STUDY PROTOCOL

Effect of Postextubation High-Flow Nasal Oxygen vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients

A Randomized Clinical Trial

PRIMARY INVESTIGATOR

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TRIAL SUMMARY

This is a non-inferiority multicenter randomized controlled trial comparing the efficacy of conditioned high-flow nasal cannula oxygen therapy to non-invasive ventilation (NIV) for preventing reintubation and postextubation respiratory failure in mechanically ventilated patients at high-risk for reintubation.

BACKGROUND AND INTRODUCTION

PLAIN LANGUAGE SUMMARY

Transient residual impairment in oxygenation after planned extubation is frequent and corrected with conventional oxygen therapy delivered through different conventional devices with increasing FiO2 and flow, depending on the degree of hypoxemia.

Until recently, studies centered on preventive measures to avoid postextubation respiratory failure have focused on specific causes of reintubation, with most evidence limited to patients with high-risk factors for these causes of reintubation, mainly laryngeal edema and hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD) patients.

Preventive NIV has been tested in general critically ill populations, without proven benefits, except limited evidence after selecting the specific subgroup of patients with high risk factors for reintubation, reported by two randomized trials. Under a 10% use of NIV after planned extubation, the reintubation rate has not changed over the last 15 years, as recently reported by Esteban et al. in an international survey study, with rates close to 10% to 12%.
High-risk factors for reintubation in the general population of critically ill patients are difficult to standardize, as they depend on the subgroup of critically ill patient, comorbidities, etc. They may also include simultaneous causes, and must be considered all together in a multifaceted diagnosis approach to define high-risk patients. This approach is sometimes difficult to implement or effectively use at the bed-side. However, some high-risk factors have been validated in prospective randomized trials.

The definition of high-flow has changed along with technological improvements. With the development of new nasal cannulas for high-flow therapy, the concept includes not only constant FiO₂ during the peak inspiratory flow but also other beneficial mechanisms such as generation of low continuous positive airway pressure (CPAP) level with increased end-expiratory lung volume, dead space washout, and conditioning the inspired mixed air, which might help improve comfort, possibly reducing airway inflammation and improving respiratory secretions management.

Most clinical studies on this new device have found improvement in some clinical outcomes in general populations of critically ill patients during the acute phase of respiratory failure (e.g., oxygenation, tolerance and comfort, thoracoabdominal synchrony, facilitation of elimination of respiratory secretions, or survival).

There is also evidence of clinical benefit after extubation in specific populations like very preterm infants, patients at low risk for reintubation and cardiac surgery patients. Recently, Maggiore et al. suggested a decreased reintubation rate in a general population after planned extubation, with greater theoretical benefit in patients with no risk factors for reintubation.
**LITERATURE REVIEW**

High-flow improves conventional oxygen therapy performance, even with the addition of a low-CPAP effect on upper airway (3-5 mmHg). It heats and moistens the inspired air up to physiologic conditions, resulting in better spontaneous respiratory secretions management and alleviating inflammation of the tracheobronchial mucosa.

To date, only the randomized trial by Maggiore et al. has tested the effect of high-flow compared to conventional oxygen therapy after extubation in critically ill patients on postextubation respiratory failure and the reintubation rate in a non-selected population. To our knowledge, no trial has focused on critically ill patients at high-risk for reintubation and compared with NIV.

The reintubation rate in this subgroup of patients ranges from 9% to 32%, depending on the case mix and the high-risk criteria selected. Causes for reintubation in these patients differ from those in low-risk patients, as the percentage of non-respiratory related reintubations is lower; likewise, the percentage of reintubations for postextubation airway obstruction secondary to glottic edema. On the other hand, hypoxemic and hypercapnic respiratory failures are more common.

High-flow is better tolerated even when compared to conventional oxygen therapy, and it is applicable outside the ICU environment.

**REFERENCES**


5.- Parke RL, McGuinness SP: Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle. Respir Care 2013; 58:1621-1624.


OBJECTIVES

PRIMARY OUTCOMES AND THEIR CRITERIA

We selected two primary outcomes:
1. Reintubation within 72 hours after extubation.

2. Postextubation respiratory failure classified according to the postextubation respiratory failure definition.

Postextubation respiratory failure is a necessary diagnosis before respiratory-related reintubation but not before non-respiratory reintubations. In addition, postextubation respiratory failure is not necessary followed by respiratory-related reintubation. The lower prevalence is expected for reintubation, so the statistical power for the analysis of postextubation respiratory failure is not compromised.

Predefined criteria for reintubation and postextubation respiratory failure:

1. Immediate reintubation: any of the following major clinical events: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate <50 beats per minute with loss of alertness, and severe hemodynamic instability unresponsive to fluids and vasoactive drugs.

2. Patients will be also reintubated for persistent postextubation respiratory failure or non-respiratory reasons, such as urgent surgery or a Glasgow Coma Scale ≤8 points not related to hypercapnia.

2. Postextubation respiratory failure definition: presence any of the following criteria within 72 hours of extubation: respiratory acidosis (pH <7.35 with PaCO2 >45 mmHg), SpO2 <90% or PaO2 <60 mm Hg at FiO2 >.4, respiratory rate >35 breaths per minute, decreased level of consciousness, agitation, or clinical signs
suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical abdominal motion, or retraction of the intercostal spaces.

SECONDARY OUTCOME MEASURES

1. Respiratory infection (ventilator-associated pneumonia or ventilator-associated tracheobronchitis).
   - Ventilator-associated pneumonia (VAP) was defined as fever (temperature >38°C) or altered leukocyte count (>12,000/mL or <4,000/mL) plus new onset of purulent endotracheal secretions or change in sputum, with new and progressive or persistent infiltrate or consolidation or cavitation and a significant pathogen culture (>10^5 cfu/mL in semiquantitative endotracheal aspirate, >10^4 cfu/mL in bronchoalveolar lavage fluid, or >10^3 cfu/mL in protected brush specimens).
   - Ventilator-associated tracheobronchitis (VAT) was defined by the same criteria but without new infiltrates.

2. Sepsis or multiorgan failure.
   - Sepsis was defined according to Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012.
   - Multiorgan failure was defined according to Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012.

3. ICU and hospital length of stay.

4. ICU and hospital mortality.
5. Reason for failure of assigned treatment if applicable, including patient comfort.

6. Nasal septum or skin trauma, as referred by patients as present or absent.

7. Time to reintubation: number of hours from extubation to reintubation.

**PATIENT SELECTION CRITERIA**

**INCLUSION CRITERIA**

All adult patients receiving mechanical ventilation longer than 12 hours and ready for scheduled extubation according to tolerance of spontaneous breathing trial (see later), with at least one of the following criteria for high-risk for extubation failure:

- Age greater than 65 years.
- Heart failure as the primary indication for mechanical ventilation.
- Moderate-to-severe COPD.
- An Acute Physiology and Chronic Health Evaluation (APACHE) II >12 points on extubation day.
- Body mass index >30 kg/m².
- Airway patency problems, including high risk of developing laryngeal edema (see later).
- Inability to deal with respiratory secretions (inadequate cough reflex or suctioning >2 times within 8 hours before extubation).
- Difficult or prolonged weaning.
- Two or more comorbidities (according to the Charlson Comorbidity Index).
- Prolonged mechanical ventilation, defined as longer than 7 days.

Only the first extubation episode will be randomized and analyzed for the primary
outcomes.

EXCLUSION CRITERIA
1. Patients <18 years old.
2. Pregnant patient.
3. Patients with do-not-resuscitate orders.
4. Tracheostomized patients.
5. Hypercapnic during the spontaneous breathing trial.
6. Accidentally extubated or self-extubated.

STUDY DESIGN

This is a multicenter randomized open trial of two different methods for oxygen therapy after planned extubation: conditioned high-flow and NIV, in high-risk for reintubation adult, mechanically ventilated patients admitted to an ICU. We hypothesized that conditioned high-flow is non-inferior to NIV in terms of postextubation respiratory failure and reintubation rates in this selected population.

STUDY PROCEDURES

RECRUITMENT

Daily screening for weaning readiness according to the following criteria: recovery from the precipitating illness; respiratory criteria (PaO₂/FiO₂ ratio >150 with FiO₂ ≤0.4, positive end-expiratory pressure <8 cm H₂O, and arterial pH >7.35); and clinical criteria (absence of electrocardiographic signs of myocardial ischemia, no vasoactive
drugs or only low doses of dopamine (<5 µg/kg/min), heart rate <140 beats per minute, hemoglobin >8 g/dL, temperature <38°C, no need for sedatives, presence of respiratory stimulus, and appropriate spontaneous cough).

Patients fulfilling these criteria will undergo a spontaneous breathing trial with either T-tube or 7 cm H2O of pressure support for 30 to 120 minutes.

Patients who tolerate the spontaneous breathing trial will be reconnected with the previous ventilator settings for rest and clinical evaluation of airway patency, respiratory secretions, and upper airway obstruction (see later).

Criteria for spontaneous breathing trial failure: agitation, anxiety, depressed mental status, diaphoresis, cyanosis, evidence of increasing respiratory effort, increased accessory muscle activity, facial signs of distress, dyspnea, PaO2 lower than 60 mm Hg or SpO2 lower than 90% on inspired fraction of oxygen higher than .5, PaCO2 higher than 50 mm Hg or increased more than 8 mmHg from baseline value, arterial pH lower than 7.32 or decreased more than .07 from baseline value, respiratory rate higher than 35 breaths per minute or increased more than 50% from baseline value, heart rate higher than 140 beats per minute or increased more than 20% from baseline value, systolic arterial pressure higher than 180 mmHg or increased more than 20% from baseline value, systolic arterial pressure lower than 90 mmHg, or cardiac arrhythmias.

**RANDOMIZATION**

Patients’ relatives will be approached for recruitment of the patients the day the first spontaneous breathing trial is attempted.

Consent will be obtained by the principal investigator at the participating center or
by a co-researcher.

Patients who pass the spontaneous breathing trial will be randomized (telephone call center) to receive high-flow oxygen therapy or noninvasive ventilation (simple randomization). The phone call will take place immediately before a planned extubation, after reconnection for rest (concealed allocation).

**DATA COLLECTION**

Data will be sourced from the patient’s bedside nursing chart, medical notes, pathology results, electronic monitors, and by interviewing relatives. This data will be entered into a paper data collection form, known as a care record form (CRF), and subsequently entered into an electronic database.

Data collection will occur regularly until final discharge from hospital. There is no follow-up of patients or their families after planned discharge.

Data collected will include the primary and secondary outcomes described above. Other data will be collected including:

- At inclusion: demographic variables (age, sex, APACHE II within first 24 hours after admission) and primary diagnosis.

- At extubation: arterial blood gases, APACHE II, and administration of steroids.

- In the 72 hours after extubation: extubation-related complications, adverse events, and causes for reintubation and postextubation respiratory failure.

Patients were followed until discharge from hospital. Length of stay in the ICU and in the hospital, and status at discharge from hospital were recorded.
SAFETY AND SIGNIFICANT ADVERSE EVENTS

The trial will be conducted and supervised by medical doctors and nurses with extensive experience in critical care medicine, as well as in conducting clinical trials.

An external monitoring committee will be convened containing at least three expert critical care physicians not involved in recruitment or supervision of the trial and a specialist statistician will be convened. No interim analyses are planned.

Significant adverse events other than primary outcomes (reintubation or postextubation respiratory failure) and secondary outcomes are not expected. Any unexpected significant adverse event will be reported during the trial by the completion of a significant adverse event reporting form, which will be forwarded to the chief investigator by fax or post. Significant adverse events will be notified to within 24 hours where possible.

STATISTICAL METHODS AND ANALYSIS

SAMPLE SIZE CALCULATION

Estimation of sample size was based on a baseline reintubation rate of 20-25% for both therapies, with a pre-defined non-inferiority margin of 10%. The non-inferiority design included a 95%CI unilateral analysis with a statistical power of 80%. Non-inferiority would be established if the limit of the one-sided 95%CI for the between-group difference in reintubation or postextubation respiratory failure rates is less than 10%. With a maximum tolerated patient loss rate of 15%, 300 participants were required per study group.
STATISTICAL ANALYSIS

All analyses will be performed on a protocol basis, and on an intention-to-treat basis to detect additional biases.

Baseline comparisons: we plan to tabulate the distribution of baseline variables across the study arms and to summarize discrete variables by frequencies and percentages. We will report continuous variables as either means with SDs or as medians with interquartile ranges. Basal homogeneity will be evaluated with these analyses.

Primary outcomes: differences between high-flow and NIV groups rates will be analyzed with a unilateral 95%CI, considering statistical significance in case it is lower than the estimated 10% difference.

To test whether the marginal odds ratio was similar to the odds ratio conditioned to co-variables, we will use multivariable logistic regression, including the following variables: length of mechanical ventilation, hospital, and baseline variables associated with reintubation with p values less than .1. The results will be expressed as odds ratios and 95%CI.

Kaplan-Meier curves will be plotted to assess the time from extubation to reintubation.

For the analysis of secondary outcomes and post hoc analyses, we will use two-sided 95%CI for the between groups differences, Fisher’s exact test, Student’s t-test, Mann-Whitney U, or Cochran-Mantel-Haenszel chi-square tests (stratified for hospitals). Reasons for reintubation will be analyzed with the chi-square test, and time to reintubation with the Mann Whitney U test.

The level of significance will be set at 0.05 and the 95%CI used will be the
Newcombe-Wilson type for the differences of proportions and the Bonnet and Price for the differences of medians. We will use SPSS version 13.0 (SPSS Inc.; Chicago, IL) for all analyses.

CLINICAL PROTOCOL

DEFINITIONS

High-flow is defined as a gas (air/oxygen) mixture at a flow rate of $\geq 30$ liters/minute (L/min), delivered via heated, humidified, blended Fisher and Paykel (F&P) circuit and prongs.

NIV encompasses all the ventilator assistance methods that produce all or part of the work of breathing without requiring endotracheal intubation, the goal being to ensure sufficient alveolar ventilation. At present, bi-level positive airway pressure ventilation (BiPAP) is by far the most widely used modality.

CONDITIONED HIGH-FLOW OXYGEN THERAPY GROUP PROTOCOL

High-flow: Optiflow® system, applied prior to extubation at 37°C and 10 lpm. Immediately after extubation, flow will be titrated upwards in 5 L/min steps until patients experienced discomfort. In case the patient report it too hot, it will be titrated downward to 31°C. The inspired fraction of oxygen will be regularly adjusted to target $\text{SpO}_2 >92\%$.

The protocol starts high-flow through nasal cannula at 10 l/m just before extubation and flow is fast and steeply increased according to patient tolerance. Flow is increased rapidly up to 30 l/min. After that, flow is increased in 5 l/m steps in a few minutes window.
After 24 hours, high flow will be stopped and patients will receive conventional oxygen therapy if necessary to maintain the same oxygen target.

Rescue therapy with noninvasive mechanical ventilation for post-extubation respiratory failure was not aloud.

NON-INVASIVE MECHANICAL VENTILATION GROUP PROTOCOL

NIV (BiPAP Vision; Respironics, Inc., Murraysville, PA) will be continuously delivered immediately after extubation for a scheduled period of 24 h after extubation. Afterward, NIV will be withdrawn and oxygen will be administered by Venturi mask.

The PEEP will be initially set at 5 cm H₂O and can be increased until oxygen saturation is constantly 92%, whereas the inspiratory pressure support will be initially set at 10 cm H₂O and then increased to the maximum tolerated. In either case, both settings will be aimed to achieve respiratory rate 25 breaths/min and satisfactory gas exchange, that is, arterial oxygen saturation (SpO₂) 92%, with pH 7.35. The fractional concentration of oxygen (FiO₂) will be such to achieve an SpO₂ 92%. A full face mask will be used in all the patients to start NIV and then, if needed for patient’s comfort, substituted by a face one after the first few hours of ventilation.

Pressure support will be 8 cm H₂O initially and will be adjusted subsequently to achieve an exhaled tidal volumen of 8 mL/Kg and a respiratory rate lower than 25 breaths/min. PEEP will be initially set at 4 cm H₂O.

NIV was withdrawn in case of patient’s intolerance and perfusión of sedatives was not allowed to increase time under NIV.
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