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Effect of early post-extubation high-flow nasal cannula versus conventional low-flow oxygen therapy on reintubation in postoperative patients from prolonged general anesthesia at surgical ICU: A randomized clinical trial (Protocol)

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ABSTRACT:

Background: The main concerns following general anesthesia, especially if it lasts longer than 4 hours, are postoperative pulmonary complications, including hypoxemia, lung atelectasis, and acute respiratory failure requiring reintubation. To avoid these complications, postoperative extubation with respiratory support is crucial. The high-flow nasal cannula (HFNC) increases end-expiratory lung volume and reduces the work of breathing to improve oxygenation by delivering a flow-dependent positive airway pressure. The advantages of using HFNC to prevent reintubation have been demonstrated in patients undergoing cardiothoracic surgery. Our target population's information is still deficient, and our trial is set up to uncover this proof.

Objectives: To evaluate the effect of high-flow nasal cannula (HFNC) versus low-flow nasal cannula on the reintubation rate and clinical outcomes in the early post-extubation adult who has prolonged general anesthesia for non-cardiothoracic and non-neuro surgery that requires surgical ICU admission.

Methods: In this study, 260 patients with an intermediate to high risk of postoperative pulmonary complications following non-cardiothoracic surgery and non-neurosurgery that required general anesthesia for longer than 4 hours were randomly assigned to receive either a high-flow nasal cannula (HFNC) or a low-flow nasal cannula after extubation. The primary outcome indicator is the reintubation rate within 72 hours of tracheal extubation. Postoperative pulmonary complications, the length of stay in the ICU and hospital, and mortality are considered secondary outcome measures.

Conclusions: This study is an investigator-initiated randomized controlled trial powered to test the hypothesis that early application of a high-flow nasal cannula probably reduces the reintubation rate in patients in SICUs with prolonged durations of general anesthesia.

Keywords: High flow nasal cannula, Oxygen therapy, Reintubation, Postoperative pulmonary complications, Prolonged general anesthesia.

INTRODUCTION

Postoperative pulmonary complications (PPCs) are significant problems after surgery and influence surgical-related morbidity and mortality [1-4]. The incidence ranges from 6% to 80%, depending on the definitions and severity considered (from atelectasis to acute respiratory failure) [1-4].

In high-risk non-cardiothoracic surgery and non-neurosurgical patients, prolonged anesthesia time is the cause of remaining intubation in the surgical ICU and the factor that increases postoperative respiratory complications [5,6]. Furthermore, the surgery duration is a risk predictor in the ARISCAT score, especially if the surgical time is more than 3 hours or at least 4 hours of anesthetic duration [7,8].

Timely extubation is a way of minimizing ventilator-associated pneumonia and other complications related to mechanical ventilation. However, inappropriate extubation may be deleterious, and the need for reintubation from acute respiratory failure may be associated with high-risk patients with hospital mortality rates of up to 40% [9].

Respiratory support and oxygen therapy after extubation are necessary to prevent hypoxemia and reintubation after general anesthesia [3,4,9]. Using low-flow oxygen equipment can supplement oxygen administration. Nevertheless, this device may not always prevent postoperative respiratory function in some high-risk patients because of loss of positive airway pressure and derecruitment of lung areas [3]. As a result, loss of functional alveolar units is common, and extubated patients are prone to oxygen desaturation and respiratory failure [10,11].

High flow nasal cannula (HFNC) delivers a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume, suggesting a possible alveolar recruitment effect. It also has several physiological advantages, including constant FiO_2, decreased anatomical dead space, and good humidification [12-14].

Nevertheless, the information about reintubation rate comparing high-flow nasal oxygen and low-flow technique after extubation focusing on prolonged anesthesia patients requiring surgical ICU from previous studies is lacking [2,3,9,11-14].

Therefore, we would like to perform a randomized clinical trial to evaluate the clinical effectiveness of HFNC directly after extubation, compared with conventional low-flow oxygen therapy, after prolonged anesthesia in non-cardiothoracic and non-neuro surgical patients who required surgical ICU admission due to the incidence of reintubation.

OBJECTIVES

Primary objective

The primary objective of this study is to compare the reintubation rate between HFNC and low-flow oxygen therapy after extubation in prolonged anesthesia for non-cardiothoracic surgery and non-neurosurgical patients who required surgical ICU admission.

KEY MESSAGES:

- Postoperative pulmonary complications are the most concerning after prolonged general anesthesia, especially when the surgery requires more than 3 hours.
- The information about reintubation rates comparing high flow nasal oxygen and low flow technique after extubation focusing on prolonged anesthesia patients who required surgical ICU from previous studies is insufficient.
- This study is a randomized controlled trial to test the hypothesis that early application of a high flow nasal cannula could reduce the reintubation rate in patients in SICUs with prolonged general anesthesia.

Secondary objective

The secondary objective is to identify the patients who have benefited from HFNC after extubation from prolonged anesthesia.

MATERIALS AND METHODS

Trial design and setting

This trial is a single-centered, prospective, randomized, controlled clinical trial conducted at surgical intensive care units (SICUs). The study protocol was approved by the Siriraj Institutional Review Board (SIRB), Mahidol University, Thailand (approval number SI 391/2022) and registered via the Thai Clinical Trials Registry (TCTR20220805002). Enrollment started in June 2022 after SIRB approval. The investigators obtained written informed consent from all patients or their legal guardians if patients could not provide support.

Study population

The following inclusion criteria did identify eligible patients. All adult patients (age ≥18 years) scheduled for planned or unplanned non-cardiothoracic and non-neuro surgery with an anticipated general anesthesia duration of 4 hours or more. Patients at least grade 2 in the ASA classification system had a moderate to high risk of postoperative pulmonary complications, defined by an ARISCAT risk score of 26 points or more. After the operation, they were observed and monitored in the surgical ICU.

Patients fulfilling one or more of the following criteria were excluded: patients with a body mass index ≥35 kg/m^2, a life-threatening condition requiring emergency surgery, patients with obstructive sleep apnea, patients with a tracheostomy tube, and pregnant patients, to provide a relatively homogenous study population and avoid potential confounding in the interpretation.

The surgical procedures contraindicated by using HFNC after extubation were also excluded. The withdrawal criteria of this study were that patients needed to be reoperated within three days or needed a mechanical ventilator more than 24 hours after the end of general anesthesia.

Subject allocation

After enrollment, participants were randomly assigned in a 1:1 ratio to either the high-flow nasal cannula group (HF group) or the low-flow nasal cannula group (LF group). The randomization was performed with variable block sizes and concealed envelopes to receive either HFNC or standard oxygen therapy immediately after endotracheal extubation.

Intraoperative and postoperative period at SICUs

As previous reports and the study protocol described, anesthesiologists applied a standardized lung protective ventilation strategy to all patients during surgery and general anesthesia [1-3]. Lung protective ventilation included a tidal volume of 6 to 8 ml per kilogram of predicted body weight and a positive end-expiratory pressure (PEEP) of 5 to 8 cm of water. The recruitment maneuvers depended on the anesthesiologist, repeated every 60 minutes after tracheal intubation.

Each recruitment maneuver applied a continuous positive airway pressure of 30 cm of water for 30 seconds. During anesthesia, a peak inspiratory pressure of no more than 30 cm of water was targeted in all patients.

At the end of the surgery, endotracheal extubation was performed either in the operating room or surgical ICU. In the operating room, extubation criteria after surgery were the recovery of spontaneous ventilation with an expired tidal volume between 5 and 8 ml/kg, the respiratory rate between 12 and 25 breaths/min, peripheral oxygen saturation ≥94%, stable hemodynamics, and a body temperature ≥36°C. Then, the patients were transferred to the surgical ICUs to be observed using the standard conventional oxygen therapy delivered continuously using low-flow oxygen nasal cannulas at 3 – 5 L/min or the HFNC oxygen therapy. In the HFNC group, oxygen was constantly delivered at a gas flow rate of 40–60 L/min with FiO_2 0.3 - 0.4 and a temperature 34 – 37 degrees Celsius through an MR850 heated humidifier and an RT202 breathing circuit (Optiflow™, Fisher and Paykel Healthcare Ltd., Auckland, New Zealand).

In the surgical ICU for the remaining intubated patient, the extubation criteria followed the weaning protocol, and then the patients were randomized to each group of interventions after extubation.

The weaning protocol included daily screening for weaning readiness according to the following criteria: recovery from the precipitating illness; respiratory criteria (PaO_2:FIO_2 [partial pressure of oxygen, atrial: fraction of inspired oxygen] ratio>150 with FIO_2 ≤0.4, PEEP <8 cm H_2O, and arterial pH >7.30); and clinical criteria (absence of electrocardiographic signs of myocardial ischemia, no inotropic and vasoactive drugs, heart rate <140/min, hemoglobin>8 g/dL, temperature <38°C, no need for sedatives; appropriate spontaneous cough).

Patients fulfilling these criteria underwent a spontaneous breathing trial with 5-8 cm H_2O of pressure support for 30 to 120 minutes. Standard criteria for failure of the breathing trial were used. Patients who tolerated the spontaneous breathing trial were clinically evaluated for airway patency, respiratory secretions, and upper airway obstruction before extubation.

After 12-48 hours, the intervention stopped, and close monitoring was observed. In each group, oxygen flow was titrated by the ICU team to maintain a peripheral oxygen saturation of 94% or more. Then, the data was collected in the case record form.

All other aspects of patient care during the intraoperative and postoperative periods, including general anesthesia, fluid administration, prophylactic antibiotics, and postoperative pain management, were conducted by the attending physician according to the expertise of the staff and routine clinical practice. However, it was suggested to perform postoperative pain management to achieve a numeric rating scale (NRS) pain score <3 in non-intubated patients or a critical care pain observation tool (CPOT) score < 3 in mechanically ventilated patients.

Arterial blood gas values and respiratory rate were collected at baseline (at SICUs) before extubation and between 6 and 12 hours after extubation. Physiologic variables were recorded after 6-12 hours of conventional low-flow oxygen cannula or high-flow nasal oxygen therapy.

Outcome measurement

The primary outcome of this study was the reintubation rate within 72 hours after extubation. The clinician teams in SICUs had to evaluate patients who were necessary for reintubation. Predefined criteria for immediate respiratory-related reintubation included any of the following: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, the persistent inability to remove respiratory secretions, heart rate less than 50 beats per minute with loss of alertness, and severe hemodynamic instability unresponsive to fluids and vasoactive drugs; patients who developed persistent post-extubation respiratory failure were also reintubated.

Non-respiratory related reasons for reintubation were needed for emergency surgery or a low level of consciousness (decrease in Glasgow Coma Scale [GCS] >2 points or GCS <9 points) with $PaCO_2$ greater than 45 mm Hg.

Post-extubation respiratory failure within 72 hours of extubation was defined as the presence and persistence of any of the following criteria: respiratory acidosis (pH <7.25 with $PaCO_2$ >50 mmHg), SpO_2 less than 92% or PaO_2 less than 80 mmHg at FiO_2 higher than 0.6, respiratory rate more than 35/min, decreased level of consciousness (GCS >1 point decrease), agitation, inability to remove respiratory secretions or clinical signs suggestive of respiratory muscle fatigue or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical abdominal motion, or retraction of the intercostal spaces.

Secondary outcomes assessed during the first seven days after surgery were

- Postoperative pulmonary complications due to any causes are graded on a scale from 0 (no pulmonary complications) to 4 (the most severe complications) (Table 1) [15]

- Sepsis or multiple organ failure
- The need for additional oxygen therapy during the treatment or after the end of the treatment is defined as peripheral oxygen saturation of less than 92% on room air or using the higher devices, for example, the rebreather or non-rebreather oxygen mask.
- ICU and hospital length of stay
- In hospital mortality and the mortality rate on days 28 and 90.

The primary safety concern was delayed reintubation, defined as patients using a non-rebreather mask for at least 12 hours or switching to high-flow nasal oxygen or non-invasive mechanical ventilation to prevent intubation [16]. As a safety substitute, the time until reintubation was also measured.

DATA ANALYSIS PLAN

Sample size calculation

We calculated that the enrollment of 230 patients would provide the trial with 80% power between the two groups at a two-sided alpha level of 0.05, assuming a 3% incidence of reintubation after extubation in the HFNC group versus 13% in the conventional oxygen therapy group [10]. As a result, we enrolled 260 patients with a 10% dropout rate.

OUTCOME ANALYSIS PLAN

Statistical analysis

Statistical analysis was conducted on an intention-to-treat (ITT) basis. Baseline categorical characteristics were described as numbers (%) and quantitative variables as means (SD) or medians (interquartile range). An unadjusted chi-square or Fisher's exact test will be used for primary outcome analysis.

For the analysis of secondary outcomes, the chi-square test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. When applicable, the unpaired t-test or the Mann-Whitney U test will be used to compare continuous variables. Both normality and homoscedasticity will be evaluated using the Shapiro-Wilk and Fisher-Snedecor tests, respectively.

Stata statistical software version 17.0 was used for all analyses (StataCorp, College Station, TX, USA). Statistical significance was defined as a two-sided P-value less than 0.05.

DISCUSSION

It has become clear that postoperative pulmonary complications are the major cause of postoperative morbidity and mortality [2]. Developing PPCs also increases healthcare costs, primarily due to the increased length of stay (LOS). In times of increasing financial restrictions, PPCs represent a significant potential source of cost-savings [17].

In the previous study, the duration of surgery (more than 3 hours) and the type of surgery (airway, head, neck, thoracic, and abdominal surgery) were independent risk factors for reintubation [18].

Surgery lasting longer than three hours is one of the significant risk factors in the ARISCAT score, which is a predictive score for postoperative pulmonary complications [7].

Long-term general anesthesia can adversely affect the respiratory system, such as by decreasing respiratory mus-

Table 1. Grades of pulmonary complications [15]

Postoperative pulmonary complication grade	Definition
Grade 1	Cough, dry Microatelectasis: abnormal lung findings and temperature > 37.5 °C without other documented cause; normal chest radiograph Dyspnea, not due to other documented cause
Grade 2[a]	Cough, productive, not due to other documented cause Bronchospasm: new wheezing or preexistent wheezing resulting in a change in therapy Hypoxemia: $SpO_2 < 90$ in room air Atelectasis: gross radiological confirmation (concordance of 2 independent experts) plus either temperature > 37.5 °C or abnormal lung findings Hypercarbia ($PaCO_2 > 50$ mmHg), requiring treatment
Grade 3	Pleural effusion, resulting in thoracentesis Pneumonia: radiological evidence (concordance of 2 independent experts) plus clinical symptoms (two of the following: leukocytosis or leukopenia, abnormal temperature, purulent secretions), plus either a pathological organism (by Gram stain or culture), or a required change in antibiotics Pneumothorax Noninvasive ventilation, strictly applied to those with all of the following: (a) $SpO_2 \leq 92\%$ under supplemental oxygen; (b) need of supplemental oxygen > 5 L/min; and (c) respiratory rate ≥ 30 bpm Reintubation postoperative or intubation, period of ventilator dependence does not exceed 48 h
Grade 4	Ventilatory failure: postoperative ventilator dependence exceeding 48 h, or reintubation with subsequent period of ventilator dependence exceeding 48 h

[a]We only classified as grade 2 if two or more items in grade 2 were present

$PaCO_2$ partial pressure of arterial carbon dioxide, SpO_2 pulse oxygen saturation cle function right after induction and causing secretion obstruction from insufficient heating and humidity. Lung atelectasis results from increased spinal curvature, cephalad diaphragm displacement in dependent regions, and decreased functional residual capacity (FRC) [17].

Therefore, it is crucial to improve respiratory support during the perioperative period [2, 10, 14]. Earlier studies mentioned that using a high-flow nasal cannula instead of traditional oxygen therapy reduces the need for reintubation in critically ill patients. However, the group of patients includes both critically ill medical and surgical patients [10, 14].

This trial is a randomized controlled study examining the early use of HFNC oxygen therapy in critically ill surgical patients at intermediate to high risk of developing postoperative pulmonary complications in situations involving prolonged general anesthesia.

The primary endpoint is the reintubation rate, which is the core outcome of our study. Selecting patients who may benefit from respiratory support therapy in the postoperative period is essential to designing individually tailored management approaches.

Several confounding factors, such as postoperative pain management, intraoperative fluid administration, and respiratory chest physiotherapy, can be suggested. These points are not protocolized in this study, in contrast to the management of intraoperative mechanical ventilation. On the other hand, the study protocol stresses that intraoperative and postoperative care are to be performed as closely as possible to routine clinical care.

CONCLUSION

The purpose of our trial, an investigator-initiated randomized controlled trial, is to determine whether prompt application of HFNC lowers the reintubation rate in SICU patients undergoing prolonged general anesthesia. The prosecution also assesses the impact of high-flow oxygen therapy on the mortality rate, the lengths of ICU and hospital stays, and the majority of postoperative pulmonary complications.

CONFIDENTIALITY

The researchers only obtained informed consent in a separate, private space within the surgical ICU. The database is password-locked and encoded with patient data using hospital-based healthcare personnel. Instead of the patient's name, hospital identification number, and admission number, a code is used and recorded. A third party cannot track these patients' data. After the trial, all information will be permanently deleted from all computers and physical documents.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: S. Kongsayreepong; (II) Data curation: S. Phetuthairung; (III) Formal analysis: S. Phetuthairung, S. Kongsayreepong; (IV) Funding acquisition: S. Kongsayreepong; (V) Methodology: S. Phetuthairung, S. Kongsayreepong; (VI) Project administration: S. Phetuthairung, S. Kongsayreepong; (VII) Visualization: S. Phetuthairung, S. Kongsayreepong; (VIII) Writing: S. Phetuthairung, S. Kongsayreepong.

SUPPLEMENTARY MATERIALS

None

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