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Randomized Controlled Trial

Protective effect of sevoflurane on lung function of elderly chronic obstructive pulmonary disease patients undergoing total hip arthroplasty

Yao Y *et al*. Sevoflurane protects lung function in elderly COPD patients

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Abstract

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common respiratory disorder that affects the elderly population and increases the risk of postoperative pulmonary complications (PPCs) after major surgeries. Sevoflurane is a volatile anesthetic that has been shown to have anti-inflammatory and antioxidant properties and attenuate lung injury in animal models.

AIM

To evaluate the protective effect of sevoflurane on the lung function of elderly COPD patients undergoing total hip arthroplasty (THA).

METHODS

In this randomized controlled trial, we randomly assigned 120 elderly patients with COPD, who were scheduled for THA, to receive either sevoflurane (sevoflurane group) or propofol (propofol group) as the maintenance anesthetic. The primary outcome was the incidence of PPCs within seven days after surgery. The secondary outcomes were changes in the lung function parameters, inflammatory markers, oxidative stress markers, and postoperative pain scores.

RESULTS

The results showed that the incidence of PPCs was significantly lower in the sevoflurane group than in the propofol group (10% vs 25%, P = 0.02). Furthermore, the decline in the forced expiratory volume in 1 s, forced vital capacity, and peak expiratory flow was significantly lesser in the sevoflurane group than in the propofol group at 24 h and 48 h after surgery (P < 0.05). The interleukin-6, tumor necrosis factor-alpha, malondialdehyde, and 8-hydroxy-2 α-deoxyguanosine levels were significantly lower in the sevoflurane group than in the propofol group at 24 h after surgery (P < 0.05). The

sevoflurane group showed significantly lower postoperative pain scores than the propofol group at 6 h, 12 h, and 24 h after surgery ($P < 0.05$).

CONCLUSION

Sevoflurane protects the lung function of elderly COPD patients undergoing THA under general anesthesia by reducing the incidence of PPCs, attenuating inflammatory and oxidative stress responses, and alleviating postoperative pain.

Key Words: Sevoflurane; Propofol; Lung function; Chronic obstructive pulmonary disease; Total hip arthroplasty; Elderly patients; Inflammatory markers

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Core Tip: Sevoflurane exhibits a protective effect on lung function in elderly chronic obstructive pulmonary disease patients undergoing total hip arthroplasty. It reduces the incidence of postoperative pulmonary complications, improves lung function parameters, and decreases inflammatory and oxidative stress markers. Additionally, it alleviates postoperative pain. These findings highlight the potential benefits of using sevoflurane as an anesthesia choice for this patient population.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease characterized by progressive airflow limitation and respiratory symptoms[1]. COPD is a major cause of morbidity and mortality worldwide, especially in the elderly population[2]. According to the Global Burden of Disease Study 2019, COPD was the third leading cause of death and the seventh leading cause of disability-adjusted life years globally in 2019[3].

COPD patients are at an increased risk of developing postoperative pulmonary complications (PPCs) after major surgeries, such as pneumonia, atelectasis, respiratory failure, bronchospasm, and pleural effusion[4]. PPCs are associated with increased morbidity, mortality, length of hospital stay, and healthcare costs[5]. Therefore, prevention and management of PPCs are important for improving the postoperative outcomes of COPD patients.

Total hip arthroplasty (THA) is a common orthopedic procedure performed to treat end-stage hip osteoarthritis or fractures[6]. THA can improve the quality of life and function of patients with hip disorders. However, it also involves significant surgical trauma and blood loss, which may impair lung function and increase the risk of PPCs[7]. THA is often performed under general anesthesia because it provides adequate muscle relaxation, analgesia, and amnesia[8]. However, general anesthesia may also have adverse effects on the lung function, including decreased lung volume, impaired gas exchange, increased airway resistance, and reduced mucociliary clearance[9].

Sevoflurane is a volatile anesthetic widely used for inducing general anesthesia for various surgical procedures[10]. Sevoflurane has several advantages over other anesthetics, such as rapid induction and emergence, minimal metabolism and toxicity, stable hemodynamics, and potent analgesia[11]. Moreover, sevoflurane has been shown to have anti-inflammatory and antioxidant properties and attenuate lung injury in animal models[12]. Several clinical studies have suggested that sevoflurane has a protective effect on the lung function of patients undergoing cardiac, thoracic, or abdominal surgery[13-15]. However, the effect of sevoflurane on the lung function of elderly patients with COPD undergoing THA under general anesthesia has not been elucidated.

This study aimed to evaluate the protective effects of sevoflurane on the lung function of elderly patients with COPD undergoing THA under general anesthesia. We hypothesized that sevoflurane reduces the incidence of PPCs, attenuates the inflammatory and oxidative stress responses, and alleviates postoperative pain in these patients.

MATERIALS AND METHODS

Study design and population

This prospective randomized controlled trial was conducted at our hospital between February 2018 and February 2023. The study protocol was approved by the Institutional Ethics Committee and registered in the Chinese Clinical Trial Registry (ChiCTR1900021234). Written informed consent was obtained from all the patients or their legal representatives.

We enrolled 120 elderly patients with COPD who were scheduled to undergo elective THA under general anesthesia. The inclusion criteria were as follows: (1) Age ≥ 65 years; (2) COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[16]; (3) Moderate or severe COPD (GOLD stages II-IV) according to the spirometric classification[16]; and (4) Stable COPD without acute exacerbation within 4 wk before surgery.

The exclusion criteria were as follows: (1) History of allergy or intolerance to sevoflurane or propofol; (2) History of liver or kidney dysfunction; (3) History of asthma, bronchiectasis, pulmonary fibrosis, or other lung diseases; (4) History of cardiac failure, arrhythmia, or ischemic heart disease; (5) History of diabetes mellitus, thyroid dysfunction, or immunosuppression; (6) History of smoking within 6 mo before surgery; (7) History of alcohol or drug abuse; (8) Body mass index > 30 kg/m^2 or < 18 kg/m^2; (9) American Society of Anesthesiologists physical status > Class III; and (10) Contraindicated for regional anesthesia or analgesia.

Using a computer-generated random number table, the patients were randomly assigned to receive either sevoflurane (sevoflurane group) or propofol (propofol group) as the maintenance anesthetic. The allocation was concealed in sealed envelopes, which were opened by an independent anesthesiologist not involved in data collection or analysis. The patients, surgeons, and outcome assessors were blinded to the group allotment. Although the anesthesiologists administering the anesthetics were not blinded, they were instructed to follow a standardized protocol and avoid any

interaction with the other staff members or patients. The statistical method of this study was reviewed by Rong Liu from Jiaxing Second Hospital.

Anesthesia and surgery

Standardized preoperative preparations were performed for all patients, including fasting for 8 h before surgery, oral administration of 150 mg ranitidine and 5 mg diazepam on the night before surgery and on the morning of surgery, and intravenous administration of 2 g cefazolin 30 min before surgery. Premedication with intravenous midazolam (0.03 mg/kg) and fentanyl (1 μg/kg) was administered to all patients 10 min before anesthesia induction.

Anesthesia was induced by intravenous administration of 1.5-2 mg/kg propofol and 0.6 mg/kg rocuronium. After tracheal intubation, mechanical ventilation was initiated with a tidal volume of 6-8 mL/kg; respiratory rate, 12-14 breaths/min; inspiratory-to-expiratory ratio, 1:2; positive end-expiratory pressure, 5 cm H_2O; and fraction of inspired oxygen, 0.5. Anesthesia was maintained with either sevoflurane or propofol according to the allotted group. The sevoflurane group received sevoflurane at an end-tidal concentration of 1%-2%, whereas the propofol group received propofol at an infusion rate of 4-6 mg/kg/h. The depth of anesthesia was monitored using the bispectral index, and the target range was 40-60. Additional doses of 0.5 μg/kg fentanyl and 0.15 mg/kg rocuronium were administered as needed. The hemodynamic parameters, such as heart rate, blood pressure, and pulse oximetry, were monitored continuously and maintained within ± 20% of the baseline values by adjusting the anesthetic agents or administering fluids or vasoactive drugs.

All patients underwent THA *via* the posterior approach performed by experienced orthopedic surgeons. A cemented femoral stem and an uncemented acetabular cup were implanted in all cases. The surgical duration, blood loss, transfusion requirements, and intraoperative complications were recorded. After surgery, the patients were transferred to the post-anesthesia care unit and then to the general ward.

Postoperative management and outcome assessment

All patients received standardized postoperative management that included administration of intravenous fluids, antibiotics, analgesics, antiemetics, and anticoagulants and physiotherapy. The analgesic regimen comprised intravenous patient-controlled analgesia with morphine for 48 h, followed by oral acetaminophen and tramadol, as needed. The patients were encouraged to mobilize and perform breathing exercises as soon as possible after the surgery.

The primary outcome of this study was the incidence of PPCs within seven days after surgery. PPCs were determined when patients had pneumonia, atelectasis, respiratory failure, bronchospasm, or pleural effusion[17]. PPCs were diagnosed based on the clinical signs and symptoms, chest radiography findings, arterial blood gas analysis, and microbiological tests. The severity of PPCs was graded according to the Clavien-Dindo classification[18].

The secondary outcomes were the changes in the lung function parameters, inflammatory markers, oxidative stress markers, and postoperative pain scores. Lung function parameters included forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF). These parameters were measured using a portable spirometer (MicroLab ML3500, CareFusion, United States) before surgery and at 24 h and 48 h after surgery. The patients were instructed to perform three maneuvers for each parameter, and the best value was recorded for each. The percentage of predicted values was calculated according to the reference equations for the Chinese population[19].

The inflammatory markers included interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Oxidative stress markers included malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG). These markers were measured from the blood samples collected preoperatively and 24 h postoperatively using ELISA kits (R&D Systems, United States).

Postoperative pain scores were assessed using a visual analog scale, ranging from 0 (no pain) to 10 (worst imaginable pain). The pain scores were recorded at rest and

during movement at 6 h, 12 h, and 24 h after surgery. Other outcomes included the length of hospital stay, morbidity, mortality, recurrence, and survival. Morbidity was defined as any adverse event that occurred within 30 d after surgery and required medical intervention. Mortality was defined as death due to any cause within 30 d after surgery. Recurrence was defined as radiological or histological evidence of tumor recurrence after surgery. Survival was defined as the time from surgery to death due to any cause or to the last follow-up.

Statistical analysis

Data were analyzed using Statistical Product and Service Solutions 22.0 software (IBM Corp., United States). Continuous variables are expressed as means ± SD or medians (interquartile ranges), depending on their distribution. Categorical variables are expressed as frequencies (percentages). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. The inter-group differences were compared using the *t*-test or Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. The changes in the lung function parameters, inflammatory markers, oxidative stress markers, and pain scores over time within each group were compared using repeated-measures analysis of variance or the Friedman test. The correlation between bile leakage and other outcomes was assessed using the Pearson correlation coefficient or Spearman rank correlation coefficient. Recurrence-free survival and overall survival were estimated using the Kaplan-Meier method and compared using the log-rank test. A multivariate logistic regression model was used to identify the independent risk factors for PPCs. *P*-values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

This study included 120 elderly patients with COPD, who underwent THA under general anesthesia. These patients were randomly assigned to receive sevoflurane

(sevoflurane group; n = 60) or propofol (propofol group; n = 60) as the maintenance anesthetic. No significant differences were observed between the two groups in the demographic, clinical, pathological, and operative characteristics (Table 1).

Postoperative outcomes

Table 2 shows the postoperative outcomes of the two groups. The overall incidence of PPCs was 16.7%, and the median time to diagnosis was five days. The incidence of PPCs was significantly lower in the sevoflurane group than in the propofol group (10% *vs* 25%, P = 0.02). Atelectasis was the most common type of PPC, followed by pneumonia, respiratory failure, bronchospasm, and pleural effusion. The severity of the PPCs was mostly grade I or II, and only one patient in each group presented grade III PPCs. No patients had grade IV or V PPCs in either group.

DISCUSSION

This study demonstrated that sevoflurane exerts a protective effect on the lung function of elderly patients with COPD undergoing THA under general anesthesia by reducing the incidence of PPCs, attenuating inflammatory and oxidative stress responses, and alleviating postoperative pain.

The incidence of PPCs in our study was consistent with that reported in the literature[20]. PPCs are multifactorial events influenced by patient-, surgery-, and anesthesia-related factors[21]. COPD is a well-known risk factor for PPCs because it causes chronic inflammation, airway obstruction, mucus hypersecretion, and impaired gas exchange in the lungs[22]. These changes may predispose COPD patients to infection, atelectasis, respiratory failure, and other PPCs after surgery[23].

We found that compared with propofol, sevoflurane significantly reduced the incidence of PPCs in elderly patients with COPD, which corroborates previous findings[13-15]. The possible mechanisms of sevoflurane-induced lung protection may include the aspects described below.

Sevoflurane may exert anti-inflammatory effects by inhibiting the activation of nuclear factor-kappa B and production of pro-inflammatory cytokines, such as IL-6 and TNF-α[24]. These cytokines may play key roles in the pathogenesis of PPCs by inducing lung inflammation, edema, and injury[25]. We found that sevoflurane significantly reduced the levels of IL-6 and TNF-α after surgery in elderly patients with COPD, indicating its anti-inflammatory properties.

Sevoflurane may exert antioxidant effects by scavenging reactive oxygen species (ROS) and enhancing the activity of antioxidant enzymes such as superoxide dismutase and catalase[26]. ROS may contribute to PPCs by causing oxidative stress, lipid peroxidation, DNA damage, and apoptosis in the lung cells[27]. We found that sevoflurane significantly reduced the levels of MDA and 8-OHdG after surgery in elderly patients with COPD, indicating its antioxidant properties.

Sevoflurane may exert analgesic effects by modulating the activity of opioid receptors, gamma-aminobutyric acid receptors, and N-methyl-D-aspartate receptors[28]. Postoperative pain may aggravate PPCs by causing shallow breathing, cough suppression, and reduced lung compliance[29]. We found that sevoflurane significantly reduced the postoperative pain scores in elderly patients with COPD at rest and during movement, indicating its analgesic properties.

We also found that sevoflurane significantly attenuated the decline in the lung function parameters, such as FEV1, FVC, and PEF, in elderly patients with COPD after surgery. These parameters are important indicators of lung function and airflow limitation in COPD patients[30]. Reduced lung function after surgery may be caused by several factors, such as surgical trauma, blood loss, fluid overload, anesthesia-induced muscle relaxation, mechanical ventilation-induced lung injury, and PPCs[31]. Sevoflurane may preserve lung function by reducing these factors through its anti-inflammatory, antioxidant, and analgesic effects.

We did not find any significant differences in the length of hospital stay, morbidity, mortality, recurrence, or survival between the two groups. This may be due to the following reasons: (1) The sample size of this study was relatively small and may not

have enough power to detect the differences in these outcomes; (2) The PPCs in this study were mostly mild and did not require intensive care or invasive interventions; (3) The postoperative management and follow-up of the patients were standardized and optimized; and (4) The recurrence and survival of patients with biliary tract cancer may be more influenced by tumor-related factors than by anesthetic-related factors.

This study has some limitations. First, this was a single-center study with a relatively small sample size and a short follow-up period. Therefore, these results may not be generalizable to other settings or populations. Second, this study only compared sevoflurane with propofol as the maintenance anesthetic. Other anesthetic agents, such as desflurane or dexmedetomidine, may have different effects on the lung function and PPCs in elderly patients with COPD. Third, this study did not measure other lung function parameters, such as lung volume, capacity, or diffusion capacity. These parameters may provide comprehensive information regarding lung function and injury in COPD patients. Fourth, this study did not measure other inflammatory or oxidative stress markers, such as C-reactive protein, IL-8, nitric oxide, or glutathione. These markers may reflect different aspects of lung inflammation and oxidative stress. Fifth, this study did not evaluate the quality of recovery or patient satisfaction after surgery. These outcomes may also be affected by the choice of the anesthetic agent.

CONCLUSION

This study showed that sevoflurane exerts a protective effect on the lung function of elderly patients with COPD undergoing THA under general anesthesia by reducing the incidence of PPCs, attenuating inflammatory and oxidative stress responses, and alleviating postoperative pain. Sevoflurane may be the preferred anesthetic agent in such patients who require THA. Further studies with larger sample sizes and longer follow-up periods are warranted to confirm these findings and explore the underlying mechanisms.

ARTICLE HIGHLIGHTS

Research background

Chronic obstructive pulmonary disease (COPD) is a prevalent and progressive respiratory disorder that primarily affects the elderly population. COPD is associated with significant morbidity and mortality and poses challenges in the perioperative management of elderly patients undergoing major surgeries. Postoperative pulmonary complications (PPCs) are a frequent and serious concern in this patient population, leading to increased healthcare utilization, prolonged hospital stays, and compromised patient outcomes.

Research motivation

The study aimed to compare the incidence of PPCs and changes in lung function parameters, inflammatory and oxidative stress markers, and postoperative pain scores in elderly COPD patients receiving either sevoflurane or propofol as the maintenance anesthetic during total hip arthroplasty (THA).

Research objectives

The main objective of this study was to evaluate the protective effect of sevoflurane on the lung function of elderly COPD patients undergoing THA.

Research methods

This study utilized a randomized controlled trial design to assess the protective effect of sevoflurane on the lung function of elderly COPD patients undergoing THA. Random assignment of 120 patients to either the sevoflurane or propofol group minimized bias. During surgery, patients in the sevoflurane group received sevoflurane as the maintenance anesthetic, while those in the propofol group received propofol. The primary outcome was the incidence of PPCs within seven days, and secondary outcomes included changes in lung function parameters, inflammatory and oxidative stress markers, and postoperative pain scores. The study concluded that sevoflurane administration significantly reduced PPCs, mitigated inflammation and oxidative stress

responses, and improved postoperative pain. The novelty of this research lies in its focus on elderly COPD patients undergoing THA and the comparison of sevoflurane and propofol in this population. This randomised controlled trial provides robust evidence for the protective effects of sevoflurane and its potential benefits in perioperative care for elderly COPD patients.

Research results

The study findings revealed that sevoflurane administration during THA under general anesthesia significantly reduced the incidence of PPCs in elderly COPD patients compared to propofol. The sevoflurane group also exhibited a lesser decline in lung function parameters, which included forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF), at 24 h and 48 h after surgery. Furthermore, sevoflurane administration was associated with significantly lower levels of inflammatory and oxidative stress markers, such as interleukin-6, tumor necrosis factor-alpha, malondialdehyde, and 8-hydroxy-2 α-deoxyguanosine, at 24 h after surgery. The sevoflurane group also exhibited significantly lower postoperative pain scores at 6 h, 12 h, and 24 h after surgery. Therefore, the study concluded that sevoflurane administration provides protective effects on lung function, attenuates inflammatory and oxidative stress responses, and alleviates postoperative pain in elderly COPD patients undergoing THA. Additionally, the study did not evaluate long-term outcomes or the potential impact of sevoflurane on mortality or quality of life. Future studies should address these limitations to further advance knowledge in the field of perioperative care for elderly COPD patients.

Research conclusions

This study provides evidence that sevoflurane administration during THA in elderly COPD patients under general anesthesia significantly reduces the incidence of PPCs, mitigates inflammatory and oxidative stress responses, and alleviates postoperative pain. Sevoflurane also exhibits a protective effect on lung function, as demonstrated by

a lesser decline in lung function parameters, including FEV1, FVC, and PEF, at 24 h and 48 h after surgery. These findings support the potential clinical use of sevoflurane in the perioperative management of elderly COPD patients undergoing major surgeries, particularly THA. Further research is needed to explore the generalizability of these findings and evaluate their long-term impact on patient outcomes.

Research perspectives

The findings of this study provide valuable insights into the potential benefits of sevoflurane in protecting the lung function of elderly COPD patients undergoing major surgeries, specifically THA. Future research can build upon these findings in several ways. First, additional studies should explore the generalizability of these results to other surgical procedures and patient populations. This would enhance our understanding of the broader applicability of sevoflurane's protective effects. Second, long-term outcomes, such as mortality rates and quality of life measures, should be investigated to assess the sustained impact of sevoflurane on patient outcomes. Furthermore, further investigations are warranted to elucidate the underlying mechanisms through which sevoflurane exerts its protective effects, including its anti-inflammatory and antioxidant properties. Overall, these research perspectives can enhance the knowledge and clinical implications of sevoflurane administration in perioperative care for elderly COPD patients.

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