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D'ANESTHESIE-REANIMATION

par

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« PREOXYGENATION PAR CANNULES NASALES D'OXYGENATION A HAUT DEBIT COMPAREE AU MASQUE FACIAL STANDARD DANS LE CADRE DE LA GESTION DES VOIES AERIENNES DIFFICILES : UNE ETUDE OUVERTE, MONOCENTRIQUE ET RANDOMISEE (L'ETUDE PREOPTIDAM) »

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Abréviations

BMI	Body Mass Index
CI	Confidence Interval
DI	Difficult Intubation
FeO2	Expired oxygen fraction
FeCO2	Expired carbon dioxide fraction
FOI	Fiberoptic Intubation
HFNC	High Flow Nasal Cannula
PaO2	Arterial Partial Pressure of Oxygen
RSI	Rapid Sequence Intubation
SD	Standard Deviation
SpO2	Oxygen saturation measured by pulse oximetry
Vs.	Versus

Table des matières

Preoxygenation in difficult airway management with high-flow oxygenation by nasal cannula versus standard facemask: an open-label, monocenter, randomised study (the PREOPTIDAM study)

Summary

Objective To assess the effect of nasal high flow nasal cannula (HFNC) therapy for the prevention of oxygen desaturation during intubation procedure, for patient at risk of difficult intubation.

Design Phase III, randomised, monocenter, open-label, controlled trial.

Setting Nantes University Hospital, from September 2018 to March 2021.

Participants 186 adults requiring general anesthesia with an anticipated difficult intubation. The expected duration of the study was 24 months.

Interventions Participants were randomised to HFNC or standard facemask as preoxygenation device. Randomisation was a priori stratified on the intubation method, fiberoptic intubation or laryngoscopic rapid sequence intubation (RSI).

Main outcomes measure The primary outcome was the incidence of hypoxemia during endotracheal intubation procedure. Hypoxemia was defined as desaturation below 95% or preventive facemask ventilation. Intubation techniques as well as patient safety and morbidity were monitored as secondary outcomes.

Results Of the 186 participants who underwent randomisation, 1 withdrew consent and 185 (99.5%) were included in the final analysis. In the modified intention-to-treat population, the incidence of the primary outcome was not significantly different between the HFNC group and the standard facemask group, respectively 2% vs. 8%, adjusted odds ratio 0.26, 95% confidence interval (CI) 0.05 to 1.27; P=0.10. However, in the per-protocol population, the incidence was significantly reduced in the HFNC group as compared to the standard group, respectively 0% vs. 8%; P=0.006. In the fiberoptic intubation stratum, tolerance of the procedure was better in the HFNC group as compared to the standard group (P=0.003) and the mean (SD) EtO2 at the end of the intubation procedure was higher in the HFNC group than in the standard group, respectively 71% (8%) vs. 60% (8%), adjusted group difference of 11%, 95% CI 4.52 to 17.16%; P=0.001. None of the patients experienced desaturation in the HFNC group. There was no significant difference between the two groups in the incidence of at least one moderate or severe complication, respectively 30% vs. 40%, adjusted odds ratio 0.60, 95% CI 0.32 to 1.10; P=0.10.

Conclusions In the intent-to-treat analysis, HFNC did not significantly reduce the incidence of desaturation <95% or preventive facemask ventilation in adults requiring general anesthesia with an expected difficult intubation. Results of the per-protocol analysis and the fiberoptic intubation stratum analyses encourage further studies.

Trial registration ClinicalTrials.gov NCT0360412

Préoxygénation par canules nasales d'oxygénation à haut débit comparée au masque facial standard dans le cadre de la gestion des voies aériennes difficiles : une étude ouverte, monocentrique et randomisée (l'étude PREOPTIDAM)

Résumé

Objectif Évaluer l'effet de l'oxygénation à haut débit par voie nasale sur la prévention de l'hypoxémie pendant la procédure d'intubation, chez des patients présentant un risque d'intubation difficile.

Design Étude de phase III, randomisée, ouverte et contrôlée.

Cadre Hôpital Universitaire de Nantes, de septembre 2018 à mars 2021.

Participants 186 adultes nécessitant une anesthésie générale avec intubation endotrachéale et ayant une intubation difficile prévue. Le délai prévu de recrutement était de 24 mois.

Intervention Selon leur groupe de randomisation, les patients ont reçu comme dispositif de préoxygénation soit des canules nasales d'oxygénation à haut débit, soit un masque facial standard. La randomisation a été stratifiée à priori sur la méthode d'intubation, à savoir par fibroscopie ou par laryngoscopie.

Critères de jugement Le critère de jugement principal était l'incidence de l'hypoxémie pendant la procédure d'intubation. L'hypoxémie a été définie comme une désaturation <95 % ou une ventilation préventive par masque facial, réalisée pour éviter la survenue d'une désaturation. Les techniques d'intubation ainsi que la sécurité et la morbidité des patients ont également été évaluées comme critère de jugement secondaires.

Résultats Sur les 186 participants randomisés, un seul a retiré son consentement et 185 (99,5%) ont donc pu être inclus dans l'analyse finale. Dans la population en intention-de-traiter modifiée, l'incidence du critère de jugement principal n'était pas significativement différente entre le groupe HFNC et le groupe masque facial, respectivement 2% contre 8%, odds ratio ajusté à 0,26, intervalle de confiance (IC) à 95 % 0,05 à 1,27 ; P=0,10. Cependant, dans la population per-protocole, l'incidence du critère de jugement principal était significativement réduite dans le groupe HFNC, respectivement 0% contre 8% ; P=0,006. Dans la strate d'intubation fibroscopique, la tolérance de la procédure était meilleure (P=0,003) et aucun patient du groupe HFNC n'a désaturé. De plus le pourcentage d'oxygène expirée (EtO2) à la fin de la procédure d'intubation était plus élevé, respectivement 71% vs 60%, avec une différence ajustée de 11%, IC 95% 4,52 à 17,16% ; P=0,001. Il n'y avait pas de différence significative en ce qui concerne la survenue de complications modérées ou sévère, respectivement 30% vs. 40%, odds ratio ajusté à 0.60, IC à 95% 0.32 to 1.10; P=0.10.

Conclusion Dans la population en intention de traitée, l'HFNC n'a pas significativement réduit l'incidence de désaturation <95% ou de ventilation préventive au masque facial, chez des adultes bénéficiant d'une anesthésie générale et ayant des critères prédictifs d'intubation difficile. Cependant, les résultats positifs de l'analyse per-protocole et de l'analyse du sous-groupe de patient intubés par fibroscopie encouragent la réalisation de nouvelles études de plus grande envergure.

Enregistrement de l'essai ClinicalTrials.gov NCT03604120

Introduction

Each year 313 million surgical procedures are performed worldwide, resulting in 4.2 million deaths [1,2]. Successfully reducing this mortality is a major public health challenge [2]. In large observational studies, hypoxia due to airway management failure has emerged as the leading cause of death or serious adverse event related to anesthesia [3,4] . Despite the establishment of rigorous management algorithms, incorporating modern efficient ventilation and intubation devices, mortality has not decreased recently [5,6]. In order to identify patients at risk of difficult airway management, predictive criteria for difficult intubation and ventilation have been identified [5,7]. These patients are particularly exposed to hypoxia and should be managed carefully [8].

Guidelines for the management of difficult airway [9–11] advise to perform awake fiberoptic intubation (Fiberoptic intubation) under sedation for patients with risk factor of impossible manual ventilation or with limited mouth opening. This technique maintains the patient's spontaneous breathing and avoids "cannot intubate cannot ventilate" situation [12]. During fiberoptic intubation, the patient's oxygenation is achieved with specific facial mask or standard nasal cannula. Guidelines also recommend to perform laryngoscopic rapid sequence intubation (RSI) for patient with risk factor of difficult intubation without fiberoptic intubation indication. RSI requires the use of short-action drugs to achieve optimal intubation conditions while limiting apnea duration [9–11]. The key message of current guidelines is to focus on oxygenation. They place a strong emphasis on achieving effective preoxygenation procedures. During preoxygenation patients achieve denitrogenation of their lungs and fill them with pure oxygen. The aim is to extend safe apnea time and reduce hypoxia occurrence. It is currently the cornerstone of patient safety during intubation procedures [13,14]. In addition to preoxygenation, guidelines promote apnoeic oxygenation, a complementary technique that could enhance anesthesia security [9,10].

The physiological principle of apneic oxygenation is based on an aventilatory flow of oxygen, from the upper airways to the alveoli, due to external oxygen supply on one side and blood oxygen extraction on the other [15]. It was historically performed with low-flow nasal or nasopharyngeal cannula [16] and has already proven its efficiency [17]. A new device could optimize this old concept. High-Flow oxygenation by Nasal Cannula (HFNC) can deliver up to

60 L/min gas flow, humidified and heated, with a fraction of inspired oxygen (FiO2) of 100%. HFNC is able to generate a moderate positive supraglottic end expiratory pressure, to flush nasopharyngeal dead space and to guaranty a constant FiO2 [18]. It was initially used to palliate respiratory failure in intensive care [19,20] or to prevent postoperative respiratory failure [21]. In the indication of preoxygenation and apnoeic oxygenation [22], its results are controversial, depending on patient's characteristics [23–27]. In the specific indication of anticipated difficult intubation, HFNC has many theoretical advantages. Indeed, in the case of RSI, nasal cannula can be left in place after preoxygenation and perform apneic oxygenation. In the case of fiberoptic intubation, HFNC may limit facemask leakage and thus improve patient per-procedure oxygenation. It may also enhance patient and operator comfort. Indeed, two recent preliminary studies have reported very encouraging results in this indication [28,29]. For all these reasons, some authors call for its systematic implementation in difficult airway algorithm [30], but its relevance must first be objectively assessed in a large randomised study.

Recent anesthetic guidelines encourage further research in the area of apneic oxygenation. Indeed, it appears to be an effective way to protect patients at risk of hypoxia [9–11]. Anticipated difficult intubation patients present a high risk of oxygen desaturation and preliminary results of HFNC in this indication seem to be very promising. We conducted a randomised, controlled, trial to assess HFNC efficiency for preoxygenation of patients with anticipated difficult intubation procedures. We hypothesize that HFNC, used as a preoxygenation and apneic oxygenation device, could reduce the incidence of oxygen desaturation or preventive facemask ventilation in this indication.

Methods

Trial design and setting

This trial was conducted in a French hospital (Nantes University Hospital). It is a pragmatic, investigator initiated, monocenter, parallel-group, open-label, randomised, controlled trial to compare HFNC with standard facemask for hypoxia prevention during intubation sequence, in patients at risk of difficult intubation. Patients provided written informed consent before participation. The study protocol and statistical analysis plan were submitted before the inclusion of the first participant (Reference of the central ethics committee approval: 2018-

04-04 RIPH2) and published [31]. The department of research at the University hospital of Nantes conducted data monitoring and data quality check. Investigators reported any adverse events within seven days. Blinding of clinicians and patients to the type of preoxygenation device was impossible. Indeed, the two preoxygenation devices have a completely different presentation and way of use.

Adult patients with at least one severe or two moderates risk factor of difficult intubation and requiring RSI or fiberoptic intubation were eligible for enrolment [31]. Supplementary file provides complete lists of exclusion criteria and anticipated difficult intubation criteria (supplementary table A).

An independent research unit at the University Hospital of Nantes performed the randomisation. A statistician, not involved in patient recruitment, randomised the participants using a computer-generated random number in fixed blocks (1:1 ratio). Randomisation was stratified on a single prespecified criterion, the intubation sequence, which depended on clinician decision (RSI or Fiberoptic intubation). Before anesthetic induction, a local investigator randomised participants using a dedicated encrypted website (CSOnline; Clinsight) to allow immediate and concealed allocation.

Intervention

Study intervention is summarized in Figure 1. For anticipated difficult intubation, current guidelines recommend to perform fiberoptic intubation for patients with risk factors of impossible mask ventilation or limited mouth opening, or RSI in the other cases. Thus, depending on patient's history and anatomical features, the clinician chooses an intubation technique. Patients of the 2 strata (Fiberoptic intubation or RSI) were then randomly allocated to the intervention group or the standard group.

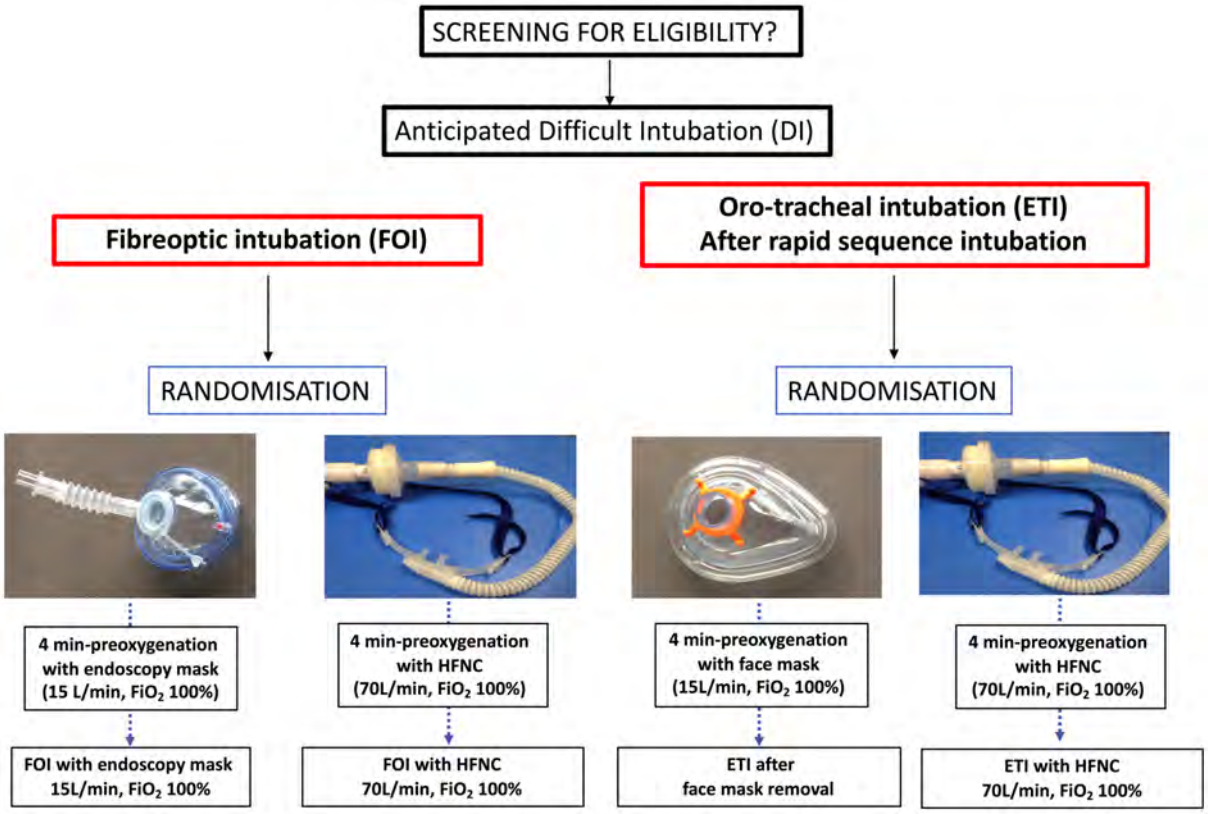
In the intervention group preoxygenation was performed with HFNC (Fisher & Paykel Healthcare, Auckland, New Zealand) for four minutes. HFNC was set at 60 L/min flow rate of pure (100% inspired oxygen fraction) and humidified oxygen (temperature at 37°). Patients were asked to keep their mouths closed to avoid air contamination. Large or medium nasal cannula were chosen according to patient's nostril size, to avoid air contamination. After induction, HFNCs were maintained throughout the intubation procedure, until successful

intubation had been confirmed. The aim was to achieve apneic oxygenation during laryngoscopic RSI or adequate oxygenation while the patient was spontaneously breathing for fiberoptic intubation.

In the standard group, preoxygenation was performed with standard facemasks for four minutes. A fitted facemask was chosen according to patient's anatomy in order to avoid oxygen leaks (size 3 to 6 for adult patients). The ventilation system was set to 15 L/min of fresh gas, with 100% inspired oxygen fraction. No inspiratory support or positive expiratory pressure was allowed. After induction, in the RSI stratum, the facemask (Economy, Intersurgical, Fontenay Sous Bois, France) was removed to enable laryngoscopy. While in the fiberoptic intubation stratum, the specific facemask (Fibroxy, VBM, Sulz, Germany) was kept in place, throughout the intubation procedure, with the same ventilator settings, to achieve continuous oxygenation. This required another caregiver to maintain the mask, ensure proper positioning and airtightness. These masks allow the passage of the fiberscope and the intubation tube, through a thin resealable opening. In both groups, the first operator was a senior or a junior supervised by a senior.

All other interventions were at the discretion of the clinician, in particular the choice of intubation technique and anesthetic drugs, the decision to proceed to facemask ventilation and the choice of alternative rescue oxygenation technique. The attending physician was free to withdraw the oxygenation device if it disrupted the intubation process or rescue oxygenation.

Figure 1: Study design. After attending physician decision to perform RSI or fiberoptic intubation, patients were randomised to receive HFNC or facemask oxygenation.



Outcomes

The primary outcome was a composite of desaturation below 95% or preventive facemask ventilation during the intubation procedure. It was assessed from the beginning of anesthesia induction to two minutes after intubation success, to avoid delayed detection of desaturation by pulse oximetry. Patients were classified into two groups: 'No event' or 'at least one event'.

This threshold of 95% comes from recent international anesthesia guidelines [9]. It has been chosen by experts, as a signal to stop intubation attempts and start oxygenation maneuvers, to ensure patient safety. Facemask ventilation is also a clinically relevant endpoint and not taking it into account would have biased the assessment of patient's desaturation. Indeed, this oxygenation technique directly impacts the arterial oxygen level of the patient. Moreover, facemask ventilation can be difficult or impossible, which can lead to dramatic situation, especially with patients at risk of difficult intubation. It can also cause gastric insufflation and pulmonary aspiration of gastric content. The level of arterial oxygen saturation was evaluated by pulse oximetry (SpO2).

Secondary outcomes were the quality of the preoxygenation, the difficulty of the intubation procedure, the intubation-related adverse events, the intraoperative as well as the post-operative care unit morbidity.

The quality of preoxygenation was assessed by the duration of the procedure, the SpO2 at the end of the procedure and the occurrence of leaks during preoxygenation. In the face mask group, EtO2 and EtCO2 at the end of the preoxygenation were also monitored.

The process of intubation was assessed by collecting intubation success rate, the need of more than one operator, first-pass attempt success rate, occurrence of desaturation <90%, number of facemask ventilation episodes, lowest SpO2, lowest EtO2 and highest EtCO2 within 2 min following intubation, duration of the intubation procedure and patient's satisfaction score (evaluated a-posteriori in post-anesthesia care unit). In the laryngoscopic stratum, the quality of exposure (Cormack score), the number of laryngoscopies, the Intubation Difficulty Scale score, the number of alternative devices and the difficult intubation rate were also monitored. In the fiberoptic intubation stratum sedation quality during fiberoptic intubation was evaluated using a dedicated scale ("patient sedation score") [32].

Per-operative respiratory monitoring was assessed by collecting higher FiO2 required to obtain SpO2 >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 maneuvers for desaturation <95% and achievement of tidal volume reduction owing to peak pressure >40 mmHg.

Morbidity in the post-anesthesia care unit was assessed by collecting rates of nausea or vomiting, occurrence of inspiratory dyspnea after extubation, lowest SpO2 after extubation, occurrence of desaturation <90% before or after extubation, occurrence of severe desaturation <80% before or after extubation, need of oxygen therapy at post-anesthesia care unit discharge, length of stay in the post-anesthesia care unit, duration of mechanical ventilation, need of non-invasive ventilation support and occurrence of reintubation for respiratory failure.

Intubation-related complications, during intubation and the following 1 hour, were divided into two groups. Severe complications included death, cardiac arrest, severe desaturation <80%, severe cardiovascular collapse (systolic blood pressure <80 mm Hg or the need to

administer ephedrine or neosynephrine or norepinephrine). Mild-to-moderate complications included intubation failure, severe ventricular or supraventricular arrhythmia, esophageal intubation, dental injury, dangerous agitation, vomiting with aspiration of gastric content, naso-laryngotracheal injury or bleeding during intubation sequence.

Severe complications were all collected in the eCRF and immediately analyzed by the vigilance unit of research department of the Nantes University Hospital.

Analysis

The rate of desaturation <90% ranged from 12% to 21% in studies on Fiberoptic intubation [33,34]. On the other hand, a rate of desaturation <95% of 16% has recently been reported during intubation procedures of patient with anticipated difficult intubation [8]. We hypothesised that HFNC would reduce the rate of our composite primary outcome from 16% to 4%. This 12% reduction was based on a previous study in the ICU [35]. 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.

For the primary outcome, a logistic model compared the incidence of desaturation <95% or preventive facemask ventilation between groups. The main analysis of the primary outcome was conducted in the modified intention-to-treat population, defined as all randomised participants except those who withdraw their consent. We also analyzed the primary outcome in the per-protocol population, defined as all randomised participants except those with major protocol violations (consent withdrawn, received the wrong intervention or device removal during intubation procedure). Prespecified exploratory subgroup analysis for the primary outcome regarding the type of intubation (Fiberoptic intubation or RSI) were also performed [31].

The secondary outcomes are 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 were adjusted to intubation sequence (Fiberoptic intubation or RSI).

Analyses were performed using SAS software (version 9.4, NC) before the breaking of the randomization code. The statistical analysis has incorporated all of the elements required by the CONSORT statement for non-pharmacological interventions.

Patient and public involvement

Except for providing written informed consent before participation, no patients or members of the public were involved in the research. However, the primary and secondary outcomes of the study impact directly patients' safety and comfort. Participant satisfaction of the intervention was assessed before post-anesthesia care unit discharge and has been analyzed as a secondary outcome.

Results

Characteristics of the population

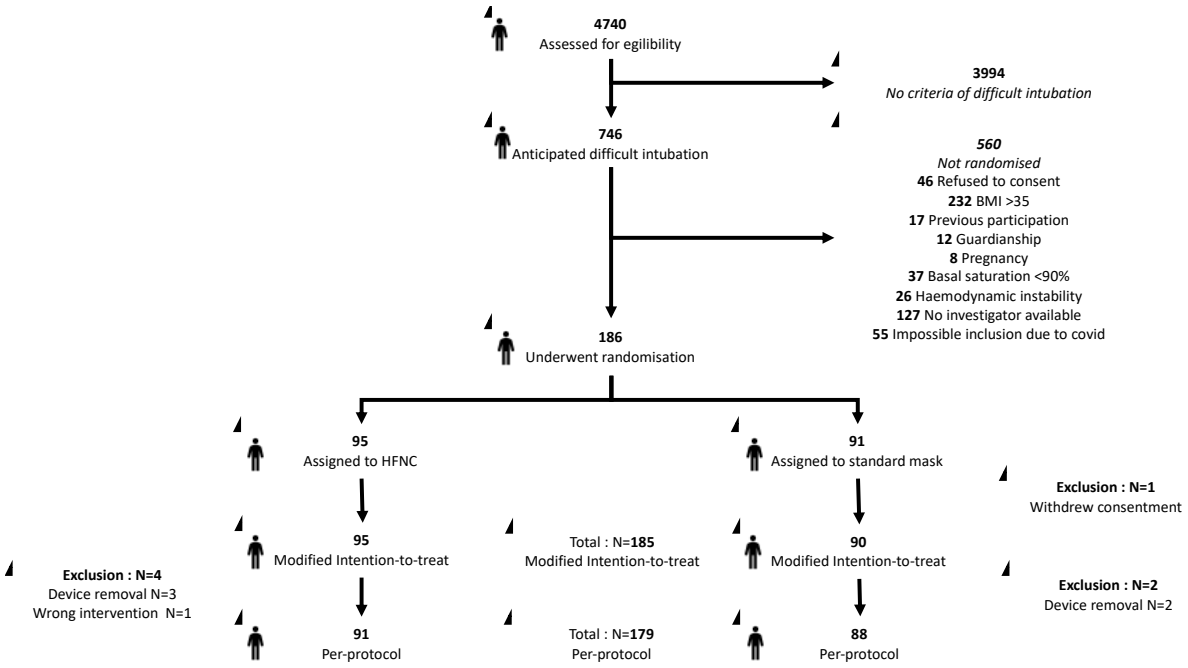
From September 2018 to March 2021, 186 patients were randomised (95 in HFNC group and 91 in standard group; Figure 1). One participant withdrew his consent after randomization and before anesthetic induction. Finally, 185 patients met the criteria for the modified intention-to-treat analysis (95 in HFNC group and 90 in standard group). After excluding six participants (one received the wrong intervention, five had device removal prohibited by the protocol during intubation procedure), 179 patients met the criteria for the per-protocol analysis (91 in HFNC group and 88 in standard group)

Baseline characteristics of the modified intent-to-treat population are described in Table 1. Patients were mostly men (75%), aged around 60 years (mean (SD) age of 62 (13) years in HFNC group and 60 (13) years in standard group), admitted for Head and Neck surgery (88%). Analysis of patient's history and co-morbidities showed no major difference between HNFC group and standard group, in particular in terms of initial cardiac or respiratory status. 35 patients (37%) in the HFNC group and 32 patients (36%) in the standard group had a McCabe scale score of 1. 28 patients (29%) in the HFNC group and 30 patients (33%) in the standard group were smokers.

Table 1. *Baseline characteristics of participants in modified intention-to-treat population*		
Characteristic	High-flow nasal cannula (n=95)	Facemask (n=90)
Sex, n (%)		
Male	71 (75)	68 (76)
Female	24 (25)	22 (24)
Mean (SD) age, years	62 (13)	60 (13)
Mean (SD) BMI, $kg.m^{-2}$	23 (4)	23 (5)
Comorbidities, n (%)		
McCabe scale 1 [a]	35 (37)	32 (36)
Chronic heart failure (NYHA III or IV) [b]	8 (8)	10 (11)
Hypertension	33 (35)	41 (45)
Chronic obstructive pulmonary disease	10 (11)	14 (15)
Obstructive sleep apnea	6 (6)	4 (4)
Active tobacco	28 (29)	30 (33)
Diabetes	4 (4)	3 (3)
Mean (SD) SpO2 in air, %	98 (2)	98 (2)
Type of surgery, n (%)		
Head and Neck	89 (94)	73 (81)
Orthopedic	5 (5)	9 (10)
Digestive, urologic, plastic or neurological	1 (1)	7 (8)
Interventional radiology	0 (0)	1 (1)

BMI=Body Mass Index, defined as the body mass divided by the square of the body height
SD=Standard Deviation
a: McCabe Scale is a subjective score that classifies patients in three categories according to their underlying diseases. It was created to predict sepsis survival. Category 1=non-fatal disease; cat 2=ultimately fatal disease (within 5 years); cat 3=rapidly fatal disease (within 1 year).
b: NYHA is a simple score that classifies cardiac dysfunction according to patients' symptoms and limitations. It starts with NHYHA 1: No limitation of physical activity and goes up to NYHA 4: Unable to carry on any physical activity without discomfort.

Figure 2: Flow chart of participants through study



Patients baseline airway and intubation parameters are described in table 2. Most of the participants had at least two criteria of difficult ventilation (63% in the two groups). The most frequent difficult intubation criteria were “a previous difficult intubation” (44% in HFNC and 59% in standard), “Previous laryngeal surgery or radiotherapy” (58% in HFNC and 54% in standard), “Mallampati score of 3 or 4” (61% in HFNC and 53% in standard). A quarter of the patients had a reduced mouth opening <25mm (28% in HFNC and 24% in standard). Fiberoptic intubation was performed in one-third of patients (33% in HFNC and 34% in standard). First operators were mainly junior (66% in HFNC and 61% in standard). Drugs used for RSI combined most often Propofol (95% in HFNC and 97% in standard) with Succinylcholine (58% in HFNC and 69% in standard). While sedation used for fiberoptic intubation combined mostly Remifentanil used in a target controlled intravenous anesthesia manner (100% in the two groups) and Ketamine (58% in the two groups).

Table 2. *Airway and intubation settings at baseline in modified intention-to-treat population*

Airway and Intubation settings	High-flow nasal cannula (n=95)	Face Mask (n=90)
Predictive factors for difficult facemask ventilation, n (%)		
Age > 55 years	70 (74)	71 (79)
Limitation of jaws protrusion	48 (51)	44 (49)
Snoring	16 (17)	15 (17)
Edentulous	41 (43)	28 (31)
Beard	3 (3)	2 (2)
BMI > 26	17 (18)	25 (28)
At least 2 difficult mask ventilation criteria	60 (63)	57 (63)
Predictive factors for difficult intubation, n (%)		
Previous difficult intubation	42 (44)	53 (59)
Previous laryngeal surgery or radiotherapy	55 (58)	49 (54)
Oral cavity or laryngeal cancer	50 (53)	38 (42)
Mallampati score 3 or 4 [a]	58 (61)	48 (53)
Thyromental distance < 6.5 centimeters	20 (21)	22 (24)
Mouth opening from 25 to 35 mm	18 (19)	20 (22)
Mouth opening < 25 millimeters	27 (28)	22 (24)
Limitation of cervical mobility <35 degrees	30 (32)	36 (40)
Retrognathism	7 (7)	3 (3)
Neck perimeter > 40 centimeters	16 (17)	14 (16)
Intubation, n (%)		
First operator: junior	63 (66)	55 (61)
Anesthetic agents for intubation		
Laryngoscopic intubation	**N = 64/95 (67)**	**N = 59/90 (66)**
Propofol	61/64 (95)	57/59 (97)
Etomidate or Ketamine	3/64 (5)	2/59 (3)
Neuromuscular blocking agent		
Rocuronium	3/64 (5)	2/59 (3)
Succinylcholine	37/64 (58)	41/59 (69)
None	28/64 (44)	14/59 (24)
Awake Fiberoptic intubation	**N = 31/95 (33)**	**N = 31/90 (34)**
Propofol	9/31 (29)	6/31 (19)
Remifentanil	31/31 (100)	31/31 (100)
Ketamine	18/31 (58)	18/31 (58)

BMI: Body Mass Index

a : Mallampati score is a score used by anesthetist to predict intubation difficulty. The test requires a visual evaluation of the oral cavity. Mallampati scoring goes from class 1: Soft palate, uvula, fauces, pillars are visible to class 4: only hard palate is visible. Class 3 but especially class 4 are associated with difficult intubation.

Primary outcome

In the modified intention-to-treat analysis, 2 of 95 participants (2%) in the HFNC group and 7 of 90 participants (8%) in the standard group experienced desaturation <95% or preventive facemask ventilation (**adjusted odds ratio 0.26, 95% confidence interval (CI) 0.05 to 1.27; P=0.10**, Table 3). HFNC did not reduce the occurrence of the composite primary outcome for the two a priori defined randomization strata. In the rapid sequence induction stratum, the primary outcome occurred in 2 of 64 participants (3%) in the HFNC group and in 3 of 59 participants (5%) in the standard group (odds ratio 0.60, CI 95% 0.10 to 3.74, P=0.59, supplementary table B). In the fiberoptic intubation stratum the primary outcome occurred in 0 of 31 participants (0%) in the HFNC stratum and in 4 of 31 participants (13%) in the standard stratum (P=0.11; supplementary table B).

In the prespecified per-protocol analysis, HFNC significantly reduced the incidence of the primary outcome 0 of 91 participants (0%) in the HFNC group and 7 of 88 participants (8%) in the standard group (**P= 0.006**, table 3). In the exploratory subgroup analyses, the occurrence of the primary outcome was still significantly reduced by HFNC in the fiberoptic intubation stratum but not in the RSI stratum. In the fiberoptic intubation stratum, 0 of 31 participants (0%) in the HFNC group and 4 of 29 participants (14%) in the standard group experienced desaturation <95% or preventive facemask ventilation (**P= 0.049,** supplementary data, table B). In the RSI stratum, the primary outcome occurred in 2 of 64 participants (3%) in the HFNC group and 3 of the 59 (5%) participants in the standard group (P=0.11, supplementary data, table B).

Table 3 (first part). *Primary outcome in the modified intention-to-treat and per-protocol population. Secondary outcomes in the modified intention-to-treat population*

Outcomes	High-flow nasal cannula (n=95)	Face Mask (n=90)	OR (95% CI)	Between group difference (95% CI)	P value
Primary outcome, desaturation <95% **or face mask ventilation, n (%)** [a,b]					
Modified intention-to-treat population	2/95 (2)	7/90 (8)	0.26 (0.05 to 1.27)		0.10[*]
Desaturation <95%	2/95 (2)	6/90 (7)	0.30 (0.06 to 1.55)		0.15[*]
Facemask ventilation	2/95 (2)	2/90 (2)	0.95 (0.13 to 6.86)		0.96[*]
Per-protocol population [c]	0/91 (0)	7/88 (8)	/		**0.006**[†]
Desaturation <95%	0/91 (0)	2/88 (2)	/		0.24[†]
Facemask ventilation	0/91 (0)	6/88 (7)	/		0.013[†]
Secondary outcomes					
Preoxygenation [d]					
4 min or more, n (%)	95 (100)	90 (100)			0.9[†]
Mean (SD) SpO2 at the end of preoxygenation	100 (0.2)	100 (0.4)		0.05 (-0.04 to 0.14)	0.28[‡]
Leaks during preoxygenation [b,e]	1 (1)	31 (34)	0.01 (0.00 to 0.10)		**<.0001**[*]
Laryngoscopic intubation	0/64 (0)	10/59 (17)	/		**0.0004**[†]
Awake Fiberoptic intubation	1/31 (3)	21/31 (68)	0.02 (0.00 to 0.13)		**0.0001**[*]
Intubation, n (%)					
Number of operators >1 [b]	17 (18)	20 (22)	0.77 (0.37 to 1.58)		0,47[†]
First pass success [b]	65 (68)	62 (69)	0.98 (0.53 to 1.83)		0.96[†]
Mean (SD) duration of procedure (min)	3 (2)	3 (3)			
Laryngoscopic intubation	2 (2)	2 (2)		0.32 (-0.32 to 0.96)	0.32
Awake Fiberoptic intubation	4 (3)	5 (3)		-1.06 (-2.49 to 0.37)	0.14

Table 3 (second part). *Secondary outcomes in the modified intention-to-treat population*					
Outcomes	High-flow nasal cannula (n=95)	Face Mask (n=90)	OR (95% CI)	Between group difference (95% CI)	P value
Secondary outcomes					
Intubation, n (%)					
Mean (SD) lowest SpO2 (%)	99 (4)	98 (4)		0.18 (-1.01 to 1.37)	0.77
Laryngoscopic intubation	98 (5)	99 (2)		-0.51 (-1.82 to 0.80)	0.44
Awake Fiberoptic intubation	99 (1)	97 (7)		1.55 (-0.90 to 3.99)	0.21
Desaturation < 90%	1 (1)	2 (2)	0.47 (0.04 to 5.25)		0.54
Mean (SD) lowest EtO2 up to 2 min after intubation (%)					
Laryngoscopic intubation	78 (8)	79 (8)		-1.37 (-4.21 to 1.47)	0.34
Awake Fiberoptic intubation	71 (11)	60 (14)		11 (4.52 to 17.16)	**0.001**
Mean (SD) highest EtCO2 up to 2 min after intubation (mHg)					
Laryngoscopic intubation	38 (7)	38 (6)		-0.21 (-2.41 to 1.99)	0.85
Awake Fiberoptic intubation	41 (7)	47 (7)		-5.55 (-9.26 to -1.84)	**0.004**
Good or excellent satisfaction score, n (%) [f]	76 (80)	53 (59)	3.10 (1.53 to 6.25)		**0.0016**
Laryngoscopic intubation	55/64 (86)	44/59 (75)	2.08 (0.83 to 5.21)		0.11
Awake Fiberoptic intubation	21/64 (68)	9/59 (29)	5.13 (1.74 to 15.13)		**0.003**
Respiratory parameters 5 minutes following intubation					
Mean (SD) plateau pressure (cm H2O)	16 (5)	15 (3)	0.73 (-0.46 to 1.91)		0.23
Mean (SD) peak inspiratory pressure (cm H2O)	20 (5)	19 (4)	0.46 (-0.94 to 1.86)		0.52
Recruitment maneuvers for desaturation <95%, n (%)	3 (3)	3 (3)	0.92 (0.18 to 4.74)		0.92

Table 3 (third part). *Secondary outcomes in the modified intention-to-treat population*

Outcomes	High-flow nasal cannula (n=95)	Face Mask (n=90)	OR (95% CI)	Between group difference (95% CI)	P value
Outcome in the PACU					
Mean (SD) length of stay (min)	109 (43)	107 (40)	1.86 (-10.94 to 14.65)		0.78
Mean (SD) duration of mechanical ventilation (min)	8 (11)	9 (14)	-0.39 (-4.25 to 3.47)		0.84
SpO2 <90%, n (%)	4 (5)	1 (1)	3.93 (0.43 to 36.27)		0.23
Non-invasive ventilation support before or after extubation, n (%)	0 (0)	0 (0)	/		/
Nausea or vomiting, n (%)	1 (1)	6 (7)	0.15 (0.02 to 1.27)		0.08

a: Evaluation period of primary outcome is extended to 2 min following intubation completion owing to possible delayed detection of desaturation with pulse oximetry
b: Details of stratum analysis are presented in supplemental data
c: In the per-protocol population, patients whose medical oxygenation device were removed by the operator without respecting protocol modalities were excluded from the analysis
d: Data about EtO2 and EtCO2 at the end of preoxygenation in the Laryngoscopic intubation stratum are presented in the supplementary results
e: The definition of leaks depended on the patient stratum. In the face mask group inward or backward leaks were defined if there was at least 15% difference between inspired and expired volume. In the HFNC group leaks were defined by patients breathing with the mouth opened.
f: Satisfaction score was collected in the recovery room. It's a patient subjective assessment of the whole intubation procedure quality from 0 (terrible experience) to 3 (excellent experience).

* Wald test for logistic regression
† Fischer's exact test (no OR or 95% CI available)
‡ Linear regression

Secondary outcomes

All participants had a preoxygenation time of more than 4 minutes (100% in the two groups, Table 3). At the end of the preoxygenation, the mean saturation was 100% in both groups and the mean FeO2 was 86% in the standard group (table 3). Leakages occurring during preoxygenation were significantly reduced by HNFC. Leakages were observed in 1% of participants in the HFNC group and 34% in the standard group (odds-ratio 0.01, 0.00 to 0.10, P<0.0001, table 3).

During intubation, severe oxygen desaturation <90% occurrence was not different between groups (1% in HFNC vs. 2% in standard; P=0.54, table 3), as lowest (SD) SpO2 (99% (4) in HFNC vs. 98% (4) in standard; P=0.77), incidence of the need for a second operator (18% in HFNC vs. 22% in standard; P=0.47, table 3) or first-pass success rate (68% in HFNC vs. 69% in standard; P=0.96, table 3). However, HFNC improved patient's tolerance of the intubation procedure, as signified by a good or excellent global satisfaction score in 76 of 95 participants (80%) in the HFNC group compared to 53 of 90 participants (59%) in the standard group, (**odds ratio 3.10 (1.53 to 6.25); P=0.0016**, table 3)**.**

In the fiberoptic stratum, the lowest EtO2 up to two minutes after intubation success was significantly higher in the HFNC group as compared to the standard group (**between group difference 11, 95% CI 4.52 to 17.16, P=0.001,** table 3) and the highest EtCO2 up to two minutes after intubation success was significantly lower in the HFNC group as compared to the standard group (**-5.55, 95% CI -9.26 to -1.84, P=0.004**, table 3).

The use of HFNC was not associated with a significant reduction of the incidence of at least one moderate complication (odds ratio 0.70, 0.36 to 1.35, P=0.28, table 4). The most frequent severe complication was severe hypotension (23% in HFNC and 29%in standard, table 4). No cardiac arrest, intubation failure, aspiration or dental injury, occurred in either group (table 4).

Table 4 Intubation related adverse events in the modified intention-to-treat population

Secondary Outcomes	High-flow nasal cannula n=95	Face Mask n=90	Odds Ratio (95% CI)	P value
At least one complications (severe + moderate) [a,b]	28/95 (30)	37/90 (40)	0.60 (0.32 to 1.10)	0.0975
Laryngoscopic intubation	21/64 (33)	22/59 (39)	0.76 (0.37 to 1.60)	0.4761
Awake Fiberoptic intubation	7/31 (23)	14/31 (45)	0.35 (0.12 to 1.06)	0.06
At least one severe complication, n (%) [a]	22/95 (23)	27/90 (27)	0.7 (0.36 to 1.35)	0.30
Laryngoscopic intubation	16/64 (25)	18/59 (31)	0.76 (0.34 to 1.68)	0.50
Awake Fiberoptic intubation	6/31 (19)	9/31 (29)	0.59 (0.18 to 1.91)	0.40
Details of severe complications [a]				
Cardiac arrest or death	0 (0)	0 (0)		
SpO2 < 80%	1 (1)	1 (1)	0.96 (0.06 to 15.61)	0.98
Severe hypotension	22 (23)	26 (29)	0.74 (0.38 to 1.43)	0.37
At least one moderate complication, n (%) [b]	11/95 (12)	13/90 (14)	0.78 (0.33 to 1.83)	0.56
Laryngoscopic intubation	8/64 (13)	8/59 (14)	0.9 (0.32 to 2.60)	0.9
Awake Fiberoptic intubation	3/31 (10)	5/31 (16)	0.56 (0.12 to 2.57)	0.45
Details of moderate complications [b]				
Nasolaryngotracheal injury or bleeding	10 (10)	9 (10)		
Esophageal intubation	0 (0)	2 (2)		
Dangerous agitation	1 (1)	3 (3)		
Severe ventricular or supraventricular arrhythmia	0 (0)	1 (1)		
Dental injury	0 (0)	0 (0)		
Aspiration	0 (0)	0 (0)		
Intubation failure	0 (0)	0 (0)		

a: Severe complications were defined as severe desaturation <80%, severe hypotension (systolic pressure < 80mmHg), cardiac arrest or death.
b: Moderate complications were defined as naso-laryngo-tracheal injury or bleeding during RSI or FOI, esophageal intubation, dangerous agitation, severe arrhythmia, dental injury, vomiting with aspiration of gastric content, or intubation failure.

Discussion

In this randomized controlled trial, the use of HFNC as a preoxygenation device did not significantly reduce oxygen desaturation <95% or preventive facemask ventilation during anticipated difficult intubation. However, HFNC significantly improved patient's experience and did not increase intubation-related complications.

Several experimental studies have shown promising results of HNFC used for apneic oxygenation [26,28,29,36]. Experts called for robust evaluation of this technique in patients at high-risk of hypoxia [9–11]. Anticipated difficult intubation has been identified as an independent risk factor for hypoxia [8,37] . Evaluating the use of HFNC in this indication appeared essential to improve patient safety. This is the first randomised controlled, trial to assess HFNC as a preoxygenation and apneic oxygenation device in anticipated difficult intubation. The sample size was large for a monocenter study. The choice of an objective criterion for the primary endpoint limited the risk of evaluation bias, even if it was an open-label study. HFNC and ventilator settings were optimised and standardised to obtain reproductible and reliable data for primary and secondary endpoints, especially FeO2 and FeCO2. After intubation and connection to the ventilator, operators maintained the following settings: FiO2=100%, limited fresh gas-flow (1L/min) and closed circuit. The aim was to limit contaminations of first patients exhalations, by pure oxygen of the circuit or ambient air of the room, and provided reliable data for post-intubation FeO2 and FeCO2. This part of the protocol had already been successfully tested in a previous study [27]. In the RSI stratum, all patients received short-acting drugs. No mask ventilation was required before intubation. Thus, it could not interfere with the primary outcome. Patients received short-acting neuromuscular blockers (67%) or high-dose remifentanil boli (33%), providing quick optimal intubation conditions [9,38]. In line with current recommendations [9], the pragmatic design of the present study ensures the replicability of these results. Similarly, the diversity of difficult intubation criteria and the choice to include patients who would be intubated with two different techniques increase the external validity of the study. The risk of unbalancing the study groups was limited by an a-priori stratification on intubation procedure.

During fiberoptic intubation, two devices are currently used for patient oxygenation: standard low flow nasal cannula or Fibroxy mask. Observational studies on fiberoptic intubation with

low flow nasal cannula reported high incidence of desaturation <90% incidences, from 12% to 20% [33,34]. Neither low flow nasal cannula nor Fibroxy mask have been evaluated in controlled, randomised studies [39,40]. HFNC has a major advantage over Fibroxy mask. It's a "hand-free" preoxygenation device [35]. There is no need for another caregiver to maintain the mask position and ensure airtightness, thus facilitating the intubation procedure and improving patient's tolerance. Furthermore, the airtightness of Fibroxy masks is not optimal. It has to be firmly applied on patient's face, causing discomfort and claustrophobia. In addition, modifications of its position are often necessary to allow the passage of the fiberscope and the tube through patient's nostrils. These modifications increase discomfort and air contaminations [41]. Our study showed a strong benefit of using HFNC over facemask during fiberoptic intubation. HFNC induced a major reduction of oxygen leaks (68% in the standard group vs. 3% in the intervention group) and significantly increased the rate of "good or excellent satisfaction score". There is only one other trial on HFNC oxygenation during fiberoptic intubation, which has also reported a comfortable experience for all patients [28]. This trial was a preliminary study, on 46 patients with no group control. It demonstrated that HFNC nasal prongs do not interfere with fiberoptic intubation procedure, which was confirmed by the PREOPTIDAM study. Preliminary study results also suggest real clinical effectiveness. No patient experienced hypoxemia with an average procedure time of 18 minutes [28]. Similarly, no patients in the HFNC group experienced desaturation <95% or preventive mask ventilation in the PREOPTIDAM study. Although the small sample size of the fiberoptic stratum did not allow for a significant difference of the primary outcome in the modified intention-to-treat population, the difference was nevertheless significant in the per-protocol population. Another interesting signal is the improvement of post-intubation EtO2 values, which reflect patient's oxygen reserves [27]. There was no difference between the two group with regard to patient's history, quality of preoxygenation and intubation's duration. This suggests that oxygen uptake during intubation procedure was more efficient with HFNC. Post-intubation highest EtCO2 values were also significantly lower, suggesting a positive effect of HFNC in CO2 clearance. All these results illustrate the poor quality of current devices for oxygenation during fiberoptic intubation. They also suggest the superiority of HFNC in this indication. Further studies should be specifically designed to definitively prove it.

Recent works on preoxygenation with HFNC in the operating room reported promising findings. Two randomised trials have compared HFNC to face mask in patients requiring RSI [24,25]. In the first one, HFNC reduced the incidence of desaturation <93%, without improving the lowest SpO2 [25]. In the second one, post-intubation arterial partial pressure of oxygen (PaO2) was similar between the two group, but apnea time was longer in the HFNC group, suggesting safer apnea time with HFNC [24]. The present study is the first randomised trial focusing on patients with anticipated difficult intubation. The only data available came from a preliminary physiological study with only 25 participants and no control group. Authors reported a median apnea time of 14 minutes with no desaturation <90% [29]. However, the PREOPTIDAM study results did not confirm these promising preliminary results. In the RSI stratum analysis, HFNC didn't succeed to reduce desaturation <95% or facemask ventilation, neither in modified intention-to-treat population nor in per-protocol population. More disappointing, there was also an episode of severe desaturation <80% in the HFNC group. This discrepancy with previous studies has several explanations. First desaturation is a rare event in anesthesia. The previous preliminary study on difficult airway patients was probably not powerful enough to detect it [29]. Second, HFNC withdrawal during intubation procedures could have limited its efficiency. Third, preoxygenation with HFNC is probably not the optimal choice for all patient categories and difficult airway patients may have characteristics limiting its efficiency. Finally, HFNC has two distinct functions: apnoeic oxygenation and preoxygenation. Apnoeic oxygenation has proven to be effective in obese patients with low flow oxygenation devices [42–44] and in children with HFNC [26]. Similarly, preliminary results on HFNC for non-obese adults were promising [29,36]. In contrast, HFNC results for preoxygenation are mixed [22,45]. Some authors point out its heterogeneity, with imperfect preoxygenation results in a substantial part of patients [22,46]. Furthermore, during preoxygenation with HFNC the monitoring of EtO2 is not feasible. The anesthetist cannot therefore assess the success of the preoxygenation. Combining facemask preoxygenation and HFNC apneic oxygenation could be an interesting option [47]. Further studies should separate the evaluation of HFNC for preoxygenation or apneic oxygenation.

This trial has several limitations. First the single-center design could limit the generalizability of the results [48]. Second, unblinded preoxygenation devices could induce an assessment bias. Third, most patients were excluded from the per-protocol analysis due to devices removal

during the intubation procedure, strictly prohibited by the protocol. Removal of these devices prevented apneic oxygenation in the RSI stratum, reducing HFNC efficiency in the modified intention-to-treat population. Four, two points of the protocol are questionable. Non-invasive ventilation used for preoxygenation was prohibited in the standard group. Bag-mask ventilation, from the induction to the start of laryngoscopy, was also forbidden in the standard group. Though this technique has recently proved to significantly reduce severe hypoxemia incidence in intensive care patients and could have been useful for participant of the standard group [49]. Fifth, the incidence of HFNC leakage during preoxygenation was very low, only 1% and may have been underestimated [45]. Finally, we chose a pragmatic protocol, with broad inclusion criteria. As a result, the incidence of the primary outcome was lower than expected which altered the study power [8,35].

PREOPTIDAM study results remain very informative. Videolaryngoscopes have been used in a large majority of participants (94% in the HFNC group and 85% in the standard group). These data reflect a major change in the management of anticipated difficult intubation, since 2017 guidelines of the French Society of Anesthesia and Intensive Care [9]. Videolaryngoscopes significantly improve first-pass success and limit failed intubation in case of anticipated difficult intubations [50]. However, despite the extensive use of videolaryngoscopes and the short duration of intubation procedures in the PREOPTIDAM study, the per-protocol analysis was still positive. This result suggests that HFNC has an impact clinically pertinent on patient safety, even with modern anesthesia practices. Furthermore, in the two study groups intubation's duration, intubation's difficulty, incidence of complications, especially incidence of severe desaturation were similar. Use of HFNC appeared to be a safe oxygenation device for anticipated difficult intubations. Future studies are needed to determine the optimal patient categories for HFNC preoxygenation and definitively conclude on its efficiency for anticipated difficult intubation patients.

Conclusion

HFNC did not significantly reduce the incidence of desaturation <95% or preventive facemask ventilation in adults requiring general anesthesia with expected difficult intubation. However, the positive results of the per-protocol analysis and the fiberoptic intubation stratum analysis encourage further large studies

What is already known on this topic

Patients with an anticipated risk of difficult intubation are at high risk of hypoxemia and severe complications.

In preliminary studies, HFNC appears to be a promising way of securing intubation procedure in high-risk patient, notably via apneic oxygenation.

What this study adds

Compared with standard facemask, preoxygenation and apneic oxygenation via HFNC was not associated with a reduction in desaturation <95% or preventive facemask ventilation during anticipated difficult intubation procedures.

There was no difference of severe or moderate complications between the two groups.

However, the positive results of the per-protocol analysis and the fiberoptic intubation stratum analysis suggest a possible clinical effectiveness of HFNC, especially for fiberoptic intubation.

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Supplementary data: Table A

Inclusion criteria

- Adults aged from 18 to 90 years
- One major or two minor criteria of anticipated DI (see below)
- And requiring RSI or fiberoptic intubation.

Anticipated Difficult Intubation criteria

Anticipated DI is defined by at least one major or two minor criteria.

Major criteria	**Minor criteria**
Past Difficult Intubation	Bone to chin distance <65 mm
Past laryngeal surgery or radiotherapy	Retrognathism
Limited mouth opening <25 mm	Limited mouth opening <35 mm and >25 mm
Fixed flexion of the cervical spine	Limitation of cervical mobility ≤35°
Mallampati IV	Mallampati III
Tumour in the oral or laryngeal region	Neck perimeter >40 cm for men and >38 cm for women

Non-inclusion criteria

- Body mass index >35 kg/m2
- Pulse oximetry <90% in ambient air
- Hemodynamic instability
- Protected adult
- Pregnancy
- Lack of consent
- Patient already enrolled in another randomised study to improve preoxygenation quality

Supplementary results : table A Primary outcome in the modified intention-to-treat and per-protocol population. Secondary otcomes in the modified intention-to-treat population					
Outcomes	High-flow nasal cannulae n=95	Face Mask n=90	Odds Ratio (95% CI)	Between group difference (95% CI)	P value
Primary outcome, desaturation ≤ 94% or face mask ventilation, n (%) [a]					
Modified intention-to-treat population					
Rapid sequence intubation stratum	2/64 (3)	3/59 (5)	0.60 (0.10 to 3.74)		0.59
Fibreoptic intubation stratum	0/31 (0)	4/31 (13)	/		0.11†
Per-protocol population [b]					
Rapid sequence intubation stratum	0/60 (0)	3/59 (5)			0.11†
Fibreoptic intubation stratum	0/31 (0)	4/29 (14)			0.049†
Secondary outcome					
Preoxygenation					
Mean (SD) EtO2 at the end of preoxygenation	/	86 (8)	-	-	-
Mean (SD) EtCO2 at the end of preoxygenation	/	33 (7)	-	-	-
Intubation					
Number of operators >1					
Rapid sequence intubation stratum	11/64 (17)	12/59 (20)	0.81 (0.33 to 2.01)		0.65
Fibreoptic intubation stratum	6/31 (19)	8/31 (26)	0.69 (0.21 to 2.29)		0.54
First pass sucess					
Rapid sequence intubation stratum	63 (98)	56 (95)	3.37 (0.34 to 33.37)		0.3
Fibreoptic intubation stratum	30 (97)	30 (97)	1.00 (0.06 to 16.74)		1
Mean (SD) patient sedation score during fibreoptic intubation [c]	6/31 (2)	6/31 (2)	0.35 (-0.65 to 1.36)		0.48
Perioperative respiratory parameters					
Intraoperative FiO2 > 50% required to achieve >94% saturation, n (%)	4 (4)	4 (4)	0.94 (0.23 to 3.87)		0.93
Mean (SD) higher FiO2 (%)	45 (15)	43 (12)	1.60 (-2.27 to 5.47)		0.42
Respiratory parameters 30 minutes following intubation					
Mean (SD) plateau pressure (cm H20)	15 (5)	14 (3)		1.01 (-0.19 to 2.22)	0.10
Mean (SD) peak inspiratory pressure (cm H20)	19 (5)	19 (5)		0.77 (-0.73 to 2.26)	0.31
Respiratory parameters 60 minutes following intubation					
Mean (SD) plateau pressure (cm H20)	14 (3)	14 (3)		0.01 (-1.12 to 1.13)	0.99
Mean (SD) peak inspiratory pressure (cm H20)	18 (4)	18 (3)		0.01 (-1.33 to 1.35)	0.99
Outcome in the PACU					
Mean (SD) lowest SpO2 (%)	95 (3)	95 (2)	0.04 (-0.75 to 0.83)		0.92
Inspiratory dyspnoea after extubation, n (%)	4 (5)	1 (1)	4.07 (0.44 to 37.29)		0.21
Tidal volume reduction owing to peak pressure >40 mm Hg	0 (0)	0 (0)			

RSI=Rapid Sequence Induction; FOI=Fibreoptic intubation.
a : Evaluation period of primary outcome is extended to 2 min following intubation completion owing to possible delayed detection of desaturation with pulse oxymetry
b : In the per-protocol population, patients whose medical oxygenation device were removed by the operator without respecting protocol modalities were excluded from the analysis
c : patient sedation score is a modification of the Steward score, specifically designed to assess sedation level during fibreoptic intubation. It's composed of three items : consciousness, airway and activity. It goes from 9 : "fully awake, eyes open, conversive - opens mouth, coughs on command - raising arm on command" to 0 : "no response - airway obstruction needing jaw retraction/oro-pharyngeal airway - no movement".
† Fischer's exact test (no OR or 95% CI available)

Open access Protocol

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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ABSTRACT

Introduction Although preoxygenation and airway management respond to precise algorithms, difficult intubation (DI) remains a daily challenge in intensive care units 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 hypothesised that HFNC can decrease the incidence of desaturation ≤94% or face mask ventilation from 16% to 4% compared with 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 randomisation, with a 1:1 allocation ratio, patients will be randomised to HFNC or face mask preoxygenation. Randomisation will be stratified on intubation sequence: Rapid sequence intubation or awake fibreoptic 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.

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 apnoeic 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 are 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 eight vital capacities or 3 min 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 fibreoptic 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) minimising 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 (ie, 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 intensive care unit (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 supraglottic 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 apnoeic 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 fibrescope in the patient's nostril to perform intubation while continuing the oxygenation and may be better tolerated.

Considering its theoretical advantages and recent recommendations,[3 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 postanaesthesia 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 with face mask preoxygenation, HFNC could reduce the incidence of desaturation ≤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
- One major or two minor criteria of anticipated DI (see below)
- And requiring RSI or FOI.

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

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

OR

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

Non-inclusion criteria

- Body mass index >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 department of Nantes University Hospital and not involved in patient recruitment. The software used to collect the data in the electronic case report form (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 min set at 60 L/min of heated and humidified pure oxygen (fraction of inspired oxygen 100%, 37°C - Optiflow; Fisher & Paykel Healthcare [FPH], 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 min with a face mask (which size will be adapted to fit the patient and ensure airtightness) connected to an Aisys CS^2 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

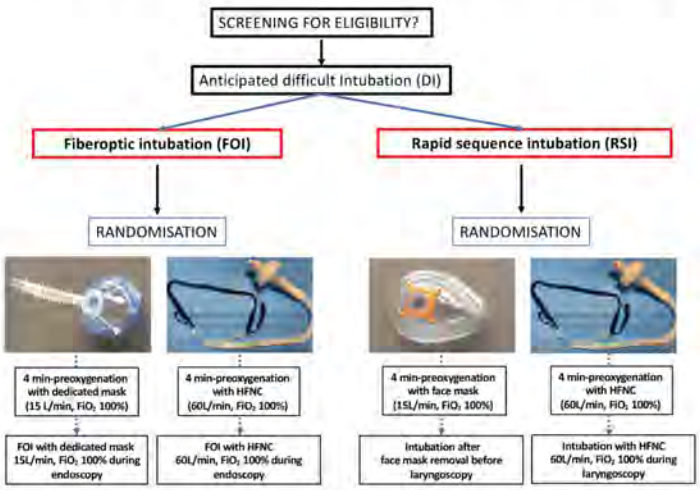

Figure 1 Study design. After attending physician decision to perform RSI or FOI, patients will be randomised to receive high-flow nasal cannula (HFNC) or face mask oxygenation. FiO **2**, fraction of inspired oxygen.

intubation procedure with a 15 L/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 programme so as to be familiar with this three oxygenation devices at the Nantes University Hospital Simulation Centre.

The current guidelines advise to interrupt intubation to focus on oxygenation (ie, 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 PACU discharge (see table 1).

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. Participant satisfaction of the intervention will be assessed before PACU discharge and will analysed as a secondary outcome.

Primary and secondary outcome

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 two groups: 'No event' or 'at least one event'.

- For RSI, the primary criterion will be assessed from the induction of general anaesthesia to 2 min following intubation.
- For FOI, the primary criterion will be assessed from the beginning of sedation to 2 min 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 min 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.

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

Table 1 Participant timeline

	Anaesthesia consultation	Preoperative visit	Inclusion	Intubation and surgery	PACU	PACU discharge
Eligibility?	X	X				
Information	X	X				
Written consent		X				
Randomisation			X			
Data collection				X	X	
Exit from the study						X

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 postanaesthesia care unit (PACU) discharge.

- Intubation Difficulty Scale score[19]
- DI 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 min following intubation
- Highest $EtCO_2$ within 2 min 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 <80 mm Hg 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 Richmond Agitation-Sedation Scale >3
  - Vomiting with aspiration of gastric content
  - Nasolaryngotracheal 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 mm Hg

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 vigilance unit of research 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 eCRF. 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 ICU (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 subgroup 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, generalised 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 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 DI, 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 data manager team of research department and 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 19 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.

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 (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 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.

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Contributors 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 data set. All authors participated in the writing the manuscript and approved the final version.

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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. KA declares personal fees from Fisher Paykel Healthcare, Baxter, LFB, Fresenius. The other authors declared to have no conflict of interest.

Patient consent for publication Obtained.

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.

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Titre de Thèse : PREOXYGENATION PAR CANNULES NASALES D'OXYGENATION A HAUT DEBIT COMPAREE AU MASQUE FACIAL STANDARD DANS LE CADRE DE LA GESTION DES VOIES AERIENNES DIFFICILES : UNE ETUDE OUVERTE, MONOCENTRIQUE ET RANDOMISEE (L'ETUDE PREOPTIDAM)

RESUME

-**Objectif**

Évaluer l'effet de l'oxygénation à haut débit par voie nasale sur la prévention de désaturation en oxygène pendant la procédure d'intubation, chez des patients présentant un risque d'intubation difficile.

-**Méthodes**

Étude de phase III, randomisée, ouverte et contrôlée.

Hôpital Universitaire de Nantes, de septembre 2018 à mars 2021.

186 adultes, nécessitant une anesthésie générale avec intubation endotrachéale et ayant une intubation difficile prévue, ont été randomisés pour recevoir comme matériel de préoxygénation soit des canules nasales d'oxygenation à haut débit, soit un masque facial standard. La randomisation était stratifiée à priori sur la méthode d'intubation, à savoir par fibroscopie ou par laryngoscopie. Le critère d'évaluation principal était l'incidence des désaturations <95% et/ou des ventilation préventives au masque faciale pendant la procédure d'intubation. Les techniques d'intubation ainsi que la sécurité et la morbidité des patients ont été évaluées en critère de jugement secondaires.

-**Résultats**

Sur les 186 participants randomisés, un seul a retiré son consentement et 185 (99.5%) ont donc pu être inclus dans l'analyse finale. Dans la population en intention-de-traiter modifiée, l'incidence du critère de jugement principal n'était pas significativement différente entre le groupe HFNC et le groupe masque facial, respectivement 2% contre 8% (odds ratio ajusté à 0,26, intervalle de confiance à 95 % (IC 95%) 0,05 à 1,27 ; P=0,10). Par contre, dans la population en per-protocole, l'incidence de ce critère était significativement réduite dans le groupe HFNC, respectivement 0% contre 8% (P=0,006). Dans la strate d'intubation fibroscopique, la tolérance de la procédure était meilleure (P=0,003), aucun patient du groupe HFNC n'a désaturé et le pourcentage d'oxygène expirée (FeO2) à la fin de la procédure d'intubation était plus élevé, respectivement 71% vs 60% (différence ajustée de 11%, IC 95% 4,52 à 17,16% ; P=0,001). Il n'y avait pas de différence significative en ce qui concerne la survenue d'au moins une complication modérée ou sévère, respectivement 30% vs. 40% (odds ratio ajusté à 0.60, IC à 95% 0.32 to 1.10; P=0.10).

-**Conclusions**

Dans la population en intention de traitée, l'HFNC n'a pas significativement réduit l'incidence de désaturation <95% ou de ventilation préventive au masque facial, chez des adultes bénéficiant d'une anesthésie générale et ayant des critères prédictifs d'intubation difficile. Cependant, les résultats positifs de l'analyse per-protocole et de l'analyse du sous-groupe des patients intubés par fibroscopie encouragent la réalisation de nouvelles études de plus grande envergure.

MOTS-CLES OXYGENATION NASALE A HAUT DEBIT; PREOXYGENATION ; OXYGENATION APNEIQUE ; INTUBATION DIFFICILE PREVUE

Titre de Thèse: PREOXYGENATION IN DIFFICULT AIRWAY MANAGEMENT WITH HIGH-FLOW OXYGENATION BY NASAL CANNULA VERSUS STANDARD FACEMASK: AN OPEN-LABEL, MONOCENTER, RANDOMISED STUDY (THE PREOPTIDAM STUDY)

ABSTRACT

-**Objectif**

To assess the effect of nasal high flow nasal cannula (HFNC) therapy for the prevention of oxygen desaturation during intubation procedure, for patient at risk of difficult intubation.

-**Methods**

Phase III, randomised, monocenter, open-label, controlled trial.

Nantes University Hospital, from September 2018 to March 2021.

186 adults requiring general anesthesia with an expected difficult intubation were randomised to HFNC or standard facemask as preoxygenation device. Randomisation was a-priori stratified on the intubation method, fiberoptic intubation or laryngoscopic rapid sequence intubation (RSI). The primary outcome was the incidence of desaturation below 95% or preventive facemask ventilation during endotracheal intubation. Intubation techniques as well as patient safety and morbidity were monitored as secondary outcomes.

-**Results**

Of the 186 participants who underwent randomisation, 1 withdrew his consent and 185 (99.5%) were included in the final analysis. In the modified intention-to-treat population, the incidence of the primary outcome was not significantly different in the HFNC group and the standard facemask group, respectively 2% vs. 8% (adjusted odds ratio 0.26, 95% confidence interval (95% CI) 0.05 to 1.27; P=0.10). However, in the per-protocol population, the incidence was significantly reduced in the HFNC group, respectively 0% vs. 8% (P=0.006). In the fiberoptic intubation stratum, tolerance of the procedure was better (P=0.003), none of the patient experienced desaturation in the HFNC group and the mean expired fraction of oxygen (FeO2) at the end of the intubation procedure was higher respectively 71% (8) vs. 60% (8) (adjusted group difference of 11%, 95% CI 4.52 to 17.16%; P=0.001). There was no significant difference in the incidence of at least one moderate or severe complications, respectively 30% vs. 40% (adjusted odds ratio à 0.60, 95% CI 0.32 to 1.10; P=0.10).

-**Conclusions**

In the intent-to-treat analysis, HFNC did not significantly reduce the incidence of desaturation <95% or preventive facemask ventilation in adults requiring general anesthesia with an expected difficult intubation. However, the positive results of the per-protocol analysis and the fiberoptic intubation stratum analyses encourage further studies.

KEYWORDS HIGH FLOW NASAL CANNULA; FACEMASK VENTILATION; PREOXYGENATION; APNEIC OXYGENATION; ANTICIPATED DIFFICULT INTUBATION; DIFFICULT AIRWAY MANAGEMENT