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Samir Jaber, Nicolas Molinari, Audrey de Jong. New method of preoxygenation for orotracheal intubation in patients with hypoxaemic acute respiratory failure in the intensive care unit, non-invasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol. *BMJ Open*, 2016, 6 (8), pp.e011298. 10.1136/bmjopen-2016-011298. hal-01799680

HAL Id: hal-01799680

<https://hal.umontpellier.fr/hal-01799680>

Submitted on 12 Mar 2020

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BMJ Open New method of preoxygenation for orotracheal intubation in patients with hypoxaemic acute respiratory failure in the intensive care unit, non-invasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

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To cite: Jaber S, Molinari N, De Jong A. New method of preoxygenation for orotracheal intubation in patients with hypoxaemic acute respiratory failure in the intensive care unit, non-invasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol. *BMJ Open* 2016;**6**: e011298. doi:10.1136/bmjopen-2016-011298

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2016-011298>).

Received 27 January 2016
Revised 27 May 2016
Accepted 18 July 2016



CrossMark

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ABSTRACT

Introduction: Tracheal intubation in the intensive care unit (ICU) is associated with severe life-threatening complications including severe hypoxaemia. Preoxygenation before intubation has been recommended in order to decrease such complications. Non-invasive ventilation (NIV)-assisted preoxygenation allows increased oxygen saturation during the intubation procedure, by applying a positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment. However, the NIV mask has to be taken off after preoxygenation to allow the passage of the tube through the mouth. The patient with hypoxaemia does not receive oxygen during this period, at risk of major hypoxaemia. High-flow nasal cannula oxygen therapy (HFNC) has a potential for apnoeic oxygenation during the apnoea period following the preoxygenation with NIV. Whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during the intubation procedure compared with NIV alone for preoxygenation in patients with hypoxaemia in the ICU with acute respiratory failure remains to be established.

Methods and analysis: The HFNC combined to NIV for decreasing oxygen desaturation during the intubation procedure in patients with hypoxaemia in the ICU (OPTINIV) trial is an investigator-initiated monocentre randomised controlled two-arm trial with assessor-blinded outcome assessment. The OPTINIV trial randomises 50 patients with hypoxaemia requiring orotracheal intubation for acute respiratory failure to receive NIV (pressure support=10, PEEP=5, fractional inspired oxygen (FiO₂)=100%) combined with HFNC (flow=60 L/min, FiO₂=100%, interventional group) or NIV alone (reference group) for preoxygenation. The primary outcome is lowest oxygen saturation during the intubation procedure. Secondary outcomes are

Strengths and limitations of this study

- One strength of the study is the blinded assessment.
- Other strengths are the inclusions performed around the clock, nights and weekend included as a routine clinical practice.
- One limitation of the study is that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who does not know the group of inclusion.
- Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of non-invasive ventilation as a method of preoxygenation. However, as previously reported and in the present study, it will be recommended to never exceed a total insufflation airway pressure (pressure support+positive end-expiratory pressure) of 15 cm H₂O, which has been shown to be safe to avoid gastric air insufflation.

intubation-related complications, quality of preoxygenation and ICU mortality.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee (CPP Sud-Méditerranée). Informed consent is required. If combined application of HFNC and NIV for preoxygenation of patients with hypoxaemia in the ICU proves superior to NIV preoxygenation, its use will become standard practice, thereby decreasing hypoxaemia during the intubation procedure and potential complications related to intubation.

Trial registration number: NCT02530957.

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.¹

Patients admitted to intensive care units (ICU) often require respiratory support. Hypoxaemia and cardiovascular collapse are the initial and most serious life-threatening complications associated with difficult airway access, both during emergency intubation in the critically ill²⁻⁶ and in planned intubations (eg, scheduled surgery or invasive procedures).^{7,8} ICU intubation conditions are worse than intubation conditions in operative rooms.^{4,9} A non-planned and urgent intubation procedure, severity of patient disease and ergonomic issues explain the morbidity associated with intubation in the ICU. To prevent and limit the incidence of severe hypoxaemia following intubation and its complications, several preoxygenation techniques and intubation algorithms have been developed,^{3,5,10,11} and specific risk factors for difficult intubation in the ICU have been identified, constituting the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening <3 cm, Coma, severe Hypoxemia (<80%) and non-Anaesthesiologist status).²

Non-invasive ventilation (NIV) for preoxygenation of patients with hypoxaemic acute respiratory failure is associated with less hypoxaemia than preoxygenation with a non-rebreather bag-valve mask during the intubation procedure.¹² Indeed, associating pressure support (PS) with positive end-expiratory pressure (PEEP) limits alveolar collapse and atelectasis formation, responsible for the hypoventilation and low perfusion ventilation ratio.^{8,13} Incidence of severe hypoxaemia, defined by a pulse oximetry (SpO₂) of <80%, can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with hypoxaemic acute respiratory failure.²

However, although NIV can be safely applied for preoxygenation before the intubation procedure, the NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Furthermore, positioning the orotracheal tube into the trachea may take time, from a few seconds to several minutes in case of difficult intubation. The patient with hypoxaemia does not receive oxygen during this period, which participates in the risk of severe hypoxaemia during intubation.

High-flow nasal cannula oxygen therapy (HFNC), which delivers high-flow heated and humidified oxygen and air via nasal prongs at a prescribed fractional inspired oxygen (FiO₂) and a maximum flow of 60 L/min,¹⁴⁻¹⁷ can be continued during the passage of the orotracheal tube through the mouth. Apnoeic oxygenation maintains blood oxygenation for a significant period of time in breathless conditions.¹⁸ Recent studies suggest that HFNC could allow apnoeic oxygenation^{16,19,20} and, as a consequence, could be

interestingly used to continue blood oxygenation during the apnoea period of intubation, especially when the NIV mask is removed. Furthermore, previous studies have shown that HFNC oxygen therapy generates a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume,²¹ thus suggesting possible associated alveolar recruitment. However, the patient's mouth must be closed to observe this effect,²² suggesting that NIV could be more efficient than HFNC to prevent alveolar derecruitment.

Using HFNC combined with NIV may have potential advantages over conventional NIV alone for preoxygenation before intubation in patients with hypoxaemia in the ICU. Some studies have assessed the preoxygenation effect of HFNC compared with the facial mask or other devices, with conflicting results.^{16,17,23} However, the technique of preoxygenation associating NIV and HFNC, respectively, combining the concepts of prevention of alveolar derecruitment and of apnoeic oxygenation, has never been assessed and the benefit remains to be established.

Objectives

Primary objective

To determine whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during the intubation procedure over NIV alone for preoxygenation in patients in the ICU needing mechanical ventilation for hypoxaemic acute respiratory failure.

Secondary objectives

To determine whether in comparison to NIV alone, application of HFNC combined with NIV could provide a better preoxygenation quality, less complications related to intubation, and decrease in ICU morbidity and mortality day-28 rate.

The OPTINIV study aims to compare the effects of preoxygenation with a combination of NIV and HFNC delivered together compared with NIV alone on lowest oxygen saturation during the intubation procedure and complications related to intubation of patients with hypoxaemia in the ICU needing mechanical ventilation for hypoxaemic acute respiratory failure.

The hypothesis is that preoxygenation combining NIV and HFNC compared with NIV alone could prevent desaturation during the intubation procedure.

Trial design

The HFNC (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand) combined with NIV for decreasing oxygen desaturation during the intubation procedure in patients with hypoxaemia in the ICU (OPTINIV) trial is an investigator-initiated single-centre randomised controlled two-arm trial.

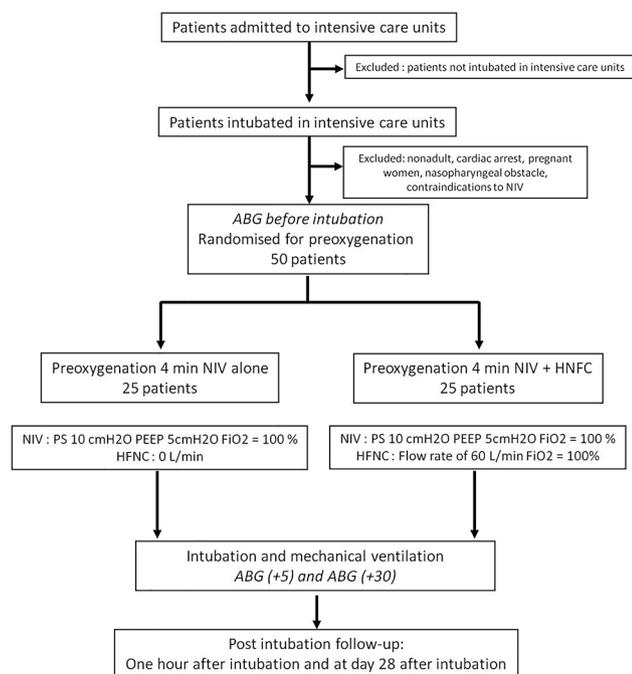


Figure 1 Consort diagram of the OPTINIV trial. ABG, arterial blood gas; FiO₂, fractional inspired oxygen; HFNC, high-flow nasal cannula oxygen therapy; NIV, non-invasive ventilation; PEEP, positive end-expiratory pressure; PS, pressure support.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the OPTINIV trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The OPTINIV study is taking place in a mixed medical and surgical 16-bed ICU in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU and require mechanical ventilation through an orotracheal tube. Hypoxaemic acute respiratory failure is defined as a respiratory rate higher than 30 breaths/min and an FiO₂ requirement of 50% or more to obtain at least 90% oxygen saturation, and an estimated arterial oxygen tension (PaO₂) to FiO₂ (PaO₂/FiO₂ ratio) below 300 mm Hg, in the 4 hours before inclusion.¹⁷

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: age <18 years, pregnant or breast-feeding woman, protected person, intubation in case of cardiocirculatory arrest, nasopharyngeal obstacle contraindicating the use of HFNC and usual contraindications to NIV.²⁴

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group or to the reference group (figure 2). The interventional group consists in applying preoxygenation at 30° of head-up inclination with NIV (PS of 10 cm H₂O, PEEP of 5 cm H₂O, FiO₂=100%, inspiratory flow trigger at 0.3 L/min, expiratory trigger at 25%, maximal inspiratory time at 1.5 s) and HFNC (humidified oxygen flow of 60 L/min, FiO₂=100%, figure 3A). We will use an ICU ventilator with NIV software (Evita V500 or XL, Dräger Lubeck). The reference group consists in applying a preoxygenation at 30° of head-up inclination with NIV only (same parameters as in the interventional group) without HFNC (nasal cannula positioned without any flow, figure 3B). The ventilator circuit will be connected to a standard soft style manual resuscitator face mask, with a capnograph inserted between the face mask and flow sensor. During preoxygenation, the operator will ensure that the jaw is pulled forward with a two-handed thenar eminence grip. After general anaesthetic induction, the NIV mask will be removed, enabling laryngoscopy vision. No ventilation will be performed during apnoea. The nasal cannula will be maintained during the laryngoscopic procedure.

Outcomes

Primary outcome measure

The primary outcome variable is the lowest oxygen saturation indicated by SpO₂ during the intubation procedure. The intubation procedure lasts from the beginning of the first laryngoscopy (the end of rapid sequence induction) to the confirmation of the orotracheal intubation by capnography after the patient is connected to mechanical ventilation.¹⁷

Secondary outcome measures

Secondary outcome variables are preoxygenation quality (duration, ability to improve SpO₂, proportion of patients in whom it is impossible to obtain a saturation >90% during preoxygenation), complications related to intubation (severe: severe hypoxaemia defined by lowest saturation <80%, severe cardiovascular collapse, defined as systolic blood pressure <65 mm Hg recorded at least once or <90 mm Hg lasting 30 min despite 500–1000 mL of fluid loading (crystalloids solutions) or requiring the introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries), morbidity in the ICU (ICU length of stay, invasive ventilator-free days and mortality rate on day 28).

A previous trial showed that preoxygenation using NIV was more effective at reducing arterial oxyhaemoglobin lowest saturation than the usual method.¹² Therefore, the study protocol stresses that NIV must be used as the

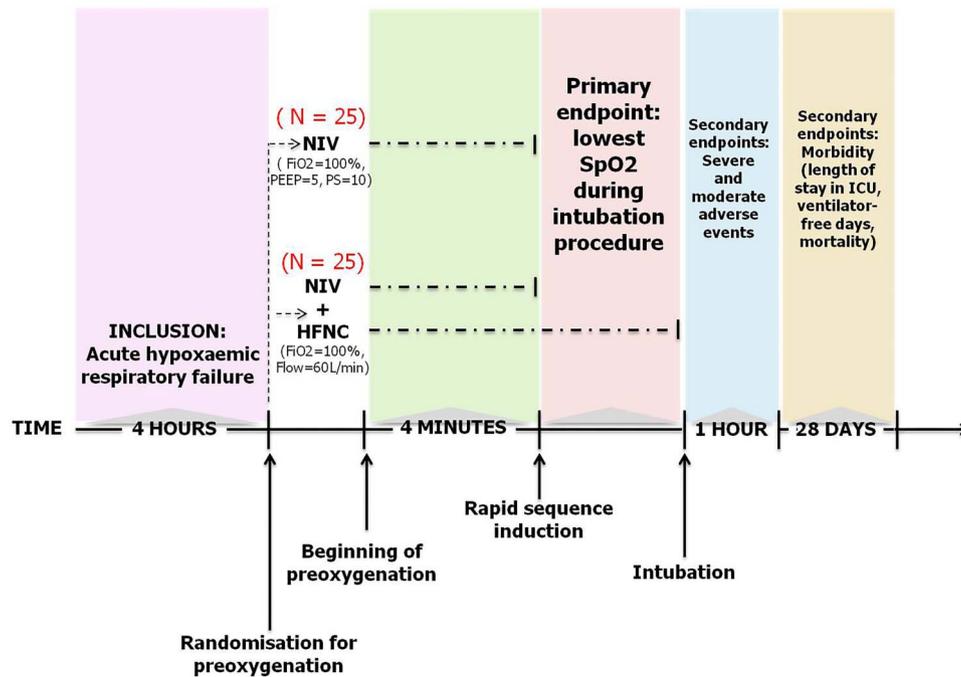


Figure 2 Study design of the OPTINIV trial. FiO₂, fractional inspired oxygen; HFNC, high-flow nasal cannula oxygen therapy; ICU, intensive care unit; NIV, non-invasive ventilation; PEEP, positive end-expiratory pressure; PS, pressure support.

reference group in the OPTINIV trial, as stated by the unit protocols,^{3 5} which are followed for each intubation procedure. Other preintubation procedures included in the unit protocols consist of fluid loading if there is no cardiogenic oedema, preparation of sedation by the nursing team and presence of two operators. The availability of equipment for management of a difficult airway will be checked. During the procedure, the patient will be ventilated in case of desaturation to <80%. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. The difficulty of intubation will be assessed using the MACOCHA score.² If a difficult intubation is predicted (MACOCHA score ≥ 3), the use of a malleable stylet and of videolaryngoscopy or combo videolaryngoscopy will be recommended. In cases of abundant secretions even after aspiration, direct laryngoscopy will be preferred rather than videolaryngoscopy. Finally, in cases of intubation failure, an intubating stylet (malleable stylet or long flexible angulated stylet) will be added first, followed successively by the use of videolaryngoscopy if not initially used, an intubation laryngeal mask airway, fiberoscopy and rescue percutaneous or surgical cricothyrotomy. The rapid sequence induction of general anaesthesia for orotracheal intubation under laryngoscopy will be used according to the unit protocol,⁵ with a Sellick²⁵ manoeuvre, a hypnotic drug (ketamine 2.5 mg/kg) in the absence of contraindications and a neuromuscular blocker (either suxamethonium 1 mg/kg in the absence of allergy and other contraindications such as hyperkalaemia, burns, rhabdomyolysis, neuromuscular disease or rocuronium 1 mg/kg). A metal blade will be used.²⁶ Just after

intubation (postintubation period), the tube's position will be checked by capnography, long-term sedation will be initiated as soon as possible (to avoid agitation)⁵ and 'protective' mechanical ventilation settings will be used, as defined by the acute respiratory distress syndrome network.²⁷ At any time, vasopressors will be mandatory in the event of severe haemodynamic collapse.

Participant timeline

The participant timeline is described in [table 1](#).

Sample size

The primary outcome is the lowest oxygen saturation during the intubation procedure. For this study, 2×23 patients are needed to detect a 5% difference in the lowest oxygen saturation during the intubation procedure, with an SD of 6%, at a two-sided α level of 0.05 and a statistical power of 80%.^{5 10 12} To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement before intubation, 25 patients will be included in each group.

Recruitment

Patients are expected to be included during a 1-year inclusion period starting July 2015.

2015: Protocol, approvals from the ethics committee and trial tool development (case report form, randomisation system).

2015–2016: Inclusion of patients.

2016: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

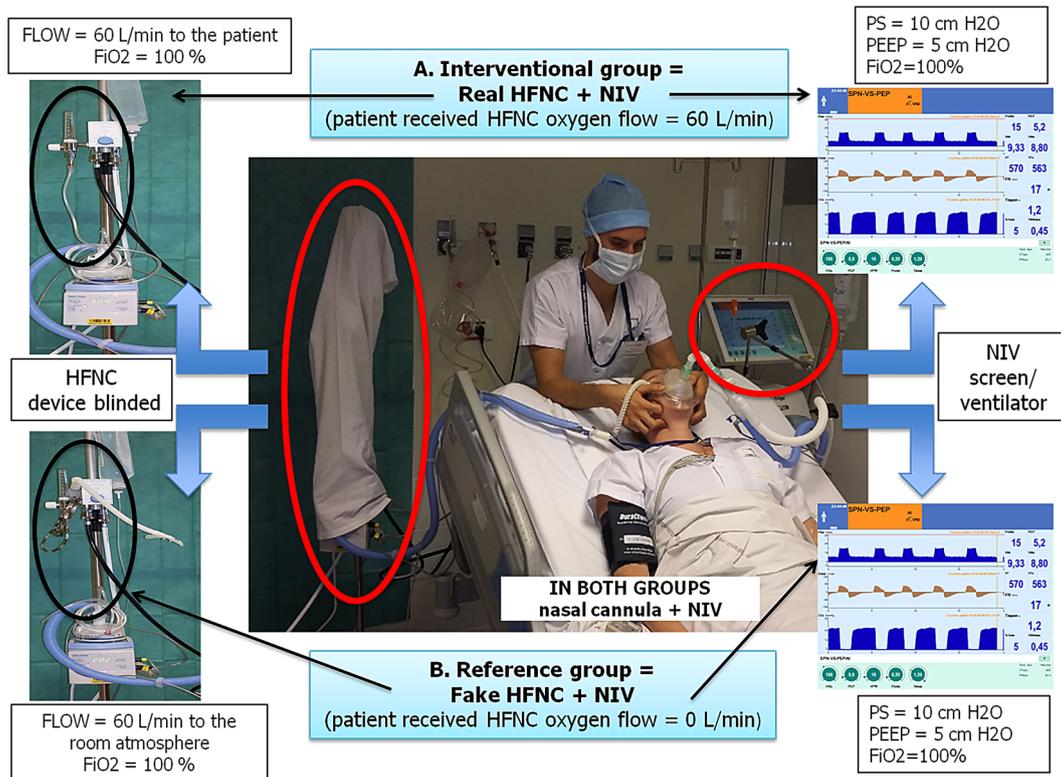


Figure 3 Blinding sequence of the OPTINIV trial. To allow blinding, a nasal cannula will be positioned in each group. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow metre. Both groups will receive non-invasive ventilation (NIV). (A) Interventional group: In the interventional group (real high-flow nasal cannula oxygen therapy (HFNC)+NIV), the nasal cannula will be connected to the oxygen flow metre via a tube and oxygen set at 60 L/min and 100% of fractional inspired oxygen (FiO₂) which will be delivered to the patient. In the interventional group, preoxygenation at 30° of head-up inclination with NIV (pressure support (PS) of 10 cm H₂O, positive end-expiratory pressure (PEEP) of 5 cm H₂O, FiO₂=100%) and oxygen HFNC set at 60 L/min and 100% of FiO₂ was applied. (B) Reference group: In the reference group (fake HFNC+NIV), no oxygen flow will be administered by the nasal cannula to the patient. The tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow metre. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow metre, with a flow also set at 60 L/min. In the reference group, preoxygenation at 30° of head-up inclination with NIV only (PS of 10 cm H₂O, PEEP of 5 cm H₂O, FiO₂=100%) without oxygen HFNC (nasal cannula positioned without any flow) was applied.

Table 1 Participant timeline

	Inclusion	Discharge from ICU	Day 28
Informed consent	X		
Eligibility: check inclusion and exclusion criteria	X		
Randomisation	X		
Filling of case report forms	X	X	X
Vital status			X

ICU, intensive care unit.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

A computer-generated randomisation will be used, which will be generated by a statistician who is not involved in determination of patient eligibility or

outcome assessment. Randomisation will be accomplished by using opaque sealed envelopes. The randomisation envelopes will contain a card stating the group to which the patient was randomised.

Blinding

The study will be blinded to the observer collecting data (figure 3). NIV will be performed and the nasal cannula positioned in both groups, to allow blinding. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow metre (figure 3). In the interventional group (called 'A. Real HFNC+NIV' in the figure 3), the nasal cannula will be connected to the oxygen flow metre via a tube and oxygen set at 60 L/min and 100% of FiO₂. In the reference group (called 'B. Fake HFNC+NIV' in the figure 3), the tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow metre. No flow of oxygen

will be administered by the nasal cannula in the reference group. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow metre, with a flow also set at 60 L/min delivered in the room atmosphere (figure 3). The blinded observer will be one of the ICU residents, a nurse or a member of the trained local research team.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on case report forms by trained local research coordinators or residents blinded to the randomised intervention. Patients will receive standard ICU monitoring consisting of ECG analysis, SpO₂ and a non-invasive blood pressure cuff. Prior to orotracheal intubation, the nurse will set the time intervals on the non-invasive blood pressure cuff monitoring and electronic medical record in the patient's room to run every minute until 15 min after successful intubation. Continuously throughout the procedure (from preoxygenation to 1 hour following intubation), vital parameters will be collected by software on an external laptop called S5/Collect by General Electric, on the General Electric CARESCAPE Monitors.

The following data will be collected and registered before intubation: demographic and epidemiological data: age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason for ICU admission, indication of intubation, comorbidities. The following parameters will be recorded during the 4 hours before intubation: nature and number of operators, and their training, arterial pressure and lowest saturation, arterial blood gases with calculated PaO₂/FiO₂ ratio, delay between the time where the intubation is decided and its realisation, presence of vasopressor drugs, prior NIV use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.²

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (oxygen saturation at the beginning and at the end of the preoxygenation, lowest oxygen saturation, lowest and highest arterial pressure and heart rate).

During the intubation procedure, the following parameters will be collected: doses of hypnotic and neuromuscular blocker used, oxygen saturation at the beginning and at the end, lowest oxygen saturation, mild (<90%), moderate (<85%) or severe (<80%) hypoxaemia, total duration of the intubation procedure, number of operators, number of attempts, Cormack-Lehane grade, traction force on the laryngoscope, Sellick manoeuvre, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale (IDS

score)²⁸ and occurrence of complications related to intubation.

After the intubation procedure (until 1 hour after): arterial blood gases with calculated PaO₂/FiO₂ ratio will be performed at 5-min and 30-min. Complications occurring will be collected: cardiac arrest, arrhythmias, pneumothorax, arterial hypotension, hypoxaemia, agitation, death.

From postoperative day 1 to 28 will be assessed: morbidity by the length of mechanical ventilation, the length of stay in the ICU and the mortality at day 28.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention-to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.3; SAS Institute; Cary, North Carolina, USA, and R V.2.14.1). A two-sided p value of <0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using n (%) for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables.

Analysis of the primary outcome

Unpaired Student's t-test or the Mann-Whitney U test when appropriate will be used for primary outcome analysis.

Analysis of secondary outcomes

The χ^2 test (or Fisher's exact test as appropriate) will be used for secondary binary outcomes. Continuous variables will be compared with the use of the unpaired Student's t-test or the Mann-Whitney U test when appropriate.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of preoxygenation used.

Auditing

An independent Data and Safety Monitoring Board, composed of three experts (Catherine Paugam, Karim Asehnoune and Emmanuel Futier) will monitor the safety of the trial.

ETHICS AND DISSEMINATION

Research ethics approval

The OPTINIV study is conducted in accordance with the declaration of Helsinki and was registered at <http://www.clinicaltrials.gov> with trial identification number NCT02530957.

Consent or assent

Three methods of consent will be used, as required by the Institutional Review Board in accordance with the 2013 Declaration of Helsinki (see online supplementary appendix 1). If possible, the patient will be included after written informed consent. However, the patient often cannot understand the information given because of hypoxaemia. These patients will be included after written informed consent is provided by the next of kin or an emergency procedure (investigator signature) if the next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

Intubation in the ICU is associated with severe hypoxaemia.²⁻⁴ Optimising preoxygenation is therefore of particular importance before the intubation procedure,

especially in patients with hypoxaemia needing mechanical ventilation for acute respiratory failure. However, although NIV preoxygenation is effective to reduce hypoxaemia during the intubation procedure,¹² the NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. The association of HFNC with alveolar recruitment by NIV could be of particular interest both for increasing administration of oxygen during preoxygenation and to allow apnoeic oxygenation during the apnoea period, a time where the patient with hypoxaemia usually receives no oxygen. This period without oxygenation can last several minutes, especially when the intubation is difficult.

The OPTINIV trial is the first randomised controlled study powered to investigate the effectiveness of combined NIV and HFNC to decrease severe hypoxaemia during the intubation procedure in patients with hypoxaemic acute respiratory failure in the ICU.

Apnoeic oxygenation is a physiological phenomenon in which, provided that a patent air passageway exists between the lungs and the exterior, the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cm H₂O that drives oxygen into the lungs.^{18 29 30} The aim of apnoeic oxygenation use throughout the intubation procedure is therefore to reduce severe hypoxaemia occurrence during the intubation procedure.³¹ Previous studies assessed the effect of apnoeic oxygenation, with conflicting results. Apnoeic oxygenation increased the time to severe desaturation during the intubation procedure in acute lung injury in an experimental study in piglets.³² Miguel-Montanes *et al*¹⁶ compared 3 min of preoxygenation using a face mask to 60 L/min of HFNC in patients with mild-to-moderate hypoxaemia. With the face mask, the median lowest SpO₂ during intubation was 94% vs 100% with HFNC. Vourc'h *et al*¹⁷ found no difference on lowest arterial oxygen during intubation in patients with hypoxaemia between 60L/min of HFNC and 4 min of preoxygenation with a face mask (92% vs 90%, p=0.44). Semler *et al*²³ performed a randomised trial in a medical ICU enrolling 150 patients. The administration of 15 L/min nasal cannula oxygen in the apnoeic oxygenation group was not associated with significantly increased arterial oxygen saturation (from 92% in the apnoeic oxygenation group to 90% in the usual care group (p=0.16)). The discrepancies between the results of these three studies^{16 17 23} could mainly be explained by the oxygen flow used for the apnoeic oxygenation group (from 15 to 60 L/min) and the different studied populations in term of hypoxaemia. Moreover, the design of these studies differs from the design of this study, which allows to specifically study apnoeic oxygenation by HFNC simultaneously combined with NIV preoxygenation. However, this study will not conclude on the superiority or not of NIV over HFNC alone, and therefore on the best means to ensure preoxygenation.

The primary end point of the trial is the lowest oxygen saturation during the intubation procedure. The incidence of severe hypoxaemia following intubation is particularly high in the ICU, reaching up to 50%.²⁻⁴ The ability to anticipate hypoxaemia occurrence is of critical importance to prevent the development of subsequent complications. Severe hypoxaemia can lead to cardiac arrest, neurological damage or multiple organ failure.² Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of combined preoxygenation on other complications.

One limitation of the study is that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported^{12-17, 26-33} and in this study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cm H₂O, which has been shown to be safe to avoid gastric air insufflation.³⁴⁻³⁶ Moreover, adding a nasal cannula under the NIV mask may generate leaks during NIV and decrease its efficacy. However, the operator performing intubation holds the mask, which limits the leaks, and the two groups are treated similarly. Finally, given the error of measure associated with SpO₂ monitors (usually around 2%) and the error associated with the oxygen blender (around 2%), one could argue that in fact the difference in SpO₂ could be solely due to the devices' imprecision. However, given the randomised design of the study, this imprecision should be evenly distributed in each group.

One strength of the study is the blinded assessment (figure 3). Moreover, the inclusions will be performed around the clock, nights and weekend included as a routine clinical practice.

In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding HFNC in combination with NIV in comparison to NIV alone allows to decrease severe hypoxaemia during the intubation procedure of patients with hypoxaemia in the ICU requiring mechanical ventilation for acute respiratory failure. The OPTINIV trial will also assess the effects of combined NIV and HFNC for preoxygenation on intubation-related complications.

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Contributors ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All the authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding The study is an investigator-initiated trial. The study promoter is Montpellier University Hospital, Montpellier, France.

Disclaimer There is no industry support or involvement in the trial.

Competing interests SJ reports receiving consulting fees from Drager, Hamilton, Maquet and Fisher & Paykel.

Patient consent Obtained.

Ethics approval The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. The study has been approved by a central ethics committee (Ethics Committee Sud-Méditerranée IV, Montpellier, France) with the registration number IDRCB 2015-A00708-41 (13 May 2015).

Provenance and peer review Not commissioned; externally peer reviewed.

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