Title:

Comparison of Two Extubation Techniques in Critically Ill Adult Patients (ExtubAR trial): Randomized Clinical Trial

Evaluated and approved by the Research Ethics Committee (#12-2018-05, approved on February 28, 2019) and registered on ClinicalTrials.gov (NCT03918811, April 18, 2019).

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Introduction

Extubation is the removal of the endotracheal tube (ETT) when it is no longer required [1]. This procedure may be associated with complications, such as desaturation, stridor, bronchospasm, and severe cough [2,3]. The complication rates reported in the literature range from 6.6% to 100% [4–6]. In some cases, these complications may lead to extubation failure [7].

Two orotracheal extubation (OTE) techniques are described in the literature [8]. The traditional extubation technique consists of introducing a suction catheter into the ETT and trachea, deflating the cuff, and removing the ETT by applying continuous endotracheal suctioning during the entire procedure. The positive pressure extubation technique, on the other hand, involves applying positive pressure through the airway during cuff deflation and extubation. Thus, the air flow passing between the ETT and the larynx pushes pooled subglottic secretions towards the oropharynx so that they can be expelled through the oral cavity. Both techniques intend to minimize the leakage of the oropharyngeal content into the distal airway. However, according to several authors, the negative pressure generated by suctioning during the traditional technique may promote rather than prevent leakage [9,10].

A noninferiority clinical trial showed that the positive pressure extubation technique was safe and noninferior to the traditional technique in terms of the incidence of immediate postextubation complications, postextubation pneumonia (PEP), OTE failure, and reintubation [11]. Although prior studies reported better clinical outcomes with the positive pressure extubation technique [6,12], its superiority has not been deeply studied yet. Therefore, the objective of our study is to determine whether the positive pressure OTE technique, compared with the traditional OTE technique, reduces the incidence of major postextubation complications (up to 60 minutes) in critically ill adult patients.

Methods

Design

A multicenter randomized clinical trial was conducted in 13 centers from Argentina. Patients admitted to the intensive care units (ICU) between April 1, 2019, and March 26, 2020, were included in the analysis. Our study was evaluated and approved by the Research Ethics Committee (#12-2018-05, approved on February 28, 2019) and registered on ClinicalTrials.gov (NCT03918811, April 18, 2019). The results were reported according to the CONSORT Statement for reporting randomized clinical trials [13].

Participants

We included patients aged > 18 years, requiring invasive mechanical ventilation (IMV) through an ETT, who had successfully completed a spontaneous breathing trial (SBT) [14] and met the following OTE criteria: an adequate level of consciousness (Glasgow Coma Scale score ≥ 8/15) [15] and effective cough (cough at order and/or at endotracheal suctioning) [16,17]. The participants' or their legal representatives' informed consent was also required. Patients with a history of upper airway (UA) injury or surgery, with a limited therapeutic effort, who had previously been extubated or tracheostomized, or who had required noninvasive mechanical ventilation (NIMV) as a weaning method were excluded from our study.

Procedure and Interventions

Patients who met the eligibility criteria and successfully completed the SBT were immediately randomized. Once OTE was performed by two operators, assessment of outcome measures within 60

min after extubation was done by a third operator (blinded). Daily monitoring of outcome measures within 72 h after extubation was performed by this same operator. If preventive NIMV or high flow nasal cannula (HFNC) had been decided, they were initiated 15 min after OTE in order not to influence monitoring of outcome measures. Extubation maneuvers were performed in accordance with the procedure reported in the literature [11]. The traditional OTE technique consisted of deflating the cuff and removing the ETT by applying continuous endotracheal suctioning during the entire procedure. In positive pressure extubation, ventilator parameters were set at 15/10 cmH2O, in PC-CSV mode. The cuff was deflated, and a suction catheter was introduced through the mouth to suction secretions from the oropharyngeal cavity [11,18,19] while the ETT was removed without endotracheal suctioning (see supplementary material).

Outcome measures

Postextubation overall complications:[11] clinical evidence of desaturation [3,5,6,20], hypertension [1,3,4,20], tachycardia [1,3,4,20], tachypnea [1,21], or poor respiratory mechanics [21] (at least one within 15 min after extubation), or clinical evidence of UA obstruction [4,22], postobstructive pulmonary edema [2,22], vomiting [3,5], bronchospasm [3,5], or severe cough [3,5,23] (at least one within 60 min after extubation).

Postextubation major complications:[11] clinical evidence of desaturation (within 15 min after extubation), or clinical evidence of UA obstruction or vomiting (at least one within 60 min after extubation).

Postextubation minor complications:[11] clinical evidence of hypertension, tachycardia, tachypnea, or poor respiratory mechanics (at least one within 15 min after extubation), or clinical evidence of postobstructive pulmonary edema, bronchospasm, or severe cough (at least one within 60 min after extubation).

Postextubation pneumonia (PEP) was defined as the presence of new or increased pulmonary infiltrate on chest radiography before OTE, in addition to the presence of fever, leukocytosis (> 10,000/mm^3), or

leukopenia (< 4,000/mm^3) compared with preextubation values and/or increase of tracheobronchial secretions or change in their quality (within 72 h after extubation) [16].

Extubation failure was defined as the need for NIMV or HFNC to treat the failure or reintubation within 72 h after extubation [1,24]. Reintubation was defined as the need for a new introduction of the ETT within 72 h after extubation [1,25].

Randomization

Randomization was performed in blocks and stratified by participating center and by the risk of extubation failure (high or low), as reported in prior studies [16,26]. Randomization assignment was blinded to the operators in charge of the procedures through an online platform (see supplementary material).

Blinding

Due to the nature of the intervention, blinding of patients and operators performing OTE was not possible. The evaluator who recorded measures of interest after extubation was blinded to the assigned extubation technique. The database was monitored by third parties with no direct participation in the study and no interest in its outcomes. The data were analyzed pursuant to the statistical analysis plan devised before the study, and the person in charge of data statistical analysis was blinded to the technique used.

Sample size

Based on a major complication rate of 37.6%, reported in a prior study [11], 778 patients (389 per group) were required to have an 80% chance of detecting, as significant at the 5% level, a decrease in

the incidence of major complications from 37.6% in the control group (traditional technique) to 28.2% in the experimental group (positive pressure technique) (relative difference of 25%).

Statistical analysis

The primary analysis of outcomes was a per-protocol analysis. An intention-to-treat analysis was also performed. Thus, a “worst case scenario” method was adopted, assigning the event of interest to the patients lost to follow-up who were randomly assigned to the positive pressure group and not allocating the event of interest to the patients lost to follow-up who were randomly assigned to the traditional group. No interim analyses were planned. Chi-square test or Fisher exact test were used for the comparison categorical variables. Continuous variables with normal distribution were presented as mean and standard deviation (SD) and were compared with the Student's t test for independent samples. Non-normally distributed variables were presented as median with 25% and 75% percentiles. For outcome measures (primary and secondary), relative risks (RR) and 95% confidence intervals (CI) were calculated. Effect estimates were also reported with their absolute risk differences (ARD) and their corresponding 95% confidence intervals (95% CI). Tests were two-tailed, and a p-value <0.05 was considered significant. Statistical analysis was performed using SPSS version 25.0; SPSS Inc, Chicago, IL, USA.

References

Supplementary Material

Spontaneous breathing trial

Patients who met the eligibility criteria and successfully completed the spontaneous breathing trial (SBT) were immediately randomized. It was conducted with a T-tube, by applying continuous positive airway pressure (continuous positive pressure in the airway) at 5 cm H2O, or by applying pressure support (PS) from 5 to 8 cm H2O for a period ranging from 30 to 120 minutes. The oxygen flow rate or FiO2 was regulated to keep an oxygen saturation over 90%. After extubation, supplementary oxygen was administered with the same FiO2 used at the end of the successful SBT. All variables were collected and recorded in specific forms.

Interventions

Both procedures were performed by two operators. In the traditional orotracheal traditional extubation (OTE), a closed suction system catheter was placed into the endotracheal tube (ETT) by the first operator, and endotracheal suctioning (ES) was initiated. The cuff was immediately deflated by the second operator, and the ETT was removed with continuous ES during the entire procedure. In the positive pressure OTE, the first operator set the ventilator parameters to PS ventilation mode, with an inspiratory pressure of 15 cm H_2O and a positive end expiratory pressure (PEEP) of 10 cm H_2O. Then, the cuff was deflated by the second operator, and the suction catheter was introduced through the mouth to suction secretions drawn to the oropharynx while the ETT was removed by the first operator without applying ES. Before the study, the participating centers were trained in both OTE procedures by means of videos.

Procedure

Patients were included in the study once they had successfully completed the SBT and met the OTE criteria. The blinded evaluator followed a preextubation checklist. It entailed discontinuing enteral nutrition, adjusting the head of the bed to 45°, suctioning oropharyngeal and tracheobronchial

secretions, and recording preextubation monitoring on the pertaining sheet. Regardless of the procedure, the alarms were silenced, and the ventilator parameters were set at PS 15/10 cmH20 by one operator, so that the blinded evaluator could not hear the maneuver or read the ventilator parameters. The blinded evaluator left and was replaced by the operators, who knew about the technique assigned. They initiated the randomization through http://extubar.ajrpt.com and were in charge of the OTE and postextubation oxygen delivery. Regardless of the OTE technique, the patients received supplemental oxygen through a nasal cannula placed before ETT removal to keep the oxygen flow used in the SBT.

Once the OTE was completed, the blinded evaluator assessed the outcome measures recorded within 60 min after extubation. Daily monitoring of outcome measures within 72 h after extubation was carried out.

The decision to perform OTE and to use NIMV or HFNC to prevent OTE failure, follow-up, and treatment was taken by the blinded evaluator, or the respiratory therapist on duty, who was blinded to randomization assignment. If preventive NIMV or HFNC had previously been decided, it was implemented 15 min after OTE so as not to affect monitoring of outcome measures.

Randomization

The randomization sequence was generated before the study by using the web site (https://www.sealedenvelope.com/) in blocks of 6 and stratified by participating center and by the risk of extubation failure (high or low). High risk of extubation failure was defined as the presence of at least one of the following criteria: age ≥66 years, moderate or severe chronic obstructive pulmonary disease (COPD), ≥2 comorbidities (COPD, peripheral artery disease, immune deficiency, liver disease, hypertension, diabetes, neurological disease, heart failure, chronic renal failure), body mass index (BMI) ≥31, congestive heart failure as main reason from IMV, difficult intubation, IMV ≥8 days, a requirement of suctioning respiratory secretions (≥3 suctions within 4 h before the OTE), difficult or prolonged

weaning and/or APACHE II (*Acute Physiology and Chronic Health disease Classification System II*) a day before the OTE ≥13. Randomization assignment was blinded to researchers in charge of recruiting patients through an online platform (http://extubar.ajrpt.com).