative tracheotomy, n (%)	53(53.5%)	58(56.9%)	0.635
Endotracheal intubation, n (%)	46(46.5%)	44(43.1%)	

Data are expressed as mean ± SD or median (IQR).

SD = standard deviation; IQR = interquartile range; PCA = patient-controlled analgesia.

The duration of surgery was calculated as the time between skin incision and closure of the incision; The duration of anesthesia was calculated as the time from the start of induction to the patient leaving the operating room; The duration of limb ischemia time was calculated as the time from the beginning of the inflation of the tourniquet in the thigh or forearm to the end of the exhalation of the tourniquet.

Table 3 Comparisons of the incidence of major complications in the propofol and sevoflurane groups

Variable	Sevoflurane N = 99	Propofol N = 102	Relative risk (95% CI)	P value	Adjusted relative risk or between- group difference (95% CI)	P Value
Primary outcome , n (%)						
PPCs Within 7 days	18(18.2)	33(32.4)	0.47(0.24- 0.90)	0.021	0.44(0.22- 0.91)	0.027
Secondary outcomes, n (%)						
Pneumonia within 7 days	11(11.1)	22(21.4)	0.52(0.26- 1.0)	0.045		
Atelectasis within 7 days	4(4.0)	6(5.8)		0.783		
Pulmonary edema within 7 days	2(2.0)	2(1.9)		1.0		
Pulmonary embolism within 7 days	1(1.0)	0(0)		0.988		
Pleural effusion within 7 days	2(2.0)	4(3.9)		0.706		

Respiratory failure within 7 days	6(6.1)	9(8.7)		0.456		
Patients with 0-1-2->2 PPCs	81-14-3-1	69-24-7-2		0.140		
Need for ventilation within 7 days	3(3.0)	5(4.9)		0.715		
PPCs in tracheotomy	13(24.5)	26(44.8)	0.40(0.18-0.90)	0.025	0.39(0.17-0.91)	0.030
PPCs in endotracheal intubation	5(10.8)	7(15.9)		0.588		
Clavien Dindo I/II/III/IV/V	11/12/3/3/0	16/23/5/5/0		0.965		
0 vs I+ II	70/23	53/39		0.013		
0+ I + II vs III +IV +V	93/6	92/10		0.436		
The time to first PPCs	3(2-4)	3(2-4)		0.021		
Extrapulmonary complications, n (%)						
Hematoma or vascular crisis	3(3.0)	5(4.9)		0.751		
Postoperative hypotension	4(4.0)	3(2.9)		0.968		
Postoperative delirium	4(4.0)	3 (2.9)		0.968		
30-day mortality	0(0)	0(0)		1		
Hospital stay	9(8-10)	9(8-11)		0.989		

(days)

median (IQR)

Data are expressed as mean (SD) or median (IQR); PPCs = postoperative pulmonary complications.

Adjusted for variables (hypertension, diabetes mellitus, tracheotomy/endotracheal intubation, duration of limb ischemia, duration of anesthesia, duration of surgery, type of flap).

Figures

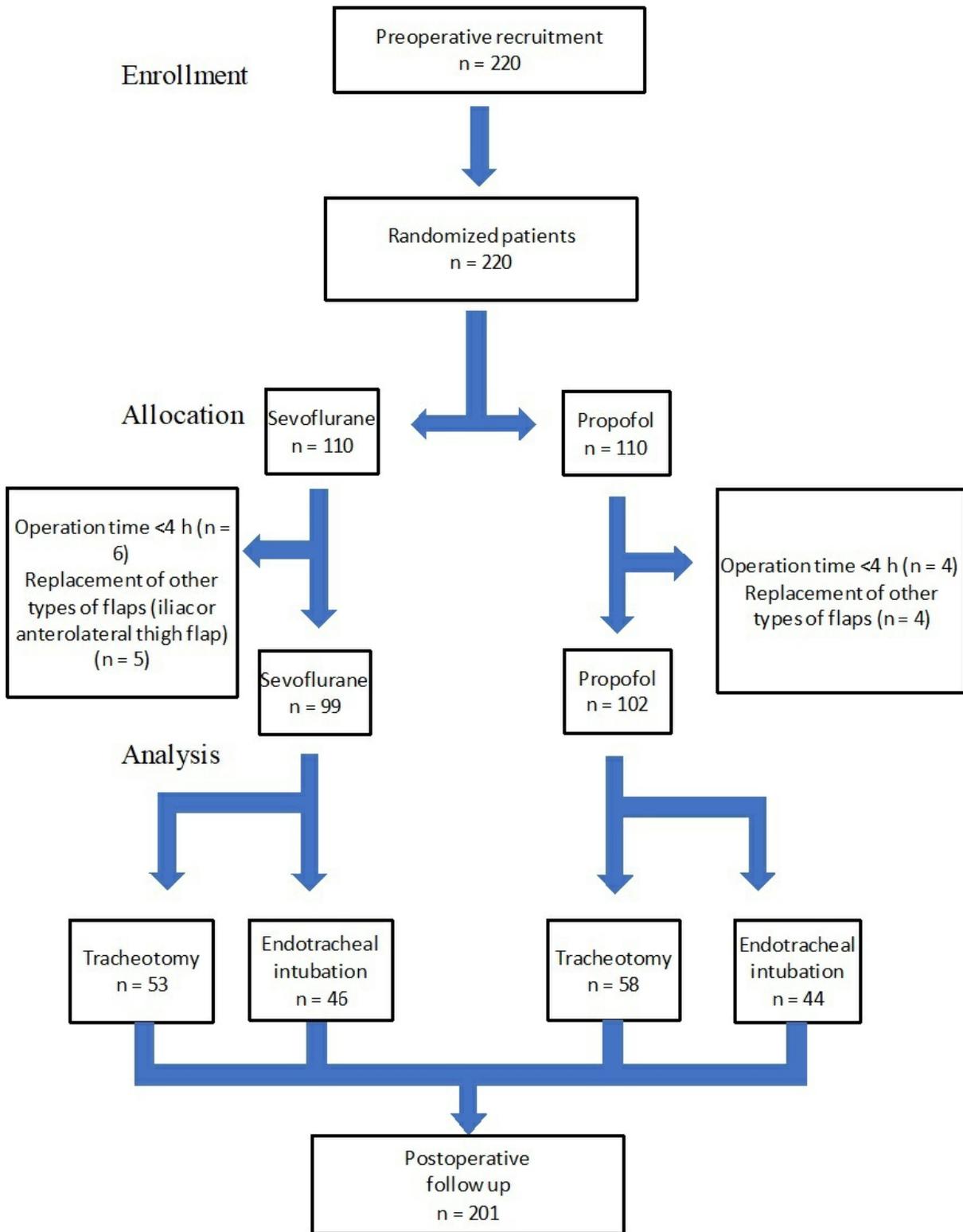


Figure 1

total of 220 patients were enrolled according to the inclusion and exclusion criteria and

randomized. Nineteen patients were excluded due to operative time and intraoperative replacement of other types of flaps. A total of 201 patients were followed up and included in the intention-to-treat analysis.

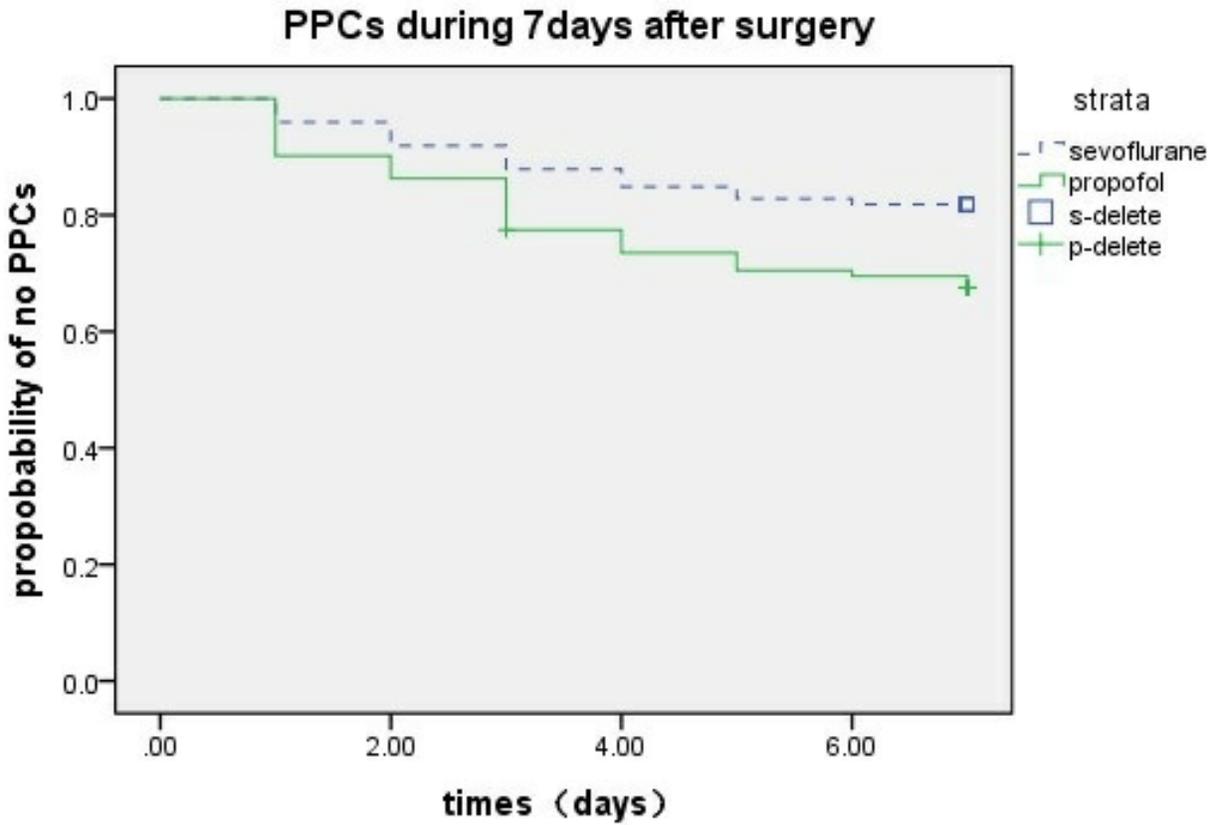


Figure 2

Kaplan-Meier curve representing the time to occurrence of PPCs after surgery in the sevoflurane and propofol groups ($P = 0.021$, log-rank test). No. at risk Sevoflurane 99 95 91 87 84 82 81 81 Propofol 102 92 88 78 74 70 69 69 S = sevoflurane; P = propofol; PPCs = postoperative pulmonary complications

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