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Keywords:	High-Flow Nasal Cannula, anticipated difficult intubation, fiberoptic intubation, video-laryngoscopy, Apneic oxygenation

TITLE PAGE

Preoxygenation optimisation in difficult airway management (PREOPTIDAM): high-flow nasal cannula oxygen versus standard device: protocol for a single-centre randomised study

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ABSTRACT

Introduction: Although preoxygenation and airway management respond to precise algorithms, difficult endotracheal intubation (ETI) remains a daily challenge in Intensive Care Units (ICU) and operating rooms because of its frequent complications, including hypoxaemia. High-flow oxygenation by nasal cannula (HFNC) could improve preoxygenation and has been reported to achieve apnoeic oxygenation. To prevent desaturation during difficult ETI, recent guidelines recommend the use of this device, but its efficiency has never been evaluated until now.

Methods and analysis: The PREOPTIDAM trial is a prospective, single-centre, randomised, controlled study in Nantes University Hospital. We hypothesized that HFNC can decrease the incidence of desaturation ≤ 94% or manual FMV along ETI from 16 to 4% compared to facial mask. Using a two-sided t-test with a first species risk of 5 % and 80 % power, a total of 186 patients with risk factors for difficult intubation (DI) and requiring ETI for planned surgery will be included. Using a computer-generated randomization, with a 1:1 allocation ratio, patients will be randomised to HFNC or standard pre-oxygenation. Randomisation will be stratified on intubation device: laryngoscopy after crash induction or fiberoptic intubation (FOI) under sedation. The primary objective is to determine whether HFNC is more efficient than standard oxygenation techniques to prevent desaturation ≤ 94% or face-mask ventilation (FMV) during DI. Intent-to-treat and per-protocol analysis are planned for the primary outcome.

Ethics and dissemination: The study project has been approved by an independent ethics committee. Oral and written information will be provided before study inclusion. Participant

recruitment begins in september 2018. Results will be submitted to international peer-reviewed medical journals.

Trial registration number: NCT03604120, registered in July 2018.

Keywords: High-Flow Nasal Cannula, anticipated difficult intubation, fiberoptic intubation, video-laryngoscopy, Apneic oxygenation

Abbreviations:

ASA: American Society of Anesthesiology

SFAR: French Society of Anesthesia and Intensive Care

HFNC: high flow nasal cannula

ETI: endo-tracheal intubation

FOI: fiberoptic intubation

DI: difficult Intubation

FMV: face-mask ventilation

FiO2: fraction of inspired oxygen

PACU: post-anaesthesia care unit

RASS: Richmond agitation-sedation scale

eCRF: electronic case report form

FPH: Fisher & Paykel Healthcare

Article Summary

Strengths and limitations of this study:

- PREOPTIDAM is the first prospective, randomized, controlled study evaluating HFNC ability to perform apneic oxygenation during anticipated difficult airway control in order to prevent desaturation
- Broad inclusion criteria and large sample size will support external validity.
- Pragmatic study protocol reflects every day practice and results will be of high clinical relevance.
- As no data is available on desaturation (<95%) incidence among anticipated DI, an interim analysis will be carried out to allow re-estimating the sample size to maintain power.

INTRODUCTION

The last French epidemiology survey pointed out that despite major safety improvement over the last decades, substantial morbidity and mortality remains in anaesthesia.[1] Hypoxaemia represented 20% of these severe adverse events.[2,3]

Although airway management and preoxygenation sequence respond to precise algorithms, anticipated DI remains a daily challenge and a major cause of hypoxaemia during anaesthesia.[4-6] Moreover, DI increases first-attempt failure and long-lasting procedure incidence leading to repeated manual face-mask ventilation (FMV) to correct or prevent desaturation. FMV often requires deepening anaesthesia, leading to severe hypotension. FMV also gives rise to gastric insufflation or active gag reflex and provokes vomiting or aspiration.

Preoxygenation, which consists in fulfilling functional residual capacity with pure oxygen, is the cornerstone of patient safety during ETI. Increasing oxygen reserve is the best way to extend safe apnoea duration and therefore to avoid hypoxaemia and its related complications.[7] Current preoxygenation guidelines suggest performing 8 vital capacities or 3 minutes of spontaneous breathing with a standard face mask, at FiO_2=1.[8,9] Despite well-conducted preoxygenation, the rate of desaturation < 90% can reach 21% in case of DI.[10] In order to reduce desaturation in anticipated DI, two options are available. The first is fiberoptic intubation (FOI) under local anaesthesia and sedation for anticipated "cannot ventilate" or limited mouth-opening patients.[11] FOI preserves the patient's spontaneous breathing and avoids major hypoxaemia in case of difficult and long lasting airway control.[12] The second option is to intubate after induction of general anaesthesia with

either a standard or a video laryngoscope and to maintain oxygenation throughout apnoea until the end of ETI.

HFNC would appear to be an innovative device to achieve apnoeic oxygenation.[13] Throughout ETI, holding the nasal prongs in place during FOI or laryngoscopy can enable the continuation of oxygenation.[14] It delivers humidified and heated oxygen up to 70 L/min with FiO_2 close to 100% and has also been reported to generate supra-glottic end expiratory pressure. Its efficacy as an apnoeic oxygenation device has already been reported during ETI.[15,16] As a preoxygenation device, HFNC has also been studied in the ICU and in operating theatres with controversial results.[17,18] However, in DI settings, recent observational studies have suggested the ability of HFNC to extend safe apnoea time and to be held during FOI.[19,20]

Considering its theoretical advantages and recent recommendations,[9,21] HFNC must be assessed during preoxygenation and apnoeic oxygenation in case of anticipated DI. Up to now, no large randomised study has compared HFNC oxygenation with standard of care. Our objective will be to evaluate HFNC accuracy as a pre-oxygenation and apnoeic oxygenation device during anticipated DI compared with standard of care. We hypothesise that HFNC could reduce desaturation during ETI and in the following two minutes.

METHOD AND ANALYSIS

Objectives

- Primary objective:

To compare the effectiveness of HFNC (interventional group) as a preoxygenation and apnoeic oxygenation device versus face mask (standard method) for anticipated DI.

- Secondary objectives:

To compare ETI related complications and patient outcome until post-anaesthesia care unit (PACU) discharge with each device.

Trial design

PREOPTIDAM will be a prospective, single-centre, open-label, randomised controlled study. The randomisation sequence will be computer-generated and stratified on intubation method (laryngoscopy or fibroscopy) according to the attending physician's decision. This study will adhere to the international recommendations for interventional trials.

Study settings

The study will take place at the Nantes University Hospital, France.

Hypothesis

We hypothesise that HFNC could reduce the incidence of desaturation ≤ 94% or the necessity for manual FMV in case of first attempt failure of ETI.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients will receive written and oral information. They will be included after investigators have obtained informed written consent.

- **Inclusion criteria**

  - Adults aged from 18 to 90 years.
  - 1 major or 2 minor criteria of anticipated DI.

Anticipated DI criteria derived from international guidelines and recent publications[22-24]:

- 1 major criterion:
  - Past DI.
  - Past laryngeal surgery or radiotherapy.
  - Limited mouth opening < 25mm.
  - Fixed flexion of the cervical spine.
  - Mallampati IV.
  - Tumour in the oral or laryngeal region.

OR

- At least 2 minor criteria:
  - Thyromental distance < 65mm.
  - Limited mouth opening < 35 mm and > 25mm.
  - Mallampati III.
  - Limitation of cervical mobility ≤ 35°.
  - Neck perimeter > 40 cm for men and > 38 cm for women.
  - Retrognathism.

- **Non-inclusion criteria**
  - BMI > 35 kg/m^2.
  - Pulse oximetry < 90% in ambient air.
  - Haemodynamic instability.
  - Protected adult.
  - Pregnancy.
  - Lack of consent.
  - Patient already enrolled in another randomised study to improve preoxygenation quality.

Assignment of interventions

- **Allocation**

Randomisation will be centralised, web-based and accessible 24 hours a day. The randomisation sequence will be carried out in blocks (1:1 ratio) and stratified according to intubation sequence (laryngoscopy or fibroscopy).

- **Sequence generation**

The randomisation sequence will be generated by a statistician working at the Clinical Research Unit of Nantes University Hospital and not involved in patient recruitment. The software used to collect the data in the eCRFs will automatically allocate patients, thereby ensuring concealment. The physicians and a clinical research nurse and/or clinical research assistant will screen the patients and include those who are eligible for the study.

- **Blinding**

Blinding of healthcare workers and patients to the type of preoxygenation device is not feasible. However, the primary outcome is assessed on the basis of an objective criterion.

Trial intervention

After anticipated DI criteria detection by the anaesthetist during the pre-operative consultation, the patients will be randomly assigned to (**see Figure 1:** Study intervention):

- HFNC preoxygenation for 4 minutes set at 70L/min air flow and FiO_2 = 1 before intubation. HFNC will be maintained throughout the FOI or laryngoscopic intubation procedure to attempt to achieve oxygenation.

or

- Standard preoxygenation for 4 minutes (15L/min, FiO_2 = 1).
  - With standard face mask for ETI under laryngoscopy after rapid sequence induction of general anaesthesia. The standard face mask will be removed after induction to enable intubation.

or

  - With an endoscopy mask for FOI under sedation and local naso-pharyngeal anaesthesia in a spontaneously breathing patient. The mask will be kept in place throughout the intubation procedure.

Clinical data will be collected throughout ETI, surgery, and until discharge of the PACU.

Concomitant medication/treatment

The drugs for general anaesthesia or sedation and ETI devices will be left to the discretion of the attending physician.

Participant withdrawal

Patients will be excluded from the trial if they withdraw their consent after randomisation. However, if the patient does not object, the data already collected until consent withdrawal will be analysed. If the patient refuses, the data will be deleted.

Participant timeline and schedule (see Table 1)

Title Table 1: Participants timeline

	Anesthesia consultation	Pre-operative visit	Inclusion	Intubation & surgery	PACU	PACU discharge
Eligibility?	X	X				
Information	X	X				
Written consent		X				
Randomization			X			
Data collection				X	X	
Exit from the study						X

Legends Table 1: After written informed consent, the patient will be randomized and preoxygenation will be performed accordingly. Patients will be followed until the Post-Anesthesia Care Unit (PACU) discharge.

Patient and Public Involvement

Patients were not directly involved in the development of the research question or the design of the study. However, the primary and secondary outcomes of the PREOPTIDAM study impact patients' safety and comfort. A written summary of the study results will be sent to requesting participants by mail.

Participants experience of the intervention will be assess before PACU discharge. This assessment is one of the secondary outcome.

Outcome measures

Primary outcome measure

We will compare the incidence of desaturation ≤ 94% or manual FMV during the procedure between the HFNC and face mask groups.

- For ETI under laryngoscopy, the primary criterion will be assessed from the induction of general anaesthesia to 2 minutes following ETI.
- For FOI, the primary criterion will be assessed from the beginning of sedation to 2 minutes following ETI.

Arterial oxygen saturation will be assessed by non-invasive transcutaneous pulse oximetry (SpO_2). The evaluation period of SpO_2 will be extended to 2 minutes following ETI completion owing to possible delayed detection of desaturation with this device.

After the first ETI attempt failure, FMV will be left to the discretion of the attending physician. In this setting, we believe that uninterrupted oxygenation by HFNC during apnoea will convince the anaesthetist not to proceed to FMV in the absence of desaturation.

Secondary outcome measure

- Preoxygenation quality:
  - SpO_2 at the beginning and the end of the preoxygenation.
- ETI procedure:
  - Quality of exposure (Cormack grade).

- ETI success, number of attempts, number of operators, number of alternative devices.
- IDS score.
- FMV with or without desaturation.
- For FOI: sedation quality, patient comfort, ease of tube and fibreoptic insertion, quality of glottis vision.

- ETI related adverse events:
  - Severe complications:
    - Death, cardiac arrest.
    - Severe desaturation with SpO_2 < 90% or < 80%.
    - Severe cardiovascular collapse (systolic blood pressure < 80mmHg or the need to administer ephedrine or neosynephrine or norepinephrine).
  - 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 laryngoscopy or FOI.

- Per-operative respiratory monitoring:
  - Higher FiO_2 required to obtain SpO_2 > 94%.
  - Higher plateau pressure at 5 min, 30 min, 1 hour after ETI.
  - Higher insufflation pressure at 5 min, 30 min, 1 hour after ETI.
  - Achievement of recruitment manoeuvres for desaturation.
  - Tidal volume reduction owing to insufflation pressure > 40 mmHg.
- Morbidity in the PACU:
  - Nausea or vomiting.
  - Inspiratory dyspnoea after extubation.
  - Lowest SpO_2 recorded after extubation.
  - Desaturation < 90% or < 80% before or after extubation.
  - Oxygen therapy requirement at PACU discharge.
  - Length of stay.
  - Duration of mechanical ventilation.
  - Non-Invasive ventilation support.
  - Reintubation for respiratory failure.

Safety issues – Severe adverse events

Severe adverse events will be immediately declared and analysed by the Pharmacovigilance Department of the Nantes University Hospital.

Expected ETI related adverse events:

- Severe desaturation <80%.
- Severe cardiovascular collapse.
- Cardiac arrest and death.

All of the expected or unexpected adverse event will be collected in the e-CRF.

The trial may be temporarily stopped for an individual patient at the discretion of the attending physician if a severe adverse event is suspected to be associated with the studied device.

Statistics analysis and sample size calculation

The primary outcome is the incidence of desaturation ≤ 94% or FMV during the ETI procedure.

We hypothesise that HFNC can decrease the incidence of desaturation ≤ 94% or manual FMV during ETI from 16% to 4% compared with the face mask. The incidence of desaturation during anticipated DI has not been described specifically in the literature up to now.[25] We hypothesise a 12% reduction in desaturation in HFNC based on our previous study in the Intensive Care Unit (unpublished data). Using a two-sided *t*-test with a first species risk of 5% and 80% power and considering 5% of consent withdrawal, we planned to include 186 patients. We anticipated approximately 50 patients with FOI indication.

An interim analysis will be performed to enable re-estimation of the sample size to maintain power.[26,27] It will be performed after inclusion of half of the total number of patients (93 patients). The overall probability of the event will be estimated from the entire sample of 93 patients.

For the primary outcome: a linear model will compare the incidence of desaturation

≤ 94% or mask ventilation. Intent-to-treat and per-protocol analysis are planned for the primary outcome.

We shall also perform sub-group analysis of the primary outcome regarding the type of ETI (FOI or laryngoscopy).

The secondary outcomes will be described and compared between the two groups with linear regression models, generalized mix models or survival models (Cox or Fine and Gray) according to the nature of the variable.

All of the analyses will be adjusted to intubation sequence (laryngoscopy or fibroscopy).

A predefined statistical analysis plan will be followed using SAS software V.9.3 (Cary, North Carolina, USA). The statistical analysis will incorporate all of the elements required by the CONSORT statement for non-pharmacological interventions.

Track record

Data will be recorded in a web-based electronic case report form (eCRF) by the research team. Characteristics at baseline will be gathered: age, sex, weight, height, medical history, indication for surgery, predictive criteria of difficult FMV DI, description of the ETI procedure (technical aspect, drugs and adverse events). During surgery, respiratory and cardiovascular parameters will be assessed.

Any protocol deviations will be recorded in the eCRF and the medical records. To preserve the confidentiality of personal information, data will be key-coded using alphanumerical numbers. To minimise missing data, to improve the quality of data collection

and tracking, an external assessor will collect the variation of SpO_2 by video recording of the cardiorespiratory monitors during ETI procedure.

Data statement

Data set will be available on reasonable request to the corresponding author.

Monitoring

Monitoring will follow "Good Clinical Practice principles" and will be performed by the independent promotion department of Nantes University Hospital Research Management Unit.

The following data will be assessed:

- Written consent after oral and written information during the anaesthesia consultation.
- Flow chart filled in for included and excluded patients.
- Trial progress.
- Primary and secondary outcome collection.
- Treatment-related severe adverse events.

The eCRF is a secure, interactive, web-response system provided and managed by the biometrics unit of the Nantes University Hospital (Nantes, France). The physicians and a clinical research nurse will ensure compliance with the study protocol and collect the study data in the eCRFs.

Trial status

A total of 186 patients are expected to be included within 15 months.

June 2018: protocol approval by the Ethics Committee.

September 2018: Start of inclusion.

December 2019: End of inclusion.

We will submit the manuscript during the second half of 2020.

ETHICS AND DISSEMINATION

Research ethics approval.

The trial will be conducted in compliance with the current version of the Declaration of Helsinki and Good Clinical Practice guidelines. The research project was approved by the appropriate Ethical Review Board (Medical Ethic Committee "PARIS, Ile-de-France 2", registration number: 2018-04-04 RIPH2).

The study was registered at http://www.clinicaltrials.gov with trial identification number: NCT03604120.

Confidentiality

The study data will be handled as requested by the French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés). All original records will be kept on file at the trial site for 15 years. The electronic trial database file will be anonymised and kept on file for 15 years.

Conflict of interests

This study was supported by institutional funds and a grant from Fisher & Paykel Healthcare (FPH) that is inferior to 20% of the total budget. FPH did not participate in the study design and will not participate in data collection, analysis and interpretation, nor in the preparation, review approval and decision to submit the manuscript for publication.

Dissemination plan

The study will be published in an international medical journal.

DISCUSSION

Among the ETI related adverse events, hypoxaemia is a life-threatening issue and this complication is mainly encountered during difficult airway management. HFNC presents several theoretical advantages compared with the standard face mask, including the ability to deliver continuous oxygen flow to perform apnoeic oxygenation. Recent expert guidelines[9,21] have advised the use of such a device to prevent desaturation during DI. However, its accuracy has never been evaluated in a large randomised study. Given the preliminary data, this device could improve patient safety. However, it must be evaluated before systematic implementation in the airway control algorithm.

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AUTHORS CONTRIBUTION

KA and MV obtained funding. KA, SJ, DH, GB, AG, MS, MT, CG and MV designed the study. FF and AC planned the statistical analysis. KA and MV will have full access to the final trial dataset. All authors participated in the writing the manuscript and approved the final version.

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The PREOPTIDAM trial is supported by the University Hospital of Nantes and a grant from Fisher & Paykel Healthcare (FPH) that is inferior to 20% of the total budget. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

DISCLAIMER

The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

COMPETING INTERESTS

MV reports personal fees from MSD, Pfizer, Baxter, grants from Fischer Paykel, outside the submitted work. SJ reports personal fees from Draeger, Fresenius-Xenios and Fisher Paykel Healthcare, outside the submitted work. No other disclosures are reported.

PATIENT CONSENT

Oral and written consent required.

ETHICS APPROVAL

By 11 june 2018 the study had been approved by a central ethics committee (Comité de Protection des Personnes Ile-de-France II, Paris, France), reference: 2018-04-04 RIPH2

Tables and Figures

Title Table 1: Participants timeline

Legends Table 1: After written informed consent, the patient will be randomized and preoxygenation will be performed accordingly. Patients will be followed until the Post-Anesthesia Care Unit (PACU) discharge.

Title Figure 1: Study design

Legend Figure 1: After attending physician decision to perform laryngoscopic or fiber-optic intubation, patients will be randomized to receive HFNC or Face mask oxygenation. **FOI**: Fiber-Optic Intubation, **ETI**: Endo-Tracheal Intubation, **HFNC**: High Flow Nasal Cannula, **FiO2**: Fraction of inspired oxygen

Figure 1: Study intervention

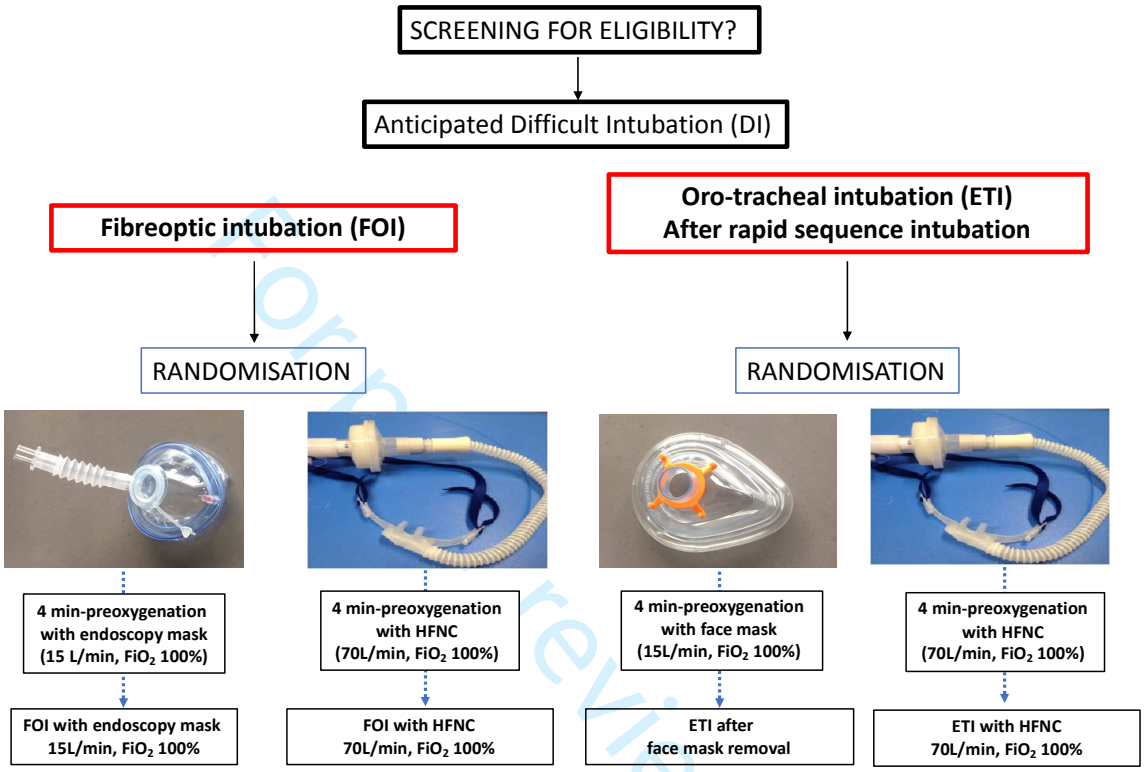

Table 1: **Participant timeline**

	Anaesthesia consultation	Pre-operative consultation	Inclusion	Intubation & surgery	PACU	PACU discharge
Eligibility?	X	X				
Information	X	X				
Written consent		X				
Randomisation			X			
Data collection				X	X	
Exit from the study						X

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+22
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17+22
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5+6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12+13+14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8+10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7+8+9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16+18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15+16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15+16
Statistics: analysis population and	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	15

missing data		statistical methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14+15+16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8+10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16+18

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18+22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16+22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Preoxygenation in difficult airway management: High-flow oxygenation by nasal cannula versus face mask (The PREOPTIDAM study): Protocol for a single-centre randomised study.

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Respiratory medicine, Anaesthesia
Keywords:	High-Flow Nasal Cannula, anticipated difficult intubation, fiberoptic intubation, video-laryngoscopy, Apneic oxygenation

TITLE PAGE

Preoxygenation in difficult airway management: High-flow oxygenation by nasal cannula versus face mask (The PREOPTIDAM study): Protocol for a single-centre randomised study.

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Word count: 3168

ABSTRACT

Introduction: Although preoxygenation and airway management respond to precise algorithms, difficult intubation (DI) remains a daily challenge in Intensive Care Units (ICU) and in the operating rooms because of its frequent complications, including hypoxaemia. To prevent desaturation during DI, high-flow oxygenation by nasal cannula (HFNC) could prove beneficial. Indeed, contrary to standard preoxygenation device, it can be held in place throughout the intubation trying to perform apnoeic oxygenation during DI. Hence, recent guidelines recommend HFNC during DI, but its relevance has never been evaluated in this setting in a large randomised study until now.

Methods and analysis: The PREOPTIDAM trial is a prospective, single-centre, randomised, controlled study in Nantes University Hospital. In anticipated DI, we hypothesized that HFNC can decrease the incidence of desaturation ≤ 94% or face mask ventilation from 16 to 4% compared to standard device. Using a two-sided t-test with a first species risk of 5 % and 80 % power, a total of 186 patients will be included. Using a computer-generated randomization, with a 1:1 allocation ratio, patients will be randomised to HFNC or face mask pre-oxygenation. Randomisation will be stratified on intubation sequence: Rapid sequence intubation or awake fiberoptic intubation. The primary objective is to determine whether HFNC is more efficient than standard oxygenation techniques to prevent desaturation ≤ 94% or face-mask ventilation during DI. Intent-to-treat and per-protocol analysis are planned for the primary outcome.

Ethics and dissemination: The study project has been approved by an independent ethics committee. Written informed consent will be obtained before study inclusion. Participant recruitment begins in september 2018. Results will be submitted to international peer-reviewed medical journals.

Trial registration number: NCT03604120, registered in July 2018.

Keywords: High-Flow Nasal Cannula, anticipated difficult intubation, fiberoptic intubation, video-laryngoscopy, Apneic oxygenation

Abbreviations:

ASA: American Society of Anesthesiology

DI: difficult Intubation

eCRF: electronic case report form

FiO2: fraction of inspired oxygen

FOI: fiberoptic intubation

HFNC: high flow nasal cannula

IDS: Intubation Difficulty Score

PACU: post-anaesthesia care unit

RASS: Richmond agitation-sedation scale

RSI: Rapid sequence intubation

SFAR: French Society of Anesthesia and Intensive Care

Article Summary

Strengths and limitations of this study:

- PREOPTIDAM is the first prospective, randomised, controlled study evaluating high-flow oxygenation by nasal cannula as a preoxygenation and apneic oxygenation device during anticipated difficult intubation (DI) in order to prevent desaturation.
- Broad inclusion criteria and large sample size will support external validity.
- Pragmatic study protocol reflects every day practice and results will be of high clinical relevance.
- As no data is available on the incidence of desaturation ≤ 94% during anticipated DI, an interim analysis will be carried out to allow re-estimating the sample size to maintain power.

INTRODUCTION

Despite major safety improvement over the last decades, substantial morbidity and mortality remains in anaesthesia.[1] Hypoxaemia represented 20% of these severe adverse events.[2,3] Although airway management and preoxygenation sequence respond to precise algorithms, anticipated difficult intubation (DI) remains a daily challenge and a major cause of hypoxaemia during anaesthesia. [4,5] Preoxygenation, which consists in fulfilling functional residual capacity with pure oxygen, is the cornerstone of patient safety during intubation. Increasing oxygen reserve is the best way to extend safe apnoea duration and therefore to avoid hypoxaemia and its related complications. Current preoxygenation guidelines suggest performing 8 vital capacities or 3 minutes of spontaneous breathing with a standard face mask, at FiO_2 = 100% in order to achieve EtO_2 of > 90%.[4,5] To reduce desaturation during anticipated DI, two options for airway management can be discussed: Rapid sequence intubation (RSI) or awake fiberoptic intubation (FOI).[4] RSI includes preoxygenation with a standard face mask, the administration of hypnotic and neuromuscular blocker with rapid onsets, and immediate intubation after mask removal without manual ventilation. RSI aims at 1) Minimizing the time from induction to intubation to reduce the risk of oxygen desaturation ;[5] 2) Ensuring a fast recovery of spontaneous breathing when intubation proves impossible with difficult face mask ventilation. FOI, usually performed under local anaesthesia and sedation, is proposed for anticipated "cannot ventilate" or “limited mouth-opening” patients. It preserves the patient’s spontaneous breathing during intubation to avoid major hypoxaemia in case of difficult airway control.After preoxygenation, a dedicated face mask guarantees continuous oxygenation during the procedure. Whatever the option, and despite well-conducted preoxygenation, DI increases first-attempt failure, long-lasting procedure incidence, and leads to frequent oxygen desaturation.[6] According to the current guidelines, when the level of pulse oximetry (SpO_2) drops below 95%, the operator has to interrupt intubation and focus on oxygenation (i.e. face mask ventilation).[7] 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.

High-flow oxygenation by nasal cannulae (HFNC) has been studied in the ICU and in the operating room as a preoxygenation device, with controversial results.[8-10] Recent observational studies have suggested the ability of HFNC to extend safe apnoea time during DI and to be held during FOI.[11,12] This device can deliver up to 60 L/min with an inspired fraction of oxygen of up to 100%,[13] and generate a moderate positive supra-glottic end expiratory pressure.[14] HFNC could prove beneficial for anticipated DI, during both the preoxygenation and the intubation:[15] After preoxygenation for RSI, HFNC makes it possible to hold nasal prongs in place during laryngoscopy, trying to perform apneic oxygenation throughout the intubation. During FOI, in a spontaneously breathing patient, the preoxygenation and the oxygenation with standard device require a dedicated operator to apply firmly the mask on the patient's face so as to ensure airtightness which is often poorly tolerated. Moreover, in toothless patients or with a beard, significant leaks around the mask can alter oxygenation. HFNC allows to insert the fiberscope in the patient's nostril to perform intubation while continuing the oxygenation and may be better tolerated.

Considering its theoretical advantages and recent recommendations,[5,7] HFNC must be assessed during preoxygenation and apnoeic oxygenation during anticipated DI. Up to now, no large randomised study has compared HFNC oxygenation with standard of care. Our objective will be to evaluate HFNC preoxygenation for anticipated DI compared with face mask. We hypothesise that HFNC could reduce oxygen desaturation during the intubation and the need of face mask ventilation accordingly.

METHOD AND ANALYSIS

Objectives

- Primary objective:

To compare the effectiveness of HFNC (interventional group) and face mask (standard method) as preoxygenation devices to prevent desaturation during anticipated DI.

- Secondary objectives:

To compare the quality of preoxygenation, intubation related complications, and patient's outcome until post-anaesthesia care unit (PACU) discharge between groups.

Trial design

The PREOPTIDAM trial will be a prospective, single-centre, open-label, randomised controlled study. The randomisation sequence will be computer-generated and stratified on the intubation method (RSI or FOI) according to the attending physician's decision. This study will adhere to the international recommendations for interventional trials.

Study settings

The study will take place at the Nantes University Hospital, France.

Hypothesis

We hypothesise that compared to face mask preoxygenation, HFNC could reduce the incidence of desaturation $\leq$ 94% or the necessity to use face mask ventilation for rescue oxygenation during anticipated DI.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients will receive written and oral information. They will be included after investigators have obtained informed written consent.

- **Inclusion criteria**

  - Adults aged from 18 to 90 years
  - 1 major or 2 minor criteria of anticipated DI (see below)
  - And requiring a rapid sequence intubation (RSI) or requiring a fiberoptic intubation (FOI).

Anticipated DI criteria derived from international guidelines and recent publications:[4,16,17]

  - 1 major criterion:
    - Past difficult intubation
    - Past laryngeal surgery or radiotherapy
    - Limited mouth opening < 25mm
    - Fixed flexion of the cervical spine
    - Mallampati IV
    - Tumour in the oral or laryngeal region

OR

  - At least 2 minor criteria:
    - Bone to chin distance < 65mm
    - Limited mouth opening < 35 mm and > 25mm
    - Mallampati III
    - Limitation of cervical mobility ≤ 35°
    - Neck perimeter > 40 cm for men and > 38 cm for women
    - Retrognathism

- **Non-inclusion criteria**

  - BMI > 35 kg/m^2
  - Pulse oximetry < 90% in ambient air
  - Haemodynamic instability
  - Protected adult
  - Pregnancy

- Lack of consent
- Patient already enrolled in another randomised study to improve preoxygenation quality

Assignment of interventions

- **Allocation**

Randomisation will be centralised, web-based and accessible 24 hours a day. The randomisation sequence will be carried out in blocks (1:1 ratio) and stratified according to intubation sequence (RSI or FOI).

- **Sequence generation**

The randomisation sequence will be generated by a statistician working at the Clinical Research Unit of Nantes University Hospital and not involved in patient recruitment. The software used to collect the data in the eCRFs will automatically allocate patients, thereby ensuring concealment. The physicians and a clinical research nurse and/or clinical research assistant will screen the patients for eligibility.

- **Blinding**

Blinding of the attending physician and patients to the type of preoxygenation device is not feasible. However, the primary outcome is assessed on the basis of an objective criterion.

Trial intervention

After written informed consent, the patients will be randomly assigned to (**see Figure 1:** Study intervention):

- 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 - Optiflow™; 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, FiO_2 = 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 (Fibroxy™, VBM, Sulz, Germany) will be kept in place throughout the intubation procedure with a 15L/min fresh gas flow, FiO_2 = 100%, ensuring airtightness.

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.

The current guidelines advise to interrupt intubation to focus on oxygenation (i.e. face mask ventilation) for oxygen desaturation ≤ 94%.[7] 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.[5] The attending physician will be free to withdraw the oxygenation device if it disrupts the intubation process or the rescue oxygenation. Clinical data will be collected throughout intubation, surgery, and until discharge of the PACU.

Concomitant medication/treatment

The drugs for sedation and general anaesthesia induction as well as intubation devices will be left to the discretion of the attending physician.

Participant withdrawal

Patients will be excluded from the trial if they withdraw their consent after randomisation. However, if the patient does not object, the data already collected until consent withdrawal will be analysed. If the patient refuses, the data will be deleted.

Participant timeline and schedule

Patients will be followed from the beginning of the preoxygenation until the Post-Anesthesia Care Unit (PACU) discharge (**see Table 1**).

Title Table 1: Participants timeline

	Anesthesia consultation	Pre-operative visit	Inclusion	Intubation & surgery	PACU	PACU discharge
Eligibility?	X	X				
Information	X	X				
Written consent		X				
Randomization			X			
Data collection				X	X	
Exit from the study						X

Legends Table 1: After written informed consent, the patient will be randomised and preoxygenation will be performed according to the allocated device. Patients will be followed until the Post-Anesthesia Care Unit (PACU) discharge.

Patient and Public Involvement

Patients were not directly involved in the development of the research question or the design of the study. However, the primary and secondary outcomes of the study impact patients' safety and comfort. A written summary of the results of the study will be sent to requesting participants by mail. Participants satisfaction of the intervention will be assess before PACU discharge and will analysed as a secondary outcome.

Primary and secondary outcome

1- Primary outcome

Proportion of patients with desaturation ≤ 94% or need to use face mask ventilation for oxygen desaturation during intubation in each group.

Measure of the primary outcome

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 (SpO_2). The evaluation period of SpO_2 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.

2- Secondary outcome

- Preoxygenation quality:
  - SpO_2 at the beginning and at the end of the preoxygenation
  - 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.
  - EtO_2 and $EtCO_2$ at the end the preoxygenation (face mask group only)
- Intubation procedure until the 2 following minutes:
  - Quality of exposure : Cormack-Lehane classification [18]
  - Intubation success
  - Number of laryngoscopy during RSI
  - Number of operators
  - Number of alternative devices
  - IDS score [19]
  - Difficult intubation rate [20]
  - Desaturation < 90%
  - Number of episode of face-mask ventilation
  - Length of intubation procedure - from general anaesthesia induction/start of sedation until the end of intubation -
  - Lowest SpO_2
  - Lowest EtO_2 within 2 minutes following intubation
  - Highest $EtCO_2$ within 2 minutes following intubation

- Sedation quality during FOI assessed by the "patient sedation score" [21]
- Patient's satisfaction score [22]

- Intubation related adverse events during intubation and the following 1 hour:
  - 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)
  - 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:
  - Higher FiO_2 required to obtain SpO_2 > 94%
  - Higher plateau pressure at 5 min, 30 min, 1 hour after intubation
  - Higher peak pressure at 5 min, 30 min, 1 hour after intubation
  - Achievement of recruitment manoeuvres for desaturation < 95%
  - Tidal volume reduction owing to peak pressure > 40 mmHg

- Morbidity in the PACU:
  - Nausea or vomiting
  - Inspiratory dyspnoea after extubation
  - Lowest SpO_2 recorded after extubation
  - Desaturation < 90% before or after extubation
  - Severe desaturation < 80% before or after extubation
  - Oxygen therapy requirement at PACU discharge
  - Length of stay
  - Duration of mechanical ventilation.
  - Non-Invasive ventilation support
  - Reintubation for respiratory failure

Safety issues – Severe adverse events

Severe adverse events will be immediately declared and analysed by the Pharmacovigilance Department of the Nantes University Hospital.

Expected intubation related adverse events are defined as:

- Severe desaturation < 80%.
- Severe cardiovascular collapse.
- Cardiac arrest and death.

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. The trial may be temporarily stopped for an individual patient at the discretion of the attending physician if a severe adverse event is suspected to be associated with the allocated device.

Statistics analysis and sample size calculation

The primary outcome is the occurrence (yes or no) of desaturation ≤ 94% or face mask ventilation during the intubation procedure and the 2 following minutes.

We hypothesise that HFNC can decrease the incidence of desaturation ≤ 94% or the need of face mask ventilation during intubation from 16% to 4% compared with the standard preoxygenation device. The incidence of desaturation during anticipated DI has not been described specifically in the literature up to now. We hypothesise a 12% reduction in desaturation with HFNC based on our previous study in the Intensive Care Unit (2019, Intensive care medicine, *in press*). Using a two-sided *t*-test with a first species risk of 5% and 80% power and considering 5% of consent withdrawal, we planned to include 186 patients. We anticipated approximately 50 patients with FOI indication.

For the primary outcome: a logistic model will compare the incidence of desaturation ≤ 94% or face mask ventilation. Intent-to-treat and per-protocol analysis are planned for the primary outcome. We shall also perform exploratory sub-group analysis for the primary outcome regarding the type of intubation (FOI or RSI). An interim analysis will be performed after inclusion of half of the total number of patients (93 patients) to enable re-estimation of the sample size to maintain power.[23,24] 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.

The secondary outcomes will be described and compared between the two groups with linear regression models, generalized mix models or survival models (Cox or Fine and Gray) according to the nature of the variable. All of the analyses will be adjusted to intubation sequence (FOI or RSI).

A predefined statistical analysis plan will be followed using SAS software V.9.3 (Cary, North Carolina, USA). The statistical analysis will incorporate all of the elements required by the CONSORT statement for non-pharmacological interventions.

Track record

Data will be recorded in a web-based electronic case report form (eCRF) by the research team. Characteristics at baseline will be gathered: age, sex, weight, height, medical history, indication for surgery, predictive criteria of difficult mask ventilation or of difficult intubation, description of the intubation procedure (technical aspect, drugs and adverse events). During surgery, respiratory and cardiovascular parameters will be assessed.

Any protocol deviations will be recorded in the eCRF and the medical records. To preserve the confidentiality of personal information, data will be key-coded using alphanumerical numbers. To minimise missing data, to improve the quality of data collection and tracking, an external assessor will collect the variation of SpO_2.

Data statement

Data set will be available on reasonable request to the corresponding author.

Monitoring

Monitoring will follow "Good Clinical Practice principles" and will be performed by the independent promotion department of Nantes University Hospital Research Management Unit.

The following data will be assessed:

- Written consent after oral and written information during the anaesthesia consultation.
- Flow chart filled in for included and excluded patients.
- Trial progress.
- Primary and secondary outcome collection.
- Treatment-related severe adverse events.

The eCRF is a secure, interactive, web-response system provided and managed by the biometrics unit of the Nantes University Hospital (Nantes, France). The physicians and a clinical research nurse will ensure compliance with the study protocol and collect the study data in the eCRFs.

Trial status

A total of 186 patients are expected to be included within 15 months.

June 2018: protocol approval by the Ethics Committee.

September 2018: Start of inclusion.

March 2020: End of inclusion.

We will submit the manuscript during the second half of 2020.

ETHICS AND DISSEMINATION

Research ethics approval.

The trial will be conducted in compliance with the current version of the Declaration of Helsinki and Good Clinical Practice guidelines. The research project was approved by the appropriate Ethical Review Board (Medical Ethic Committee "PARIS, Ile-de-France 2", registration number: 2018-04-04 RIPH2).

The study was registered at http://www.clinicaltrials.gov with trial identification number: NCT03604120 before the first inclusion.

Confidentiality

The study data will be handled as requested by the French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés). All original records will be kept on file at the trial site for 15 years. The electronic trial database file will be anonymised and kept on file for 15 years.

Conflict of interests

This study was supported by institutional funds and a grant from Fisher & Paykel Healthcare (FPH) that is inferior to 20% of the total budget (24,000 Euros). FPH did not participate in the study design and will not participate in data collection, analysis and interpretation, nor in the preparation, review approval and decision to submit the manuscript for publication.

Dissemination plan

The study will be published in an international medical journal.

DISCUSSION

Among the intubation related adverse events, hypoxaemia is a life-threatening issue and this complication is mainly encountered during difficult airway management. HFNC presents several theoretical advantages compared with the standard face mask, including the ability to deliver continuous oxygen flow to perform apnoeic oxygenation. Recent expert guidelines have advised the use of such a device to prevent desaturation during DI.[5,7] However, its relevance has never been evaluated in a large randomised study. This device could improve patient safety but, it must be evaluated before systematic implementation in the airway control algorithm.

ACKNOWLEDGEMENTS

We are grateful to the medical staff, nurses and research staff of the Anaesthesia and Critical Care Departments of Nantes University Hospital. We thank Ludivine Perrier for administrative and logistic support, Coralie Ono dit Biot for creating the eCRF, and Dr Anne Chiffoleau, MD for safety monitoring.

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AUTHORS CONTRIBUTION

KA and MV obtained funding. KA, SJ, DH, GB, AG, MS, MT, CG and MV designed the study. FF and AC planned the statistical analysis. KA and MV will have full access to the final trial dataset. All authors participated in the writing the manuscript and approved the final version.

FUNDING

The PREOPTIDAM trial is supported by the University Hospital of Nantes and a grant from Fisher & Paykel Healthcare (FPH) that is inferior to 20% of the total budget (24,000 Euros).

DISCLAIMER

The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

COMPETING INTERESTS

MV reports personal fees from MSD, Pfizer, Baxter, grants from Fischer Paykel, outside the submitted work. SJ reports personal fees from Draeger, Fresenius-Xenios and Fisher Paykel Healthcare, outside the submitted work. Karim Asehnoune declares personal fees from Fisher Paykel Healthcare, Baxter, LFB, Fresenius. The other authors declared to have no conflict of interest.

PATIENT CONSENT

Oral and written consent required.

ETHICS APPROVAL

By 11 june 2018 the study had been approved by a central ethics committee (Comité de Protection des Personnes Ile-de-France II, Paris, France), reference: 2018-04-04 RIPH2

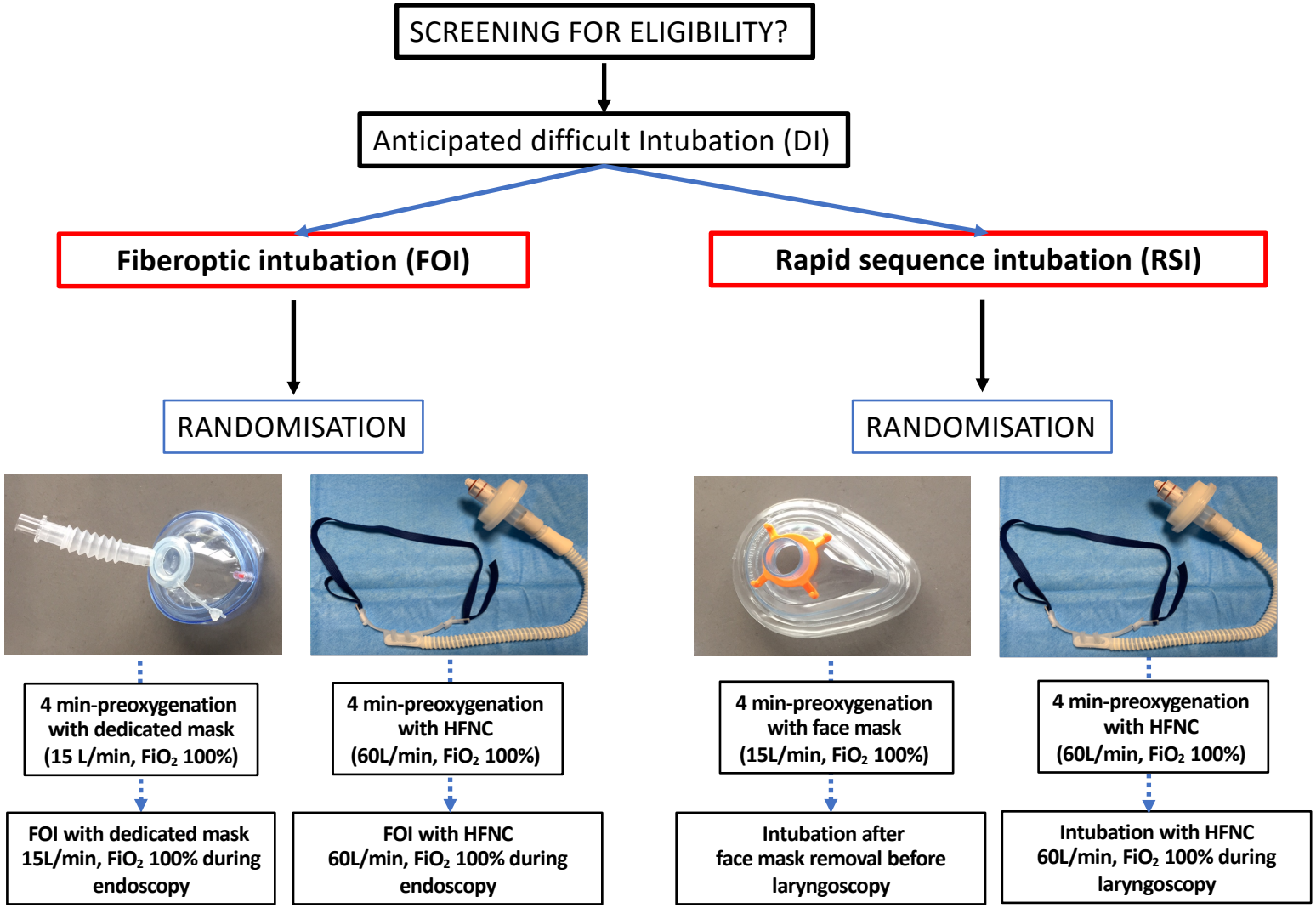
Tables and Figures

Title Table 1: Participants timeline

Legends Table 1: After written informed consent, the patients will be randomised and preoxygenation will be performed accordingly. Patients will be followed until the Post-Anesthesia Care Unit (PACU) discharge.

Title Figure 1: Study design

Legend Figure 1: After attending physician decision to perform RSI or fiberoptic intubation, patients will be randomised to receive HFNC or Face mask oxygenation. **FOI**: Fiberoptic Intubation, **HFNC**: High Flow Nasal Cannula, **FiO_2**: Fraction of inspired oxygen


SCREENING FOR ELIGIBILITY?
Anticipated difficult Intubation (DI)
Fiberoptic intubation (FOI)
Rapid sequence intubation (RSI)
RANDOMISATION
RANDOMISATION
4 min-preoxygenation with dedicated mask (15 L/min, FiO2 100%)
4 min-preoxygenation with HFNC (60L/min, FiO2 100%)
4 min-preoxygenation with face mask (15L/min, FiO2 100%)
4 min-preoxygenation with HFNC (60L/min, FiO2 100%)
FOI with dedicated mask 15L/min, FiO2 100% during endoscopy
FOI with HFNC 60L/min, FiO2 100% during endoscopy
Intubation after face mask removal before laryngoscopy
Intubation with HFNC 60L/min, FiO2 100% during laryngoscopy

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1+22
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17+22
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5+6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12+13+14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8+10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7+8+9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16+18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15+16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15+16
Statistics: analysis population and	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	15

missing data		statistical methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14+15+16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8+10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16+18

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18+22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16+22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA