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

Dan Zhou
Peking University Third Hospital

Xi Zhu
3917798@qq.com*Corresponding Author*
ORCiD: https://orcid.org/0000-0001-6091-8831

Likuan Wang
Peking University School of Stomatology

Xudong Yang
Peking University School of Stomatology

Yun Liu
Peking University School of Stomatology

Xiang Zhang
Peking University School of Stomatology

DOI:
10.21203/rs.2.12505/v1

SUBJECT AREAS
Anesthesiology & Pain Medicine

KEYWORDS
Intravenous anesthesia, Inhalational anesthesia, Postoperative pulmonary complications, Oral and maxillofacial surgery

Abstract

Background: The effects of intravenous and inhalation anesthesia on intraoperative and postoperative pulmonary inflammatory responses have been reported in many studies. However, the differences in clinical postoperative pulmonary complications (PPCs) have rarely been studied, except in cases of lung resection. 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 surgery 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 after surgery was 44.8% and 24.5% (adjusted relative risk, 0.39; 95% CI, 0.17 to 0.91; P = 0.030). 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 frequency of PPCs in intermediate-risk and high-risk patients undergoing oral and maxillofacial surgery with microvascular reconstruction. Trial registration: Clinical Trail Registration: ChiCTR1800015347; Registered March 25, 2018.

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 tracheotomy after surgery is up to 47%.[4] It is a key point for anesthesiologists to prevent and reduce the occurrence of postoperative 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' habits and hospital practice. The incremental value of anesthetics, such as their anti-inflammatory effects, have also been studied. [5] However, the immunomodulatory effects of anesthetics on the lung mostly involve biological markers, and not so much PPCs. [6,7] Current research indicates that compared to propofol, sevoflurane for anesthesia maintenance is more conducive for reducing the incidence of PPCs after lung or cardiac surgery. [7,8,9] The association with other types of surgery has been rarely reported and there is no relevant clinical evidence available. Therefore, the effect of anesthetics on clinical outcomes needs to be explored further. Recently, it has been found that anesthetics can affect the long-term survival rate of patients. [10,11]

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 maxillofacialsurgery. We hypothesized that compared to propofol, sevoflurane could improve outcomes 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 conditioning with sevoflurane leads to fewer PPCs compared to those associated with propofol within 7 days after surgery. Eligible patients were enrolled and randomly assigned to receive one of two interventions, sevoflurane or propofol.

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 were eligible for participation in the study if they were older than 18 years and younger than 80 years, were scheduled to undergo free flap (fibula or forearm) surgery with an expected duration of at least 4 h, and had a preoperative pulmonary complication risk index (Canet score) exceeding 26 points. 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. [12]

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), acute phase of chronic bronchial inflammation, uncontrolled asthma, pulmonary artery stenosis, pulmonary hypertension and congestive heart failure, complex heart deformities, severe liver or kidney dysfunction, 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 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 μg/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, and fraction of inspiration O_2 (FiO_2)of 0.4–0.5; the respiratory rate was adjusted to maintain an end-tidal carbon dioxide concentration ($ETCO_2$) 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 μg/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 was used 30 minutes before surgery and for the fourth hour during surgery.

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.

Postoperative data

Postoperative patients undergoing tracheotomy (extubation on the fifth day) or endotracheal intubation (extubation the next morning) according to intraoral conditions were observed for a night in the post-anesthesia care unit (PACU). All patients were treated with dexmedetomidine sedation (4 μg/ml) in the PACU and intravenous patient-controlled analgesia (PCA) (48 h). If there were no special circumstances, patients returned to the ward the next morning.

Patients in the ward inhaled hydrocortisone three times a day up to discharge, and the vibrating sputum clearance device was used until the sixth day after surgery. Patients with forearm flaps were treated with cefuroxime sodium until the fifth day after surgery. Cefuroxime sodium and ornidazole were used up to 6 days for patients with fibula flaps after surgery.

Furthermore, when any pulmonary complication was suspected, bedside chest radiography (CXR) was also performed. The follow-up period was 7 days. Pulmonary complications were classified according to diagnostic criteria and assessed using the Clavien-Dindo classification, whereby grade 0 indicated no complication and grade V indicated death. [13,14] PPCs were diagnosed based on objective data such as blood gas analysis data, complete blood count, X-ray findings, and medical records in real time. Surgical complications (vascular crisis or hematoma), extrapulmonary complications, hospital stay, and mortality at 30 days were also recorded.

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 20% loss rate, 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 52.5%

of the patients in the sevoflurane group and 51.0% of those in the propofol group underwent repair of the defect with a fibula flap. About 53 patients (53.5%) in the sevoflurane group and 58 (56.9%) in the propofol group underwent tracheotomy after 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 lower 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% confidence interval [CI], 0.22 to 0.91; P = 0.027) (Table 3).

Secondary Outcomes

More patients who underwent tracheotomy after surgery in the propofol group showed pulmonary complications than in the sevoflurane group (adjusted relative risk, 0.39; 95% confidence interval [CI], 0.17 to 0.91; P = 0.030). However, there were no significant differences between the two groups with respect to tracheal intubation. In addition, the Clavien-Dindo classification showed significant differences between groups in minor complications (CD I and II) but not in major complications (CD 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%]). The PPCs occurred within 7 days after surgery, Kaplan-Meier curves are shown in Figure 2. The differences between groups were statistically significant ($p = 0.021$). (Fig 2) No differences were found for hospital stay, extrapulmonary complications, and 30-day mortality (Table 3).

Discussion

This trial suggested that sevoflurane for maintenance anesthesia, in comparison with propofol, significantly reduced the incidence of postoperative PPCs after oral and maxillofacial surgery. This finding was in line with that obtained in studies by Conno et al and Gala et al. [7,8] A few randomized controlled trials (RCTs) involving patients who underwent lung surgery revealed that sevoflurane

decreased the incidence of PPCs based on the reduction in the pulmonary inflammatory response, [6] but conflicting data exist, with one study showing no difference in the incidence of major complications between the two anesthesia regimens after lung surgery. [15] However, previous studies mainly focused on the effect of the anesthetics on lung ischemia-reperfusion injury, and clinical evidence that volatile anesthetics prevent PPCs in other types of surgery are still missing. The present prospective study was the first to compare the effects of the two anesthetics on clinical outcome after extrathoracic surgery.

The anti-inflammatory effect of sevoflurane could explain the differences in the present study. [16] The duration of free flap surgery is generally longer than four hours, vascular anastomosis of the flap needs adequate perfusion, and an expanding volume is often used, and acquisition of forearm or tibial flaps often results in the effects of limb ischemia-reperfusion injury (IRI) on distant organs (lungs). Furthermore, patients may require tracheal intubation or tracheotomy for a long time after surgery. These factors contributed to the intraoperative and postoperative inflammatory response, which may provoke or aggravate PPCs. The lipopolysaccharide lung injury model in vitro has confirmed the anti-inflammatory effects of the carbon trifluoride component (CF3) in sevoflurane. [17] Strosing and colleagues also reported that the anti-inflammatory and antioxidant effects of inhaled anesthesia play a protective role in mechanical ventilation lung injury. [18] More in vitro studies have suggested that volatile anesthetics exert anti-inflammatory effects in lungs, possibly due to the activation of signaling pathways including $GABA_A$, TLR4-MyD88, ERK1/2/Akt, and others. [19] However, the effect of anesthetics on the inflammatory response in other types of surgery is controversial. [20.21] 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. Therefore, it could be postulated that sevoflurane had a certain anti-inflammatory effect, but could not prevent the occurrence of severe disease. Moreover, the lack of differences in the need for ventilation and hospital stays between the two groups could also validate this result.

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. 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. [2,22] 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. [3,23] Advanced age, male gender, prolonged operation time, tracheotomy, and delayed mobilization have been identified as risk factors for POP. [24,25] Most of our patients were male (70.7% vs. 69.6%, respectively), older (mean age 59 years vs 60 years), and underwent tracheotomy after surgery (53.5% vs 56.9%), which could have been responsible for the high incidence of POP in our study. Our results further confirmed that tracheotomy was an independent predictor for PPCs (13.3% vs 35.1%, the incidence of PPCs with endotracheal intubation versus that with tracheotomy after surgery, respectively). [26] 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. [27]

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, [28,29] and intraoperative opioid savings are thought to play a role in lower rates of PPCs development. [30] 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. [31] 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 age and ASA grade may account for the absence of cerebrovascular accidents in extrapulmonary complications, but hypotension and delirium occurred in postoperative

patients.

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) This study was aimed at patients with Canet scores indicating intermediate and high risk, while the low-risk patients were not included, considering the low incidence of PPCs. (3) This study was a single-center study, and the sample size was not large enough. Because of the particularity of free flap surgery, there is a certain gap in the operative quantity and quality between other hospitals. Therefore, further research in the future will take the above factors into account.

Conclusion

Our study provides evidence that administration of sevoflurane reduces the incidence of PPCs in moderate- and high-risk patients after oral and maxillofacial surgery with free flap reconstruction. In order to mitigate PPCs and possible sequelae, inhalation anesthesia should be popularized.

Abbreviations

PPCs: Postoperative pulmonary complications; 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; CI: Confidence interval; RCTs: Randomized controlled trials; IRI: limb ischemia-reperfusion injury; CF3: Carbon trifluoride component; POP: Postoperative pneumonia; 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 finally approved the version to be submitted. LKW designed the study and conducted follow-up examinations. XDY performed the patients' anesthesia, collected the data, revised the article and finally approved the version to be submitted. YL and XZ performed the patients' anesthesia and collected the data. All authors read and

approved the manuscript.

Funding

This work was supported by National Natural Science Foundation of China (81372043), Beijing Municipal Natural Science Foundation (7162199) and National Science and Technology Major Project (2018ZX10101004003003).

Availability of data and materials

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

Ethics approval and consent to participate

Ethics 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 before randomization from each patient.

Consent for publications

Not applicable

Competing interests

The authors declare that they have no conflict of interest.

Author details

[1]Department of Anesthesiology, Peking University Third Hospital, Beijing, China, [2]Department of Intensive Care Medicine, Peking University Third Hospital, Beijing, China, [3]Department of Anesthesiology, Peking University Hospital of Stomatology, Beijing, China.

References

1. Loeffelbein DJ, Julinek A, Wolff KD, Kochs E, Haller B, Haseneder R. Perioperative risk factors for postoperative pulmonary complications after major oral and maxillofacial surgery with microvascular reconstruction: A retrospective analysis of 648 cases. Journal of Cranio-Maxillofacial Surgery. 2016;44(8):952–7.
2. Chang YT, Wu CC, Tang TY, Lu CT, Lai CS, Shen CH. Differences between Total Intravenous Anesthesia and Inhalation Anesthesia in Free Flap Surgery of Head and Neck Cancer. Plos One. 2016;11(2):e0147713.

3. Petrar S, Bartlett C, Hart RD, Macdougall P. Pulmonary complications after major head and neck surgery: A retrospective cohort study. Laryngoscope. 2012;122(5):1057–61.
4. Ong SK, Morton RP, Kolbe J, Whitlock RM, Mcivor NP. Pulmonary complications following major head and neck surgery with tracheostomy: a prospective, randomized, controlled trial of prophylactic antibiotics. Archives of Otolaryngology–Head & Neck Surgery. 2004;130(9):1084–7.
5. Anderson SL, Duke-Novakovski T, Singh B. The immune response to anesthesia: Part 1. Veterinary Anaesthesia & Analgesia. 2014;41(2):113–26.
6. Thomas S, Alf K, Mert S, Christof H, Annegret R, G Ran H, Thomas H. Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. Anesthesiology. 2011;115(1):65–74.
7. De la Gala F, Piñeiro P, Reyes A, Vara E, Olmedilla L, Cruz P, Garutti I. Postoperative pulmonary complications, pulmonary and systemic inflammatory responses after lung resection surgery with prolonged one-lung ventilation. Randomized controlled trial comparing intravenous and inhalational anaesthesia. British Journal of Anaesthesia. 2017;119(4):655–63.
8. Elisena DC, Steurer MP, Moritz W, Zalunardo MP, Walter W, Didier S, Schimmer RC, Richard K, Neff TA, Schmid ER. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology. 2009;110(6):1316–26.
9. Uhlig C, Bluth T, Schwarz K, Deckert S, Heinrich L, De HS, Landoni G, Serpa NA, Schultz MJ, Pelosi P. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: A systematic review and meta-analysis. Anesthesiology. 2016;124(6):1230–45.
10. Dubowitz JA, Sloan EK, Riedel BJ. Implicating anaesthesia and the perioperative

period in cancer recurrence and metastasis. Clinical & Experimental Metastasis. 2018;35(4):347–58.

11. Soltanizadeh S, Degett TH, Gögenur I. Outcomes of cancer surgery after inhalational and intravenous anesthesia: A systematic review. Journal of Clinical Anesthesia. 2017;42(11):19–25.

12. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, Sabaté S, Mazo V, Briones Z, Sanchis J. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113(6):1338–50.

13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery. 2004;240(2):205–13.

14. Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, Yasuhiro T, Satoh T, Yokomizo A, Fukuda H, sasako M. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surgery today. 2016;46(6):668–85.

15. Beck-Schimmer B, Bonvini JM, Braun J, Seeberger M, Neff TA, Risch TJ, Stüber F, Vogt A, Weder W, Schneiter D. Which anesthesia regimen is best to reduce morbidity and mortality in lung surgery? A multicenter randomized controlled trial. Anesthesiology. 2016;125(2):313–21.

16. O'Gara B, Talmor D. Lung protective properties of the volatile anesthetics. Intensive Care Medicine. 2016;42(9):1487–9.

17. Urner M, Limbach LK, Herrmann IK, Müller-Edenborn B, Roth-Z'Graggen B, Schlicker A, Reyes L, Body C, Hasler M Stark WJ. Fluorinated groups mediate the immunomodulatory effects of volatile anesthetics in acute cell injury. American journal of respiratory cell and molecular biology. 2011;45(3):617–24.

18. Strosing KM, Faller S, Gyllenram V, Engelstaedter H, Buerkle H, Spassov S, Hoetzel A. Inhaled anesthetics exert different protective properties in a mouse model of ventilator-induced lung injury. Anesthesia & Analgesia. 2016;123(1):143–51.

19. Kim SH, Li M, Pyeon TH, So KY, Kwak SH. The volatile anesthetic sevoflurane attenuates ventilator-induced lung injury through inhibition of ERK1/2 and Akt signal transduction. Korean journal of anesthesiology. 2015;68(1):62–9.

20. Kvarnström AL, Sarbinowski RT, Bengtson JP, Jacobsson LM, Bengtsson AL. Complement activation and interleukin response in major abdominal surgery. Scandinavian journal of immunology. 2012;75(5):510–6.

21. Lindholm EE, Aune E, Norén CB, Seljeflot I, Hayes T. The anesthesia in abdominal aortic surgery (ABSENT) study: a prospective, randomized, controlled trial comparing troponin T release with fentanyl-sevoflurane and propofol-remifentanil anesthesia in major vascular surgery. Anesthesiology, 2013;119(4):802–12.

22. Nobel GJL, Higgins KM, Enepekides DJ. Predictors of complications of free flap reconstruction in head and neck surgery: Analysis of 304 free flap reconstruction procedures. Laryngoscope. 2012;122(5):1014–9.

23. Damian D, Esquenazi J, Duvvuri U, Johnson JT, Sakai T. Incidence, outcome, and risk factors for postoperative pulmonary complications in head and neck cancer surgery patients with free flap reconstructions. Journal of clinical anesthesia. 2016;28(2):12–18.

24. Xu J, Hu J, Yu P, Wang W, Hu X, Hou J, Fang S, Liu X. Perioperative risk factors for postoperative pneumonia after major oral cancer surgery: A retrospective analysis of 331 cases. PloS one. 2017;12(11):e0188167.

25. Yeung JK, Harrop R, Mccreary O, Leung LT, Hirani N, Mckenize D,De Haas V, Matthews TW, Nakoneshny S, Dort JC, Schrag C. Delayed mobilization after microsurgical

reconstruction: an independent risk factor for pneumonia. The Laryngoscope. 2013;123(12):2996–3000.

26. Li L, Yuan W, Zhang S, Wang K, Ruan H. Analysis of Risk Factors for Pneumonia in 482 Patients Undergoing Oral Cancer Surgery With Tracheotomy. Journal of oral and maxillofacial surgery. 2016;74(2):415–9.

27. Mazo V, Sabaté S, Canet J, Gallart L, de Abreu MG, Belda J, Langeron O, Hoeft A, Pelosi P. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology. 2014;121(2):219–31.

28. Sumikura H, Arendt-Nielsen L. MAC reduction after intrathecal coadministration of GABA A agonist and glutamate antagonist in rats. Journal of anesthesia. 2003;17(2):92–7.

29. Stabernack C, Sonner JM, Laster M, Zhang Y, Xing Y, Sharma M, Eger EI. Spinal N-methyl-d-aspartate receptors may contribute to the immobilizing action of isoflurane. Anesthesia & Analgesia. 2003;96(1):102–7.

30. Friedrich S, Raub D, Teja B, Neves S, Thevathasan T, Houle T, Eikermann M. Effects of low-dose intraoperative fentanyl on postoperative respiratory complication rate: a pre-specified, retrospective analysis. British journal of anaesthesia. 2019;122(6):180–8.

31. Ward D, Karan S, Pandit J. Hypoxia: developments in basic science, physiology and clinical studies. Anaesthesia. 2011;66(supplement s2):19–268.

Tables

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

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

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)	1700（1700-2200）	2200（1700-2200）	0.346
Colloid (ml), median (IQR)	500（0-500）	500（0-500）	0.340
Duration of anesthesia (min), median (IQR)	375（295-445）	360（300-420）	0.721
Duration of surgery (min), median (IQR)	340（264-405）	327（260-400）	0.673
Duration of limb ischemia time (min), median (IQR)	54（45-65）	51（40-64）	0.155
Blood loss (ml), median (IQR)	300（200-400）	300（200-300）	0.065
Urine output (ml), median (IQR)	500（350-650）	700（500-912）	<0.001
Sufentanil dosage (μg)	39.5±17.6	47.6±17.4	<0.001
Remifentanil dosage (mg)	1.6±0.4	2.3±0.7	<0.001
Sufentanil dosage in PCA(μg)	65.5±11.4	64.3±10.6	0.725
Postopetative			0.635
tracheotomy, n (%)	53(53.5%)	58(56.9%)	
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	55/38		0.019		
0+ I + II vs III +IV +V	93/6	93/9		0.456		
The time to first PPCs	3(2-4)	3(2-4)		0.021		
Extrapulmonary complications, n (%)						
Hematoma or vascular crisis exploration	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 (days) median (IQR)	9(8-10)	9(8-11)	0.989

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

A 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 underwent intention-to-treat analysis.

Figure 2

Kaplan-Meier curve representing the time to occurrence of PPCs after surgery between the sevoflurane group and the propofol group (P = 0.021, log-rank test).