APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
IMPACT FACTOR 2.595

Peer Review File

Article Information: https://dx.doi.org/10.21037/apm-22-647

Round 1

Reviewer A

In a retrospective analysis, the authors aimed to compare the preoxygenation efficacy between FiO2 80% and 100% using a single-center medical database. This article is well-written and the issue is of clinical importance. However, there are several flaws in methodology.

1. Some important factors related to patients' baseline pulmonary and oxygenation functions are not included, including current smoking history, COPD history, and SpO2 in room air. Please add these data and reanalyze the results.

Reply 1.) Thank you for your review and comments. We reviewed patients' medical record, and we inserted those information you mentioned such as smoking status, history of COPD and asthma, basal SpO_2, the site of surgery (abdominal or not), and the emergency of surgery, into the demographic data (Table 1). And we inserted these at the method in the manuscript.

Changes in the text 1.) demographic data included age, sex, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, smoking status, concomitant pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma, Cormack–Lehane grade (14) during intubation (grade 1, most of the glottis is visible; grade 2, only the posterior extremity of the glottis is visible; grade 3, no part of the glottis can be seen, but the epiglottis is visible; grade 4, neither the glottis or epiglottis can be seen), and type, site and emergency status of the operation. (Page 6, Line 19 ~ Page 7, Line 3); and Table 1.

2. There are some imbalances in baseline patient characteristics, including ASA class and Cormack-Lehane grade. Statistical analyses (e.g., regression or matching) are needed to adjust for these potential confounding factors.

Reply 2.) We performed propensity score match to reduce selection bias and to control for potential confounding factors. We revised our method, results and discussion about this.

Changes in the text 2.) "Propensity score matching (PSM) was performed thorough a logistic regression analysis, to reduce selection bias, to controlling for potential confounding factors including age, sex, BMI, ASA physical status, smoking status, COPD, asthma, basal SpO_2, abdominal surgery, elective surgery, and the Cormack–Lehane grade. After PSM, continuous variables were analyzed using Wilcoxon signed–rank test and categorical variables were analyzed using the McNemar test or McNemar–Bowker test, as appropriate." (Page 9, Line 14-20); Demographic data before and after PSM are presented in Table 1. Before PSM, there were no significant differences in age, sex, weight, height, BMI, the proportion of smokers, COPD, asthma, abdominal surgery and emergency surgery, or basal SpO_2 between the two groups. However, there was a significant difference in ASA physical status ($p < 0.05$). After PSM, none of the demographic characteristics differed between the two groups. (Page 11, Line 9-13); After PSM, the preoxygenation time also did not differ significantly between the two groups (median difference = -1, 95% CI: -13 to 10, p=0.605). There were also no differences in the overall rate of inadequate preoxygenation (12% vs. 6%, p =0.143) or the proportion of patients for whom > 3 min was required for adequate preoxygenation (26% vs. 28%, p=0.118). (Page 11, Line 20-23); Table 1 and Table 2.

3. The authors sought to evaluate the oxygenation and ventilation results based on a retrospective databank. Typically, a prospective study is better to accurately measure

the results. The authors are suggested to better describe the recording interval and data error processing of the used database.

Reply 3.) We agree with your comments. We are conducting prospective study to find out the effectiveness of preoxygention, including efficacy (wash-in) and efficiency (DAWD).

And we inserted sentence and supplement file to describe about the VitalDB Record program.

Changes in the text 3.) Third, we could not measure DAWD due to the retrospective nature of the study; DAWD measurements are not performed routinely in actual clinical practice. However, the efficiency of preoxygenation is also important when evaluating the effectiveness of preoxygenation. We are currently conducting a prospective study to evaluate the effectiveness of preoxygenation. (Page 10, Line 10-14); All data collected using multiple monitors are automatically recorded using the Vital Recorder tool; time-synchronized data are shown (20) in Supplement 1. (Page 6, Line 15-16)

4. The objective and conclusion of this study should be stated more clearly. Did the authors aim to compare the preoxygenation efficacy between FiO2 80% and 100%? If yes, the conclusion should be revised accordingly.

Reply 4.) We revised our conclusion according our outcome.

Changes in the text 3.) No difference in preoxygenation time was found between the 80% and 100% groups. For some patients, breathing for 3 min is not sufficient for adequate preoxygenation. EtO2 monitoring aids evaluation of whether preoxygenation was adequate. (Page 3, Line 3-5); In conclusion, we found no difference in preoxygenation time between 100% and 80% oxygen, using EtO_2 as an

end-point. Currently, preoxygenation for 3 min is considered the standard, but many patients required more than 3 min for adequate preoxygenation. Therefore, it is helpful to use EtO_2 to confirm adequate preoxygenation. EtO_2 monitoring would complement evaluations of preoxygenation adequacy. (Page 16, Line 24 ~ Page 17, Line 1-4)

Reviewer B

There is potential in this topic, and the authors correctly emphasise the value of end tidal oxygen concentration as a measure of adequate preoxygenation, however, appropriate caution needs to be applied with a lower FiO2 group during preoxygenation, and its impact on patient safety. With an FiO2 of 80%, 'successful' preoxygenation, which was not achieved in 11% of cases, still equates to an end tidal oxygen concentration of 70%, and this has been shown in the literature to significantly decrease the time to desaturation, compared to an FiO2 of 100%.

Reply) Thank you for your review and comments. Many studies on optimal oxygen concentration during preoxygenation have been reported, but no large study has been conducted yet. We described why we chose 80% oxygen compared with 100% oxygen.

Changes in the text) To prevent atelectasis, the use of lower FiO_2 (8-10) or techniques (11) such as the alveolar recruitment maneuver (ARM) and positive end-expiratory pressure (PEEP) have been suggested (6,12). Using 80% oxygen may provide many of the benefits of 100% oxygen (13), while atelectasis is not significantly different with ≤ 80% oxygen (13,14). (Page 4, Line 15-19)

- Concluding that desaturation events are rare in actual clinical practice is also an overstep in this small retrospective study.

Reply) We deleted that sentence.

- Of note, a difficult airway also occurred more frequently in the high FiO2 group.

Reply) That might be due to selection bias. We described about this at limitation in discussion.

Changes in the text) First, it was retrospective, so selection bias is inevitable. The period of data collection also differed. To reduce selection bias, we performed PSM, but many patients were excluded because we analyzed only those with objective data. (Page 15, Line 3-6)

- Future consideration could be given to a prospective study, or a higher FiO2 group selection of 100% vs 90% during preoxygenation.

Reply) We are conducting prospective study to find out the effectiveness of preoxygention, including efficacy (wash-in) and efficiency (DAWD) between 80% and 100% oxygen. It is difficult to determine which which oxygen concentration would be selected as a threshold. As you mentioned, further study comparing 90% and 100% oxygen seems to be needed.

Reviewer C

This article compares the use of 80% and 100% oxygen to preoxygenate general surgical patients, looking to see if there is a difference in time to maximal preoxygenation or in desaturation rates. They touch upon the reasons for the use of 80% oxygen with minimising absorption atelectasis but I feel this could be explored more. The study rightly adds weight to a growing argument that preoxygenation should not be a fixed 3 minutes, but individualised based on each patients ETO2, given the variation in time to maximal preoxygenation.

However the premise for this study, that 80% oxygen could be as safe as using 100% oxygen at induction is unproven. Their argument that absorption atelectasis is caused by high inspired oxygen must be weighed against the higher risk of desaturation. It would be helpful if they could explore the risks of absorption atelectasis further.

Finally from a physiological basis, I would not expect any difference between preoxygenation at different FIO2s because this is exponential wash-in physiology.3 If they had found a difference in preoxygenation time, it feel it would have most likely been due to difference in their sample population or preoxygenation technique.

The overall article reads well, however there are several grammatical errors that disrupt the flow and the article could be written more concisely.

Please see below for more in depth analysis

Reply) Thank you for your review and comments. We revised our manuscript according to your comments.

Abstract

• Some grammatical errors exist e.g. line 22 *preventing

Reply) We revised that sentence as following.

Changes in the text) Preoxygenation is a simple but very important procedure for preventing arterial desaturation. (Page 2, Line 3)

• Would refute the statement about few studies using end tidal oxygen as a measure of preoxygentation – this is the gold standard and is commonly used in modern studies.

Reply) We deleted that sentence.

• Reason for using 80% oxygen isn't clarified in abstract

Reply) We inserted sentences at introduction in abstract as following.

Changes in the text) A higher FiO_2 increases atelectasis and 80% oxygen results in significantly less atelectasis than 100% oxygen. We investigated whether there was a difference in the duration of adequate preoxygenation when using 100% and 80% oxygen. The proportion of patients for whom > 3 min was required to achieve adequate preoxygenation was also investigated. (Page 2, Line 4-7)

• Only a small number of database patients had sufficient data, which could bias the selected sample. Why did these patients have inadequate data?

Reply) We analyzed only sufficient recorded data. Due to technical errors, the loss of data could be possible. And, another reason would be that many anesthesiologists did not perform preoxygenation for sufficient time (ex, 3min) or without leakage.

Changes in the text) Of the patients who underwent general surgery under general anesthesia, only those with satisfactory EtO_2 and capnography data were included. The patients were classified into 100% and 80% groups according to the oxygen concentration used during preoxygenation. From the start to the end of preoxygenation, if a continuous exponential increase in EtO_2 was identified, and a

capnography waveform of the patient's respiration was recorded simultaneously (Figure 1), the data were considered sufficient for analysis. Patients whose data were incomplete were excluded, including those with no or irregular EtO_2 and capnography data; an absent or irregular EtO_2 graph and $EtCO_2$ waveform before anesthesia induction (Supplement 2), or no FiO_2 or EtO_2 data due to technical errors (Supplement 3). (Page 6, Line 9-17); Second, there may also have been technical problems in performing preoxygenation, although they might have been insignificant because we selected only patients with sufficient data for analysis; also, our preoxygenation protocol using tight-fitting face masks without leakage, appeared to be well implemented, and we checked for the presence of the capnography waveform, and for inflation and deflation of the reservoir bag, according to the patient's breathing. (Page 15, Line 5-10)

• One of their conclusions is a statement of fact, but is not demonstrated by their study - Line 41-42 monitoring can improve the quality of preoxygenation, ensuring patient safety.

• Line 41 'It is helpful to use EtO2 to confirm maximal preoxygenation' should be justified by the large range in required duration needed

Reply) We deleted that sentence and revised conclusion as following.

Changes in the text) No difference in preoxygenation time was found between the 80% and 100% groups. For some patients, breathing for 3 min is not sufficient for adequate preoxygenation. EtO2 monitoring aids evaluation of whether preoxygenation was adequate. (Page 3, Line 3-5)

Introduction

• Line 17-18: A higher FIO2 or at least higher ETO2 will provide a longer apnoea duration1

Reply) We revised that sentence as you recommended.

Changes in the text) A higher FiO_2 or EtO_2 will lead to longer duration of apnea without desaturation (DAWD); (Page 4, Line 11)

• Lines 23-25: The authors note that no studies have investigated the time difference between 100% & 80% oxygen. Considering the exponential washout physiology behind this process, one would have hypothesised no difference.2 The use of different oxygen concentrations on time to preoxygenation has been studied before. 3

Reply) Based on constructed database, we wondered if there was a difference in efficacy of preoxygenation when using 80% and 100% oxygen. As you mentioned, it would be the same, naturally by the physiological law of wash-in. However, we wanted to compare actual time between two groups and wondered how it would turn out in actual clinical practice, so we started investigating on it. We revised that sentence as you and reviewer 3 mentioned.

Changes in the text) however, few studies have measured the time required for EtO_2 to reach 70% when using 80% oxygen. (Page 4, Line 17-18); However, there was no difference in the adequate preoxygenation rate between 80% and 100% oxygen, which may be a result of the physiological law of exponential wash-in. (Page 14, Line 12-14)

• Line 15-16 Maximal preoxygenation is considered to have been achieved when the difference between the FiO2 and EtO2 fractions approaches 10%. Considering

physiology this is broadly true (5% remaining CO2 and 5% nitrogen), but other studies have found patients achieving >90% and nearly ETO2 of 95%. Therefore stopping proxygenation when patients reach a 10% difference may not be maximally preoxygenating all participants. In addition the references attached to this line do not seem to verity the 10% margin.

Reply) We agreed with your comment. Therefore, we corrected “maximal preoxygenation” to “adequate preoxygenation” in all manuscript.

Changes in the text) Given that end-tidal oxygen (EtO_2) reflects the alveolar fraction of oxygen, EtO_2 can be used as an index of adequate preoxygenation, and as a means of monitoring leakage. Adequate preoxygenation is considered to have been achieved when the difference between the FiO_2 and EtO_2 fractions approaches 10% (2-5). (Page 4, Line 6-10)

• Line 23-25 – the time to ETO2 90% has been extensively studied, not in several studies.

Reply) We revised that sentence as following, and cited more references.

Changes in the text) Many studies have reported on the time required for EtO_2 to reach 90% when using 100% oxygen for preoxygenation (3,8-10); (Page 4, Line 16-17)

• Appropriate secondary outcomes of desaturation incidence and inadequate preoxygenation

Reply) We revised those sentences as following.

Changes in the text) DAWD is naturally shortened when 80% oxygen is used; thus, the occurrence of desaturation was also investigated. We also wanted to determine the proportion of patients for whom > 3 min was required to achieve adequate preoxygenation. (Page 4, Line 20-22)

• It would be helpful to include any studies that show clinical effects of worsening absorption atelectasis e.g. post op hypoxaemia

Reply) We inserted sentence and references as following.

Changes in the text) this can reduce the functional residual capacity (6), impair gas exchange, and cause respiratory dysfunction and lung injury (7). (Page 4, Line 14-15)

Methodology

Data selection

• Clearly defined groups

Reply) We inserted sentence as following at Data selection in methods.

Changes in the text) The patients were classified into 100% and 80% groups according to the oxygen concentration used during preoxygenation. (Page 6, Line 10-12)

• It is unclear why this date range was selected.

Reply) We were asked to show sample size calculation during IRB approval despite of retrospective study. Total 326 patients was estimated, and total 330 patients' data were collected during the above period.

Changes in the text) Bhatia *et al*. reported that the time taken for EtO_2 to reach 90% when using 100% oxygen in young adults was 157 ± 32 s (8). Assuming that a 5% difference in preoxygenation time is clinically significant, 326 patients were estimated to be needed to achieve 80% power with a two-sided significance level of 0.05 using the two-sample *t*-test. (Page 6, Line 5-9)

• General surgical population so lower risk of difficult airways and therefore desaturation

Reply) We revised our manuscript as following.

Changes in the text) Although there was only one desaturation case in our series, our sample was small, and difficult mask ventilation or intubation cannot be predicted. (Page 14, Line 15-16)

• Were these elective or emergency operations

Reply) We reviewed our data and described the emergency of surgery at demographic data.

Changes in the text) demographic data included age, sex, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, smoking status, concomitant pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma, Cormack–Lehane grade (14) during intubation (grade 1, most of the glottis is visible; grade 2, only the posterior extremity of the glottis is

visible; grade 3, no part of the glottis can be seen, but the epiglottis is visible; grade 4, neither the glottis or epiglottis can be seen), and type, site and emergency status of the operation.(Page 5, Line 19-23 ~ Page 7, Line 3)

• No clear study size defined or power calculation

Reply) We inserted sentences about that as following.

Changes in the text) Bhatia *et al*. reported that the time taken for EtO_2 to reach 90% when using 100% oxygen in young adults was 157 ± 32 s (8). Assuming that a 5% difference in preoxygenation time is clinically significant, 326 patients were estimated to be needed to achieve 80% power with a two-sided significance level of 0.05 using the two-sample *t*-test. (Page 6, Line 5-9)

Preoxygentaion

• First paragraph has some grammatical errors – e.g line 22-23

Reply) We sent our manuscript to the English editing service, and revised our manuscript after the English editing service.

Changes in the text) All preoxygenation and anesthesia methods were performed in accordance with the protocols of our institution. We routinely used 100% oxygen during preoxygenation in the supine position. A head-up or ramped position could be used at the anesthesiologist's discretion. A tight-fitting face mask without leakage, and the use of 100% oxygen, is essential during preoxygenation, but many anesthesiologists in our institution do not perform preoxygenation properly; sometimes there is a gap between the patients' face and the face mask, resulting in leakage. This leakage in turn results in the entrainment of > 20% room air, thus

lowering the FiO_2 and EtO_2 (15,16). After a journal club session on airway management aimed at reducing atelectasis, we performed preoxygenation properly by using a tight-fitting face mask without leakage, using 80% or 100% oxygen at the anesthesiologist's discretion, with a fresh gas flow rate of 6–10 L/min. We also used EtO_2 as an endpoint, rather than the preoxygenation time. This enabled us to collect data using different oxygen concentrations during preoxygenation. (Page 6, Line 20-23 ~ Page 7, Line 1-8)

• As this is a sequential trial rather than a randomised trial, practice may have changed at the institution e.g. knowing monitoring was occurring could affect preoxygenation technique and affected validity of result. Did practitioners know about the study?

Reply) No. We discussed about how we could use our database, and we thought the efficacy of preoxygenation could be analyzed by objectively recorded database, so we started to collect data about this.

• Line 20: It would be helpful to have the conference attended referenced, with a link to the evidence which triggered a change in practice at this institution. The suggestions in line 22-26 do not clearly make sense. If preoxygenation is often performed inadequately in real world practice this suggests all the more reason to use 100% oxygen, than 80% oxygen alongside poor preoxygenation.

Reply) We have weekly journal meeting, and we called that as "journal conference", not real the conference. It may be more appropriated calling as "journal club". We revised our manuscript as following.

Changes in the text) A tight-fitting face mask without leakage, and the use of 100% oxygen, is essential during preoxygenation, but many anesthesiologists in our institution do not perform preoxygenation properly; sometimes there is a gap between the patients' face and the face mask, resulting in leakage. This leakage in turn results in the entrainment of > 20% room air, thus lowering the FiO_2 and EtO_2 (15,16). After a journal club session on airway management aimed at reducing atelectasis, we performed preoxygenation properly by using a tight-fitting face mask without leakage, using 80% or 100% oxygen at the anesthesiologist's discretion, with a fresh gas flow rate of 6–10 L/min. We also used EtO_2 as an endpoint, rather than the preoxygenation time. (Page 6, Line 22-23 ~ Page 7, Line 1-7)

• Line 24-25: don't clearly reflect the papers referenced which show a varied ETO2 depending on the degree of mask leak

Reply) We revised that sentence as following.

Changes in the text) This leakage in turn results in the entrainment of > 20% room air, thus lowering the FiO_2 and EtO_2 (15,16). (Page 7, Line 3-4)

• Clear description of methods.

Reply) We revised our manuscript as you and other reviewers recommended.

• Line 38 – I question whether two intubation attempts can be detected via the use of capnography alone. Two attempts could occur without ventilation and therefore capnography in the middle

Reply) We agree with your comment. We deleted that sentence, and revised sentence in result as following.

Changes in the text) Her Cormack–Lehane grade was 4 and tracheal intubation was attempted at least twice, judging from the capnography waveform (supplement 3). (Page 11, Line 6-7)

• It would be helpful to know the exact protocol for preoxygenation in this institution: alongside FIO2, do they specify a target ETO2, or a required duration, do clinicians strictly follow this protocol. After what period of time do clinicians continue with induction if the threshold ETO2 is not being met? Are patients lying flat for preoxygenation, ramped or is it at clinician preference? How are they being asked to breathe? Were patients face mask ventilated after induction of anaesthesia?

Reply) We revised first paragraph as following.

Changes in the text) All preoxygenation and anesthesia methods were performed in accordance with the protocols of our institution. We routinely used 100% oxygen during preoxygenation in the supine position. A head-up or ramped position could be used at the anesthesiologist's discretion. A tight-fitting face mask without leakage, and the use of 100% oxygen, is essential during preoxygenation, but many anesthesiologists in our institution do not perform preoxygenation properly; sometimes there is a gap between the patients' face and the face mask, resulting in leakage. This leakage in turn results in the entrainment of > 20% room air, thus lowering the FiO_2 and EtO_2 (15,16). After a journal club session on airway management aimed at reducing atelectasis, we performed preoxygenation properly by using a tight-fitting face mask without leakage, using 80% or 100% oxygen at the anesthesiologist's discretion, with a fresh gas flow rate of 6–10 L/min. We also used

EtO_2 as an endpoint, rather than the preoxygenation time. This enabled us to collect data using different oxygen concentrations during preoxygenation. (Page 6, Line 20-23 ~ Page 7, Line 8)

Results

• Large group of patients not analysed due to no or irregular capnography, leaving remaining small group at risk of bias. Patients with a poor mask seal and therefore a poor capnography trace may be more likely to be in this group.

Reply) Yes. We agree your comments. Due to a poor mask seal, capnography waveform was not recorded, and many patients were excluded. We inserted sentence at the limitation part in discussion about this.

Changes in the text) To reduce selection bias, we performed PSM, but many patients were excluded because we analyzed only those with objective data. (Page 15, Line 3-4)

• Lines 39-46: it is helpful to know that time to intubation did not vary in the groups as this could affect rates of desaturation, but discussing the use of Levin tubes etc does not seem relevant to their outcomes. Of note 'Levin tube' is not a common term in the UK – nasogastric tube is more commonplace.

Reply) We deleted about the part of Levin tube at results and Table 2.

• The authors did not find a difference in desaturation rates. I suspect that their study was not powered to find a difference.

Reply) We revised our manuscript as following.

Changes in the text) Although there was only one desaturation case in our series, our sample was small, and difficult mask ventilation or intubation cannot be predicted. (Page 14, Line 15-16)

• The authors defined desaturation at SPO2 <90%, in many other studies the agreed threshold has been set higher at 95%.5 It would be interesting to know is this threshold affected the desaturation rates and incidence in each group.

Reply) We reviewed database and added the threshold of desaturation, SpO2<95% at result and Table 2.

Changes in the text) We also checked whether there was a desaturation event, defined as a peripheral oxygen saturation (SpO_2) lower than 95% or 90% (reflecting "abnormal" and "significant" arterial oxygen desaturation, respectively (18-20)). (Page 7, Line 19-21)

• Table 1. It would be helpful to know the urgency of surgery in the demographics table, as this may affect both efficacy of preoxygenation and risk of desaturation.

Reply) We added emergency of surery at demographic data and table.

Changes in the text) Demographic data before and after PSM are presented in Table 1. Before PSM, there were no significant differences in age, sex, weight, height, BMI, the proportion of smokers, COPD, asthma, abdominal surgery and emergency surgery, or basal SpO_2 between the two groups. However, there was a significant

difference in ASA physical status ($p < 0.05$). After PSM, none of the demographic characteristics differed between the two groups. (Page 10, Line 9-13); Table 1

Discussion

• Would be helpful to have discussion of the reasons why the authors felt there was no difference between 80 & 100% oxygen groups, including the physiological basis for this.

Reply) As you mentioned, this results may be natural by the physiologic law of exponenctial wash-in. We added this sentence in discussion.

Changes in the text) However, there was no difference in the adequate preoxygenation rate between 80% and 100% oxygen, which may be a result of the physiological law of exponential wash-in. (Page 14, Line 12-14)

• Acknowledging potential bias in the missing data group would seem beneficial

Reply) We added sentence at limitation in discussion.

Changes in the text) To reduce selection bias, we performed PSM, but many patients were excluded because we analyzed only those with objective data. (Page 15, Line 3-4)

• One of the authors arguments appears to be that not all anaesthetists preoxygenate people and when they do it may not be 'maximal'. Therefore a use of an ETO2 <90%

may be 'relatively' safe as evidenced by a low desaturation rate of around 0.5%. I would suggest that it is better to 'inadequately' preoxygenate patients with 100% oxygen and have a safety margin, than routinely use 80% oxygen where inadequate preoxygenation could result in very rapid desaturation. In addition using 100% oxygen would achieve an ETO2 of 70% in a much quicker time than using 80%. If the authors have this data, this would be interesting to compare. For example a small study (using healthy volunteers) found that using 100% oxygen, patients reached ETO2 >70% within 60 seconds.4

Reply) We changed all "maximal preoxygenation" as "adequate preoxygenation" in entire manuscript. We didn't have data about DAWD, but we are now conducting prospective study of the effectiveness of preoxygenation using 80% and 100% oxygen. Instead, we reviewed database and analyzed the induction time defined from start of propofol to end of intubation. Based on DAWD of Edmark et al., we added sentences about the safety as following.

Changes in the text) Edmark *et al.* reported DAWD values of 414 ± 84 and 303 ± 59 s using 100% and 80% oxygen, respectively (40). Based on those values, the safety of only 75% of the patients would have been guaranteed in the event of "cannot intubate, cannot oxygenate" when using 100%, while that of < 50% would have been guaranteed when using 80% oxygen. Therefore, 100% oxygen should be used during preoxygenation with CPAP, ARM and PEEP to reduce atelectasis, until a large study proves that 80% oxygen differs in safety from 100% oxygen during the induction period. (Page 14, Line 19-24 ~ Page 15, Line 1)

• It is worth noting that the absorption atelectasis the authors are trying to prevent should be preventable with recruitment manoeuvres after induction, such as 40cm3 pressure. 5

Reply) We added sentences about other technique to reduce atelectasis in the manuscript as you recommended.

Changes in the text) To prevent atelectasis, the use of lower FiO_2 (8-10) or techniques (11) such as the alveolar recruitment maneuver (ARM) and positive end-expiratory pressure (PEEP) have been suggested (6,12). (Page 4, Line 15-17); Many studies reduced atelectasis using 100% oxygen by applying continuous positive airway pressure (CPAP), the ARM, or PEEP (11,47-50). In addition, the median total induction time was 353.5 s (IQR: 322.75–406.5 s) after PSM. Edmark *et al* reported DAWD values of 414 ± 84 and 303 ± 59 s using 100% and 80% oxygen, respectively (8). Based on those values, the safety of only 75% of the patients would have been guaranteed in the event of "cannot intubate, cannot oxygenate" when using 100%, while that of < 50% would have been guaranteed when using 80% oxygen. Therefore, 100% oxygen should be used during preoxygenation with CPAP, ARM and PEEP to reduce atelectasis, until a large study proves that 80% oxygen differs in safety from 100% oxygen during the induction period. (Page 15, Line 16-24 ~ Page 16, Line 1)

• The authors note a low desaturation rate of 0.5%, from a thai study – this study excluded patients who looked to have a difficult airway, so could be falsely low.6 This larger study of a wider range of patients and operations found a higher incidence of 6.6%. 7

Reply) We agreed your comments and deleted about that sentence.

• Lines 3-5 are confusing. Are they saying that of the large number of excluded patients, few of these desaturated?

Reply) We deleted those sentences.

• I agree with the authors conclusions that ETO2 monitoring should be used actively to determine preoxygenation duration.

Reply) We revised our conclusion as following.

Changes in the text) In conclusion, we found no difference in preoxygenation time between 100% and 80% oxygen, using EtO_2 as an end-point. Currently, preoxygenation for 3 min is considered the standard, but many patients required more than 3 min for adequate preoxygenation. Therefore, it is helpful to use EtO_2 to confirm adequate preoxygenation. EtO_2 monitoring would complement evaluations of preoxygenation adequacy. (Page 16, Line 24 ~ Page 17, Line 1-4)

• The authors have not drawn significant conclusions based on their finding of no difference in duration of preoxygenation between the 100% and 80% oxygen groups – it would be helpful to know which FIO2 they recommend and why.

Reply) We added sentences about that as following.

Changes in the text) Although there was only one desaturation case in our series, our sample was small, and difficult mask ventilation or intubation cannot be predicted. Many studies reduced atelectasis using 100% oxygen by applying continuous positive airway pressure (CPAP), the ARM, or PEEP (11,47-50). In addition, the median total induction time was 353.5 s (IQR: 322.75–406.5 s) after PSM. Edmark *et al* reported DAWD values of 414 ± 84 and 303 ± 59 s using 100% and 80% oxygen, respectively (8). Based on those values, the safety of only 75% of the patients would have been guaranteed in the event of "cannot intubate, cannot oxygenate" when using 100%, while that of < 50% would have been guaranteed when using 80% oxygen. Therefore, 100% oxygen should be used during preoxygenation with CPAP, ARM and PEEP to

reduce atelectasis, until a large study proves that 80% oxygen differs in safety from 100% oxygen during the induction period. (Page 15, Line 15~24 ~ Page 16, Line 1)

References

1. Edmark L, Kostova-Aherdan K, Enlund M, et al. Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 2003;98:28-33.

2. Nimmagadda U, Salem MR, Joseph NJ, et al. Efficacy of preoxygenation with tidal volume breathing. Comparison of breathing systems. Anesthesiology. 2000;93:693698.

3. McGowan P, Skinner A. Preoxygenation--the importance of a good face mask seal. Br J Anaesth 1995;75:777-8.

4. Berry CB, Myles PS. Preoxygenation in healthy volunteers: a graph of oxygen "washin'
using end-tidal oxygraphy. British Journal of Anaesthesia 1994; 72: 116-118

5. Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G. Dynamics of re-expansion of atelectasis during general anaesthesia. Br J Anaesth. 1999;82:551556.

6. Uakritdathikarn T, Chongsuvivatwong V, Geater AF, et al. Perioperative desaturation and risk factors in general anesthesia. J Med Assoc Thai 2008;91:1020-9.

7. C. Baillard, M. Boubaya, E. Statescu, M. Collet, A. Solis, J. Guezennec, V. Levy, O. Langeron. Incidence and risk factors of hypoxaemia after preoxygenation at induction of anaesthesia. British Journal of Anaesthesia. 2019;122(3): 388-394.

Reviewer D

The purpose of this article is clearly stated. However, there are various concerns and criticisms regarding the manuscript, which are itemized below.

Main concern: This is a retrospective study. The study is simple to be carried out through a randomized clinical trial. Without a randomization process, the selection of the technique is conditioned by variables such as patient comorbidities or the existence of difficult airway predictors, so the results are conditioned by multiple biases.

1. The title does not reflect the study carried out. I suggest authors to follow the "PICO" formulation

Reply) Thank you for your review and comments. We revised our title as following.

Changes in the text) Efficacy of preoxygenation with end-tidal oxygen when using different oxygen concentrations in patients undergoing general surgery: A single-center retrospective observational study (Page 1, Line 1-2)

2. Introduction: Authors should summarize the initial hypothesis under study, primary aim and secondary aims.

Reply) We revised our introduction as following.

Changes in the text) For this reason, we attempted to determine if there is a difference in preoxygenation time, using EtO_2 as an endpoint, between different oxygen concentrations (100% vs. 80%). DAWD is naturally shortened when 80% oxygen is used; thus, the occurrence of desaturation was also investigated. We also wanted to determine the proportion of patients for whom > 3 min was required to achieve adequate preoxygenation. (Page 4, Line 22-24 ~ Page 5, Line 1-2)

3. Methods.

• I suggest that the inclusion and exclusion criteria be presented more explicitly.

Reply) We added more information in the method and inserted figure and supplements files to show inclusion and exclusion criteria more clearly.

Changes in the text) From the start to the end of preoxygenation, if a continuous exponential increase in EtO_2 was identified, and a capnography waveform of the patient's respiration was recorded simultaneously (Figure 1), the data were considered sufficient for analysis. Patients whose data were incomplete were excluded, including those with no or irregular EtO_2 and capnography data; an absent or irregular EtO_2 graph and $EtCO_2$ waveform before anesthesia induction (Supplement 2), or no FiO_2 or EtO_2 data due to technical errors (Supplement 3). (Page 7, Line 13-18)

• Who was in charge of data collection?

Reply) Database is managed and controlled by Sang-Hyun Kim and Misoon Lee. Data were collected by Jaewoong Jung, Seri Park, and Misoon Lee under the supervision of Bon-Sung Koo.

• Laryngeal grades. authors should use a more standardized classification, reference it and define the different grades

Reply) We revised "laryngeal grade" to "Cormack-Lehane grade" and cited it.

Changes in the text) demographic data included age, sex, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, smoking status, concomitant pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma, Cormack–Lehane grade (21) during intubation (grade 1, most of the glottis is visible; grade 2, only the posterior extremity of the glottis is

visible; grade 3, no part of the glottis can be seen, but the epiglottis is visible; grade 4, neither the glottis or epiglottis can be seen), and type, site and emergency status of the operation. (Page 6, Line 20-23 ~ Page 7, Line 4); Assuming that Cormack–Lehane grades 1 and 2 represent easy intubation, and grades 3 and 4 difficult intubation (28), the rate of difficult airway was 9.5% (31 of 327 patients) and 9.1% (26 of 285 patients) before and after PSM, respectively. (Page 12, Line 11-13)

• The justification of the sample size study should be incorporated in the paragraph dedicated to the statistical analysis although it is a retrospective study

Reply) We added sentences about sample size calculation as following.

Changes in the text) Bhatia *et al*. reported that the time taken for EtO_2 to reach 90% when using 100% oxygen in young adults was 157 ± 32 s (15). Assuming that a 5% difference in preoxygenation time is clinically significant, 326 patients were estimated to be needed to achieve 80% power with a two-sided significance level of 0.05 using the two-sample *t*-test. (Page 7, Line 6-10)

4. Results: Authors must add the numerical values of the variables in the text despite being presented in the table.

Reply) We described the numerical values and revised our results as you recommended.

Changes in the text) Before PSM, the preoxygenation time did not differ significantly between the two groups (median difference = 3, 95% confidence interval [CI]: -8 to 13, p=0.625) when using EtO_2 as the endpoint (Table 2). The percent of inadequate

preoxygenation was also similar between the two groups (11% vs. 6%, p=0.131), and the overall rate of inadequate preoxygenation was 8%. No demographic characteristics were associated with inadequate preoxygenation. Overall, for 28% of the patients > 3 min was required for adequate preoxygenation (28% vs. 28%, p=0.993). After PSM, the preoxygenation time also did not differ significantly between the two groups (median difference = -1, 95% CI: -13 to 10, p=0.605). There were also no differences in the overall rate of inadequate preoxygenation (12% vs. 6%, p =0.143) or the proportion of patients for whom > 3 min was required for adequate preoxygenation (26% vs. 28%, p=0.118). (Page 11, Line 14-23); Despite the significant group difference in laryngeal grade (p=0.000 before PSM and 0.004 thereafter), the intubation time did not differ significantly between the two groups (p=0.315 before PSM and 0.722 thereafter). Assuming that Cormack–Lehane grades 1 and 2 represent easy intubation, and grades 3 and 4 difficult intubation (28), the rate of difficult airway was 9.5% (31 of 327 patients) and 9.1% (26 of 285 patients) before and after PSM, respectively. BMI (OR, 1.12; 95% CI: 1.03 to 1.22; p=0.009 before PSM; OR, 1.14; 95% CI: 1.04 to 1.24; p=0.004 after PSM) was identified as a risk factor for difficult airway by logistic regression. (Page 12, Line 9-15)

5. Discussion:

• The two authors do not specify the main preoxygenation methods. I suggest you use the reference: Garzón JC, Sastre JA, Gómez-Ríos MÁ, López T, Garzón-Sánchez A, Pandit JJ. Comparing the dynamics of changes in regional cerebral oxygen saturation with arterial oxygen partial pressure with two techniques of preoxygenation in healthy adults. J Clin Anesth. 2021 Feb;68:110091.

Reply) We read the journal you mentioned. Our study is a retrospective study, and we analyzed only obejectively recorded data via VitalDB Record, so we cannot describe the method of preoxygenation as in the above journal. We have no choice but to

describe the protocol of our hospital, and we revised the method sections as following.

Changes in the text) All preoxygenation and anesthesia methods were performed in accordance with the protocols of our institution. We routinely used 100% oxygen during preoxygenation in the supine position. A head-up or ramped position could be used at the anesthesiologist's discretion. A tight-fitting face mask without leakage, and the use of 100% oxygen, is essential during preoxygenation, but many anesthesiologists in our institution do not perform preoxygenation properly; sometimes there is a gap between the patients' face and the face mask, resulting in leakage. This leakage in turn results in the entrainment of > 20% room air, thus lowering the FiO_2 and EtO_2 (22,23). After a journal club session on airway management aimed at reducing atelectasis, we performed preoxygenation properly by using a tight-fitting face mask without leakage, using 80% or 100% oxygen at the anesthesiologist's discretion, with a fresh gas flow rate of 6–10 L/min. We also used EtO_2 as an endpoint, rather than the preoxygenation time. This enabled us to collect data using different oxygen concentrations during preoxygenation. (Page 7, Line 21-23 ~ Page 8, Line 9)

• P5L8: "other studies"… Authors should reference such studies

Reply) We cited the references as following.

Changes in the text) other studies have tended to report the EtO_2 at 3 min after preoxygenation (4,15,29). (Page 13, Line 7)

• P5L45: "..or whether leakage is present.." This assertion is not correct. Delete

Reply) We deleted that sentence.

• “Due to this low probability, it may be considered excessive to supply oxygen until maximal preoxygenation is reached in all patients.” This assertion is not correct. Delete

Reply) We deleted that sentence.

6. A grammatical revision of the manuscript could be convenient

Reply) We sent our manuscript to the English editing service, and revised our manuscript after the English editing service.

Round 2

Review Comments:

I commend the authors for taking on board comments by all of the reviewers and significantly improving their manuscript in the process.

The have obviously not been able to alter the inherent methodological flaws present in a retrospective database analysis, which still raises questions over the validity of their data as a degree of bias may remain. Especially because the use of 80% or 100% oxygen appears to have been at anaesthetist discretion rather than protocolised. Given the 100% oxygen group has a higher proportion of high Cormack and lehane intubation grades and a longer induction time, this would suggest to me that the patients in this group may have been at higher risk of desaturation. Patients with difficult airways may also be more difficult to preoxygenate so would represent a fundamental difference in the two groups studied here.

Answer) Thank you for your reviewing of our research. Even after a propensity score matching, there still was a significant difference in the Cormack-Lehane grade between the two groups. As you mentioned, it would be a methodologic limitation in our research. We plan to investigate the effectiveness of preoxygenation through a randomized study. We believe that the result of a randomized study could compensate for the flaws in our research. Once again, we thank the reviewers for their dedication of reviewing our work.

Please see further comments on individual sections below:

Abstract

Line 3 – use of however between the first and second sentences may improve the flow

Answer) We inserted "however" between first and second sentences. as following: "Preoxygenation is a simple but very important procedure for preventing arterial desaturation. However, a higher FiO_2 increases atelectasis and 80% oxygen results in significantly less atelectasis than 100% oxygen." (Page 2, Line 3-5)

Introduction

• Line 9 – the nitrogen in the alveoli does not 'run out' is it washed out

Answer) We revised that words as following: "When the nitrogen used to splint alveoli washed out, oxygen absorption exceeds carbon dioxide (CO_2) excretion, potentially accelerating resorption atelectasis;" (Page 4, Line 12-14)

• Line 13 – slightly confusing text, does this mean that using 80% oxygen gives similar absorption atelectasis to air?

Answer) We revised that sentence and corrected the citation as following: "Using 80% oxygen may provide many of the benefits of 100% oxygen (13), while atelectasis is much less than 100% oxygen, but comparable to 30% oxygen (8,13)." (Page 4, Line 17-19)

Methodology

Preoxygenation and induction methods

• Line 2 – the lack of standardised supine or ramped position could affect results

Answer) We did not routinely record the patient's position during preoxygenation, just supine position. It is a limitation of our research due to its retrospective nature, so we revised our limitations in discussion as following; "Second, there may also have been technical problems in performing preoxygenation, although they might have been insignificant because we selected only patients with sufficient data for analysis. The preoxygenation time was influenced by several factors, such as position (supine, head-up or ramped) or respiratory pattern (minute ventilation). Some patients breathed shallowly and rapidly, while others breathed deeply and slowly; hyperventilation can achieve adequate preoxygenation in a short period of time (50). Precise tidal volume breathing, through education or guidance of patients, would improve preoxygenation times. Further protocolized and randomized studies were needed to confirm our results." (Page 15, Line 21-24 ~ Page 16, Line 1-5)

• Line 6 – it cannot be guaranteed that preoxygenation was performed 'properly' after the education session. Perhaps ' anaesthetists were reminded of the importance of using an appropriately fitting face mask without leakage'

Answer) We revised that sentences as you recommended; “After a journal club session on airway management aimed at reducing atelectasis, we were reminded of the importance of using an appropriately fitting face mask without leakage, using 80% or 100% oxygen at the anesthesiologist’s discretion, with a fresh gas flow rate of 6–10 L/min.” (Page 8, Line 4-7)

• Lines 6-7: the choice of 80% or 100% oxygen being at anaesthetist discretion could induce significant bias

Answer) We agreed with your comment. We added the limitation in discussion about this as following; “First, our study was retrospective, and the method of preoxygenation was not protocolized, and was adjusted at the anesthesiologist’s discretion. And the period of data collection differed, so selection bias is inevitable. The choice of which oxygen concentration to be used could also affect. For those reasons, we performed PSM to reduce selection bias, but many patients were already excluded because we analyzed only those with objective data, and there was still a significant difference in Cormak-Lehane grade between the two groups.” (Page 15, Line 15-21)

Results

• The use of data prior to and after PSM is confusing. Could this be simplified into using either the data before or after this process, not citing all data twice.

Answer) We revised our results as you mentioned. Only demographic data remained original to compare the results before and after PSM; “After PSM, the preoxygenation time also did not differ significantly between the two groups (median difference = -1, 95% CI: -13 to 10, p=0.605). There were also no differences in the overall rate of

inadequate preoxygenation (12% vs. 6%, p =0.143) or the proportion of patients for whom > 3 min was required for adequate preoxygenation (26% vs. 28%, p=0.118) (Table 2). No demographic characteristics were associated with inadequate preoxygenation." (Page 11, Line 14-18);

Despite the significant group difference in laryngeal grade (p=0.004 after PSM), the intubation time did not differ significantly between the two groups (p=0.722 after PSM). Assuming that Cormack–Lehane grades 1 and 2 represent easy intubation, and grades 3 and 4 difficult intubation (28), the rate of difficult airway was 9.1% (26 of 285 patients) after PSM. BMI (OR, 1.14; 95% CI: 1.04 to 1.24; p=0.004 after PSM) was identified as a risk factor for difficult airway by logistic regression." (Page 12, Line 4-9); Table 2.

Discussion

• Lines 5-11 – would benefit from a new paragraph. A lot of this seems to be a justification of the authors choice to use 80% oxygen and the harms of absorption atelectatsis. Would this fit better in the introduction section.

Answer) We revised our manuscript as you recommended; "A higher FiO_2 or EtO_2 will lead to longer duration of apnea without desaturation (DAWD); however, it may also increase resorption atelectasis (2). Since nitrogen in air is not taken up, the alveoli are kept open by nitrogen. When the nitrogen used to splint alveoli washed out, oxygen absorption exceeds carbon dioxide (CO_2) excretion, potentially accelerating resorption atelectasis; this can reduce the functional residual capacity (6), impair gas exchange, and cause respiratory dysfunction and lung injury (7). This may

explain why preoxygenation using 100% oxygen precipitates more atelectasis; this would be consistent with Reber *et al.*, who reported that preoxygenation and hyperoxygenation produced more atelectasis (8). To prevent atelectasis, the use of lower FiO_2 (9-11) or techniques (12) such as the alveolar recruitment maneuver (ARM) and positive end-expiratory pressure (PEEP) have been suggested (6,13).

However, because a high fraction of oxygen is essential to avoid hypoxia, questions have been raised regarding the optimal oxygen concentration (14-16). While ≤ 80% oxygen could reduce atelectasis (6,9,14), 80% oxygen does not worsen pulmonary gas exchange, or the lung volumes (17). Despite a modest shortening of DAWD (18), we thought that 80% oxygen could be an alternative to 100% oxygen, if it can enhance the efficacy of preoxygenation. Using 80% oxygen may provide many of the benefits of 100% oxygen (17), while atelectasis is much less than 100% oxygen, but comparable to 30% oxygen (9,17)." (Page 4, Line 11-24 ~ Page 5, Line 1-4)

• Line 10-11 would benefit from referencing. E.g. Nimmagadda U, Salem MR, Joseph NJ, et al. Efficacy of preoxygenation with tidal volume breathing. Comparison of breathing systems. Anesthesiology. 2000;93:693698.

Answer) We revised our manuscript, and added the reference as following; "We found that the preoxygenation time, defined as the time taken to achieve a 10% difference between FIO_2 and EtO_2, did not differ significantly between the 100% and 80% groups (median difference = -1, 95% CI: -13 to 10 after PSM). To our knowledge, no studies have compared the time taken for adequate preoxygenation using 100% and 80% oxygen, although this results may be a result of the physiological law of exponential wash-in (33)." (Page 13, Line 2-6)

• Line 15-2 are slightly confusing. How have they determined the safety of these patients in a CICO scenario

Answer) We revised our manuscript as following; “Based on those values, only 75% and <50% of the patients would be able to endure in the event of “cannot intubate, cannot oxygenate” when using 100%, and 80% oxygen, respectively.” (Page 15, Line 10-12)

• Line 4- can the authors expand on what they mean here?

Answer) We revised our manuscript as following; “EtO2 monitoring might be an essential element of preoxygenation and is of sufficient value for continuous monitoring and evaluation.” (Page 15, Line 3-4)