Supplementary Online Content 1

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STUDY PROTOCOL

Conditioned high-flow nasal cannula oxygen therapy for preventing reintubation in mechanically ventilated patients at low risk for extubation failure

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TRIAL SUMMARY

This is a randomized controlled trial comparing the efficacy of conditioned high-flow nasal cannula oxygen therapy to conventional oxygen therapy for preventing reintubation in mechanically ventilated patients at low 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 FiO_2 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 oedema and hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD) patients.

Preventive noninvasive mechanical ventilation (NIMV) 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 NIMV 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 rounding 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 conditioned high flow nasal cannula oxygen therapy has changed along with technological improvements. With the development of new nasal cannulas for high-

flow therapy, the concept includes not only constant FiO_2 during the peak inspiratory flow but also other beneficial mechanisms such as generation of low 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 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

Conditioned high-flow oxygen therapy improves conventional oxygen therapy performance, even with the addition of a low-CPAP effect on upper air-way (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 therapy after extubation in critically ill patients on postextubation respiratory failure and the reintubation rate in a nonselected population. To our knowledge, no trial has focused on critically ill patients at low-risk for reintubation.

The reintubation rate in this subgroup of patients ranges from 5% to 13%, depending on the case mix and the high-risk criteria selected. Causes for reintubation in these patients differ from those in high-risk patients, as the percentage of non-respiratory related reintubations are higher; likewise, the percentage of reintubations for post-extubation air-way obstruction secondary to glottic edema is higher. On the other hand, hypoxemic and hypercapnic respiratory failures are less common.

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

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OBJECTIVES

PRIMARY OUTCOME AND FAILURE CRITERIA

Primary outcome: reintubation within 72 hours after extubation.

Predefined criteria for immediate reintubation:

1. 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.

SECONDARY OUTCOME MEASURES

1. Postextubation respiratory failure classified according to the postextubation respiratory failure definition, and according to a clinical diagnosis of extubation failure if applicable.

   o Postextubation respiratory failure definition: presence any of the following criteria within 72 hours of extubation: respiratory acidosis (pH <7.35 with $PaCO_2$ >45 mmHg), SpO_2 <90% or PaO_2 <60 mmHg at FiO_2 >0.4, 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.

2. Respiratory infection (ventilator-associated pneumonia or ventilator-associated tracheobronchitis).

   • Ventilator-associated pneumonia (VAP) was defined as fever (temperature >38ºC) 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.

3. 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.

4. ICU and hospital length of stay.

5. ICU and hospital mortality.

6. Reason for failure of assigned treatment if applicable, including patient comfort.

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

8. 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).

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

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.
7. Presence of any of the following high-risk factors for extubation failure:
   o Age greater than 65 years.
   o Heart failure as the primary indication for mechanical ventilation.
   o Moderate-to-severe COPD.
   o An Acute Physiology and Chronic Health Evaluation (APACHE) II >12 points on extubation day.
   o Body mass index >30 kg/m^2.
   o Airway patency problems, including high risk of developing laryngeal edema (see later).
   o Inability to deal with respiratory secretions (inadequate cough reflex or suctioning

>2 times within 8 hours before extubation).
- o Difficult or prolonged weaning.
- o Two or more comorbidities (according to the Charlson Comorbidity Index).
- o Prolonged mechanical ventilation, defined as longer than 7 days.

STUDY DESIGN

This is a randomized open trial of two different methods for oxygen therapy after planned extubation: conditioned high-flow and conventional oxygen therapy, in adult, mechanically ventilated patients admitted to an ICU. We hypothesized that conditioned high-flow is superior to conventional oxygen therapy in terms of post-extubation 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 (PaO_2/FiO_2 ratio >150 with FiO_2 ≤0.4, positive end-expiratory pressure <8 cmH_2O, 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 cmH_2O 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).

Patients considered at high risk for postextubation laryngeal edema with the presence of at least two of the following: female gender, orotracheal intubation lasting 3 days or longer, and difficult intubation. These patients will undergo an auscultation cuff-leak test.

If no leak or only a mild leak is heard through a stethoscope (excluding cases in which the leak is heard without a stethoscope), a cuff-leak volume test will be performed, according to the following protocol: the actual tidal volume at expiration is measured before and after deflation of the endotracheal tube cuff.

Patients with a cuff leak volume >24% of tidal volume during inflation will receive 20 mg intravenous methylprednisolone every 4 hours during 12 hours and extubation delayed for that period.

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, PaO_2 lower than 60 mmHg or SpO_2 lower than 90% on inspired fraction of oxygen higher than 0.5, $PaCO_2$ higher than 50 mmHg or increased more than 8 mmHg from baseline value, arterial pH lower than 7.32 or decreased more than 0.07 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 conventional oxygen therapy or high-flow therapy in permuted blocks, stratified according to Hospital. 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.
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 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 an absolute reduction in reintubation rate from 13% to 5% (absolute reduction of 8%). The calculated sample size for a bilateral contrast analysis is 260 patients per group, ensuring an alpha level of 0.05% and power of 80% and a maximum patient loss rate of 15%.

STATISTICAL ANALYSIS

All analyses will be performed on an intention-to-treat basis.

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.

Reintubation rates will be compared with the Cochran-Mantel-Haenszel chi-square test and will be stratified according to hospital of inclusion.

To test whether the marginal odds ratio was similar to the odds ration conditioned to co-variables Odd ratios, we will use multivariable logistic regression, including the following variables: high-flow oxygen therapy, length of mechanical ventilation, hospital, and baseline variables associated with reintubation with p values less than 0.1. The results will be expressed as odds ratios. The 95%CI and the number needed to treat will be calculated with the Newcombe-Wilson method. Reasons for reintubation will be analyzed with the chi-square test, and time to reintubation with the Mann Whitney U test

Kaplan-Meier curves will be plotted to assess the time from extubation to reintubation and compared by means of the log-rank test.

For the analysis of secondary outcomes and post hoc analyses, we will use Fisher's exact test, Student's t-test, Mann-Whitney U, or Cochran-Mantel-Haenszel chi-square tests (stratified for hospitals).

The level of significance was set at 0.05. We will use SPSS version 13.0 (SPSS Inc.; Chicago, IL) for all analyses.

CLINICAL PROTOCOL

DEFINITIONS

Conditioned high-flow nasal cannula oxygen therapy is defined as a gas (air/oxygen) mixture at a flow rate of ≥30 liters/minute (L/min), delivered via heated, humidified, blended Fisher and Paykel (F&P) circuit and prongs.

Conventional oxygen therapy is defined as a blended air/oxygen that is not heated or humidified at a flow rate <15 liters/minute (L/min), applied though nasal cannula or non-rebreather face mask.

CONDITIONED HIGH-FLOW OXYGEN THERAPY GROUP PROTOCOL

High-flow oxygen therapy: Optiflow® system, applied prior to extubation at 37ºC 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 31ºC. The inspired fraction of oxygen will be regularly adjusted to target 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 strongly discouraged.

CONVENTIONAL OXYGEN THERAPY GROUP PROTOCOL

Conventional oxygen therapy will be applied continuously through nasal cannula or

nonrebreather face mask, and oxygen flow adjusted according to the inspired fraction of oxygen needed to maintain SpO_2 >92%.

Rescue therapy with noninvasive mechanical ventilation for postextubation respiratory failure was strongly discouraged.

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