Abstract

I. Title of Project: Effects of Preoxygenation with Lower Fraction of Inspired Oxygen during Induction of Anesthesia.

II. Name of Principal Investigator: Lam, Chen-Fuh

III. Background:

During the induction period of general anesthesia, surgical patients are inevitably experienced a short period of apnea (no spontaneous or assisted ventilation) for endotracheal intubation or other airway manipulation. In order to minimize the risks of hypoxemia during the establishment of artificial airway, pure oxygen (oxygen partial pressure FiO2= 1) is commonly applied to the patients throughout the preoxygenation and induction period. The administration of 100% oxygen for 3 minutes in a normal subject may replace the nitrogen content in the lung cavity (de-nitrogenation) with higher alveolar concentrations of oxygen (greater then 95%). Elevation of oxygen reserve in the lung and oxygen partial pressure in the blood circulation may thus delay the development of hypoxemia (oxygen desaturation; defined as the tissue oxygen saturation below 90%) up to 10 minutes after apnea.

However, there is currently no clinical evidence indicating that preoxygenation with lower oxygen partial pressure (i.e. FiO2= 0.5 or 0.6) during the induction of anesthesia increases the incidence of hypoxemia or other complications. Most recently, two elegant large-scale clinical trials reported that the supplement of oxygen to patients with acute myocardial infarction or acute ischemic stroke did not provide any clinically beneficial effects in the prognosis of diseases. Oxygen has traditionally been recommended as a “standard” therapy for acute myocardial infarction and stroke. However, the results of these two important trials did not support the routine supplement of oxygen in these acute diseases. In addition, high concentrations of

oxygen therapy are potentially deleterious, as oxygen toxicity may result in direct tracheobronchial and alveolar damage, absorption atelectasis (lung tissue collapse) and central nervous system toxicity. In cellular levels, hyperoxia increases the production of reactive oxygenn species, such as the superoxide anion, the hydroxyl radical, and hydrogen peroxide, which in turn may cause cellular apoptosis and inflammatory response. Therefore, oxygen therapy in clinical settings has been recognized as a two-edged sword and excessive oxygen supplement should be guided closely for its potential toxicity.

Currently, there is no clinical evidence that supports the routine administration of 100% oxygen prior to intubation is essential or beneficial. In the contrary, it also remains undetermined if lower fractions of inspiratory oxygen during the induction period of anesthesia may attenuate lung injury or other cellular damage derived from the oxygen toxicity. Therefore, the findings of this proposed clinical study may provide fundamental evidence for the use of different oxygen concentrations in clinical anesthesia during the induction period, and determine the effects of inspiratory oxygen concentrations on the general postoperative outcomes after general anesthesia.

IV. Purpose of the study

The aim of this study is to determine the effect of preoxygenation with pure oxygen (FiO2=1) or lower partial pressure of oxygen (FiO2=0.6) on the development of hypoxemia during anesthesia and major complications at 3 days after surgery. These measurements include hemodynamic parameters, acute lung injury, wound healing, pain, other systemic complications, all cause mortality, and hospital length of stay.

V. Study design: this is a randomized, open-label, observer-blind and non-inferiority clinical trial.

1. Research model: Two-group parallel interventional study.
2. Control group: Preoxygenation with 100% oxygen during the induction phase of anesthesia
3. Blind method: Open-label, observer-blind.
4. Randomization: Block randomization using randomization generator software.

VI. The number of subjects:

This study anticipates in enrolling 500 participants in each month and it will take three months to enroll a total of approximate 1500 participants.

VII. Inclusion criteria:

1. A patient who is scheduled for an elective surgery and required for anesthesia with endotracheal intubation.
2. Age of the patient is between 18 and 65 years old.
3. Patient's American Society of Anesthesiologists (ASA) Physical Status is I-III.

VIII. Exclusion criteria.

Patients who:

1. Have difficult airway for ventilation or intubation.
2. Have severe lung disease (including any acute respiratory infection).
3. Were diagnosed of coronary artery disease or myocardial infarction.
4. Have severe heart failure (NYHA Fc ≥III).
5. Have liver cirrhosis (Child-Pugh's score ≥B).

6. Have acute or chronic kidney disease (Creatinine ≥2 mg/dl).
7. Have severe anemia (hemoglobin ≤8 mg /dl).
8. Have a body mass index ≥35.
9. Are currently pregnant.
10. Have not enough fasting time, intestinal obstruction or severe gastroesophageal reflux.
11. Received emergency surgery, cardiac surgery, craniotomy, or pulmonary surgery.
12. Have mental incapacitation, confusion, dementia, mental retardation, or are unable to complete the consent independently.
13. Refuse to participate in this study.

IX. Research processes:

This research study is a randomized, open-label and observer-blind trial. Patients who meet the eligibility criteria (without any exclusion criteria) and agree to join the study are randomly assigned to either high oxygen (FiO2=1) or lower oxygen (FiO2=0.6) group. A research assistant, who is not involved directly in patient care, will randomly assign the patients to the high oxygen (FiO2=1) or lower oxygen (FiO2=0.6) group.

After entering the operating room on the day of surgery, a pulse oximeter will be applied to the patient to determine the baseline levels SpO2. Preoxygenation with different percentages of inspiratory oxygen will be administered via a face mask for 8-10 minutes before intubation of an endotracheal tube. Pulse oximeter and other standard hemodynamic parameters will be continuously monitored throughout the entire induction period. After the endotracheal tube is successfully established, the patient will be processed for maintenance of anesthesia and surgical procedure

according to the clinical practice.

X. Assessment Indicators (objective measures based on research objectives)

1. The primary endpoint of this study is the development of hypoxemia (defined as SpO2< 92%) during the induction of anesthesia.
2. The composite secondary endpoint is the development of complications within three days after surgery, which include acute lung injury, lung collapse, pneumonia, wound infection, delayed wound healing, severe postoperative pain, prolonged hospital stay and mortality.

XI. Withdrawal from the study (Please provide a brief description of the assessment criteria and conditions for withdrawal from the study)

1. Patient or his/her family voluntarily withdraws from the study.
2. A baseline level of SpO2 < 92% measured at operating room.
3. A Data & Security Monitoring Board (DSMB) will be established to monitor the progress of the study. This monitoring board consists of a clinical expert, a biometric expert and a human rights expert. The adverse events, number of patients who dropped out of the trial, compliance with the test, the integrity, timeliness, and the quality of the data will be closely monitored by the board members.

XII. Consent form acquisition process

The physician anesthesiologists will illustrate the purpose of study, research procedures, potential risks and follow-up of the study during the preanesthesia visit. The informed consent will then be obtained from the patient.

XIII. The expected risks, side effects and treatment

Expected risks and side effects: the administration of lower oxygen concentration (FiO2= 0.6) during preoxygenation period may cause hypoxemia. Since tissue oxygenation will be continuously monitored throughout the anesthesia period, the development of hypoxemia during this period will be detected by the anesthesia team. Hypoxemia will be treated by the in-charge anesthesiologist according to the standard clinical guidelines, including increased concentrations of inspiratory oxygen, application of positive pressure ventilation, and increased minute ventilation.

XIV. Data Collection and Management

1. Data collection:

■Medical records □Questionnaire □Interview □Photography or photography

□Others_____

2. Person who may contact with the participants' information:

■Principal Investigator ■Co- principal Investigator ■Research Assistant

■Program auditing staff □Others_____

3. Data processing

■Encoding identification □Encryption □De-linking □Others_____

4. Data preservation:

The time for keeping the data: □Destruction after the end of the project

■Continue to save and reuse after the end of the project.

■Location of keeping the data: in the Department of Anesthesiologist Office in E-da Hospital.

■The data in-charge person: Dr. Lam, Chen-Fuh (Vice-superintendent in E-da Cancer Hospital)

XV. Sample collection and samples derivative management

■Does collect any specimen? NO.

XVI. Statistical analysis

All quantitative variables will be using a two-way RM ANOVA or unpaired t-test. And all qualitative variables will be using $\chi 2$ test followed by the posthoc 2×2 Fisher exact test.