Efficacy of Corticosteroids Treatment on Reducing the Risk of Post-Extubation Stridor: Study Protocol for a Randomized Controlled Trial

Jingyi Wang
Peking Union Medical College Hospital
Joseph Walline
Chinese University of Hong Kong
Yili Dai
Peking Union Medical College Hospital
Lu Yin
Peking Union Medical College Hospital
Jiayuan Dai
Peking Union Medical College Hospital
Huadong Zhu
Peking Union Medical College Hospital
Xuezhong Yu
Peking Union Medical College Hospital
Jun Xu (xujunfree@126.com)
Peking Union Medical College Hospital https://orcid.org/0000-0001-5014-4238

Study protocol

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Abstract

Background: Laryngotracheal injury is one of common complications of airway intubation, with severe cases leading to stridor or even extubation failure (need for reintubation within 48 hours after extubation). As corticosteroids have anti-inflammatory effects, they may play an important role in reducing the risk of post-extubation stridor and extubation failure among adult patients.

Aim: To investigate the efficacy of corticosteroids on reducing the risk of post-extubation stridor.

Methods: A multicenter, randomized, placebo-controlled trial will be performed. The trial will enroll 232 patients undergoing extubation from mechanical ventilation. The patients will be randomly assigned to treatment four hours prior to extubation either with intravenous methylprednisolone 40mg or placebo. The primary endpoint is the occurrence of laryngeal stridor within 48 hours, and the secondary endpoints are the need for respiratory support or reintubation secondary to post-extubation stridor within 48 hours after extubation, side effects or corticosteroids, hospital length of stay, and 30-day mortality.

Discussion: The trial will examine if corticosteroid therapy before extubation is effective at reducing the risk of post-extubation stridor-related complications among adult patients.

Trial registration: Chictr.org.cn, ChiCTR2000030349. Registered on 29 Feb 2020.

Background

Despite great improvements in invasive mechanical ventilation in past decades, the potential risks of extubation failure remain high. Upper airway intubation with an endotracheal tube (ETT) may cause laryngotracheal injury, although the associated laryngeal damage is ordinarily well-tolerated in most of patients[1], severe cases can lead to upper airway obstruction (UAO), which presents clinically as stridor. Moreover, severe stridor may lead to extubation failure (i.e. the need for reintubation within 48 hours after extubation), which is associated with a higher risk of acquiring ventilator associated pneumonia, a prolonged hospital length of stay and an increased mortality rate[18].

Corticosteroids play a role in inhibiting the release of inflammatory factors, along with reducing vascular permeability and edema[12], thus making them theoretically applicable to preventing post-extubation stridor and extubation failure. Although previous trials conducted among pediatric patients clearly demonstrated that corticosteroids reduced the prevalence of post-extubation stridor [2, 3, 23] and the need for re-intubation[10], their effect on mechanically ventilated adults remains far from clear and consistent[4, 8, 31, 33], particularly since mechanically ventilated adults have lower re-intubation rates for UAO than pediatric patients, whose re-intubation rate may up to 37% in critically ill pediatric patients[5].

As we have increasingly encountered patients with intubation times lasting over 24 hours, we plan to analyze and evaluate the efficacy of pre-extubation corticosteroids on reducing the risk of post-extubation stridor and extubation failure among adult patients who were treated with invasive mechanical

ventilation. We will develop this study using a multi-center, double-blind, randomized, placebo-controlled trial.

Methods

Trial design and setting

This is an investigator-initiated, multicenter, parallel-group, non-inferiority, randomized controlled trial that will include 232 participants from 6 large tertiary hospitals in China. The study was prospectively registered with Chictr.org.cn on February 29, 2020 (identifier: ChiCTR 2000030349).The Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College in Beijing have also approved the trial protocol. The schedule of enrollment, intervention data collection and assessment follows the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and checklist is presented in Fig. 1 (also see Additional File 1 for more detail).

Study Population

Previous studies have found several risk factors for post-extubation stridor and extubation failure, including: female sex, intubation duration > 36 hours, age ≥ 80 years, short stature, intubation with a larger internal diameter sized-tube (males > 8 mm, females > 7 mm), ETT to laryngeal size ratio (> 45%), patients intubated after traumatic injury, GCS score < 8, a higher APACHE II score, an asthma history, presence of a nasogastric tube, and excessive tube mobility due to insufficient fixation[4, 8, 15, 24, 31–34]. Epstein[33] believed that the focus of using steroids should continue be on patients at greater risk, so our study population will be restricted to patients with at least one of the above risk factors for developing stridor. Some studies recommended a cuff-leak test (CLT) as an efficient way of identifying patients with the highest risks, with a threshold volume less than 110 ml-130 ml or 12% of inspiratory VTs[6, 11, 17]. The sensitivity and specificity of the CLT is suboptimal[6, 7, 10, 11], as the volume amount is also influenced by other factors such as inspiratory flow rates, and system compliance or resistance[7]. In addition, CLT may even lead to unnecessary prolongation of intubation time[33]. Therefore, we will not use CLT in our inclusion criteria.

The inclusion criteria and exclusion criteria are as follows.

Inclusion criteria

1. Age ≥ 18 years old
2. Patients receiving mechanical ventilation for at least 24 hours
3. Patients with confirmed consent
4. Patients undergoing extubation from mechanical ventilation within the next 12 hours
5. 18.5 ≤ BMI□27

*6. Age ≥ 80 years old

*7. Patients receiving mechanical ventilation for at least 36 hours

*8. Patients intubated with a larger tube (male > 8 mm, female > 7 mm)

*9. Patients intubated after traumatic injury

*10. Patients with a medical history of asthma

*11. Patients with a GCS < 8 or a higher APACHE II score

Note

Patients should meet all items of 1–5 and at least one items of *6–11.

Exclusion criteria

1. 1. Patients with a prior history of laryngotracheal disease, surgery or tracheostomy
2. 2. Pregnant or breastfeeding patients
3. 3. Patients with a history of post-extubation UAO
4. 4. Unplanned or self-extubation, where immediate reintubation is deemed necessary
5. 5. Patients chronically using anti-inflammatory drugs or corticosteroids
6. 6. Patients has been treated with corticosteroids within a week prior to extubation
7. 7. Patients being extubated for comfort measures or family request
8. 8. Patients or family refusing extubation
9. 9. Patients with vocal cord dysfunction
10. 10. Patients in deep sedation (RASS score≤-4)
11. 11. Patients suffered gastrointestinal hemorrhage within 3 months

There will be a research coordinator at each hospital to promote and monitor the trial. Patients and their guardians will be informed of the purpose, procedures, potential risks and benefits of the study. The participants' written consent will be obtained. Participants will be allowed to withdraw from the trial at any time without consequence.

Treatment Arms And Co-interventions

Once the registered patients meet the extubation standards (Table 1), they will be allocated to either the corticosteroid group or the placebo group, and the planned extubation will be implemented within 12 hours after allocation. Patients from the corticosteroid group and placebo group will be treated with an

intravenous injection of methylprednisolone 40 mg or an equivalent volume of isotonic saline (placebo), respectively, four hours prior to the planned extubation.

Table 1
Extubation Standards

Successfully complete a spontaneous breathing trial (SBT)
* No or mild amount of endotracheal secretions (last suctioning > 2.5 hours prior)
* Cough strength (grades 3–5)[21]
* Cough peak expiratory flow (PCEF) > 35 L/min[26]
* Positive white card test (WCT) result[21]
Patients ready for extubation should meet the first item (SBT) along with at least one *item.
General treatment measures include precautions and countermeasures to increase the UAO risk and guarantee the safety of all patients as could as possible. The precautions include gentle extubation to avoid laryngotracheal mucosal injury; strict EET fixation to avoid repeated friction between EET and laryngotracheal mucosal; emphasizing EET disinfection to reduce contamination rick. The countermeasures to UAO are applied in accordance to the patient's condition, including oxygen therapy with corticosteroid inhalation for mild airway edema; same as mild with intravenous infusion of hydrocortisone 100 mg for moderate airway edema; NIV implementation and re-intubation assessment will be carried out when the above treatments are invalid.

Study Endpoints

The primary endpoint is the occurrence of laryngeal stridor within the first 48 hours after extubation. Secondary end-points include: the need for respiratory support (both invasive and non-invasive ventilation, NIV) and reintubation secondary to post-extubation stridor within 48 hours after extubation, clinical assessments will be done at 5, 15, 30, and 60 minutes, and then at 3, 6, 12, 24,36 and 48 hours after extubation. Any side-effects, hospital length of stay and 30-day mortality will also serve as secondary endpoints.

Sample Size Calculation

We reviewed the international critical care literature concerning the incidence of post-extubation stridor and extubation failure. We sought to estimate using a Chi-Squared statistical analysis the minimum sample size required to evaluate the effect of corticosteroids on our study outcomes. François[8] in 2007 performed a randomized double-blind single-center trial of methylprednisolone 12 hours prior to extubation in 698 patients (343 placebo, 355 steroid). They found methylprednisolone significantly reduced the incidence of post-extubation laryngeal edema from 22–3%, reduced reintubations from 8–4% and the proportion of reintubations secondary to edema from 54–8%. Cheng[15] found in 2006 that both single- and four-dose regimens of methylprednisolone reduced rates of post-extubation stridor compared

to placebo (11.6% vs. 7.1% vs. 30.2%, respectively). Lee, Peng and Wu[25] in 2007 reported decreased post-extubation stridor of 10% vs. 27.5% after dexamethasone was given 24 hours prior to extubation.

We therefore anticipate a post-extubation stridor rate of 10% in the treatment group and 25% in the control group. With an 80% power to detect a difference and an alpha of 0.05(two-sided), we anticipate requiring 97 subjects in each group. Assuming a drop-out rate of 20%, this gives a total minimum sample size of 232 subjects.

Randomization And Blinding

As female sex has been reported to be an independent risk factor for stridor and extubation failure[4, 8, 15], a gender-stratified block randomization will be performed. Within each stratum, a random block size of 4 will be used. After completion of the pre-extubation assessment and written informed consent is obtained, participants will be randomly assigned to either the intervention group or control group. Patients and medical staff involved will both be blinded to treatment allocation. All analyses will be performed in an un-blinded fashion.

Data Collection And Management

For each participant, anthropometric data (gender, age, body mass index) and baseline characteristics such as GCS score, APACHE II score, vital signs (blood pressure, heart rate, respiratory rate, blood oxygen saturation and temperature) and arterial blood gases (ABGs) will be recorded as long as the patients are in-hospital. Blood oxygen saturation (SaO2), as well as end tidal carbon dioxide tension (PETCO2) if available, will be in continuous record. In order not to cause unnecessary pain to patients, ABGs will be collected only for necessity during the follow-up operation, while the baseline characteristics will be recorded at set times.

We will also record rates of the following for each enrolled patient:

1. laryngeal stridor
2. respiratory support, as defined by:

   presence of respiratory acidosis (an arterial pH of less than 7.35 with a partial pressure of arterial carbon dioxide of more than 45 mmHg)
   clinical signs of increased respiratory effort (use of accessory muscles, intercostal retractions, or paradoxical motion of the abdomen)
   respiratory rate > 30 breath/min for two consecutive hours
   hypoxemia (an arterial oxygen saturation of < 90% with an FiO_2 > 50%)
3. reintubations, noting which are secondary to post-extubation stridor
4. reported side-effects due to corticosteroids

5. hospital length of stay
6. 30-day mortality.

Clinical data will be collected locally via the Research Electronic Data Capture (REDCap) system, an Internet-based electronic case report form (CRF). The research coordinators at each hospital will form a steering committee, which provides training and reviews study process, to improve adherence to the protocol and resolve problems. In addition, they will regularly check CRFs and contact responsible medical staff members every 3 months to ensure data quality and accuracy.

Statistical Methods

The primary endpoint will be analyzed on an intention-to-treat basis, regardless of whether they complete the originally allocated treatment study protocol. Any reasons for protocol violations will be recorded and described. All p-values are two-tailed, and the significance level will be a p-value < 0.05. Data will be presented as frequencies and percentages for categorical variables. Continuous variables will be expressed as means and standard deviations (normal distribution) or median with interquartile range (skewed distribution). Student's t-test (normal distribution) or Mann-Whitney U test (skewed distribution) will be used for group comparisons. Categorical variables will be compared using Pearson's chi-squared test or Fisher's exact test as appropriate. Statistical uncertainty will be expressed in terms of a relative risk and 95% confidence intervals.

Discussion

Although only a small portion of intubated adult patients develop severe post-extubation complications, laryngotracheal injuries due to endotracheal intubation are not uncommon, ranging from ulcerations to tracheitis, which have statistical correlation with high cuff pressures, infections and severe respiratory failure[27]. To minimize the adverse effects of endotracheal intubation, corticosteroids have been applied due to their anti-inflammatory action, and Cheng KC[28] also found an up-regulation of IL-4 and IL-10, which have been regarded anti-inflammatory cytokine, in patients treated with methylprednisolone. However, to date there have been no adequate studies to support the use of corticosteroids for this indication, and controversy still exists regarding their effectiveness. A trial developed with intubated rabbit models showed that dexamethasone could not ameliorate laryngeal inflammation and necrosis[29]. This finding was consistent with the clinical results from Darmon[24], where corticosteroids showed little preventive effect. However, contrary to these previous studies, Bruno François[8] found that a 12 hour pretreatment with methylprednisolone significantly reduced the incidence of post-extubation edema, and Lee[25] reported that multiple-does of dexamethasone during the 24 hours prior to extubation resulted in a lower incidence of stridor. As for adverse effects, previous studies have reported negligible results for corticosteroids, and potential complications such as an increased risk of infection, gastrointestinal bleeding or high blood sugar were rarely observed[14–16, 25].

This project will be a multicenter trial aimed at rigorously examining the effectiveness of corticosteroids on reducing the risk of post-extubation stridor and extubation failure among adult patients. The previous relevant studies were developed at different dosages and frequencies of injection. A systematic review and meta-analysis by McCaffrey[18] also found that, although use of corticosteroids was associated with a reduced rate of laryngeal edema, the type and dose of corticosteroid used were more varied in adult populations, compared with the relatively standard dosing in neonatal and pediatric patients. Medical staff currently use different criteria for deciding on a planned extubation and may use different policies for preparing for an extubation. Therefore, an improved understanding of corticosteroids will on one hand assess the effectiveness and necessity of pre-extubation corticosteroid use among patients with risk-factors for extubation failure and on the other hand decrease the unnecessary use of corticosteroids among other patients. This trial will provide the groundwork for further research on pre-extubation interventions for improved patient safety. Our final objective is to work toward an evidence-based adult safe-extubation preparation guideline.

Currently, there are two recommended modes of pre-extubation corticosteroid administration. One is to give a single dose of 40 mg of methylprednisolone four hours before the planned extubation, and the other is to give four doses of 20 mg of methylprednisolone every four hours until the planned extubation. Although several studies found that the multiple dose strategy may be more efficient than the single dose strategy[4, 18, 19, 30], few medical institutions apply the latter due to its poor practicality, and longer-term inventions such as the multiple dose strategy are believed to potentially cause unnecessary prolongation of extubation and increase the risk of complications. Therefore, this trial will treat patients with a single dose.

There are some potential limitations in this study. First, this trial mainly focuses on patients at higher risk, but Andrés found that the survival of patients receiving mechanical ventilation depended on not only a patient's condition when initiating mechanical ventilation, but also on the development of complications and changes in other monitored variables, which increases the uncertainty of potential complications[9]. Further research may be required to find the overall efficacy of corticosteroids for an "average" patient. Second, we include extubation failure as one of our secondary outcomes, but it's important to mention that other factors such as pulmonary edema can also lead to extubation failure, and can be alleviated by corticosteroids as well. Third, there is currently no universally acknowledged standard extubation protocol, so extubation standards in this trial mainly originate from previous studies[20–22] and the authors' clinical experience.

Definitions

1. Cough strength grading system: 0 = no cough on command, 1 = audible movement of air through the endotracheal tube but no audible cough, 2 = weakly (barely) audible cough, 3 = clearly audible cough, 4 = stronger cough, and 5 = multiple sequential strong coughs[21].

1. 2. White card test (WCT): A white file card is placed 1 to 2 cm away from the end of the endotracheal tube, asking patients to cough, up to three to four times, if any wetness appears on the card, it was

classified as a positive WCT result[21].

2. 3. Cough Peak Expiratory Flow (CPEF): A respiratory muscle function test designed to evaluate a patient's ability to protect their airway. It is measured by connecting an electronic peak flow meter to the connecting piece of the endotracheal tube[26].

Trial Status

The trial plans to start recruiting patients on 1 May 2020. Protocol version 3.0 was applied (25 March 2020). The recruitment is expected to be completed before March 2021.

Abbreviations

UAO
upper airway obstruction; ETT:endotracheal tube; APACHE II:Acute Physiology and Chronic Health; GCS:Glasgow Coma Scale; CLT:cuff-leak test; BMI:Body Mass Index; RASS:Richmond agitation-sedation scale; ABGs:arterial blood gases; SBT:spontaneous breathing trial; PCEF:cough peak expiratory flow; WCT:positive white card test; SaO_2:blood oxygen saturation; $PETCO_2$:end tidal carbon dioxide tension; NIV:non-invasive ventilation.

Declarations

Ethical approval and consent to participate

The Ethics Committee of Peking Union Medical College Hospital, Beijing approved the trial protocol under reference number JS-2334 on April 9, 2020. Informed consent will be obtained from all study participants.

Consent for publication

Not Applicable.

Availability of data and materials

The dataset generated and/or analyzed during the current study are available from the principal investigator (Jingyi Wang and Jun Xu) on reasonable request.

Competing interests

The authors declare that there is no competing interest.

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Authors' contributions

JyW drafted the manuscript. JW co-authored the writing of the manuscript and offered revision, YlD, LY and JyD co-authored the writing of the manuscript. JX designed the study and edited the manuscript. HdZ and XzY critically assessed the study design. All authors read and approved the final manuscript.

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Figures

	STUDY PERIOD													
	Pre-randomization		Primary study period											
TIMEPOINT	**enrollment**	**allocation**	**-4h**	**0h**	**5min**	**15min**	**30min**	**1h**	**3h**	**6h**	**12h**	**24h**	**36h**	**48h**
ENROLLMENT														
-Eligibility screen	×													
-Informed consent	×													
-Allocation		×												
INTERENTIONS														
-Methylprednisolone therapy			×											
-Placebo therapy			×											
EXTUBATION				×										
DATA COLLECTION AND ASSESSMENT														
Anthropometric data	×													
*ABGs	×													
Baseline variables	×		×	×	×	×	×	×	×	×	×	×	×	×
Primary endpoint					×	×	×	×	×	×	×	×	×	×
Secondary endpoints				×	×	×	×	×	×	×	×	×	×	×
Continuous points			◆	—	—	—	—	—	—	—	—	—	—	◆

Figure 1

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule of enrolment, intervention and assessments. Anthropometric data: age, gender, body mass index (BMI).*ABGs: collected for necessity only. Baseline variables: GCS score, APACHE II score, vital signs. Primary endpoint: occurrence of laryngeal stridor. Secondary endpoints: need for respiratory support, reintubation secondary to post-extubation stridor, side effects, hospital length of stay and in-hospital mortality. Cotinuous points: Blood oxygen saturation (SaO2) and end tidal carbon dioxide tension (PETCO2).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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