Original Article

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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

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Objective: High inspiratory oxygen fraction (FiO_2) is associated with increased perioperative pulmonary morbidity and postoperative mortality. However, the use of 100% oxygen is still currently recommended during the anesthesia induction.

Methods: This open-label randomized non-inferiority trial was conducted in 302 surgical patients [American Society of Anesthesiologists (ASA) physical classification ≤ III] who received endotracheal tube intubation general anesthesia (ETGA), and they 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 ($SpO_2 \leq 92\%$) 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 with increased body mass indexes (BMI > 30 kg/m^2) reached the primary endpoint. 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; $p = 0.064$).

Conclusion: 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.

Key words: acute respiratory distress, general anesthesia, induction, oxygen

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Introduction

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 FiO_2 = 1.0) has been recommended throughout the preoxygenation and induction period.[1,2] Elevated oxygen reserve in the lungs and oxygen partial pressure in the blood circulation can significantly delay the development of hypoxemia after apnea.[3,4] Compared with the FiO_2 1.0 treatment, the mean time to reach a peripheral oxygen saturation (SpO_2) below 90% was significantly reduced in patients preoxygenated with FiO_2 0.6 (411 vs. 213 minutes, $p < 0.01$).[4] Furthermore, high intraoperative FiO_2 has also been shown to reduce postoperative surgical site infection (SSI)[5] and postoperative nausea/vomiting (PONV).[6]

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.[7] 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.[8,9] At the cellular levels, hyperoxia increases the production of reactive oxygen species, include superoxide anion, the hydroxyl radical, and hydrogen peroxide, which cause cellular apoptosis and induce inflammatory responses.[10] Therefore, oxygen therapy in clinical settings has been recognized as a two-edged sword and excessive oxygen supplement should be closely monitored for potential toxicity.[11,12] In clinical anesthesia, a low optimal oxygen supplement (as low as FiO_2 0.4) is recommended to maintain $SpO_2 \geq 92\%$ during intraoperative mechanical ventilation for nonobese patients.[13,14]

Currently, there is no consensus on whether lower fractions of inspiratory oxygen during the induction period of anesthesia can attenuate lung injury or other cellular damage by oxygen toxicity, or pure oxygen should be used.[15] The aim of this non-inferiority trial was to determine whether the use of a lower inspiratory oxygen concentration was as effective as pure oxygen during induction of anesthesia in prevention of desaturation before establishment of endotracheal ventilation and 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) ≤ III who were scheduled for surgical procedures that required endotracheal tube intubation general anesthesia (ETGA). The study was approved by the ethics committee and the institutional review board (approval number EMRP15107N). The trial was registered in September 2018 with clinical trials registration: NCT03665259.

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/m^2, 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 (FiO_2 1.0) or lower oxygen fraction (FiO_2 0.6) in a 1:1 ratio. The allocation of treatment 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.

Anesthesia and intervention protocols

Patients were given oxygen (FiO_2 1.0 or FiO_2 0.6) via a face mask at a flow rate of 6 L/min for at least 3 minutes before the administration of a hypnotic agent. 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 by the electroencephalographic devices, and the attending anesthetist decided the optimal duration of assisted mask ventilation. An appropriate 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 ventilator setting included a tidal volume of 8 mL/kg predicted body weight and a positive end expiratory pressure (PEEP) of 2 – 5 cmH_2O. 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 (FiO_2 0.6) at a flow rate of 1 L/min during maintenance of anesthesia. High flow rate of oxygen (FiO_2 0.6, 6 L/min) was used to wash out the anesthetic gases during the emergence phase of anesthesia. Oxygen fraction was switched to 100% whenever arterial desaturation (defined as a SpO_2 of ≤ 92%)[16] 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 postanesthesia care unit (PACU). The standard protocol of anesthesia is shown in Figure 1.

Measurements

The primary endpoint of this study was the development of arterial desaturation (SpO_2 ≤ 92%) during the induction of anesthesia.[16] 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, SSI, unplanned admission to intensive care unit (ICU), severe postoperative pain, prolonged hospital stays and mortality. 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 (SpO_2 < 90%) during induction of anesthesia ranges from 1.4% to 7.4%.[17,18] 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) treatments. We speculated a p-value < 0.05 would indicate non-inferiority of FiO_2 0.6 to induce desaturation during

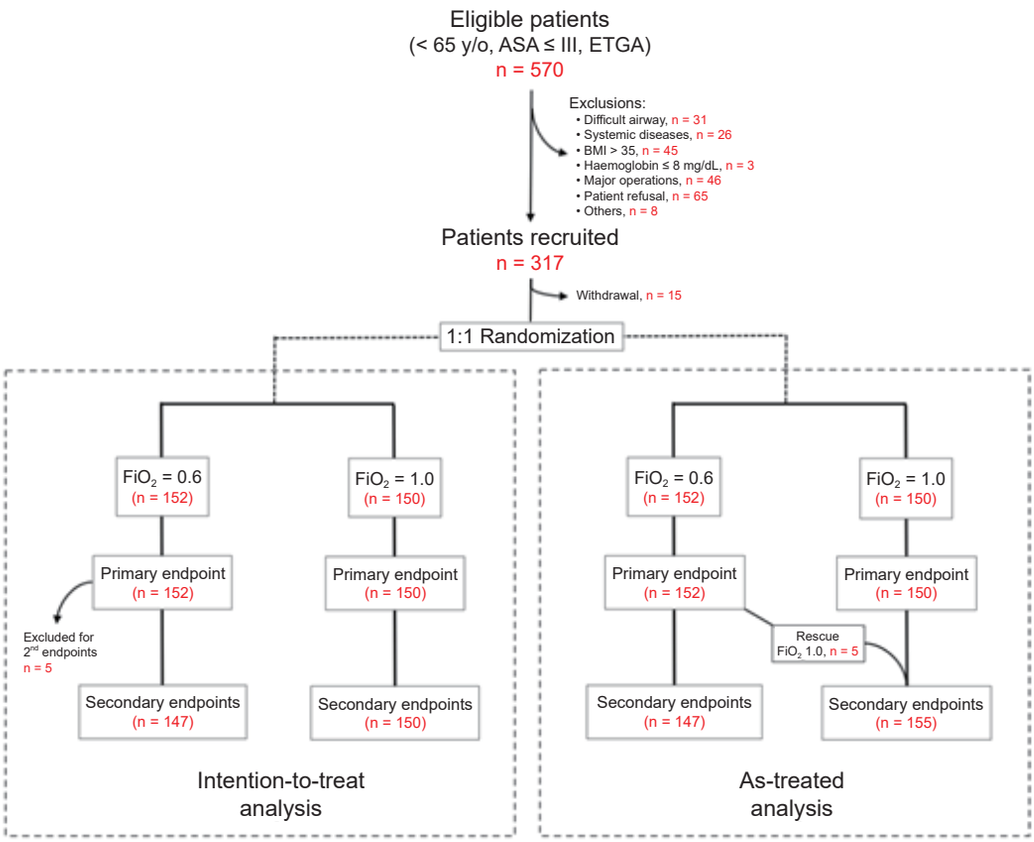

*Fig. 1 Protocol of anesthesia and postoperative care. *Mixed air (FiO_2 0.6) or pure oxygen (FiO_2 1.0) was administered via a face-mask for preoxygenation. Following the loss of consciousness, mixed air or pure oxygen was delivered by the bag-mask assisted ventilation. ASA: American Society of Anesthesiologists; BMI: body mass index; ETGA: endotracheal tube intubation general anesthesia; FiO_2: oxygen partial pressure.*

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 1,000 patients). 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. Binary logistic regression model was used to compare the associations between the presence of primary endpoint and patient characteristics or other perioperative factors. 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 570 eligible patients were included in the study (Fig. 2). This study was prematurely terminated after recruitment of 302 patients due to safety concerns addressed by the institutional Data and Safety Monitoring Board (DSMB). A total of 15 patients decided

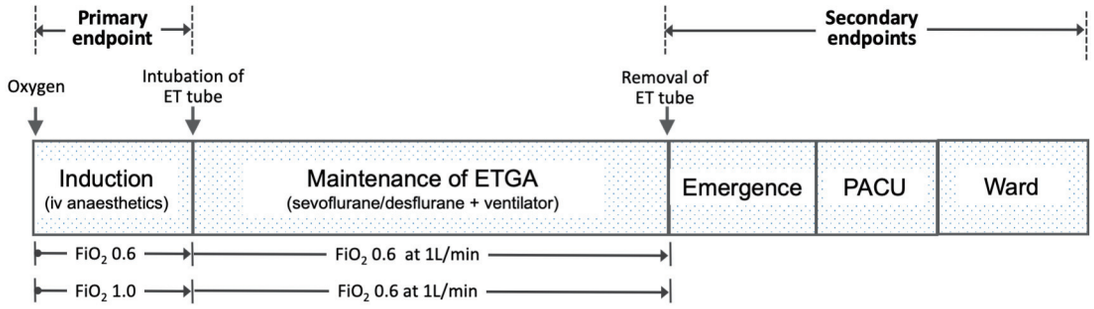

Fig. 2 Study flow chart.

to withdraw from the study before randomization, and there were no cases dropped off after entering the trial (Fig. 2). The patient characteristics are listed in Table 1. There were no significant differences between the two group in the baseline SpO_2 at room air (97.2 ± 2.0% vs. 97.4 ± 2.2% for FiO_2 0.6 vs. FiO_2 1.0, respectively; $p = 0.370$) (Table 1).

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; FiO_2: oxygen partial pressure; 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 hypoxemia ($SpO_2 \leq 92\%$) during the induction phase of anesthesia, and all 5 patients received FiO_2 0.6 for preoxygenation. 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 FiO_2 0.6 and FiO_2 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 SpO_2 in the FiO_2 0.6 group was also significantly lower than that in the FiO_2 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

Table 2. Primary endpoint.

Incidence of desaturation during induction (intention-to-treat analysis)					
	FiO_2 0.6 (N = 152) n (%) or mean (SD)	FiO_2 1.0 (N = 150) n (%) or mean (SD)	97.5% upper confidence border	*p* value	NNH
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†	-

* Unconditional test for non-inferiority using difference of two binomial proportions (one-sided).

† Unpaired t-test.

NNH: number-needed-to harm; FiO_2: oxygen partial pressure; SpO_2: peripheral oxygen saturation.

cancellation of surgery (eTable 1 in the supplement).

Secondary endpoints

Intention-to-treat and as-treated principles were applied to the analysis of the incidence of desaturation after removal of endotracheal tube for the secondary endpoints (Fig. 2). 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 the development of desaturation (Fig. 2). Two patients in the FiO_2 0.6 group developed desaturation after removal of endotracheal tube in the operating room (1.4%, 2/147). The incidences of desaturation in the FiO_2 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 FiO_2 0.6 group while the patients were cared for in the PACU (0% vs. 1.9% for FiO_2 0.6 vs. FiO_2 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 FiO_2 0.6

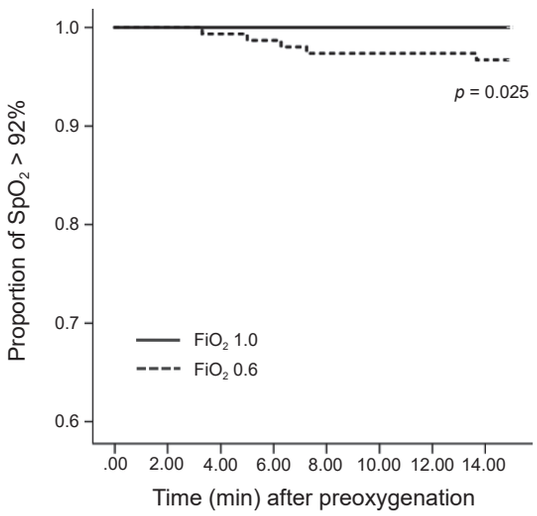

Fig. 3 Kaplan-Meier plot of estimating the development of primary endpoint ($SpO_2 \leq 92\%$) during induction of general anesthesia following administration of pure oxygen (FiO_2 1.0) or 60% oxygen (FiO_2 0.6).

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	-	-	

* Patients who developed primary endpoint were excluded from the FiO_2 0.6 group, and included in the FiO_2 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.

ALI: acute lung injury; CI: confidence interval; FiO_2: oxygen partial pressure; ICU: intensive care unit; NNH: number-needed-to harm; OR: operating room; PACU: postanesthesia care unit.

and FiO_2 1.0 groups, respectively (p = 0.064) with an odd ratio 0.22 (95% CI 0.05 – 1.05) (Table 3). The characteristics of patients who developed desaturation after extubation are summarized in eTable 2 in the supplement. 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 (Table 3).

Regression analysis of risk factors for desaturation

A logistic regression model was used to determine the potential risk factors associated with the development of desaturation during the induction phase of anesthesia (Table 4). Amongst the commonly reported factors for developing hypoxemia due to prolonged apnea-hypopnea period,[1,3] the analysis showed that increased body weight was the only characteristic parameter that was positively associated with the development of desaturation during induction (OR 1.43, 95% CI 1.09 – 1.87). Indeed, four out of the five patients who reached primary endpoint had BMI's greater than 30 kg/m^2 (eTable 1 in the supplement).

Discussion

Routine pure oxygen supplementation for non-critical or generally healthy patients during induction is still a debated topic.[15] Patients with low oxygen reserve due to reduced functional residual capacity and increased closing volume, or who were pre-defined as intolerable to prolonged apnea were excluded from this study due to safety concerns.[19] There is currently no clinical evidence demonstrating the advantages of routine use of pure oxygen during induction of anesthesia, while intraoperative oxygen overexposure defined as hyperoxemia (SpO_2 > 98%) and substantial oxygen exposure (FiO_2 > 0.5) can potentially be harmful and increase postoperative complications.[20] Two recent large-scale clinical trials also found routine oxygen supplementation for patients with acute myocardial infarction or acute ischemic stroke with no clinical sign of hypoxia did not provide any clinically evident benefits in prognosis.[21,22] Therefore, this non-inferiority trial investigated the grounds for the current common practice of routine pure oxygen supplementation 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 FiO_2 0.6 and the null hypothesis of non-inferiority could not be rejected. Furthermore, time-to-event analysis and the lowest mean SpO_2 confirmed the increased hypoxemic events during the induction period of anesthesia in the FiO_2 0.6 study group. The incidence

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

	Coefficient value	p value	OR	95% CI	
				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: confidence interval; LL: lower limit; OR: operating room; SpO_2: peripheral oxygen saturation; UL: upper limit.

[*] Binary logistic regression model was computed from the FiO_2 0.6 group (n = 152).

of hypoxemia during induction phase by giving 60% inspired oxygen was 3.9% in our study, which is considerably higher than the previous report.[17] Supplementation of 60% FiO_2 during induction phase may provide an estimated number needed-to-harm (NNH) of 31 in developing desaturation that requires urgent medical intervention. The lowest SpO_2 in the FiO_2 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. Lower inspiratory oxygen fraction (i.e., FiO_2 0.6) during preoxygenation and assisted ventilation before endotracheal intubation increased risk of desaturation in patients with ASA PS I – III. Several important potential risk factors were included for analysis, including patient's age, gender, ASA class, BMI, STOP-Bang score for obstructive sleep apnea and status of smoking history. The analysis indicated that increased BMI is the only patient characteristic factor associated with the development of desaturation during induction. In fact, four out of the five patients who developed the primary endpoint had BMI's greater than 30 kg/m^2. Obese patients have increased oxygen demand and CO_2 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.[23,24]

Since the patients who developed primary endpoint were switched to 100% oxygen therapy during induction, these patients were included in the FiO_2 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 FiO_2 0.6 group, two case developed a $SpO_2 \leq 92\%$ in the OR, but none developed desaturation at PACU. However, there were 9 cases of desaturation in the FiO_2 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 FiO_2 0.6 vs. FiO_2 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 FiO_2 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 FiO_2 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 hours, emergency operation, high-risk surgery and perioperative fluid overload.[25-28] Our database showed that there were no differences in average operation time or total fluid administered during operation between the two groups (Table 1).

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.[29,30] 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 FiO_2 0.6 (10 cm^2 vs. 0.3 cm^2, $p < 0.001$).[4] Compared with FiO_2 0.3, the degree of atelectasis (1.6 ± 1.6 cm^2 vs. 4.7 ± 4.5 cm^2) and intrapulmonary shunt (3.2 ± 2.7% to 9.8 ± 5.7%) were significantly increased in the FiO_2 1.0 group.[30] 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.[31,32] Our study provides further evidence that pure oxygen administration during induction may aid in 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 low fraction oxygen supplementation (FiO_2 0.6) during induction of ETGA increases incidence of desaturation during induction, but seems to have protective effects against respiratory distress after endotracheal tube removal. Our study examining lower risk population showed that the overall incidence of hypoxemia after removal of endotracheal tube in the FiO_2 1.0 group was 6.0%, which is comparable with the incidences reported in general population (9.3 – 21%).[17,33,34] Given that more than 200 million major surgical procedures are performed worldwide each year,[35] a NNH of 23 to 26 by administrating FiO_2 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, this was an open-label trial in which our anesthesia team was not blinded to the treatment groups, as it is not practical to conceal the inspired oxygen fractions during anesthesia. Nevertheless, the research team members who recorded the secondary endpoints in the ward were blinded to the treatment. Secondly, obese patients have been recognized as an independent risk factor for early desaturation during apnea,[1,36] but they were included in this study and might confound the primary endpoint. Although we excluded patients with BMI > 35 kg/m^2 (class II obesity), our study specifies that class I obese (BMI 30 – 34.9 kg/m^2 patients may also benefit from high inspired oxygen fraction during induction. Thirdly, 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, different timing of endotracheal intubation and extubation might result in different time points of developing desaturation in this study. Fourthly, this study failed to specify the optimal oxygen concentration for anesthesia induction, and can only provide the estimated range of 60% to 100%, such as 80%. FiO_2 0.8 can serve as an optimal oxygen fraction balanced between hyperoxic toxicity and hypoxemia due to unmet oxygen demand intraoperatively. Furthermore, the WHO committee also recommends use of an intraoperative FiO_2 of 0.8 in all intubated patients.[6] Fifthly, 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. Sixthly, our study did not show any difference in SSI occurrence, as some studies have suggested that higher fraction oxygen supplementation can reduce risk of SSI's.[5,37] Since high risk procedures and patients with major comorbidities were excluded, the incidence of postoperative SSI was relatively low in our study, thereby attenuating the ability to detect difference between the two groups. Lastly, cumulating evidence suggests that critically ill patients might also benefit from low optimal oxygen therapy.[38,39] However, our results are not applicable to patients with ASA ≥ IV or advanced systemic diseases, active lung diseases, difficult airway and those who receive emergency and major operations.

This randomized control trial investigated the differences between two oxygen supplementation fractions on non-critically ill patients (ASA PS ≤ III) receiving ETGA. Our study reports the supplementation of FiO_2 0.6 in surgical patients with ASA PS I – III, who receive ETGA, significantly increases the risk of hypoxemia during induction. Obese patients (BMI > 30 kg/m^2) are particularly at higher risk of developing desaturation when FiO_2 0.6 is

administered for preoxygenation and induction phase of anesthesia. However, administration of pure oxygen during anesthesia induction increases the incidence of hypoxemic events after removal of endotracheal tube and the return of spontaneous ventilation in the OR and at PACU. Although our study is underpowered to conclude the statistical difference, the brief period of substantially high oxygen exposure at the beginning of anesthesia could be an important contributing factor to postoperative acute respiratory distress in patients receiving general anesthesia.

Supplementary Material

eTable 1: Characteristic data of patients present with primary endpoint.
eTable 2: Patient characteristics and perioperative factors present with hypoxaemia after extubation.

Author Contributions

Study Design, Tzu-Huan Su, Kuang-Yao Li, Yi-Kai Su and Chen-Fuh Lam; Data Collection, Tzu-Huan Su, Kuang-Yao Li and Shu-Ching Chang; Statistical Analysis, Tzu-Shan Chen, Chung-Yi Li and Chen-Fuh Lam; Data Interpretation, Tzu-Huan Su, Kuang-Yao Li, Yi-Kai Su and Chen-Fuh Lam; Manuscript Preparation, Tzu-Huan Su and Chen-Fuh Lam; Literature Search, Tzu-Huan Su and Kuang-Yao Li; Funding Acquisition, Yi-Kai Su and Chen-Fuh Lam. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was approved by the institutional review board of the E-Da Hospital, Kaohsiung, Taiwan (approval number EMRP15107N). The trial was registered in March 2021 with Clinicaltrials.gov registration: NCT03665259. All procedures in this study were conducted in accordance with the institutional ethical standards and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Statement

Informed written consent was obtained from all the participants before the commencement of the study.

Data Availability Statement

Data and associated documentation will be available to users from the corresponding authors on reasonable request. All requests for data will go through a data request committee which will include the corresponding authors, who will review any requests and will oversee data sharing procedures. If the request is deemed reasonable by the committee, we will proceed with a data sharing agreement and secure data sharing plan, using a secure file transfer system to ensure data security and compliance.

Conflicts of Interest

The authors declare no conflict of interest.

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