High-flow oxygen therapy versus facemask preoxygenation in anticipated difficult airway management (PREOPTI-DAM): an open-label, single-centre, randomised controlled phase 3 trial

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Summary

Background Difficult airway management remains a critical procedure with life-threatening adverse events. Current guidelines suggest high-flow therapy by nasal cannulae (HFNC) as a preoxygenation device in this setting. However, there is an evidence gap to support this recommendation.

Methods The PREOPTI-DAM study is an open-label, single-centre, randomised controlled phase 3 trial done at Nantes University Hospital, France. Patients were aged 18–90 years with one major or two minor criteria of anticipated difficult airway management, and requiring intubation for scheduled surgery, were eligible. Patients with body mass index >35 kg/m^2 were excluded. Patients were randomly allocated (1:1) to receive 4-min preoxygenation by HFNC or facemask. Randomisation was stratified according to the intubation strategy (laryngoscopic versus fiberoptic intubation). The primary outcome was the incidence of oxygen desaturation ≤94% or of bag-mask ventilation during intubation. The primary and safety analyses included the intention to treat population. This trial is registered with ClinicalTrials.gov (NCT03604120) and EudraCT (2018-A00434-51).

Findings From September 4 2018 to March 31 2021, 186 patients were enrolled and randomly assigned. One participant withdrew consent and 185 (99.5%) were included in the primary analysis (HFNC, N = 95; Facemask, N = 90). The incidence of the primary outcome was not significantly different between the HFNC and the facemask groups, respectively 2 (2%) versus 7 (8%); adjusted difference, −5.6 [95% confidence interval (CI), −11.8 to 0.6], P = 0.10. In the HFNC group, 76 patients (80%) versus 53 (59%) in the facemask group, reported good or excellent intubation experiences; adjusted difference 20.5 [95% CI, 8.3–32.8], P = 0.016. Comparing HFNC with facemask, severe complication occurred in 22 (23%) versus 27 (30%) patients (P = 0.29), and moderate complication in 14 (15%) versus 18 (20%) patients (P = 0.35). No death or cardiac arrest occurred during the study.

Interpretation Compared with facemask, HFNC did not significantly reduce the incidence of desaturation ≤94% or bag-mask ventilation during anticipated difficult intubation but the trial was underpowered to rule out a clinically significant benefit. Patient satisfaction was improved with HFNC.

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Keywords: Preoxygenation; High-flow oxygen therapy; Intubation; Fiberoptic intubation; Apnoeic oxygenation; Difficult intubation

Research in context

Evidence before this study

While endotracheal intubation is performed daily in the operating room, difficult intubation remains a risky procedure with up to 30% serious adverse events. Recent guidelines recommend the use of apnoeic oxygenation in this setting in order to secure intubation considering the promising preliminary results of high-flow therapy by nasal cannulae (HFNC) in this indication. In order to assess the level of evidence supporting these recommendations, we completed a non-systematic PubMed search, using a combination of terms including, but not limited to, 'intubation', 'difficult airway management', 'apnoeic oxygenation' and 'high-flow oxygenation'. It only included randomized clinical trials with a search date starting on January 1, 2000 and ending on July 1, 2018. Our conclusion was that strong evidence was lacking to support these recommendations.

Added value of this study

This is the first randomised controlled study comparing HFNC with facemask for the preoxygenation of patients with anticipated difficult intubation. In this study which included 186 patients, the incidence of desaturation ≤94% or bag-mask ventilation was not significantly reduced in the HFNC versus facemask groups, respectively 2 (2%) versus 7 (8%), P = 0.10. The trial was underpowered to rule out a clinically meaningful benefit from HFNC. Nevertheless, patient satisfaction was significantly improved in the HFNC group.

Implications of all the available evidence

HFNC preoxygenation did not reduce oxygen desaturation during anticipated difficult intubation. While not statistically significant, the 71% relative risk reduction in hypoxemia or bag-mask ventilation observed with HFNC as well as patient satisfaction, warrant investigation in future studies.

Introduction

Hypoxemia during intubation is a leading cause of serious adverse events or death in the operating room.[1,2] Patients with anticipated difficult intubation are at high risk of oxygen desaturation. Depending on the patient's condition, current guidelines recommend intubating with either fiberscopy (i.e., limited mouth opening or anticipated difficult manual ventilation) to avoid apnoea,[3] or laryngoscopy.[4,5] Preoxygenation before induction of anaesthesia is intended to maximise the oxygen reserve and thereby delay the onset of oxygen desaturation during the intubation.[6,7] Nevertheless, the risk of oxygen desaturation persists despite well-conducted preoxygenation. This is explained by a mandatory phase of apnoea after the induction of general anaesthesia for laryngoscopic intubation and hypoventilation related to sedation during fiberoptic intubation.

High-flow oxygenation by nasal cannulae (HFNC) is a widespread oxygenation device in the operating room which can deliver up to 60 Litres per minute (L/min) of humidified and heated gas with 100% inspired oxygen fraction (FiO_2).[8] After preoxygenation, nasal cannulae can be held in place during attempted intubation under fiberscopy or throughout laryngoscopy (i.e., trying to perform apnoeic oxygenation). Recent observational studies have suggested that HFNC could theoretically achieve apnoeic oxygenation including during difficult intubation and therefore prevent oxygen desaturation.[9,10] Current guidelines for the management of difficult intubation therefore suggest the use of apnoeic oxygenation techniques to reduce the risk of oxygen desaturation. However, there is no randomised controlled study to support these recommendations. It is for this reason that experts have called for a robust evaluation of HFNC in patients at high-risk of oxygen desaturation during intubation.[4]

In this randomised, controlled trial, the main objective was to assess whether HFNC as a preoxygenation and apnoeic oxygenation device could reduce the incidence of oxygen desaturation during intubation compared with facemask. Secondary objectives were to compare the quality of preoxygenation, intubation-related complications, post-operative morbidity between groups and patient satisfaction.

Methods

Study design

This investigator-initiated, monocentre, parallel-group, open-label, randomised, controlled trial was conducted at Nantes University Hospital, France. The study protocol was submitted and published before the first inclusion.[11] The study was approved by an institutional review board (Comité de Protection des Personnes Ile-de-France II, Paris, France, registration number #2018-04-04). The study was conducted in accordance with the Declaration of Helsinki, and was registered before the first inclusion (NCT03604120, https://clinicaltrials.gov/ct2/show/NCT03604120). The report of the study follows CONSORT guidelines.

Participants

Participants were adults aged 18–90 years with one major or two minor criteria for anticipated difficult

intubation. Gender was collected according to self-report (i.e., male or female). Major criteria were previous difficult or failed intubation, past laryngeal surgery or radiotherapy, mouth opening less than 25 mm, Mallampati score of 4, oral cavity or laryngeal cancer. Minor criteria were bone-to-chin distance less than 65 mm, retrognathism, mouth opening of 25–35 mm, limited cervical mobility less than 35°, Mallampati score of 3, neck circumference greater than 40 cm for men or 38 cm for women. Non-inclusion criteria were: Hemodynamic instability, protected adult, pregnancy, lack of consent, patient already enrolled in another randomised study assessing a preoxygenation device. Patients with body mass index greater than 35 kg per meter^2 or pulse oximetry (SpO_2) below 90% in ambient air were not eligible considering the strong evidence against the use of HFNC in these conditions.[12,13] Written informed consent was obtained from all patients following oral and written information.

Randomisation and masking

Patients were randomised into one of the two preoxygenation strategies (allocation list generated by the study statistician, ratio of 1:1, variable block sizes). Patient allocation was performed using a secure computer-generated online remote system (CSOnline; Clinsight). This was controlled by the independent research promotion unit of the Nantes University Hospital which had no role in patient recruitment. Randomisation was stratified on the intubation strategy (i.e., laryngoscopic versus fiberoptic intubation) which was left to the discretion of the physician. Fiberoptic intubation was primarily intended for patients with several criteria for difficult bag-mask ventilation (i.e., age >55 years, limited jaw protrusion, snoring, edentulism, beard, body mass index greater than 26) or with limited mouth opening which hindered the insertion of the laryngoscope for suitable glottis vision. There was no masking strategy.

Procedures

In the intervention group, preoxygenation was performed with HFNC (Optiflow™ Fisher & Paykel Healthcare, Auckland, New Zealand) for 4 min. HFNC was set at a flow rate of 60 L/min, 100% FiO_2, at 37 °C. To avoid air contamination, patients were asked to keep their mouths closed while breathing and the size of the nasal cannulae (i.e., large or medium) was chosen according to the patient's nostril. At the end of preoxygenation, general anaesthetic agents were administered (i.e., in the laryngoscopic intubation stratum) or fiberoptic intubation was started while the patient was breathing spontaneously during conscious sedation (i.e., in the fiberoptic intubation stratum).

In the control group, preoxygenation was performed for 4 min with a fitted facemask in order to avoid gas leaks (ventilator settings: spontaneous breathing, 15 L/min, 100% FiO_2 without inspiratory support). Facemask references were "Economy, Intersurgical, Fontenay Sous Bois, France" in the laryngoscopic intubation stratum and "Fibroxy, VBM, Sulz, Germany" in the fiberoptic intubation stratum (i.e., allowing the endotracheal tube to be nasally inserted along the fiberoptic through a perforated flexible diaphragm). At the end of preoxygenation, general anaesthetic agents were administered and the facemask was removed (i.e., in the laryngoscopic intubation stratum) or fiberoptic intubation was started while the nurse was holding the facemask in place to ensure proper positioning and airtightness, and the patient was breathing spontaneously during conscious sedation (see Fig. 1).

HFNC was maintained throughout the intubation procedure, including laryngoscopy or fiberscopy, until successful intubation was confirmed. In the same way, facemask was maintained during fiberscopy whereas it was removed during laryngoscopy. The choice of laryngoscopes (i.e., standard blade or video laryngoscope), alternative devices, the size of fiberoptic and anaesthetic drugs were left to the discretion of the attending physician. Unless oxygen desaturation occurred, systematic bag-mask ventilation was not allowed in either group.

Follow-up began when patients entered the operating room and ended on discharge from the post-anaesthesia care unit.

Outcomes

The primary outcome was the occurrence of oxygen desaturation ≤94% measured by pulse oximetry (Nellcor OxiMax Durasensor DS 100A) or bag-mask ventilation whatever the value of SpO_2. Bag-mask ventilation was included in the primary outcome to account for the potential use of bag-mask ventilation to prevent hypoxemia in this unblinded trial. This criterion was assessed from the end of the preoxygenation time to 2 min following intubation (i.e., detection of oxygen desaturation by pulse oximetry may be delayed by 60 s according to manufacturer instructions).

Secondary outcomes were the quality of preoxygenation, intubation-related adverse events,[14] and respiratory outcomes during and after surgery. Quality of preoxygenation was assessed by pulse oximetry at the end of preoxygenation, leaks during preoxygenation (i.e., 15% difference between inspired and expired volume in the facemask group or leaks though the mouth in the HFNC group), the end-tidal oxygen (EtO_2) and the end-tidal carbon dioxide ($EtCO_2$) levels at the end of preoxygenation. During intubation, the following items were recorded: first operator, the number of operators, first pass success, the number of laryngoscopy and alternative device, the duration of the procedure (from the injection of anaesthetic drugs to the start of mechanical ventilation), the Intubation Difficulty Score, the lowest SpO_2, oxygen desaturation below 90%, EtO_2 and $EtCO_2$ levels within 2 min of intubation (Fig. 2). Severe

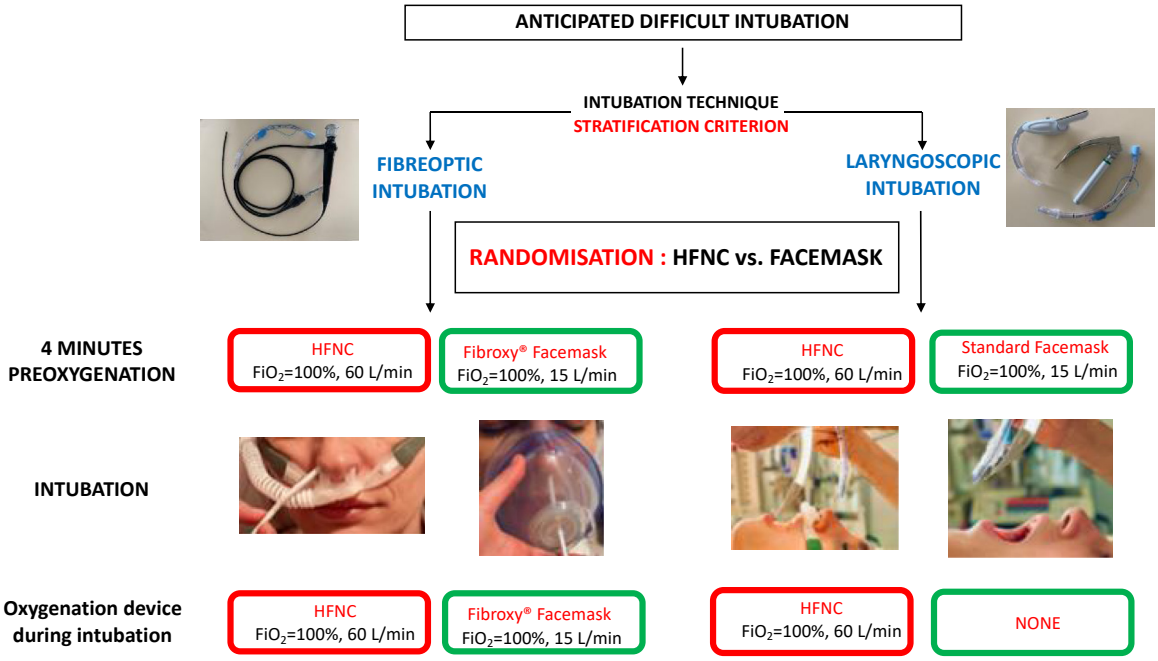

Fig. 1: Study design. The decision between fiberoptic or laryngoscopic intubation was left at the physician discretion. Randomisation was stratified on the intubation strategy (i.e., Fiberoptic versus Laryngoscopic). Patients received preoxygenation during 4 min according the randomisation group before intubation. **HFNC**: High-flow therapy by nasal cannulae, **L/min**: Liter per minute. **FiO_2**: Inspired oxygen fraction.

intubation-related adverse events during intubation and the following hour included: death, cardiac arrest, severe desaturation <80%, severe hypotension with systolic blood pressure <80 mm of mercury (mmHg) or the need for a vasopressor (i.e., ephedrine, neosynephrine or norepinephrine). Mild-to-moderate complications included: Nasolaryngotracheal injury or bleeding, oesophageal intubation, dangerous agitation defined by a Richmond Agitation–Sedation Scale >3, ventricular or supraventricular arrhythmia, dental injury, vomiting with aspiration of gastric content, intubation failure. Respiratory outcomes during surgery were: the highest FiO_2 (i.e., to achieve an SpO_2 ≥95%), the highest peak and plateau pressure at 5, 30 and 60 min after intubation, need for recruitment manoeuvres (i.e., for oxygen desaturation below 95%) or need for tidal volume reduction owing to peak pressure >40 cm of water. After surgery, in the post-anaesthesia care unit, the following outcomes were assessed: length of stay, respiratory status (duration of mechanical ventilation, oxygen desaturation below 90% or below 80%, the lowest SpO_2 recorded after extubation, non-invasive ventilation support, inspiratory dyspnoea after extubation, extubation failure), the occurrence of nausea or vomiting. Satisfaction scores (1 = Excellent, 2 = Good, 3 = Reasonable, 4 = Poor) were noted before discharge from the post-anaesthesia care unit.[15]

In the laryngoscopic intubation stratum, the following items were specifically assessed: the first attempt device, alternative devices, and the quality of exposure (i.e., glottis vision graded by the Cormack score for standard laryngoscope or Percentage Of Glottic Opening score, POGO).

Statistical analysis

The statistical analysis plan was submitted and published before the first inclusion.[11] In patients with anticipated difficult intubation, the incidence of desaturation ≤94% during intubation can reach 16%.[16] To detect a 12% absolute reduction for the primary outcome in the HFNC group,[17] with an α risk of 5%, using a 2-sided test and 80% power and considering 5% withdrawal of consent, we needed to include 186 patients.

In the primary analysis, all patients were analysed according to their randomisation group except for those who withdrew consent. The primary outcome was also analysed in the per-protocol population that excluded patients who did not receive the protocol-specified intervention: Wrong preoxygenation device, preoxygenation for less than 4 min, premature removal of the preoxygenation device unless desaturation already occurred. The incidence of the primary outcome was compared between groups with a logistic regression model adjusted to stratification criteria. The difference in probability (adjusted risk difference) was estimated after predicting the probability of outcome for each participant based on the logistic model. When zero event was observed in an arm, the risk difference is not

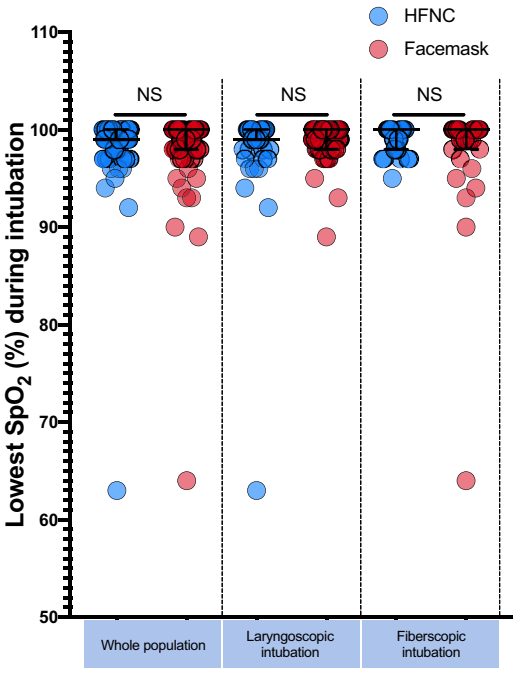

Fig. 2: Lowest oxygen saturation during intubation. This figure presents the lowest oxygen saturation during intubation and the two following minutes. Results are presented as median and Interquartile range. **HFNC**, High-Flow therapy by nasal cannulae; **NS**, Non-significative; **SpO_2**, Pulse oximetry.

adjusted on the stratification criteria and a non-parametric Fisher test was applied. There was no missing data for the primary outcome. For each randomisation stratum, prespecified exploratory subgroup analyses were also performed. Interaction between the two groups and the subgroup covariate was tested in logistic regression models using the same adjustment as for the primary analysis. To investigate whether the association between randomisation groups and the primary outcome differs according to intubation strategy (i.e., an interaction), a chi-square test of homogeneity of association was applied with a Haldane-Anscombe correction (added 0.5 to each of the cells of the stratum with the zero cell count. For secondary outcomes all analyses were adjusted to stratification criteria. Categorical data were analysed with logistic regression models and quantitative data with linear regression models. The adjusted differences (proportion or mean) were estimated with 95% CI but were not adjusted for multiplicity. Owing to the potential for type I error due to multiple comparisons, findings for secondary end points should be therefore interpreted as exploratory.

Analyses were performed using SAS software (version 9.4, NC) before the breaking the randomisation code. The statistical analysis incorporated all of the elements required by the CONSORT statement for non-pharmacological interventions. In addition to electronic data base monitoring, onsite monitoring was performed to ensure the completeness and quality check of data collection.

This trial is registered with ClinicalTrials.gov (NCT03604120) and EudraCT (2018-A00434-51).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 4740 patients were assessed for eligibility from September 4, 2018 to March 31 2021. Finally, among 746 patients with criteria for anticipated difficult intubation, 560 were excluded and 186 were randomised (95 in the HFNC group and 91 in the facemask group, including 62 patients (33%) in the fiberoptic intubation stratum (Fig. 3). One participant withdrew consent after randomisation immediately before anaesthesia, 185 patients were therefore included in the primary analysis (95 in the HFNC group and 90 in the facemask group). The prespecified per-protocol analysis of 179 patients (91 in the HFNC group and 88 in the facemask group) excluded 1 patient who received the wrong intervention in the HFNC group, and 5 patients whose devices were removed before the end of intubation (2 from the facemask group in the fiberoptic intubation stratum and 3 from the HFNC group). These 5 latter patients did not present desaturation before the device was removed.

Baseline patient characteristics were similar in the two groups and are reported in Table 1. Of the 185 patients in the primary analysis, 46 (25%) were women, with a mean (Standard Deviation, SD) age of 61 years (13). The mean SpO_2 in ambient air was 98% in both groups and 58 (31%) patients were active smokers. Patients were mostly admitted for scheduled Head and Neck (89%) or orthopaedic surgeries (8%).

Airway and intubation parameters are described in Table 2. In both groups, 63% of the participants had at least two criteria of difficult ventilation. In the HFNC group, previous difficult intubation was reported in 42 patients (44%) compared with 53 patients (59%) in the facemask group. In the HFNC group, 58 patients (61%) had a Mallampati score of 3 or 4 compared with 48 patients (53%) in the facemask group. Anaesthetic agents for laryngoscopic intubation were mainly propofol (96%) and succinylcholine (63%) in both groups, whereas conscious sedation for fiberoptic intubation combined mostly ketamine and remifentanil (i.e., target-controlled intravenous anaesthesia). In the laryngoscopic intubation stratum, video laryngoscope was used as the first attempt intubation device in 60 (94%) patients of the HFNC group and 50 (85%) in the facemask group (see Supplemental Table S1).

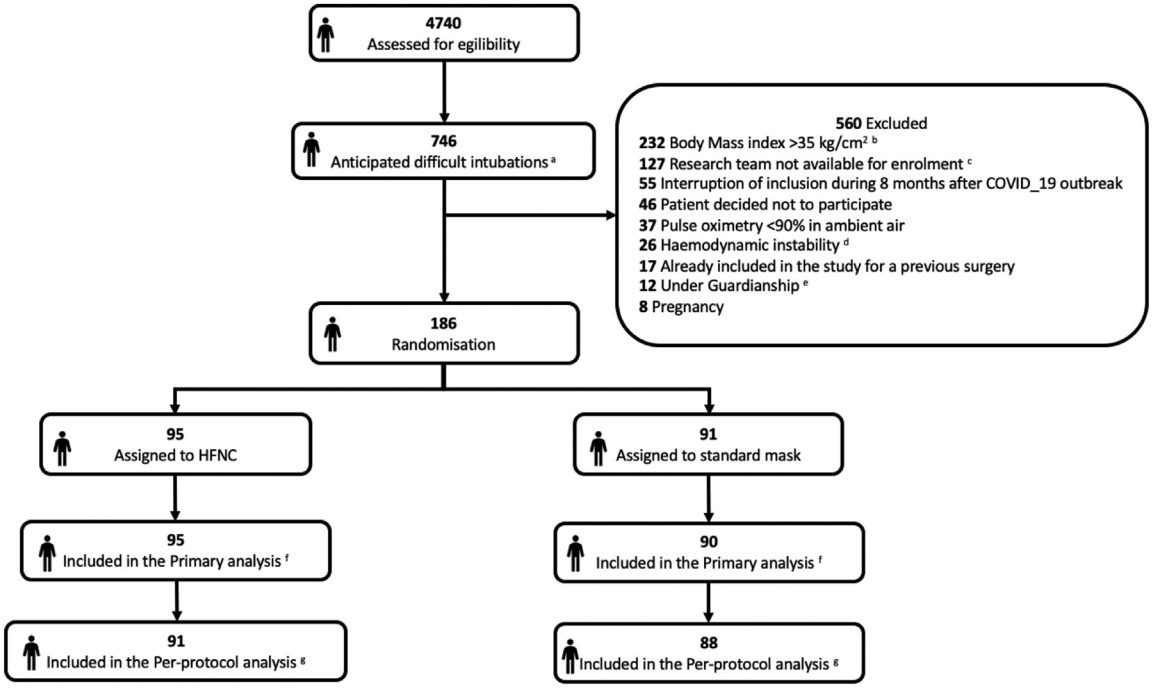

Fig. 3: Flowchart of the study. **HFNC**: High-flow therapy by nasal cannulae.[a] According to the inclusion criteria.[b] Body mass index was calculated by the weight in kilograms divided by the square of the height in meters.[c] Stands for unavailability of the research or medical teams within the inclusion window.[d] Haemodynamic instability was defined as hypotension requiring vasopressive drugs before the induction of anaesthesia.[e] According to French law.[f] The primary analysis included all the patients randomised in the study. No imputation was applied for missing data (1 full withdrawal of consent before intubation).[g] The per-protocol analysis excluded patients with protocol violation (one patient received the wrong intervention in the HFNC group, the device was removed before the end of intubation in three patients in the HFNC group and two patients in the facemask group).

In the primary analysis, 2 of 95 participants (2%) in the HFNC group versus 7 of 90 participants (8%) in the facemask group met the primary outcome; adjusted difference, −5.6 [95% confidence interval (CI), −11.8 to 0.6], P = 0.10 (Table 3)

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 facemask group met the primary outcome; difference, −8.0 [95% CI, −13.6 to −2.3], P = 0.0061 (Supplemental Table S1). This difference was mainly observed in the fiberoptic intubation stratum. The intubation strategy did not modify the relationship between the intervention and the primary outcome (test of homogeneity P = 0.28). Further analyses are available for subgroup interaction with the primary outcome (Supplemental Fig. S1).

At the end of preoxygenation, mean SpO_2 was 100% in both groups (Table 3). Other characteristics of the preoxygenation period are described in Supplemental Table S1. During intubation, the number of operators, the first pass success rate and the lowest saturation were not different between groups (Table 3) or between strata (Supplemental Table S1). HFNC did not improve the lowest SpO_2 during intubation (HFNC, 99% versus facemask 98%; adjusted difference, 0.18 [95% CI, −1.01 to 1.37], P = 0.77) and did not reduce severe oxygen desaturation <90% compared with facemask preoxygenation, respectively 1% versus 2%; adjusted difference, −1.2 [95% CI, −4.8 to 2.5], P = 0.54 (Table 3).

Additional details on the intubation of each stratum are available in Supplemental Table S1. Notably, in the fiberoptic intubation stratum, the mean (SD) EtO_2 after intubation was significantly higher in the HFNC group compared with the facemask group, respectively 71% (11) versus 60% (14); adjusted difference, 11 [95% CI, 4.52–17.16], P = 0.0011) and the mean (SD) $EtCO_2$ was significantly lower in the HFNC group compared with the facemask group, respectively 41 mmHg (7) versus 47 mmHg (7); adjusted difference, −5.55 [95% CI, −9.26 to −1.84], P = 0.0040 (Table 3). There was no difference for the latter two in the laryngoscopic intubation stratum. Quality of exposure, device and Intubation Difficulty Scores for the laryngoscopic intubation stratum are also available in Supplemental Table S1.

There was no significant difference in the occurrence of at least one severe or moderate complication in the HFNC group compared with the facemask group: 30

Characteristic	High-flow nasal cannulae (N = 95)	Facemask (N = 90)
Gender, n (%)		
Male	71 (75)	68 (76)
Female	24 (25)	22 (24)
Mean (SD) age, years	62 (13)	60 (13)
Mean (SD) BMI, $kg.m^{-2}$[a]	23 (4)	23 (5)
Comorbidities, n (%)		
McCabe scale 1[b]	35 (37)	32 (36)
Chronic heart failure (NYHA III or IV)[c]	1 (1)	3 (3)
Hypertension	33 (35)	41 (46)
Chronic obstructive pulmonary disease	10 (11)	14 (16)
Obstructive sleep apnoea	6 (6)	4 (4)
Active tobacco	28 (29)	30 (33)
Diabetes	4 (4)	3 (3)
Mean (SD) SpO_2 in ambient air, %	98 (2)	98 (2)
Type of surgery, n (%)		
Head and Neck	89 (94)	73 (81)
Orthopaedic	5 (5)	9 (10)
Other surgeries[d]	1 (1)	8 (9)

SD, Standard Deviation; **kg/m^{-2}**, Kilogram per meter square, **SpO_2**, Pulse Oximetry. [a]Body mass index (BMI) was calculated by the weight in kilograms divided by the square of the height in meters. [b]McCabe Scale is a score that classifies patients in three categories according to their underlying diseases. Category 1, Non-fatal disease; Category 2, Ultimately fatal disease (within 5 years); Category 3, Rapidly fatal disease (within 1 year). [c]The New York Heart Association (**NYHA**) classification for cardiac dysfunction according to patient symptoms and limitations. NYHA 1: No limitation of physical activity, up to NYHA 4: Unable to carry on any physical activity without discomfort. [d]Other surgeries stands for digestive, urologic, plastic, neurological surgery or interventional radiology.

Table 1: **Baseline characteristics of the participants.**

(32%) versus 39 (43%); adjusted difference, −11.8 [95% CI, −25.6 to 2.1], P = 0.10 (Table 3). During the study period, no cardiac arrest, dental injury, aspiration of gastric content, or intubation failure occurred in either group.

There was no difference between groups for respiratory outcomes during surgery, including plateau pressure at 5, 30 and 60 min after intubation (Supplemental Table S1). Details of the other respiratory outcomes during surgery can be found in Supplemental Table S1.

In the post-anaesthesia care unit, there was no difference between groups in patient length of stay, duration of mechanical ventilation and oxygen desaturation below 90% (Table 3). Interestingly, more patients in the HFNC group reported good or excellent intubation experiences compared with those in the facemask group: 76 (80%) versus 53 (59%); adjusted difference, 20.5 [95% CI, 8.3–32.8], P = 0.0016. This difference was mainly reported in the fiberoptic intubation stratum.

Discussion

This single-centre, randomised controlled clinical trial compared HFNC with facemask during the preoxygenation of patients with anticipated difficult intubation. While the difference failed to reach statistical significance, the 71% relative risk reduction in the primary outcome and significant differences in exploratory outcomes like EtO_2, suggest a potential benefit from HFNC that should be evaluated in future research. After excluding patients with protocol violation, the per-protocol analysis found a significant reduction for the primary outcome in the HFNC group. Patient satisfaction was markedly improved in the HFNC group compared with facemask. Finally, the incidence of moderate or severe complications did not differ between groups.

Despite scheduled surgery with trained medical staff, severe complications occurred in 25% of the patients and 30% required more than one laryngoscopy in the present study. This therefore confirms that difficult intubation is a challenging topic in terms of patient safety. Anticipated difficult intubation has already been identified as an independent risk factor for hypoxia.[16,19] In this setting, experimental studies have reported promising results with HFNC used as a preoxygenation and an apnoeic oxygenation device to prevent hypoxia.[9,10,20] This explains why current guidelines for difficult airway management suggest that HFNC may prove beneficial.[4]

In neonatal endotracheal intubation, HFNC improved the likelihood of successful intubation without deep desaturation.[21] In contrast to neonates, supra-glottic positive pressure generated by HFNC in adults may be unable to prevent general anaesthesia-related airway obstruction,[9] which could therefore

Airway and intubation settings	High-flow nasal cannulae (N = 95)	Facemask (N = 90)
Predictive factors for difficult bag-mask ventilation, n (%)		
Age >55 years	70 (74)	71 (79)
Limitation of jaw protrusion[a]	48 (51)	44 (49)
Snoring	16 (17)	15 (17)
Edentulous	41 (43)	28 (31)
Beard	3 (3)	2 (2)
BMI >26[b]	17 (18)	25 (28)
At least 2 difficult bag-mask ventilation criteria	60 (63)	57 (63)
Predictive factors for difficult intubation, n (%)		
Past 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[c]	58 (61)	48 (53)
Bone-to-chin distance below 65 mm	20 (21)	22 (24)
Mouth opening <25 mm	27 (28)	22 (24)
Mouth opening from 25 to 35 mm	18 (19)	20 (22)
Limited cervical mobility below 35°	30 (32)	36 (40)
Retrognathism	7 (7)	3 (3)
Neck perimeter >40 cm (Men) or >38 cm (Women)	16 (17)	14 (16)
Anaesthetic agents for laryngoscopic intubation, n (%)[d]	**N = 64**	**N = 59**
Propofol	61 (96)	57 (97)
Ketamine	3 (4)	2 (3)
Neuromuscular blocking agent		
Succinylcholine	37 (58)	41 (69)
Other	27 (42)	18 (31)
Anaesthetic agents for fiberoptic intubation, n (%)[d]	**N = 31**	**N = 31**
Propofol	9 (29)	6 (19)
Remifentanil	31 (100)	31 (100)
Ketamine	18 (58)	18 (58)

SD, Standard Deviation; **Cm**, Centimetre. [a]Defined as lower incisors cannot be protruded edge to edge with upper incisors.[18] [b]Body mass index **(BMI)** was calculated by the weight in kilograms divided by the square of the height in meters. [c]Mallampati score is used 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). Classes 3 and 4 are predictive of difficult intubation. [d]Patients could receive multiple anaesthetic agents during the intubation process.

Table 2: **Airway and intubation setting at baseline.**

jeopardise apnoeic oxygenation, and explain our results in the laryngoscopic stratum. At the opposite, in the fiberoptic stratum, patients from the HFNC group had higher EtO_2 than in the facemask group suggesting that oxygenation remains efficient during conscious sedation (see Supplemental Table S1). Similarly, HFNC which was reported to flush nasopharyngeal dead space (i.e., a key determinant of carbon dioxide clearance),[22] led to significantly lower $EtCO_2$ level after intubation in the fiberoptic stratum. Unlike HFNC, facemask oxygenation requires firm maintenance of the interface to ensure airtightness which may cause discomfort or claustrophobia, especially during fiberoptic intubation. This could explain the marked improvement in patient satisfaction in the HFNC group.

This is the first randomised clinical trial comparing HFNC with facemask for the preoxygenation of adults with anticipated difficult intubation. This trial has some limitations. During COVID-19 pandemic, physicians preferred not to use HFNC to avoid virus aerosolization. The recruitment period was therefore longer than expected, raising financial issues. Hence, the interim analysis which was planned to adjust the sample size according to the incidence of the primary outcome, was cancelled. Consequently, the incidence of the primary outcome which is poorly reported in the literature was lower than expected in the control group and therefore altered the power of the study. Moreover, the hypothesis of a 12% reduction of the primary outcome in the HFNC group may have been overestimated. The sample size and the single-centre design may have underestimated the treatment effect and could limit generalisation of the results.[23] The unblinded preoxygenation device could have interfered with the results. Nevertheless, blinding would have required combining both of the devices which was not feasible, especially in the fiberoptic stratum. The choice of the primary outcome is questionable: current

Outcomes[a]	High-flow nasal cannulae (n = 95)	Facemask (n = 90)	Adjusted difference (95% CI)	P value
Primary outcome, desaturation ≤94% or bag-mask ventilation, n (%)[b]				
Primary analysis	2 (2)	7 (8)	−5.6 (−11.8 to 0.6)	0.10[k]
Laryngoscopic intubation stratum	2/64 (3)	3/59 (5)	−2.0 (−9.0 to 5.1)	0.59[k]
Fiberoptic optic intubation stratum	0/31 (0)	4/31 (13)	−12.9 (−24.7 to 1.1)[l]	0.11[l]
Details of the composite primary outcome				
Desaturation ≤94%	2 (2)	6 (7)	−4.5 (−10.4 to 1.4)	0.15[k]
Bag-mask ventilation for rescue oxygenation[c]	2 (2)	2 (2)	−0.2 (−4.4 to 4.0)	0.96[k]
Secondary outcomes				
Mean (SD) SpO_2 at the end of preoxygenation, %	100 (0.2)	100 (0.4)	0.05 (−0.04 to 0.14)	0.28[m]
Intubation, n (%)				
First operator, junior	63 (66)	55 (61)	5.6 (−7.9 to 19.1)	0.41[k]
Number of operators >1	17 (18)	20 (22)	−4.3 (−15.8 to 7.3)	0.47[k]
First pass success[d]	65 (68)	62 (69)	0.4 (−13.0 to 13.7)	0.96[k]
Mean (SD) duration of procedure, minutes[e]	2.8 (2.4)	3.0 (2.7)	−0.1 (−0.8 to 0.5)	0.66[m]
Mean (SD) lowest SpO_2, %[f]	99 (4)	98 (4)	0.18 (−1.01 to 1.37)	0.77[m]
Desaturation <90%[f]	1 (1)	2 (2)	−1.2 (−4.8 to 2.5)	0.54[k]
Mean (SD) lowest end-tidal oxygen after intubation (%)[f]	76 (10)	73 (14)	2.8 (−0.2 to 5.7)	0.065[m]
Mean (SD) highest end-tidal carbon dioxide after intubation (mmHg)[f]	39 (7)	41 (7)	−2.0 (−4.0 to −0.1)	0.041[m]
Total number of complications[g]	47	58		
At least one complication (severe or moderate), n (%)	30 (32)	39 (43)	−11.8 (−25.6 to 2.1)	0.10[k]
Laryngoscopic intubation stratum	22/64 (34)	24/59 (41)	−6.3 (−23.4 to 10.8)	0.47[k]
Fiberoptic intubation stratum	8/31 (26)	15/31 (48)	−22.6 (−46.0 to 8.0)	0.069[k]
At least one severe complication, n (%)	22/95 (23)	27/90 (30)	−6.9 (−19.6 to 5.8)	0.29[k]
Cardiac arrest or death	0 (0)	0 (0)	–	
SpO_2 <80%	1 (1)	1 (1)	0.0 (−3.0 to 3.0)	0.98[k]
Severe hypotension or need for a vasopressor[h]	22 (23)	26 (29)	−5.8 (−18.4 to 6.8)	0.37[k]
At least one moderate complication, n (%)[i]	14 (15)	18 (20)	−5.3 (−16.2 to 5.7)	0.35[k]
Nasolaryngotracheal injury or bleeding	10 (11)	9 (10)	0.4 (−8.3 to 9.1)	0.92[k]
Oesophageal intubation	0 (0)	2 (2)	−2.3 (−5.3 to 0.8)	0.15[k]
Dangerous agitation	1 (1)	3 (3)	−2.2 (−6.2 to 1.9)	0.32[k]
Ventricular or supraventricular arrhythmia	0 (0)	1 (1)	−1.1 (−3.1 to 1.0)	0.31[k]
Outcome in the post-anaesthesia care unit				
Mean (SD) length of stay, minutes	109 (43)	107 (40)	1.86 (−10.94 to 14.65)	0.77[m]
Mean (SD) duration of mechanical ventilation, minutes	8 (11)	9 (13)	−0.39 (−4.25 to 3.47)	0.84[m]
SpO_2 <90%, n (%)	4 (5)	1 (1)	3.2 (−1.5 to 8.0)	0.23[k]
Satisfaction score, good or excellent experience, n (%)[j]	76 (80)	53 (59)	20.5 (8.3–32.8)	**0.0016**[k]

SD, Standard Deviation; **SpO_2**, Pulse Oximetry; **CI**, Confidence Interval. [a]See Supplemental Table S1 for other outcomes. [b]Primary analysis: The primary analysis included all the patients randomised in the study. No imputation was applied for missing data (1 full withdrawal of consent before intubation). The primary outcome was recorded during intubation and the following 2 min. [c]For oxygen desaturation below 95%, the protocol advised the physician to interrupt intubation in order to focus on oxygenation by facemask. [d]Defined as successful intubation after one attempt with correct placement of the endotracheal tube in the trachea as confirmed by end-tidal CO_2 capnometry. [e]Measured from the injection of anaesthetic drugs until the beginning of mechanical ventilation. [f]Measured during intubation and the 2 min following intubation. [g]Complications were recorded during intubation and the following 1 h. [h]Severe hypotension was defined as systolic blood pressure <80 mmHg or vasopressor introduction (i.e., ephedrine, neosynephrine, or norepinephrine). [i]There was no intubation failure, dental injury, or aspiration in the 2 groups. [j]Collected in the post-anaesthesia care unit. The satisfaction score (1 = Excellent, 2 = Good, 3 = Reasonable or, 4 = Poor) was monitored before the discharge from the post-anaesthesia care unit.[15] [k]Wald test for logistic regression, adjusted on the intubation stratum. [l]Non adjusted risk difference Fisher's exact test. [m]Linear regression, adjusted on the intubation stratum.

***Table 3*: Primary and secondary outcomes.**

guidelines advise interrupting the intubation attempt to focus on oxygenation (i.e., bag-mask ventilation) as soon as SpO_2 drops below 95% during intubation.[24] In order not to underestimate the primary outcome, bag-mask ventilation which could avoid desaturation, regardless of the preoxygenation device, was also included in the primary outcome. Bag-mask ventilation for rescue oxygenation can lead to serious complications (i.e., gastric insufflation, regurgitation). Oxygen desaturation below 95% or rescue bag-mask ventilation during difficult intubation is therefore a patient-centred outcome. This parameter is not as accurate as the measurement of oxygen partial pressure (PaO_2) to assess patient oxygenation,[25] especially because the reduction of $EtCO_2$ in the HFNC group could have shifted to the right the haemoglobin saturation curve and bias SpO2. However, it is a non-invasive and a mandatory standard of monitoring during all

anaesthesia, available worldwide. Given the limitations of SpO_2 measurement, an external observer was specifically dedicated to SpO_2 monitoring to improve data collection. In addition, systematic arterial catheterisation to measure PaO_2 could not be ethically justified for scheduled non-bleeding surgery. In the HFNC group, EtO_2 monitoring at the end of the preoxygenation was not feasible (i.e., non-occlusive device) which hindered the comparison of patients between groups at the end of the preoxygenation period. Moreover, the incidence of leakage during preoxygenation in the HFNC may have been underestimated since it could only be objectively quantified in the facemask oxygen group. The mechanism of the expected benefit of HFNC during laryngoscopic and fiberoptic intubation is different. Hence, analysing these 2 strata together could limit interpretation of results. However, the risk of unbalancing groups was limited by stratification of the randomisation.

In conclusion, compared with facemask, HFNC did not significantly reduce the incidence of desaturation ≤94% or bag-mask ventilation during anticipated difficult intubation but the trial was underpowered to rule out a clinically significant benefit. The results of the fiberoptic intubation stratum analysis encourage further studies focusing on fiberoptic intubation.

Contributors

MV and KA have accessed and verified the data and all authors were responsible for the decision to submit for publication.

Study concept and design: MV, PJM, DH, CG, and KA.

Data acquisition: All of the authors participated in data collection and acquisition.

Data analysis and interpretation: KA, MV, PJM, DH, MM, MLP, RD, MS, and AR.

Verification of the underlying data: KA and MV.

Drafting of the manuscript: KA, MV, PJM, BR, MLP, RD, MS, and AR.

Critical revision of the manuscript for important intellectual content: All of the authors.

Statistical analysis: FF.

Funding obtained: MV and KA.

Administrative, technical or material support: All of the clinician authors.

Study supervision: MV and KA.

Data sharing statement

Deidentified data about the individual participants are to be shared for further studies. Request for data sharing will be handled in line with the data access and sharing policy of Nantes University.

Declaration of interests

MV declares personal fees from MSD, Pfizer, Baxter, Grants from Fisher Paykel, outside the submitted work. KA reprorts grants from Fischer & Paykel and Biomerieux, and consulting fees from Baxter, LFB, and Edward Lifesciences. AR reports receiving consulting fees from MSD and bioMerieux. BR reports receiving lecture fees from NordicPharma, Aguettant, and LFB and support for attending meetings NordicPharma. Other authors declare that they have no conflict of interest involving the work under consideration for publication. No compensation was received for this study.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. The present study presents no discrepancies from the study as originally planned.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101998.

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