

Efficacy of prophylactic methylprednisolone on reducing the risk of post-extubation stridor in patients after an emergency intubation: study protocol for a randomized controlled trial

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Abstract

Background: Post-extubation stridor (PES) is one of the most common complications of invasive respiratory support, with severe cases leading to possible extubation failure (reintubation within 48 hours) and increased mortality. Previous studies confirmed that prophylactic corticosteroids play an important role in reducing the risk of PES and extubation failure. However, few studies have looked at the efficacy of corticosteroids on preventing PES in patients after an emergency intubation.

Aim: To evaluate whether a single dose of methylprednisolone given over a set timeframe before extubation is effective in preventing PES in patients after an emergency intubation.

Methods: A multicenter, randomized, placebo-controlled trial will be performed in an emergency department (ED) setting. The trial will include 132 patients who fail a cuff-leak test (CLT) prior to the intervention. Patients will be randomly assigned to either intravenous methylprednisolone (40mg) or placebo four hours prior to extubation. Other eligible patients who pass the CLT will be included in a non-intervention (observation) group. The primary endpoint is the incidence of PES within 48 hours after extubation. Secondary endpoints include oxygen therapy, respiratory support requirements, reintubation secondary to PES, adverse effects within 48 hours after extubation, hospital length of stay and hospital mortality.

Discussion: Patients who are intubated on an emergency basis have a higher risk of intubation-related complications. Previous studies have examined treatment regimens involving more than 10 different variations on corticosteroid treatments for PES

prevention, while for ED therapy only a simple and effective treatment would be appropriate. Corticosteroid administration is usually accompanied by adverse effects, thus this study will be important for further risk stratification among intubated ED patients.

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

Keywords: Post-extubation stridor, corticosteroid, emergency airway management, multicenter, randomized controlled trial

Background

Endotracheal intubation with mechanical ventilation is a common life support method in emergency resuscitation. However, intubation/extubation and invasive mechanical ventilation may lead to the development of complications such as post-extubation stridor (PES) or extubation failure (defined as reintubation within 48 hours). Both of these complications are associated with a higher risk of ventilator associated pneumonia, prolonged hospital length of stay and increased mortality[1].

Corticosteroids have a broad anti-inflammatory effect which is well described in previous studies[2,3]. They also have a vasopressor effect that contributes to reduced airway edema and less microvascular fluid leakage[4], which may help prevent laryngeal edema and PES. While a large body of evidence has revealed that prophylactic corticosteroids effectively reduce the incidence of PES and reintubation among high-risk patients[5], few studies have evaluated their effectiveness in patients after an emergency intubation. Due to the large ED population and inpatient ward shortage, many patients are both intubated and extubated while remaining in the ED setting. Comparing with the previous studies developed in intensive care units(ICUs)[18], Shinohara[6] found the incidence of PES was higher in patients intubated on an emergency basis. This may be due to multiple factors, including lack of familiarity with a patient's history, limited time for airway evaluation and management, contraindications to many sedative agents due to an unstable clinical condition (e.g. hypotension or altered mental status), massive intravenous fluid therapy, or patient-endotracheal tube size mismatch.

89 Ideally, patients at high risk for PES should be identified before extubation. The
90 cuff-leak test (CLT), defined as the difference in the actual tidal volume before and
91 after cuff deflation, has been proposed for this purpose[7, 8]. Previous studies
92 described a cuff leak volume less than 110ml or 24% of tidal volumes as
93 insufficient[9-11], and evidence showed absent or insufficient cuff leak volume
94 suggested an increased risk of PES and extubation failure[7]. Several studies showed
95 the CLT has a good specificity but poor sensitivity, and the accuracy for predicting
96 PES varied with different studies[13-15]. Moreover, the measured tidal volume could
97 also be influenced by other factors such as system compliance or airflow
98 resistance[13]. However, the CLT is still preferred as it has been showed to decrease
99 the risk of PES and reintubation[8].

100 We conceived the present protocol in order to evaluate whether a single dose of
101 methylprednisolone given over a set timeframe before extubation is effective in
102 reducing the incidence of PES in patients who had been intubated on an emergency
103 basis and were approaching extubation. We hope to answer this question through a
104 multicenter, double-blind, randomized controlled trial.

106 **Methods**

107 **Trial design and setting**

108 This is an investigator-initiated, multicenter, superiority, randomized controlled trial
109 that will include 132 participants in intervention arm. Six large tertiary hospitals in
110 China will be involved in this trial. This 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 and Peking Union Medical College in Beijing has approved the trial protocol. The schedule of enrollment, intervention, data collection and assessment follows the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Figure 1 for checklist and Additional File 1 for more details).

Study population

Patients will be eligible for inclusion if they are aged 18-80 years, admitted into the Emergency Department(ED) and intubated emergently for one of the following conditions: (1)severe traumatic injury, (2)Glasgow Coma Scale (GCS) score<8, (3)hypoventilation, (4)persistent hypoxemia ($\text{SaO}_2 \leq 90\%$) despite supplemental oxygen, (5)persistent hypotension despite vasopressor treatment, or (6)cardiac arrest. Since most participants in our study will have no capacity to make decisions, written informed consent will be acquired from each patient's next of kin prior to inclusion. Patients or their next of kin will be informed of the purpose, procedures, potential risks, and benefits of the study. Participants will be allowed to withdraw from the trial at any time without consequence.

Patients will be excluded if they meet at least one of the following criteria: pregnant or breastfeeding, chronically treated with corticosteroids or other anti-inflammatory drugs, extubated for patient comfort or on family request, unplanned or self-extubation, vocal cord dysfunction, deep sedation (defined as a Richmond Agitation-Sedation Scale (RASS) score $\leq$ -4), or those diagnosed with gastrointestinal

hemorrhage within the past three months.

There will be a research coordinator at each hospital to promote and monitor the trial.

Intervention, control and observation groups

Once eligible patients successfully pass a spontaneous breathing trial (SBT), a CLT will be performed to evaluate their risk for developing PES. Patients who had a cuff-leak volume (CLV) less than 24% of vital volume will be included in the intervention arm, where they will be randomly allocated to either the corticosteroid group or the placebo group. The planned extubation will be implemented within six hours after allocation. Patients in the corticosteroid group and placebo group will be treated with an intravenous injection of methylprednisolone 40mg (corticosteroid) or an equivalent volume of isotonic saline (placebo) four hours prior to extubation.

Patients with a CLV >24% of tidal volume will serve as a control group, where extubation will be performed within two hours after CLT completion.

All other standard precautions or treatments will be implemented in all patients.

Precautions include gentle extubation to avoid laryngotracheal mucosal injury, strict endotracheal tube (EET) fixation to avoid repeated friction between the EET and laryngotracheal mucosa, EET nursing to reduce contamination risk. Any treatments for PES will be applied in accordance with each patient's condition, including: oxygen therapy with inhaled corticosteroid for mild airway edema, intravenous administration of hydrocortisone (100mg) for moderate airway edema. Non-invasive ventilation or re-intubation will be carried out as clinically indicated if the above treatments are ineffective.

Study endpoints

The primary endpoint is the occurrence of PES within the first 48 hours after extubation. Secondary endpoints include oxygen therapy after extubation, respiratory support requirements, reintubation secondary to PES within 48 hours after extubation , adverse effects (glycemic change, gastrointestinal bleeding or neuropsychiatric events). 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. Hospital length of stay and hospital mortality will also serve as secondary endpoints. (see Figure 2 for study flow chart).

Sample size calculation

We used a Chi-Squared statistical analysis of minimum sample size required to evaluate the effect of corticosteroids on our study outcomes. Cheng[9] showed that either a single or multiple doses of methylprednisolone six hours before extubation reduced the incidence of PES compared to placebo (11.6%/7.1% vs 30.2%,). Cheng[10] later reported that a single dose of methylprednisolone four hours before extubation significantly reduced the incidence of PES from 39.4% to 15.8%. Other studies treating with prophylactic dexamethasone showed that it decreased the incidence of PES from 27.5-30.2% to 8.8-11.5% [11, 12]. We therefore anticipate an incidence of PES of 10% in the treatment group and 30% in the placebo group. With an 80% power to detect a difference and a two-sided alpha of 0.05, we anticipate needing 59 subjects in each group. Assuming a drop-out rate of 10%, we calculate a total minimum sample size of 132 subjects.

Randomization and blinding

As female sex has been reported to be an independent risk factor for stridor and extubation failure [5,6, 9,16,17], a gender-stratified block randomization will be performed in a 1:1 ratio. Within each stratum, a random block size of four will be used. After completion of the pre-extubation assessment and obtaining written informed consent, participants will be randomly assigned to either the intervention group or the control group. Staff not assigned to patient therapy or assessment will be responsible for injecting the intervention, thus both patients and therapists involved will be blinded to treatment allocation. All analyses will be performed on an intention-to-treat basis.

Data collection and management

For each participant, anthropometric data (gender, age, body mass index (BMI)) and baseline characteristics such as GCS score, Acute Physiology and Chronic Health II (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. Arterial blood oxygen saturation (SaO₂), as well as end tidal carbon dioxide (PETCO₂) if available, will be continuously recorded. In order not to cause unnecessary pain to patients, ABGs will be collected when deemed clinically necessary during follow-up, while other baseline characteristics will be recorded at set times.

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

1. PES, defined as a presence of an audible high-pitched sound with respiration

2. Oxygen therapy after extubation (e.g. nasal catheter, reservoir mask or venturi mask)
3. Requiring a respiratory support , as defined by:
 - a. Presence of respiratory acidosis (an arterial pH of less than 7.35 with a partial pressure of arterial carbon dioxide of more than 45mmHg)
 - b. Clinical signs of increased respiratory effort (use of accessory muscles, intercostal retractions, or paradoxical motion of the abdomen)
 - c. Respiratory rate >30 breaths/min for two consecutive hours
 - d. Hypoxemia (SaO₂ of <90% with an FiO₂ >50%)
4. Reintubation secondary to PES
5. Adverse effects due to corticosteroids
6. Hospital length of stay
7. Hospital 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 processes, to improve adherence to the protocol and resolve problems. In addition, they will regularly audit CRFs and contact responsible medical staff members every three months to ensure data quality and accuracy. All data use will be limited to study analysis only, and no individuals' personal information will be published. Data confidentiality will be under the supervision of the study coordinators and the Ethics Committee of Peking Union Medical College Hospital.

Statistical methods

The primary endpoint will be analyzed on an intention-to-treat basis, regardless of whether subjects complete their originally allocated treatment study protocol. Any reasons for protocol violations will be recorded and described. All p-values will be two-tailed, and significance 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 with standard deviations (when normally distributed) or as medians with interquartile ranges (for 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

Endotracheal intubation remains a challenging procedure, with multiple potential complications such as mucosal edema, ulcerations or vocal cord injuries[18]. Although most complications are generally reversible, some patients develop severe symptoms[19]. Previous reviews showed the incidence of PES varied widely from 1.5 % to 26.3 %, and the incidence of reintubation due to laryngeal edema or PES was also quite variable at 1.1–10.5 % [18]. While a recent study reported 29% of the patients intubated on an emergency basis had symptoms of stridor on extubation, 45% of these patients who required reintubation had symptoms of post-extubation upper

airway obstruction[6], illustrating that PES and extubation failure were much more common in ED patients. Moreover, a study conducted among ED intubated patients showed 35% under multiple intubations, which was associated with a higher incidence of adverse events[20].

The type and dose of prophylactic corticosteroid used varied in adult populations. There were over 10 corticosteroid treatments reported in previous studies, all with different dosing and timings[5]. Although several studies found a multiple dose strategy may be more efficient than a single dose strategy [1,17,22,23], this is not optimal for ED use due to relative complexity over a single-dose. In addition, a multiple dose strategy requires a longer pre-extubation period, which may cause unnecessary delays and increase the risk of complications in the ED setting.

Methylprednisolone achieved a peak plasma concentration at about 0.8 hours after intravenous administration[10], and possesses a half-life of approximately 2.5 hours[26]. The pharmacology of methylprednisolone makes it a good choice for a single dose, ED-based strategy.

Although few studies reported severe complications associated with prophylactic corticosteroids before extubation [9,17,22,25], a recent study led by Kuriyama [23] reported significantly increased blood glucose levels caused by corticosteroid use, especially among patients with underlying diabetes mellitus. Hyperglycemia, considered as an adaptive-stress response, is frequently present in critically ill patients[24]. A two-day monitoring for the changes in blood glucose after

263 methylprednisolone treatment will be implemented in our study, with temporary
264 insulin therapy implemented if blood glucose levels increase more than 100mg/dl.
265 There are some limitations to this study. First, our study mainly focuses on the initial
266 conditions of intubated patients in the ED. Esteban[27] found that survival in patients
267 receiving mechanical ventilation depended on not only each patient's condition when
268 initiating mechanical ventilation, but also on how the condition changes and
269 complications develop subsequently. Although we will attempt to control for
270 complications, these may still affect the outcomes. Second, we include extubation
271 failure as one of our secondary outcomes, but it's important to mention that other
272 factors such as pulmonary edema also lead to extubation failure, and could be
273 alleviated by corticosteroids as well. Third, there is currently no universally
274 acknowledged extubation standard, so extubation decision made mainly on clinical
275 experience.
276 This will be the first study looking at the prophylactic methylprednisolone for
277 preventing PES in patients after an emergency intubation. As more patients spend
278 longer periods of time in the ED, it is important to understand the best method for
279 minimizing the complications and maximizing ED patient safety during extubation. .

281 **Trial status**

282 This trial plans to start recruiting patients by the time this article is published.

283 Recruitment is expected to be finished within 10 months.

List of Abbreviations

PES: post-extubation stridor; CLT: cuff-leak test; GCS: Glasgow Coma Scale;
APACHE II: Acute Physiology and Chronic Health; RASS: Richmond
agitation-sedation scale; ABGs: arterial blood gases; SBT: spontaneous breathing
trial; SaO₂: arterial blood oxygen saturation; PETCO₂: end tidal carbon dioxide; BMI:
body mass index; ED: Emergency Department.

Ethical approval and consent to participate

The Ethics Committee of Peking Union Medical College Hospital approved this trial
protocol (reference number JS-2334) on April 9, 2020. Informed consent will be
obtained from all participants' next of kin.

Consent for publication

Not Applicable.

Availability of data and materials

Dataset generated and/or analyzed during the current study are available from the
corresponding author (Jun Xu) upon reasonable request.

Competing interests

The authors declare no competing interest.

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Authors' contributions

JyW and JHW drafted the manuscript. LY, YID and JyD co-authored the writing of the manuscript. JX proposed the research question and helped conceptualize the protocol. HdZ and XzY critically assessed the study design. All authors read and approved the final manuscript.

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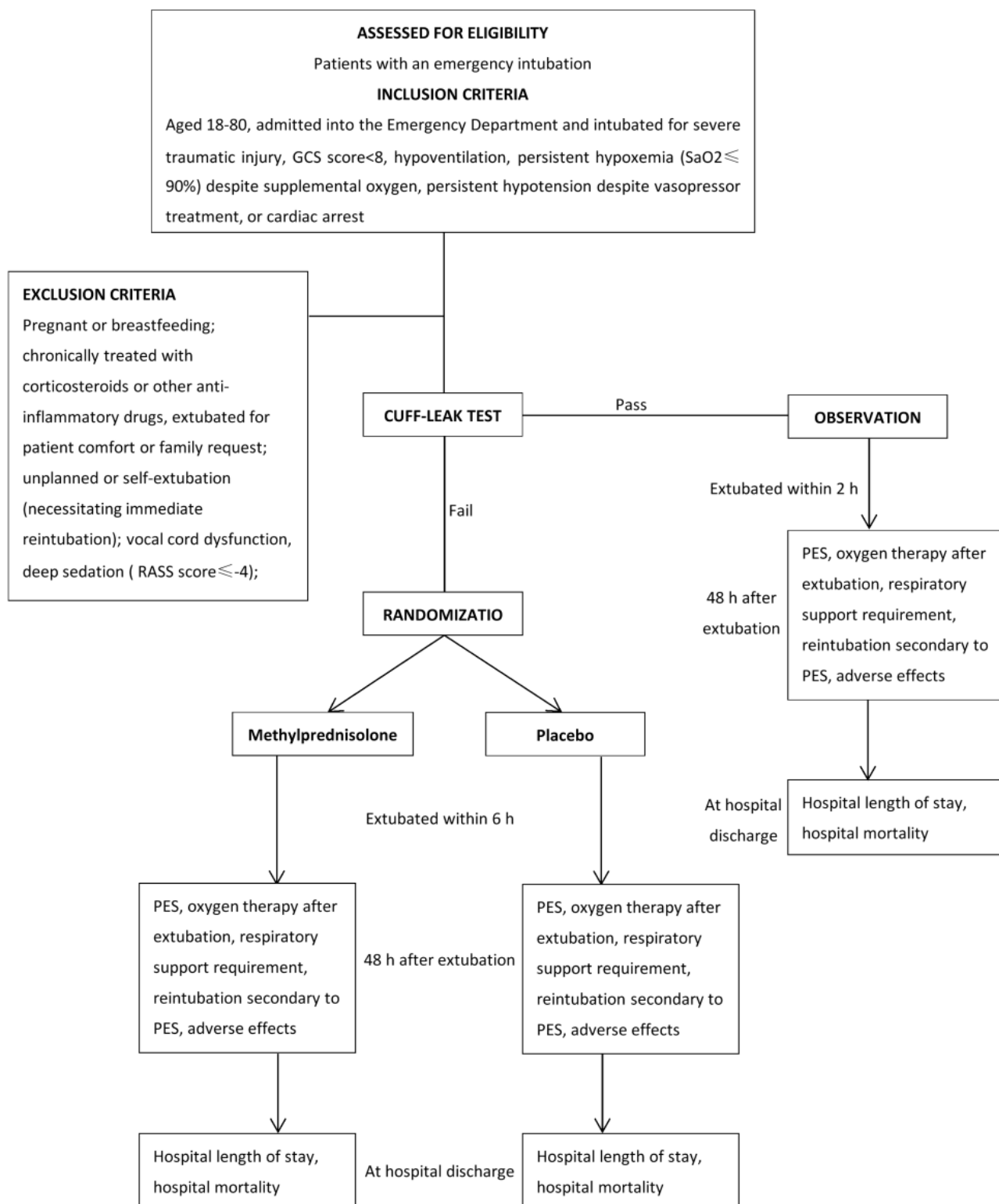
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Figure 1 - Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule of enrolment, intervention and assessments. Anthropometric data: age, gender, body mass index (BMI).*ABGs: collected for necessity only. Baseline variables: GCS score, APACHE II score, vital signs. Primary endpoint: occurrence of PES. Secondary endpoints (a): postextubation oxygen therapy, respiratory support requirement, reintubation secondary to PES, adverse effects. Secondary endpoints (b): hospital length of stay and hospital mortality. Continuous points: SpO_2 and $PETCO_2$.



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428 *Figure 2-Study flow chart.*