PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Preoxygenation in difficult airway management: High-flow oxygenation by nasal cannula versus face mask (The PREOPTIDAM study): Protocol for a single-centre randomised study.
AUTHORS	VOURC'H, Mickael; Huard, Donatien; FEUILLET, Fanny; BAUD, Gabrielle; GUICHOUX, Arthur; SURBLED, Marielle; TISSOT, Melanie; CHIFFOLEAU, Anne; GUITTON, Christophe; Jaber, S.; Asehnoune, Karim

VERSION 1 – REVIEW

REVIEWER	Sangsari Razieh Children Medical Center hospital,Tehran Iran
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	Please, replace face mask instead of standard device in title. Please,add indication of FMV in article. Please,define primary and secondary outcome correctly. please,define severe desaturation as <80% in pages 15. Thank you.

REVIEWER	Dr. Nuttapol Rittayamai Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	The investigators presented the study protocol comparing high-flow nasal cannula vs standard oxygen therapy before endotracheal intubation in patients with anticipated difficult airway management in the theater. The hypothesis of the study is HFNC will result in better oxygenation than standard oxygen therapy before and after endotracheal intubation by the mechanism of apneic oxygenation. I have some comments and suggestions as follows: Introduction • Page 5, last paragraph: please correct typo - at FiO2 = 1.0 (not at FiO2 = 1.) Patient eligibility • Page 8 and 9: I would suggest the investigators to add termination or withdrawal criteria for patient safety issue Trial intervention • The investigators should provide more information regarding the HFNC device and standard oxygen device. In addition, HFNC device in the market can generate the maximum flow rate of 60 LPM but they are going to use flow rate at 70 LPM in this study. Is

	this the new device? • Who will perform endotracheal intubation (attending physician, trainee, etc)? • They should explain more details regarding how to manage patient who develop desaturation during the study protocol? When to perform face mask ventilation? When to terminate the protocol? Because one of the main objective of the study is the number (or time) of manual FMV and this should have some standard criteria to initiate FMV. • I am aware that patient who receive standard face mask for ETI under laryngoscopy will develop hypoxemia because the face mask will be removed and patient will not get any oxygen during such period. Outcome • Page 13: In terms of severe complication please clarify the definition of severe desaturation that < 90% or < 80%? • Page 14: please check the definition of desaturation in the section of morbidity in the PACU whether it is defined < 90% or < 80%.

REVIEWER	Jörn Grensemann Universitatsklinikum Hamburg-Eppendorf, Intensive Care
REVIEW RETURNED	10-Nov-2018

GENERAL COMMENTS	The planned study compares the preoxygenation by standard face-mask or high-flow-nasal-cannula in patients with predicted difficult intubation in an elective anesthesia setting. This is a very interesting question that certainly needs to be studied since it may have great impact on routine clinical practice with the potential to improve patients' safety for predicted difficult intubation. The study protocol is concisely written and covers all aspects necessary to duplicate the study. However, I have some remarks. Unfortunately, the study seems to be recruiting patients already so that an amendment of the study protocol is probably not feasible anymore. As far as I understand the protocol, the "standard" group receives preoxygenation with a non-rebreather mask with 15 L/min O2? By this method, a FiO2 of 1.0 cannot be delivered for preoxygenation and this method may not reflect the routine clinical practice with a half-closed rebreathing anesthesia circuit. In my opinion, the delivery of a FiO2 of 1.0 is mandatory especially in predicted difficult intubation. Please discuss why no anesthesia circuit is used in your study. Please explain how the sample size calculation allows for the pre-specified sub-group analysis. Is it possible to amend the planned sample size after the interim analysis, should the achieved power prove to small? Some items in the study protocol currently differ from the clinicaltrials.gov record. Please clarify and check for further inconsistencies. - inclusion criteria (rapid sequence induction!) - estimated study complete date - HFNC delivered at 60 vs. 70 L/min Please amend the inclusion criteria to only include patients requiring a rapid sequence induction as stated on clinicaltrials.gov.

	further minor comments: please check if all abbreviations are explained at their introduction (e.g. Abstract: FMV, Manuscript body: DI, IDS,…) P6 L22 I would suggest to add the citation of the following studies: - Simon M et al. High-flow nasal cannula versus bag-valve-mask for preoxygenation before intubationin subjects with hypoxemic respiratory failure. Respir Care 2016; 61: 1160 – 1167. - Jaber S et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med 2016; 42: 1877 – 1887. I wish the authors every success in their study and look forward to the results as I expect this study to have a large impact on clinical practice in the future.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Q1) Please state any competing interests or state ‘None declared’: None declared
R1) Thank you for your comment, the conflicts of interest of Karim Asehnoune have been added as follows (Lines 14-15, page 23): Karim Asehnoune declares personal fees from Fisher Paykel Healthcare, Baxter, LFB, Fresenius.

Q2) Please, replace face mask instead of standard device in title.
R2) Thank you for this remark, the title was modified as suggested (Line 4 page 1)

Q3) Please, add indication of FMV in article.
R3) Thank you for this comment, FMV has been removed from the manuscript since it was not a usual abbreviation. This term has been replaced by “Face mask ventilation” throughout the manuscript.

Q4) Please, define primary and secondary outcome correctly.
R4) Thank you. We agree that the definitions of the primary and secondary outcomes were not precise enough. This could have been deleterious for further publication an for the clarity of the study design. Moreover, some secondary criteria were missing. As required the primary and secondary outcome were described more precisely as follows:
(Line 11-12, page 11): Primary outcome Proportion of patients with desaturation ≤ 94% or need to use face mask ventilation for oxygen desaturation during intubation in each group.
(Line 25, page 11 to Line 10 page 14): Secondary outcomes
Preoxygenation quality:
1-SpO2 at the beginning and at the end of the preoxygenation
2-Leaks during preoxygenation defined as:

- In the face mask group: Inward or backward leaks with at least 15% difference between inspired and expired volume.
- In the HFNC group: Leaks though the mouth for patients breathing with the mouth opened.
3-EtO2 and EtCO2 at the end the preoxygenation (face mask group only)

Intubation procedure until the 2 following minutes:
1-Quality of exposure : Cormack-Lehane classification [1]
2-Intubation success
3-Number of laryngoscopy during RSI
4-Number of operators
5-Number of alternative devices
6-IDS score [2]
7-Difficult intubation rate [3]
8-Desaturation < 90%
9-Number of episode of face-mask ventilation
10-Length of intubation procedure - from general anaesthesia induction/start of sedation until the end of intubation -
11-Lowest SpO2
12-Lowest EtO2 within 2 minutes following intubation
13-Highest EtCO2 within 2 minutes following intubation
14-Sedation quality during FOI assessed by the “patient sedation score” [4]
15-Patient’s satisfaction score [5]

Intubation related adverse events during intubation and the following 1 hour:
1-Severe complications :
- Death
- Cardiac arrest
- Severe desaturation < 80%
- Severe cardiovascular collapse (systolic blood pressure < 80mmHg or the need to administer ephedrine or neosynephrine or norepinephrine)

2-Mild-to-moderate complications:
- Intubation failure
- Severe ventricular or supraventricular arrhythmia
- Oesophageal intubation
- Dental injury
- Dangerous agitation defined as RASS >3 (Richmond Agitation-Sedation Scale)
- Vomiting with aspiration of gastric content
- Naso-laryngo-tracheal injury or bleeding during RSI or FOI

Per-operative respiratory monitoring:
1-Higher FiO2 required to obtain SpO2 > 94%
2-Higher plateau pressure at 5 min, 30 min, 1 hour after intubation
3-Higher peak pressure at 5 min, 30 min, 1 hour after intubation
4-Achievement of recruitment manoeuvres for desaturation < 95%
5-Tidal volume reduction owing to peak pressure > 40 mmHg

Morbidity in the PACU:
1-Nausea or vomiting
2-Inspiratory dyspnoea after extubation
3-Lowest SpO2 recorded after extubation
4-Desaturation < 90% before or after extubation

5-Severe desaturation < 80% before or after extubation
6-Oxygen therapy requirement at PACU discharge
7-Length of stay
8-Duration of mechanical ventilation.
9-Non-Invasive ventilation support
10-Reintubation for respiratory failure

Q5) Please, define severe desaturation as <80% in pages 15.
R5) Thank you. As suggested we defined severe desaturation < 80% (Line 6, page 13)

References for reviewer# 1:

1 Cormack RS. Cormack-Lehane classification revisited. British Journal of Anaesthesia 2010;105:867–8. doi:10.1093/bja/aeq324
2 Adnet F, Borron SW, Racine SX, et al. The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology 1997;87:1290–7.
3 American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 2003;98:1269–77.
4 Rai MR, Parry TM, Dombrovskis A, et al. Remifentanil target-controlled infusion vs propofol target-controlled infusion for conscious sedation for awake fibreoptic intubation: a double-blinded randomized controlled trial. British Journal of Anaesthesia 2008;100:125–30. doi:10.1093/bja/aem279
5 Dhasmana SC. Nasotracheal fiberoptic intubation: patient comfort, intubating conditions and hemodynamic stability during conscious sedation with different doses of dexmedetomidine. J Maxillofac Oral Surg 2014;13:53–8. doi:10.1007/s12663-012-0469-0

Reviewer: 2
Reviewer Name: Dr. Nuttapol Rittayamai

Introduction

Q1) Page 5, last paragraph: please correct typo - at FiO2 = 1.0 (not at FiO2 = 1.)
Patient eligibility
R1) Thank you for this comment. As required we modified the wording for FiO2 = 100% (Line 10, page 4)

Q2) Page 8 and 9: I would suggest the investigators to add termination or withdrawal criteria for patient safety issue
R2) Thank you for your comment, we inserted a statement in this section as follows (Lines 19-20, page 14): All of the expected or unexpected adverse events (occurring from the beginning of the preoxygenation to the discharge of the PACU) will be collected in the e-CRF.

Trial intervention
Q3) The investigators should provide more information regarding the HFNC device and standard oxygen device. In addition, HFNC device in the market can generate the maximum flow rate of 60 LPM but they are going to use flow rate at 70 LPM in this study. Is this the new device?
R3) Thank you for your comment. We added details regarding the 2 standards face mask (for RSi or FOI) and the HFNC as well, as follows (From Line 21, page 8 to line 12 page 9):

The intervention group: HFNC preoxygenation for 4 minutes set at 60L/min of heated and humidified pure oxygen (fraction of inspired oxygen 100%, 37°C - OptiflowTM; Fisher & Paykel Healthcare®, Auckland, New-Zealand). Large or medium nasal cannulae will be chosen according to the patient's nostril size to limit air contamination. Throughout the intubation procedure, HFNC will be maintained trying to achieve:
- Continuous oxygenation while the patient will be spontaneously breathing during FOI,
- Or apnoeic oxygenation during laryngoscopy for RSI

The standard group: preoxygenation for 4 minutes with a face mask (which size will be adapted to fit the patient and ensure airtightness) connected to an Aisys CS2 ventilation system (General Electric, GE Healthcare®, Oy, Finland). In this group, the ventilation system is set with 15 L/min of fresh gas, FiO2 = 100%, without inspiratory support or expiratory positive pressure.
- For RSI, the face mask (Economy, Intersurgical®, Fontenay Sous Bois, France) will be removed after induction to enable intubation.
- For FOI the face mask (FibroxyTM, VBM, Sulz, Germany) will be kept in place throughout the intubation procedure with a 15L/min fresh gas flow, FiO2 = 100%, ensuring airtightness.

We fully agree that the device we are studying can deliver until 60 L/min and not (70 L/min). We modified the flow rate throughout the manuscript as well as in the Figure 1.

Q4) Who will perform endotracheal intubation (attending physician, trainee, etc)?
R4) Thank for your comment. The following information was inserted in the manuscript (Lines 14-16, page 9): In both groups, the first operator will be a senior or a junior supervised by a senior. All operators will have assisted a three half-day formation program so as to be familiar with this 3 oxygenation devices at the Nantes University Hospital simulation centre.

Q5) They should explain more details regarding how to manage patient who develop desaturation during the study protocol? When to perform face mask ventilation? When to terminate the protocol? Because one of the main objective of the study is the number (or time) of manual FMV and this should have some standard criteria to initiate FMV
R5) Thank you for this relevant comment. Indeed, the decision to use face mask ventilation is sometimes difficult to assess and to protocolized. That's why, our primary outcome is: The number of patients with at least one event among - desaturation ≤ 94% or need to use face mask ventilation for oxygen desaturation during intubation or the following 2 minutes – between groups.
The primary outcome was built so as not to miss any events among oxygen desaturation or face mask ventilation (which can hide oxygen desaturation). As a result:
- If the attending physician decides not to use face mask ventilation despite desaturation ≤ 94%, the event "desaturation" will lead the patient to be considered as "with an events"
- In the same way, systematic face mask ventilation preventing desaturation ≤ 94% will also lead the patient to be considered as "with an events".
We added precision regarding the primary outcome definition as well as a comment in the introduction and in the intervention sections with the recommendations for face ventilation in case of desaturation.
Line 13-22, page 11: The patients will be classified in 2 groups: "No event" or "at least one event".
- For RSI, the primary criterion will be assessed from the induction of general anaesthesia to 2 minutes following intubation.
- For FOI, the primary criterion will be assessed from the beginning of sedation to 2 minutes following intubation.
Arterial oxygen saturation will be evaluated by level of oxygen saturation measured by pulse oximetry (SpO2). The evaluation period of SpO2 will be extended to 2 minutes following intubation completion owing to possible delayed detection of desaturation with this device. Face mask ventilation will be noted if it occurs after general anaesthesia (RSI) or sedation (FOI) induction.
From line 23, page 4 to line 2, page 5: According to the current guidelines, when the level of pulse

oximetry (SpO2) drops below 95%, the operator has to interrupt intubation and focus on oxygenation (i.e. face mask ventilation).[6] Nevertheless, face mask ventilation could be difficult or impossible in patients with anticipated DI, and could give rise to gastric insufflation or active gag reflex and provoke vomiting or aspiration. It also often requires deepening anaesthesia, leading to severe hypotension. As a result, to limit face mask ventilation during DI could also reduce adverse events, driving research effort in this field.
Lines 17-23, page 9: The current guidelines advise to interrupt intubation to focus on oxygenation (i.e. face mask ventilation) for oxygen desaturation ≤ 94%.[6] Nevertheless, the decision to proceed to face mask ventilation mainly depends on the progression of intubation procedure. Thus, mask ventilation is left at the discretion of the physician as well as the algorithm for rescue oxygenation. However, International recommendation will be presented to all of the investigators before the start of the study.[7] The attending physician will be free to withdraw the oxygenation device if it disrupts the intubation process or the rescue oxygenation.

Outcome
Q6) Page 13: In terms of severe complication please clarify the definition of severe desaturation that < 90% or < 80%?
R6) Thank you for your precise reviewing. As suggested by reviewer #1 and yourself, we defined severe desaturation as < 80% (Line 6, page 13)

Q7) Page 14: please check the definition of desaturation in the section of morbidity in the PACU whether it is defined < 90% or < 80%.
R7) Thank you for this comment. We defined severe desaturation as < 80% (Line 5, page 14)

References for reviewer# 2:
6 Langeron O, Bourgain J-L, Francon D, et al. Difficult intubation and extubation in adult anaesthesia. Anesthésie & Réanimation 2017;3:552–71. doi:10.1016/j.anrea.2017.09.003
7 Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults†. BJA: British Journal of Anaesthesia 2015;115:827–48. doi:10.1093/bja/aev371

Reviewer: 3
Reviewer Name: Jörn Grensemann

Q1) As far as I understand the protocol, the “standard” group receives preoxygenation with a non-rebreather mask with 15 L/min O2? By this method, a FiO2 of 1.0 cannot be delivered for preoxygenation and this method may not reflect the routine clinical practice with a half-closed rebreathing anesthesia circuit. In my opinion, the delivery of a FiO2 of 1.0 is mandatory especially in predicted difficult intubation. Please discuss why no anesthesia circuit is used in your study.
R1) Thank you for your comment, we fully agree that Non-rebreather mask face mask would not have been able to deliver 100% FIO2. We have added precisions regarding the standard oxygenation device. Indeed, the control arm consists in a Face mask connected to an anesthesia ventilation system. The intervention section was modified as follows (Lines 4-12, page 9):
The standard group: preoxygenation for 4 minutes with a face mask (which size will be adapted to fit the patient and ensure airtightness) connected to an Aisys CS2 ventilation system (General Electric, GE Healthcare®, Oy, Finland). In this group, the ventilation system is set with 15 L/min of fresh gas, FiO2 = 100%, without inspiratory support or expiratory positive pressure.
- For RSI, the face mask (Economy, Intersurgical®, Fontenay Sous Bois, France) will be removed after induction to enable intubation.
- For FOI the face mask (FibroxyTM, VBM, Sulz, Germany) will be kept in place throughout the intubation procedure with a 15L/min fresh gas flow, FiO2 = 100%, ensuring airtightness.

Q2a) Please explain how the sample size calculation allows for the pre-specified sub-group analysis
R2a) Thank you for this question. The initial sample size (186 patients) is calculated to have a power to show a 12% difference between the two randomizations groups for the primary outcome in the intent-to-treat population. The pre-specified sub-group analysis is exploratory. We inserted this notion in the text (Line 13, page 15): We shall also perform exploratory sub-group analysis for the primary outcome regarding the type of intubation (FOI or RSI).

Q2b) Is it possible to amend the planned sample size after the interim analysis, should the achieved power prove to small?
R2b) No data is available on the incidence of desaturation for planned difficult intubation. If the interim analysis highlights a lack of power, the sample size will be increased. As previously reported by Friede et al. [8,9], during interim analysis overall event probability can be estimated during the ongoing trial based on the pooled data of both treatment groups. If necessary, the sample size will be adjusted accordingly and an amendment to the protocol will be made. This information has been inserted in the text as follows (Lines 16-18, page 15): The overall probability of the event will be estimated from the pooled data of both treatment groups. If necessary, the sample size will be adjusted accordingly and an amendment to the protocol will be made.

Q3) Some items in the study protocol currently differ from the clinicaltrials.gov record. Please clarify and check for further inconsistencies.
- inclusion criteria (rapid sequence induction!)
- estimated study complete date
- HFNC delivered at 60 vs. 70 L/min
Please amend the inclusion criteria to only include patients requiring a rapid sequence induction as stated on clinicaltrials.gov.
R3) Thank you for your precise reviewing. We agree there were inconsistencies between clinical trial registration and the manuscript. We modified the manuscript according to the clinical trial registration:
- We have added the missing information in the inclusion section (Lines 4-5, page 7): Patients requiring a rapid sequence intubation (RSI) or requiring a fiberoptic intubation (FOI)
- The end of the study is planned on March 2020 (Line 9, page 17)
- In the experimental arm HFNC will be set at 60L/min (Line 21, page 8)

Further minor comments:

Q4) Please check if all abbreviations are explained at their introduction (e.g. Abstract: FMV, Manuscript body: DI, IDS,…)
R4) Ok thank you, we added the definition of RSI and IDS in the abbreviation section (Lines 8 & 11,page 3)

Q5) P6 L22 I would suggest to add the citation of the following studies:
- Simon M et al. High-flow nasal cannula versus bag-valve-mask for preoxygenation before intubationin subjects with hypoxemic respiratory failure. Respir Care 2016; 61: 1160 – 1167.
- Jaber S et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med 2016; 42: 1877 – 1887.
R5) Thank you for your recommendations. The references were inserted as suggested (Line 4, page

5).

References for reviewer# 3:

8 Friede T, Kieser M. Sample size recalculation for binary data in internal pilot study designs. Pharmaceutical Statistics 2004;3:269–79. doi:10.1002/pst.140
9 Friede T, Kieser M. Sample size recalculation in internal pilot study designs: a review. Biom J 2006;48:537–55.

VERSION 2 – REVIEW

REVIEWER	Dr. Nuttapol Rittayamai Division of Respiratory Diseases and Tuberculosis, Department fo Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	The investigators have responded all of my comments and I satisfy with these responses. I have no further comments or suggestions.

REVIEWER	Jörn Grensemann University Medical Center Hamburg-Eppendorf Center of Anesthesiology and Intensive Care Medicine Dept. of Intensive Care Medicine, Hamburg, Germany
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	The authors have addressed all reviewers' questions and remarks and amended their manuscript accordingly. I have no further remarks and wish the auth