

Short-Term Outcomes of Low Versus High Inspiratory Oxygen Fraction During Induction of General Anesthesia in Noncardiac Surgery: A Pragmatic Open-Label Randomized Non-Inferiority Trial

Tzu-Huan Su

E-Da Hospital

Kuang-Yao Li

E-Da Hospital

Tzu-Shan Chen

E-Da Hospital

Shu-Ching Chang

E-Da Hospital

Yi-Kai Su

E-Da Hospital

Chung-Yi Li

National Cheng Kung University Hospital

Chen-Fuh Lam (✉ lamcf@mail.ncku.edu.tw)

E-Da Hospital <https://orcid.org/0000-0002-8419-9912>

Research

Keywords: acute respiratory distress, general anesthesia, induction, oxygen

Posted Date: July 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-40108/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background. High inspiratory oxygen fraction (FIO_2) is associated with increased perioperative pulmonary morbidity and postoperative mortality. However, the use of pure oxygen is still currently recommended during the anesthesia induction.

Methods, This open-label randomized non-inferiority trial was conducted in two metropolitan hospitals at Southern Taiwan. A total of 302 surgical patients (ASA PC \leq III) who received endotracheal general anesthesia (ETGA) were randomized to receive 100% (FIO_2 1.0) or 60% (FIO_2 0.6) oxygen during induction. The primary endpoint was presence of hypoxemia ($\text{SpO}_2 \leq 92\%$) during the induction of anesthesia. The secondary endpoint was the development of major complications immediately and within 3 days after surgery.

Results. A total of 5 patients in the FIO_2 0.6 group developed hypoxemia during induction (3.9% vs 0% for FIO_2 0.6 vs FIO_2 1.0, respectively; $P=0.167$ for non-inferiority), suggesting that FIO_2 0.6 was inferior than FIO_2 1.0 for anesthesia induction. The mean lowest SpO_2 during induction was also significantly lower in FIO_2 0.6 group. Four patients reached the primary endpoint had increased body mass indexes ($\text{BMI} > 30 \text{ kg/m}^2$). However, the overall incidence of desaturation developed after removal of endotracheal tube was higher in FIO_2 1.0 group (1.4% vs 5.8%, FIO_2 0.6 vs FIO_2 1.0; odd ratio 0.22, 95% confidence interval 0.05-1.05; $P=0.064$).

Conclusions. High fractions of oxygen should be used for oxygenation during induction of ETGA in general population, especially in the obese patients. However, the supplement of high FIO_2 during induction was associated with increased hypoxemic events after removal of endotracheal tube that might have a more significant impact on perioperative care.

Background

Surgical patients often experience transient apnea before endotracheal intubation or other airway instrumentation during the induction of general anesthesia. In order to minimize the risks of hypoxemia during establishing artificial airway, the use of pure oxygen (oxygen partial pressure $\text{FIO}_2 = 1.0$) has been recommended throughout the preoxygenation and induction period (Bouroche and Bourgain 2015; Martin and Grocott 2015). Elevated oxygen reserve in the lungs and oxygen partial pressure in the blood circulation can significantly prolong the development of hypoxemia after apnea (Nimmagadda et al. 2017; Edmark et al. 2003). It has been found that it took significantly less time for patients preoxygenated with FIO_2 0.6 to drop their peripheral oxygen saturation (SpO_2) to below 90% compared with patients oxygenated with FIO_2 1.0 (411 vs 213 min, $P < 0.01$) (Edmark et al. 2003).

However, a recent study illustrated that high intraoperative inspiratory oxygen fractions are associated with a dose-dependent increase of respiratory complications and increased 30-day mortality (Staeher-Rye et al. 2017). Other sources have also pointed to the potentially damaging effects of high concentration

oxygen therapy, as oxygen toxicity may result in direct tracheobronchial and alveolar damage, absorption atelectasis and central nervous system toxicity (van Ooij et al. 2016; Hafner et al. 2015). Therefore, oxygen therapy in clinical settings has been recognized as a two-edged sword and excessive oxygen supplementation should be closely monitored for potential toxicity (Horner and O'Driscoll 2018; Martin and Grocott 2013), and use of $\text{FIO}_2 > 0.8$ is a topic of ongoing debate in the perioperative care (Weenink et al. 2020). In clinical anesthesia, a low optimal oxygen supplement (as low as $\text{FIO}_2 0.4$) is recommended to maintain $\text{SpO}_2 \geq 92\%$ during intraoperative mechanical ventilation for nonobese patients (LAS VEGAS Investigators 2017; Guldner et al. 2015).

Currently, there is no consensus on whether lower fractions of inspiratory oxygen during the induction period of anesthesia can decrease the risk of lung injuries and other cellular damage (Ball et al. 2017). In addition, higher perioperative oxygen supplement ($\text{FIO}_2 \geq 80\%$) has been suggested to be associated with a greater incidence of atelectasis and postoperative pulmonary complications (Li et al. 2019). Therefore, this non-inferiority trial hypothesized that in patients receiving anesthesia with endotracheal intubation, an induction FIO_2 of 0.6 was inferior to the standard $\text{FIO}_2 1.0$ in regards to desaturation prevention before endotracheal ventilation establishment and the development of postoperative complications.

Materials And Methods

Study population

This pragmatic, open-label, randomized (1:1 ratio), non-inferiority clinical trial was conducted in E-Da Hospital and E-Da Cancer Hospital (Kaohsiung, Taiwan) from October to December 2018. Eligible participants included adult aged 18–65 years with American Society for Anesthesiologist physical statuses (ASA PS) \leq III who were scheduled for surgical procedures and required endotracheal tube intubation general anesthesia (ETGA). The study was approved by the Institutional Review Board of E-Da Hospital (Kaohsiung, Taiwan) on 2 August 2018 (approval number EMRP15107N), and patients were enrolled after obtaining official IRB approval. The trial was also registered in September 2018 with clinical trials registration: NCT03665259. Written informed consent was obtained from the patients or their legal surrogates.

Exclusion criteria

Patients with anticipated difficult intubation, active lung disease, history of myocardial infarction or coronary artery disease, any advanced organ dysfunction (i.e. heart failure, renal insufficiency and/or liver cirrhosis), severe anemia (hemoglobin ≤ 8 mg/dl), body mass index (BMI) ≥ 35 kg/m², pregnancy, inadequate preoperative fasting time, or those receiving major operations (i.e. emergency, cardiac surgery, chest surgery and craniotomy) were excluded from the study.

Allocation to intervention

Eligible patients were randomized in permuted blocks of 10 using a computer-generated list to receive either pure oxygen (FIO₂ 1.0) or lower oxygen fraction (FIO₂ 0.6) in a 1:1 ratio. Treatment allocation for each patient was concealed in an opaque envelope according to the randomization sequence. The envelope was opened by the attending anesthetist immediately before preoxygenation, and the assigned treatment oxygen fraction was disclosed to the anesthesia team. Patient allocation and study flow diagrams are shown in Fig. 1.

Anesthesia and intervention protocols

Before administration of intravenous hypnotic agents, patients were given oxygen (FIO₂ 1.0 or FIO₂ 0.6) for at least 3 minutes via a face mask at a flow rate of 6 L/min. Anesthesia was induced through intravenous injection of fentanyl (2 µg/kg), propofol (1.5-2.0 mg/kg) and rocuronium (0.8-1.0 mg/kg). Following the loss of consciousness, bag-mask assisted ventilation was provided by the attending anesthetist through the face mask connected to the semi-closed circuit of anesthesia machine. Depth of anesthesia was not routinely monitored with the electroencephalographic devices, and the attending anesthetist decided the optimal duration of assisted mask ventilation during the induction phase. An appropriately size of endotracheal tube was intubated into the trachea under direct laryngoscopy, and the patient was then mechanically ventilated using the volume-control mode. The standard intraoperative ventilator setting followed the recent clinical practice recommendations, included a tidal volume of 8 mL/kg predicted body weight and a positive end expiratory pressure (PEEP) of 2-5cmH₂O (Li et al. 2019). Intraoperative anesthesia was maintained by volatile anesthetics (desflurane or sevoflurane) at optimal levels of minimal alveolar concentration (MAC). Inhaled anesthetics were delivered by 60% oxygen (FIO₂ 0.6) at a flow rate of 1L/min during maintenance of anesthesia. High flow rate of oxygen (FIO₂ 0.6, 6L/min) was used to wash out the anesthetic gases during the emergence phase of anesthesia. Neuromuscular monitoring system was not routinely used during the perioperative period. Oxygen fraction was switched to 100% whenever arterial desaturation (defined as a SpO₂ of ≤ 92%) (Futier et al. 2013) developed during the induction phase of anesthesia. Increases in the fraction of inspired oxygen and changes in ventilatory settings were also made to compensate for any episodes of arterial desaturation happened at any time points during maintenance or emergence phases of anesthesia. After patients had recovered to adequate spontaneous ventilation, the endotracheal tube was removed by the anesthetist and patients were transferred to the postanesthesia care unit (PACU). The standard protocol of anesthesia is shown in Fig. 2.

Measurements

The primary endpoint of this study was the development of arterial desaturation (SpO₂ ≤ 92%) during the induction of anesthesia (Futier et al. 2013). Desaturation during induction was closely monitored by the anesthetic team. The composite secondary endpoint was the development of postoperative complications (from removal of endotracheal tube to three days after surgery), which included events such as desaturation, acute lung injury, pneumonia, surgical site infection (SSI), unplanned admission to

intensive care unit (ICU), severe postoperative pain, prolonged hospital stays and mortality (supplementary Table 1). The clinical staff who recorded the secondary endpoints developed after discharged from PACU were blinded to the treatment groups.

Statistics

The reported overall incidence of hypoxemia ($\text{SpO}_2 < 90\%$) during induction of anesthesia ranges from 1.4–7.4% (Ehrenfeld et al. 2010; Baillard et al. 2019). With a reference probability of 0.05, the study defined an arbitrary non-inferiority margin of 5% in the development of desaturation during induction between the FIO_2 0.6 (alternative) and FIO_2 1.0 (standard or reference) treatments. We speculated a P -value < 0.05 would indicate non-inferiority of FIO_2 0.6 to induce desaturation during induction of anesthesia (alternative hypothesis), and would correspond to the upper limit of the one-sided 95% confidence interval (CI) of the difference not exceeding the 5% based on the type I error at 0.05 (one-sided) and a 90% statistical power. Under 1:1 sampling ratio in the two groups with an expected 10% withdrawal or drop-off rate, the calculated sample size in each group was approximately 500 patients (a total of 1000 patients) (PASS 15, NCCS, Utah, USA). Categorical variables were compared using the χ^2 statistics or Fisher's exact test. Continuous variables were compared using the Student's t -test or Mann-Whitney test. The Kaplan-Meier method was used to analyze the time to development of desaturation during induction, and time-to-event data between the groups were compared with the long-rank test. Intention-to-treat and as-treated analyses are presented for the development of desaturation after removal of endotracheal tube (a secondary endpoint), while the other secondary endpoints were analyzed in the as-treated population. All analyses were carried out using the SAS software, version 9.1 (SPSS software, version 24.0 (IBM, Armonk, NY).

Results

General outcomes and baseline patient characteristics

A total of 541 patients were assessed for eligibility of enrolment and 15 patients decided to withdraw from the study before randomization, and there were no cases dropped off after entering the trial (Fig. 1). This study was prematurely terminated after recruiting of 302 patients due to safety concerns addressed by the institutional Data and Safety Monitoring Board (DSMB), as there was a significant increase in the number of patients who reached the primary endpoint. The patient characteristics are listed on Table 1. There were no significant differences between the two group in the baseline SpO_2 at room air ($97.2 \pm 2.0\%$ vs $97.4 \pm 2.2\%$ for FIO_2 0.6 vs FIO_2 1.0, respectively; $P = 0.370$) (Table 1). The study did not record any patients with unanticipated difficult intubation who required advanced intubating devices, such as fiberoptic bronchoscope or surgical airway during induction. Types of operation are listed in Supplementary Table 2.

Table 1
Patient characteristics and perioperative factors

	FiO ₂ 0.6 (n = 152)	FiO ₂ 1.0 (n = 150)	P value
Age (years)	45.5 ± 11.8	46.6 ± 11.9	0.404
Gender (F:M)	90/62	84/66	0.571
ASA PS (I:II:III)	27/115/10	27/114/9	0.978
BMI	25.9 ± 5.0	24.9 ± 5.6	0.095
Active smoker	32	29	0.781
STOP Bang score	2.2 ± 1.6	2.3 ± 1.7	0.917
Baseline SpO ₂ (%)	97.2 ± 2.0	97.4 ± 2.2	0.370
Total anesthesia time (h)	195 ± 89	190 ± 80	0.613
Total intraoperative fluid (ml)	731 ± 501	707 ± 437	0.655
ASA PS: American Society of Anesthesiologists physical status; BMI: body mass index; SpO ₂ : peripheral oxygen saturation. Data were analyzed by unpaired t-test or χ^2 test, as appropriate.			

Primary endpoint

A total of 5 patients developed severe hypoxemia (SpO₂ ≤ 92%) during the induction phase of anesthesia. All the five patients received FiO₂ 0.6 for preoxygenation and they were switched to receive FiO₂ 1.0 for rescue therapy. Non-inferiority was not met (P = 0.167 for non-inferiority), as the upper margin 95% CI of 0.074 was greater than the pre-specified non-inferiority margin of 0.05 (Table 2). The incidences of desaturation during induction were 3.9% and 0% in the FiO₂ 0.6 and FiO₂ 1.0 groups, respectively (P = 0.03, Fisher Exact test) (Table 2). Time-to-event analysis by the Kaplan-Meier survival curves also confirmed that there was a significant difference between the two groups in regards to desaturation during induction (Fig. 3). Furthermore, the mean lowest SpO₂ in the FiO₂ 0.6 group was also significantly lower than that in the FiO₂ 1.0 group (98.7 ± 3.0% vs 99.7 ± 0.8%, respectively; P = 0.01). All the patients who developed the primary endpoint were successfully managed through increasing the fraction of oxygen supplementation to 100% via the bag-mask assisted ventilation. None of the patients required additional treatment or cancellation of surgery (supplementary Table 3).

Table 2
Primary endpoint

Incidence of desaturation during induction (intention-to-treat analysis)					
	FiO ₂ 0.6 (N = 152)	FiO ₂ 1.0 (N = 150)	97.5% upper confidence border	P value	NNH
	n (%) or mean (SD)	n (%) or mean (SD)			
Desaturation during induction	5 (3.9)	0 (0)	0.074	0.167*	31
Mean lowest SpO ₂ (%)	98.7 (3.0)	99.7 (0.8)	-	< 0.001 [†]	-

CI: confident interval; NNH: number-needed-to harm; OR: odd ratio; SpO₂: peripheral oxygen saturation.
*Unconditional test for non-inferiority using difference of two binomial proportions (one-sided).
[†]Unpaired t-test.

Secondary endpoints

The five patients who developed primary endpoint were excluded from the intention-to-treat analysis, but they were included in the as-treated analysis since they were all switched to receive 100% oxygen treatment after developing desaturation (Fig. 1). Two patients in the FIO₂ 0.6 group developed desaturation after removal of endotracheal tube in the operating room (1.4%, 2/147). The incidences of desaturation in the FIO₂ 1.0 group in the operating room (OR) were 3.3% (5/150) and 3.9% (6/155) for intention-to-treat and as-treated analysis, respectively (Table 3). Lower incidence of desaturation was also recorded in the FIO₂ 0.6 group while the patients were cared for in the PACU (0% vs 1.9% for FIO₂ 0.6 vs FIO₂ 1.0; P = 0.25). According to as-treated analysis, the overall incidences of desaturation after extubation (in OR and at PACU) were 1.4% (2/147) and 5.8% (9/155) in the FIO₂ 0.6 and FIO₂ 1.0 groups, respectively (P = 0.064) with an odds ratio of 0.22 (95% CI 0.05–1.05) (Table 3). The characteristics of patients who developed desaturation after extubation are summarized in supplementary Table 4. There were no cases of mortality or unplanned ICU admission in this study, and only one definite case developed SSI after operation (Table 3). The lengths of hospital stays were similar between these two groups (5.9 ± 3.0 vs 5.4 ± 2.4 days for FIO₂ 0.6 vs FIO₂ 1.0, respectively; P = 0.163) (Table 3).

Table 3
Secondary endpoints

Incidence of desaturation after extubation					
Intention-to-treat analysis*	FiO ₂ 0.6 (N = 147) n (%)	FiO ₂ 1.0 (N = 150) n (%)	P value	OR (95%CI)	NNH
Desaturation in OR after extubation (a)	2 (1.4)	5 (3.3)	0.448	-	-
Desaturation at PACU after extubation (b)	0 (0)	3 (2.0)	0.248	-	-
Desaturation after extubation (a + b)	2 (1.4)	8 (5.3)	0.105	0.24 (0.05–1.17)	26
As-treated protocol*	FiO ₂ 0.6 (N = 147) n (%)	FiO ₂ 1.0 (N = 155) n (%)	P value	OR (95%CI)	NNH
Desaturation in OR after extubation (a)	2 (1.4)	6 (3.9)	0.285	-	-
Desaturation at PACU after extubation (b)	0 (0)	3 (1.9)	0.248	-	-
Desaturation after extubation (a + b)	2 (1.4)	9 (5.8)	0.064	0.22 (0.05–1.05)	23
Complications within 3 days after operation (as-treated analysis)*					
	FiO ₂ 0.6 (N = 147) n (%)	FiO ₂ 1.0 (N = 155) n (%)	P value	OR (95%CI)	
Pneumonia or ALI	0	0	-	-	
Surgical site infection	1	0	0.495	-	
Unplanned ICU admission	0	0	-	-	
Length of hospital stays (days) [¶]	5.9 ± 3.0	5.4 ± 2.4	0.163	-	
Mortality	0	0	-	-	
<p>ALI: acute lung injury; CI: confidence interval; ICU: intensive care unit; NNH: number-needed-to-harm; PACU: postanesthesia care unit; SpO₂: peripheral oxygen saturation. *Patients who developed primary endpoint were excluded from the FiO₂ 0.6 group, and included in the FiO₂ 1.0 group for analysis of secondary endpoints (as-treated analysis); [¶]Data is shown as mean ± SD. Results were analyzed by the Fisher exact test (two-sided) or unpaired t-test, as appropriate.</p>					

Table 4
Logistic regression analysis of perioperative factors with primary endpoint*

				95% CI	
	Coefficient value	P value	OR	LL	UL
Age	-0.002	0.952	0.998	0.925	1.076
Gender	-0.034	0.971	0.967	0.157	5.961
BMI	0.356	0.010	1.428	1.091	1.869
ASA PS					
I	Ref				
II-III	-17.89	0.999	0.000	0.000	
STOP Bang score	0.083	0.765	1.087	0.629	1.876
Smoker	-0.067	0.953	0.935	0.101	8.673
Baseline SpO ₂	-25.961	0.978	0.000	0.000	
ASA PS: American Society of Anesthesiologists physical status; BMI: body mass index; CI: confident interval; LL: lower limit; OR: odd ratio; SpO ₂ : peripheral oxygen saturation; UL: upper limit. *Binary logistic regression model was computed from the FiO ₂ 0.6 group (n = 152).					

Discussion

The main factor of interest in this study was the relationship between oxygen supplementation fraction received during anesthesia induction and the development of desaturation or post-operative respiratory distress in non-critically ill patients. Routine pure oxygen supplementation for non-critical or generally healthy patients during induction is still a debated topic (Ball et al. 2017). There is currently no clinical evidence demonstrating the advantages of routine pure oxygen during induction of anesthesia, while intraoperative oxygen overexposure defined as hyperoxemia (SpO₂ > 98%) and substantial oxygen exposure (FIO₂ > 0.5) can potentially be harmful and increase postoperative complications (Suzuki et al. 2018). Although the time duration to reach desaturation (SpO₂ < 90%) was significantly prolonged in patients receiving higher fractions of inspired oxygen (FIO₂ > 0.8) (Edmark et al. 2003), an apneic time for more than 200 seconds with the supplement of FIO₂ 0.6 during induction should be sufficient for establishing a secure airway in generally healthy patients. Therefore, this trial tested the alternative hypothesis that FIO₂ 0.6 was non-inferior to the current common practice of routine pure oxygen supplementation in the prevention of desaturation during anesthesia induction.

This study was prematurely terminated after recruitment of 302 patients due to the safety concerns raised by the DSMB members, as all patients who developed primary endpoint received FIO₂ 0.6, and

time-to-event analysis and the lowest mean SpO₂ confirmed the increased hypoxemic events during the induction period of anesthesia in the FIO₂ 0.6 study group. Therefore, the null hypothesis of non-inferiority could not be rejected. The incidence of hypoxemia during induction phase by giving 60% inspired oxygen was 3.9% in our study, which is considerably higher than the previous report (Ehrenfeld et al. 2010). It was found that supplementation of 60% FIO₂ during induction phase may provide an estimated number needed-to-harm (NNH) of 31 in developing desaturation that requires urgent medical intervention. The lowest SpO₂ in the FIO₂ 0.6 group ranged from 78–92%, and these patients were switched to receive pure oxygen for rescue therapy. None of these patients developed any clinically significant consequences. Since there were no differences in patient characteristics and proportion of difficult intubation between the two groups, lower inspiratory oxygen fraction (i.e. FIO₂ 0.6) during preoxygenation and assisted ventilation before endotracheal intubation increased risk of desaturation in patients with ASA PS I-III. Our results indicated that four out of the five patients who developed the primary endpoint had BMI's greater than 30 kg/m². Obese patients have increased oxygen demand and CO₂ production, and as a result they are prone to rapid desaturation during apnea or hyponea due to reduced functional residual capacity and expiratory reserve volume, while the total lung compliance is decreased exponentially (Pelosi et al. 1998; Peppard et al. 2009).

Since the patients who developed primary endpoint were switched to 100% oxygen therapy during induction, these patients were included in the FIO₂ group for the subsequent analysis of the secondary endpoints (as-treated analysis). The main short-term outcomes after ETGA is concerned with the occurrence of acute respiratory distress or desaturation following removal of endotracheal tube. A total of 11 cases of desaturation after extubation in the OR or at PACU were found during the study. In the FIO₂ 0.6 group, two case developed a SpO₂ ≤ 92% in the OR, but none developed desaturation at PACU. However, there were 9 cases of desaturation in the FIO₂ 1.0 group, including one patient who developed the primary endpoint was switched to pure oxygen treatment. Although the incidence of desaturation was not statistically different (1.4% vs 5.8% for FIO₂ 0.6 vs FIO₂ 1.0; P = 0.064) between the two study groups, this unanticipated result highlights that the odds of developing desaturation after removal of endotracheal tube in ETGA patients is 78% lower in patients receiving FIO₂ 0.6 than those with pure oxygen exposure (odd ratio 0.22, 95% CI 0.22–1.05) during induction of anesthesia. Since the effect size of pure oxygen is considered high (i.e. 4.4 times higher than FIO₂ 0.6) in the development of post-extubation hypoxemia, the clinical impact of oxygen fractions used for anesthesia induction should not be overlooked. Previous studies suggested that surgical- and anesthesia-related risk factors for postoperative acute respiratory distress include long surgical duration > 2 h, emergency operation, high-risk surgery and perioperative fluid overload (Morris et al. 1998; Chapman et al 2005; Gupta et al. 2011; Attaallah et al. 2019). As high-risk and emergency surgeries were excluded, perioperative fluid overload and prolonged operation times are the two main potential confounding factors for postoperative respiratory distress in this trial. Our database showed that there were no differences in average operation time or total fluid administered during operation between the two groups (Table 1).

Pulmonary atelectasis occurs in 85–90% of healthy anesthetized adults and is one of the leading causes of postoperative hypoxemic events (Karcz and Papadacos 2013). Besides procedure- and anesthetic-related factors, the composition of inspired gas is another important factor that influences the formation of pulmonary atelectasis during general anesthesia (Sun et al. 2015; Quintero-Cifuentes et al. 2018). Edmark *et al.* found that the mean areas of lung atelectasis immediately after apnea was higher in patients received 100% oxygen compared to those oxygenated with FIO₂ 0.6 (10 cm² vs 0.3 cm², P < 0.001) (Edmark et al. 2003). Another clinical observational study compared the effects of gas composition on the formation of atelectasis and gas exchange during the induction of general anesthesia (Rothen et al. 1995). Compared with FIO₂ 0.3, the degree of atelectasis (1.6 ± 1.6 cm² vs 4.7 ± 4.5 cm²) and intrapulmonary shunt (3.2 ± 2.7% to 9.8 ± 5.7%) were significantly increased in the FIO₂ 1.0 group (Rothen et al. 1995). Therefore, some early studies have suggested that a lower concentration of oxygen mixed with nitrogen may ameliorate the early formation of atelectasis and pulmonary shunt during anesthesia induction (Rothen et al. 1996; Edmark et al. 2011). Our study provides further evidence that high FIO₂ administration during induction may increase the formation of absorption atelectasis and pulmonary shunt, which in turn, may impact the gas exchange and tissue oxygenation at the emergence and recovery phases of anesthesia.

The results of this study indicate that, in generally healthy patients (ASA PS I-III), low fraction oxygen supplementation (FIO₂ 0.6) during induction of ETGA appears to affect tissue oxygen tension at two ways: it increases incidence of desaturation during induction, but seems to have protective effects against respiratory distress after endotracheal tube removal. Since increased BMI could be a confounding factor for the development of desaturation during induction, it would be reasonable to repeat follow-up studies in non-obese patients who receive ETGA. Our study examining lower risk population showed that the overall incidence of hypoxemia after removal of endotracheal tube in the FIO₂ 1.0 group was 6.0%, which is comparable with the incidences reported in general population (9.3–21%) (Ehrenfeld et al. 2010; Sun et al. 2015; Quintero-Cifuentes et al. 2018). Given that more than 200 million major surgical procedures are performed worldwide each year (Weiser et al. 2008), a NNH of 23 to 26 by administrating FIO₂ 1.0 during induction could be clinically significant to result in post-anesthesia hypoxemic events.

It should be noted that there are several limitations in this study. First, the fact that the trial was early terminated may have reduced the statistical power needed to determine the difference between the two treatment groups. Secondly, this was an open-label trial in which our anesthetic team was not blinded to the treatment groups. However, it is not practical to conceal the inspired oxygen fractions during anesthesia. Furthermore, blinding the anesthetist-in-charge to oxygen concentrations may be unethical, as tissue desaturation usually progresses very rapidly after the patient has been paralyzed. Nevertheless, the research team members who recorded the secondary endpoints in the ward were blinded to the treatment. Thirdly, obese patients have been recognized as an independent risk factor for early desaturation during apnea (Bouroche and Bourgain 2015; Goudra et al. 2014), but they were included in this study and might confound the primary endpoint. Our initial study design aimed to investigate the effect of inspired oxygen fractions on the perioperative outcomes in relatively healthy patients (ASA PS I-

III), as they are more likely to achieve beneficial outcomes from lower oxygen fractions than critically ill patients (Nimmagadda et al. 2017). Although we excluded patients with BMI > 35 kg/m² (class II obesity), our study specified that class I obese (BMI 30-34.9 kg/m²) patients may also benefit from high inspired oxygen fractions during induction. Fourthly, this was a pragmatic clinical trial testing the outcomes of two different oxygen fractions used for anesthesia induction in a broad routine clinical practice. Therefore, endotracheal intubation and extubation timing was primarily decided by the anesthetist-in-charge based on the patient's clinical responses and anesthetic depth, which resulted in a number of different time points in regards to development of desaturation. Fifthly, this study failed to specify the optimal oxygen concentration for anesthesia induction, and can only provide the estimated range of 60% to 100%. Future studies may wish to look into more specific oxygen concentrations for optimal anesthesia induction. Sixthly, we did not routinely measure the recovery of neuromuscular function before extubation of endotracheal tube. The residual curarisation effect of neuromuscular blocking agents on spontaneous ventilation could affect the occurrence of respiratory distress after extubation. Seventhly, our study did not show any differences in SSI occurrence, as some studies have suggested that higher fraction oxygen supplementation can reduce risk of SSI's (Belda et al. 2005; Chu et al. 2018). Since high risk procedures and patients with major comorbidities were excluded from this study, the incidence of postoperative SSI was relatively low in our study, thereby limiting our ability to detect difference between the two groups. Lastly, growing evidence suggests that critically ill patients might also benefit from low optimal oxygen therapy (Chu et al. 2018; Damiani et al. 2018). However, our results are not applicable to patients with ASA ≥ IV, advanced systemic diseases, active lung diseases, difficult airway and those who receive emergency and major operations.

As compared with FIO₂ 1.0, this clinical study shows that FIO₂ 0.6 supplementation in with ASA PS I-III surgical patients receiving ETGA significantly increases the risk of hypoxemia during induction. Obese patients (BMI > 30 kg/m²) are associated with higher risk of developing desaturation when FIO₂ 0.6 is administered during the preoxygenation and induction phases of anesthesia. However, administration of 100% FIO₂ during anesthesia induction may increase incidence of hypoxemic events after endotracheal tube removal and the return of spontaneous ventilation in the OR and at PACU. Although our study was underpowered to conclude the statistical difference, the brief period of substantially high oxygen exposure at the beginning of anesthesia could be a potential contributing factor to postoperative acute respiratory distress in patients receiving general anesthesia.

Abbreviations

ASA PC

American Society of Anesthesiologists physical class; BMI:body mass index; CI:confidence interval; DSMB:Data and Safety Monitoring Board; ETGA:endotracheal intubation general anesthesia; ICU:intensive care unit; IRB:institutional review board; FIO₂:inspiratory oxygen fraction; MAC:minimal alveolar concentration; NNH:number needed-to-harm; OR:operating room; PACU:postanesthesia care unit; PEEP:positive end expiratory pressure; SSI:surgical site infection SpO₂:peripheral oxygen saturation

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (approval number EMRP15107N) of E-Da Hospital, Kaohsiung, Taiwan. Ethical approval was granted according to the Taiwan government's requirements. The trial was also registered in September 2018 with clinical trials registration: NCT03665259. Written informed consent was obtained from the patients or their legal surrogates.

Consent for publication

Not applicable

Availability of data and material

The data and materials used in the study are available on request from the corresponding author.

Competing interests

We declare that the authors have no competing interests in conducting this study.

Funding

This work was supported by research grants obtained from the Ministry of Science and Technology, Taiwan (grant number MOST 108-2314-B-650-002 to CFL) and an institutional grant obtained from the E-Da Hospital, Taiwan (grant number EDAHP108055 to YKS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

THS contributed to study conception, enrolment of clinical cases, data collection and processing, writing the article. KYL and YKS performed data analysis and interpretation. SCC contributed to patient enrolment and data collection; TSC and CYL contributed to study design, data analysis, critical appraisal of manuscript. CFL conceived of the study, participated in its design and coordination and obtained research fund. All authors read and approved the final manuscript

Acknowledgements

The authors wish to express our deepest gratitude to Ms. Pei-Jung Tsai (Department of Nursing, E-Da Hospital, Kaohsiung, Taiwan) for assistance in the application of IRB approval and registration with the ClinicalTrial.gov.

References

1. Attaallah AF, Vallejo MC, Elzamzamy OM, Mueller MG, Eller WS. Perioperative risk factors for postoperative respiratory failure. *J Perioper Pract*. 2019;29:49–53.
2. Baillard C, Boubaya M, Statescu E, Collet M, Solis A, Guezennec J, Levy V, Langeron O. Incidence and risk factors of hypoxaemia after preoxygenation at induction of anaesthesia. *Br J Anaesth*. 2019;122:388–94.
3. Ball L, Lumb AB, Pelosi P. Intraoperative fraction of inspired oxygen: bringing back the focus on patient outcome. *Br J Anaesth* 2017;119:16–18. Bouroche G, Bourgain JL. Preoxygenation and general anesthesia: a review. *Minerva anestesiol* 2015;81:910 – 20.
4. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, Rodriguez R, Company R, Sessler DI, Aguilar G, Botello SG, Orti R. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA*. 2005;294:2035–42.
5. Chapman MJ, Myburgh JA, Kluger MT, Runciman WB. Crisis management during anaesthesia: pulmonary oedema. *Qual Saf Health Care*. 2005;14:e8.
6. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schunemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391:1693–705.
7. Damiani E, Donati A, Girardis M. Oxygen in the critically ill: friend or foe? *Curr Opin Anaesthesiol*. 2018;31:129–35.
8. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during induction of general anesthesia. *Anesthesiology*. 2003;98:28–33.
9. Edmark L, Auner U, Enlund M, Ostberg E, Hedenstierna G. Oxygen concentration and characteristics of progressive atelectasis formation during anaesthesia. *Acta Anaesthesiol Scand*. 2011;55:75–81.
10. Ehrenfeld JM, Funk LM, Van Schalkwyk J, Merry AF, Sandberg WS, Gawande A. The incidence of hypoxemia during surgery: evidence from two institutions. *Can J Anaesth*. 2010;57:888–97.
11. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369:428–37.
12. Goudra BG, Singh PM, Penugonda LC, Speck RM, Sinha AC. Significantly reduced hypoxemic events in morbidly obese patients undergoing gastrointestinal endoscopy: Predictors and practice effect. *J Anaesthesiol Clin Pharmacol*. 2014;30:71–7.
13. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 2000;342:161–7.
14. Guldner A, Kiss T, Serpa Neto A, Hemmes SN, Canet J, Spieth PM, Rocco PR, Schultz MJ, Pelosi P, Gama de Abreu M. Intraoperative protective mechanical ventilation for prevention of postoperative

- pulmonary complications: a comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. *Anesthesiology*. 2015;123:692–713.
15. Gupta H, Gupta PK, Fang X, Miller WJ, Cemaj S, Forse RA, Marrow LE. Development and validation of a risk calculator predicting postoperative respiratory failure. *Chest*. 2011;140:1207–15.
 16. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive care*. 2015;5:42.
 17. Horner D, O'Driscoll R. Oxygen therapy for medical patients. *Br Med J*. 2018;363:k4436.
 18. Karcz M, Papadakos PJ. Respiratory complications in the postanesthesia care unit: A review of pathophysiological mechanisms. *Can J Respir Ther*. 2013;49:21–9.
 19. LAS VEGAS Investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries. *Eur J Anaesthesiol*. 2017;34:492–507.
 20. Li XF, Jiang D, Jiang YL, Yu H, Jiang JL, He LL, Yang XY, Yu H. PROtective Ventilation with a low versus high Inspiratory Oxygen fraction (PROVIO) and its effects on postoperative pulmonary complications: protocol for a randomized controlled trial. *Trials*. 2019;20:619.
 21. Martin DS, Grocott MP III. Oxygen therapy in anaesthesia: the yin and yang of O₂. *Br J Anaesth*. 2013;111:867–71.
 22. Martin DS, Grocott MP. Oxygen therapy and anaesthesia: too much of a good thing? *Anaesthesia*. 2015;70:522–7.
 23. Morris RW, Buschman A, Warren DL, Philip JH, Raemer DB. The prevalence of hypoxemia detected by pulse oximetry during recovery from anesthesia. *J Clin Monitor*. 1988;4:16–20.
 24. Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: Physiologic Basis, Benefits, and Potential Risks. *Anesth Analg*. 2017;124:507–17.
 25. Pelosi P, Croci M, Ravagnan I, Tredici S, Pedoto A, Lissoni A, Gattinoni L. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. *Anesth Analg*. 1998;87:654–60.
 26. Peppard PE, Ward NR, Morrell MJ. The impact of obesity on oxygen desaturation during sleep-disordered breathing. *Am J Respir Crit Care Med*. 2009;180:788–93.
 27. Quintero-Cifuentes IF, Pérez-López D, Victoria-Cuellar DF, Satizábal-Padridín N, Billefals-Vallejo ES, Castaño-Ramírez DA. Incidence of early postanesthetic hypoxemia in the postanesthetic care unit and related factors. *Col J Anesthesiol*. 2018;46:309–16.
 28. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995;345:1387–91.
 29. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Atelectasis and pulmonary shunting during induction of general anaesthesia—can they be avoided? *Acta Anaesthesiol Scand*. 1996;40:524–9.

30. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, Vidal Melo MF, Gatke MR, Walsh JL. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. *Br J Anaesth.* 2017;119:140–9.
31. Sun Z, Sessler DI, Dalton JE, Devereaux PJ, Shahinyan A, Naylor AJ, Hutcherson MT, Finnegan PS, Tandon V, Darvish-Kazem S, Chugh S, Alzayer H. and Kurz A. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. *Anesth Analg.* 2015;121:709–15.
32. Suzuki S, Mihara Y, Hikasa Y, Okahara S, Ishihara T, Shintani A, et al. Current Ventilator and Oxygen Management during General Anesthesia: A Multicenter, Cross-sectional Observational Study. *Anesthesiology.* 2018;129:67–76.
33. van Ooij PA, Sterk PJ, van Hulst RA. Oxygen, the lung and the diver: friends and foes? *Eur Respir Rev.* 2016;25:496–505.
34. Weenink RP, de Jonge SW, van Hulst RA, Wingelaar TT, van Ooij PAM, Immink RV, Preckel B, Hollmann MW. Perioperative Hyperoxyphobia: Justified or Not? Benefits and Harms of Hyperoxia during Surgery. *J Clin Med.* 2020;9(3):642.
35. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008;372:139–44.

Figures

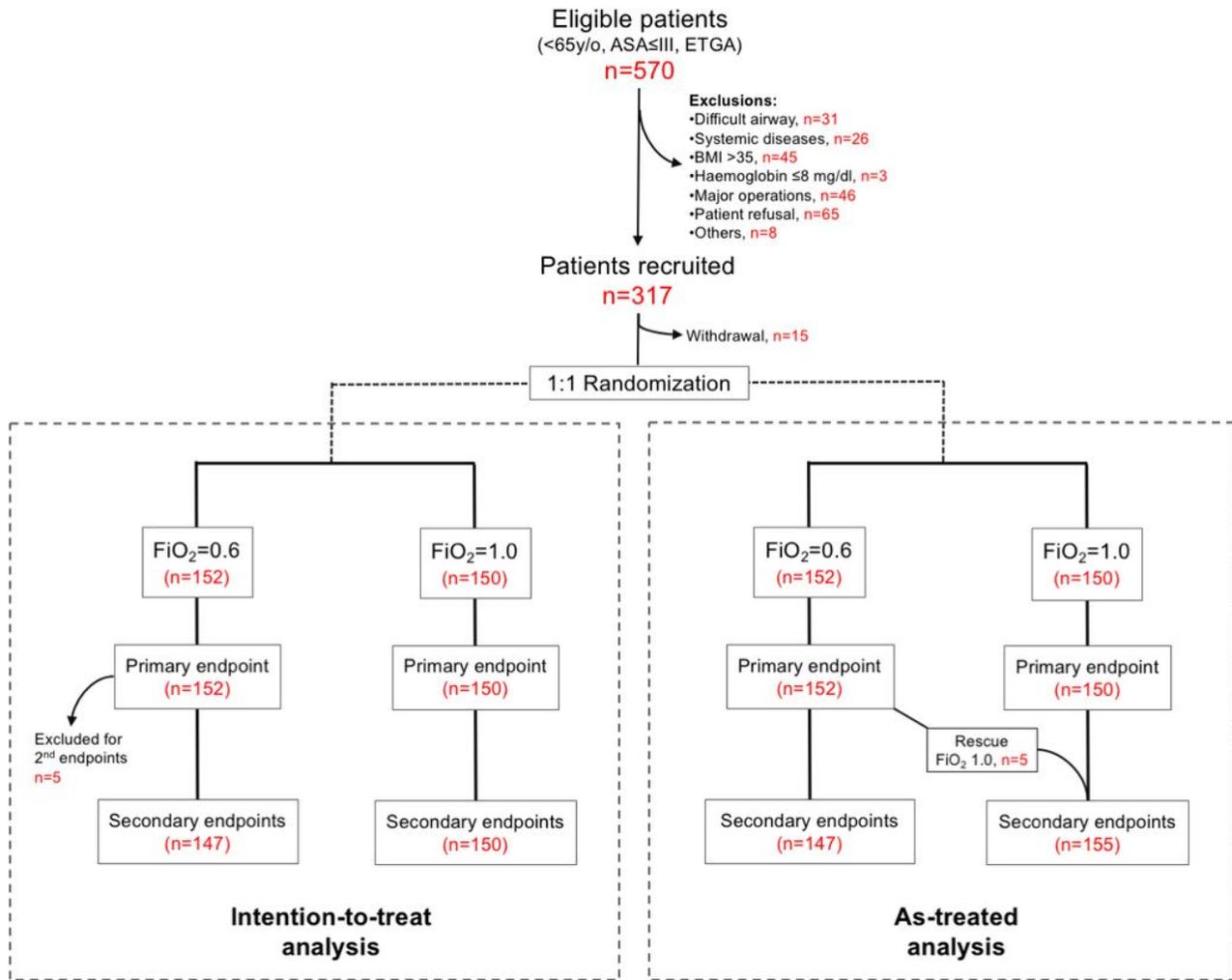


Figure 1

CONSORT study flow diagram. PACU: postanesthesia care unit; OR: operating room

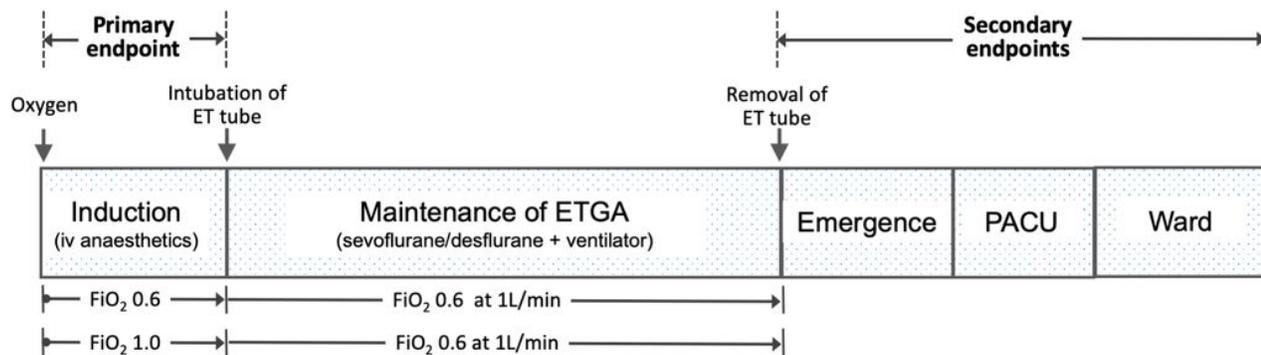


Figure 2

Protocol of anesthesia and postoperative care. *Mixed air (FiO_2 0.6) or pure oxygen (FiO_2 1.0) was administered via a face-mask for preoxygenation. Following the loss of consciousness, mixed air or pure oxygen was delivered by the bag-mask assisted ventilation. ETGA: endotracheal intubation general anesthesia; ET tube: endotracheal tube; PACU: postanesthesia care unit.

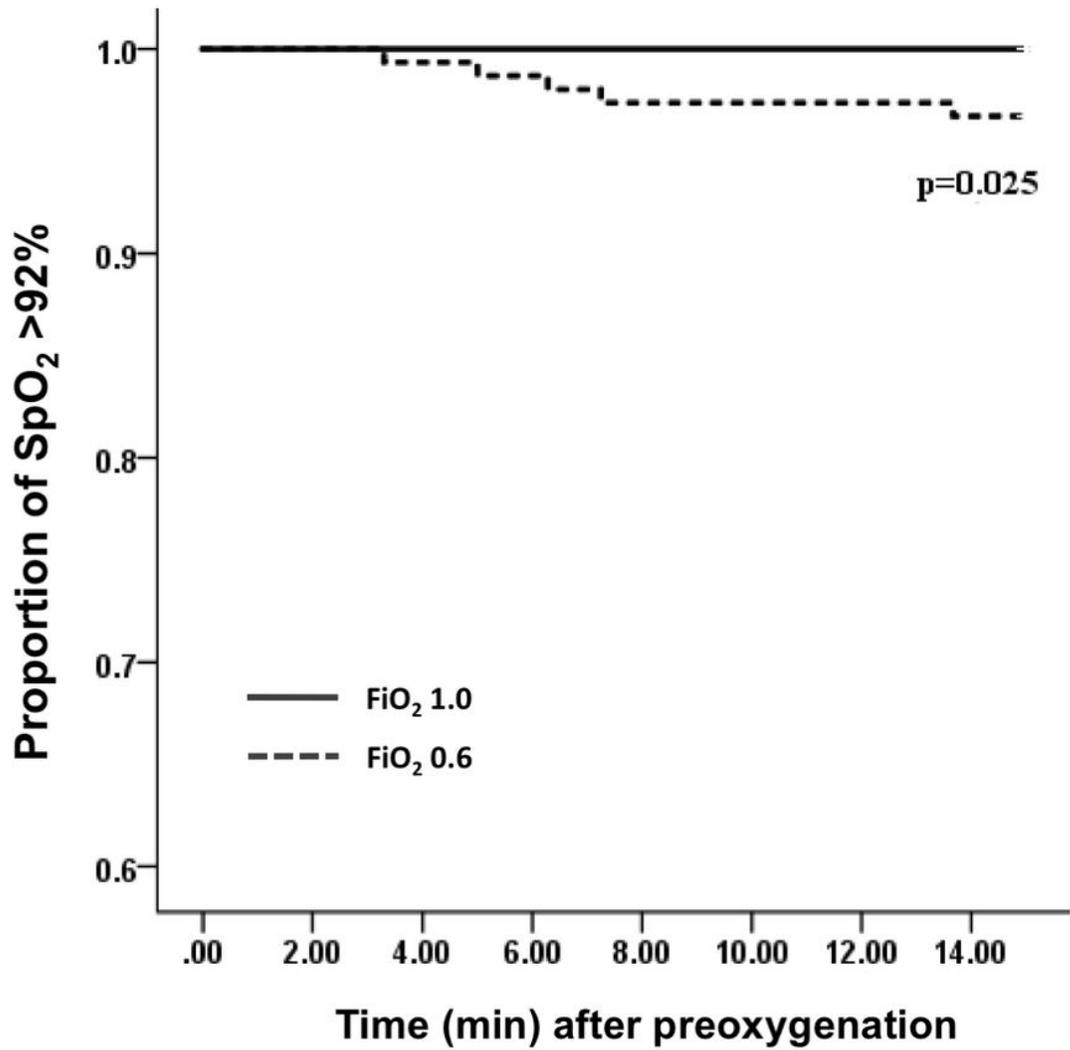


Figure 3

Kaplan-Meier plot of estimating the development of primary endpoint (SpO₂ ≤ 92%) during induction of general anesthesia following administration of pure oxygen (FIO₂ 1.0) or 60% oxygen (FIO₂ 0.6).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)