



**Cuff Leak Test and Airway Obstruction in Mechanically Ventilated ICU Patients
(COMIC): A Pilot Trial**

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Cuff Leak Test and Airway Obstruction in Mechanically Ventilated ICU Patients (COMIC): A Pilot Randomized Controlled Trial Protocol

ABSTRACT

Introduction: Endotracheal intubation and mechanical ventilation are lifesaving interventions that are commonly done in the intensive care unit (ICU). The act of intubating someone can cause laryngeal edema that, if extensive enough, can cause airway obstruction after a patient is extubated. To date, the only test that is available to predict this complication is the cuff leak test (CLT). However, its diagnostic accuracy is uncertain as there have been no randomized controlled trials (RCT) examining this. Herein, we report the protocol for the Cuff leak and airway Obstruction in Mechanically ventilated ICU patients (COMIC) Pilot Trial to determine the feasibility of conduction a powered RCT to examine the impact of CLT on postextubation stridor and reintubation. Subsequently, describing the diagnostic accuracy of this test.

Methods: This will be a multi-center centered, pragmatic, double blinded RCT. We will include mechanically ventilated patients in the ICU, who are deemed ready to be extubated. All patients will have a CLT done prior to extubation. The results of the CLT in the intervention arm will be communicated to the treating physician, and decision to extubate will be left to the treating team, while the results of the CLT for patients in the control arm will not be communicated to the treating physician, and the patient will be extubated, regardless of the result of the CLT.

Objective: Although we will examine all clinical outcomes relevant for the future COMIC RCT, the primary outcomes of the COMIC Pilot Trial will be feasibility outcomes including: consent rate, recruitment rate, and protocol adherence. Clinical outcomes will include postextubation stridor, reintubation, emergency surgical airway, ICU mortality, in hospital mortality, duration of mechanical ventilation, and ICU length of stay in days.



INTRODUCTION

Endotracheal intubation and mechanical ventilation are lifesaving interventions. However, as with acute interventions, can be associated with serious complications. One such complication is laryngeal edema (LE) that occurs in 4-55% of patients¹⁻⁵. LE is thought to be caused by marked polymorphonuclear infiltration to the traumatized upper airway postintubation⁶. The incidence of LE increases as the duration of intubation accrues, but it can occur as early as the first 24 hours of intubation⁵. LE can result in airway narrowing and increased airflow velocity. It is postulated that narrowing of the lumen by 50% or more may result in postextubation stridor and respiratory distress⁷. As a result, 3.5% (range 0-10.5%) of patients with LE will fail an extubation attempt and require reintubation⁵. For various reasons, reintubation has a significant morbidity and mortality⁸⁻¹³.

Identifying patients with LE can be challenging, the presence of the endotracheal tube (ETT) precludes direct visualization of the upper airway prior to extubation, therefore, clinicians cannot accurately predict airway obstruction before it occurs. A cuff-leak test (CLT) was first described in 1988 as a surrogate for direct visualization and a screening for airway edema prior to extubation¹⁴. This test involves deflating the balloon cuff on an ETT and observing if the patient is able to breathe around it. If air can pass around the ETT, it suggests that the airway is patent and clinicians may proceed with extubation¹⁴. A small leak or complete absence of one, would suggest an airway obstruction.

There are conflicting results on the utility and accuracy of a CLT. To date, two meta-analyses of observational studies examined the diagnostic accuracy of a CLT^{5,15}. One meta-analysis reports

that a failed CLT is insensitive but a specific predictor of LE (pooled sensitivity and specificity 0.56; 95% CI, 0.48-0.63 and 0.92; 95% CI, 0.90-0.93, respectively) and reintubation (pooled sensitivity and specificity for reintubation 0.63; 95% CI, 0.38-0.84 and 0.86; 95% CI, 0.81-0.90, respectively)¹⁵. While the second meta-analysis also states that the failed CLT was associated with postextubation LE, particularly in patients with > 5 days duration of intubation (odds ratio [OR]=2.09; 95% CI, 1.28-2.89), it was not associated with higher odds of reintubation (OR=0.94; 95% CI, 0.32-1.57)⁵.

Despite the lack of high quality studies, an absent cuff leak usually results in delayed extubation and exposure to corticosteroids to empirically treat airway edema. A recent meta-analysis of 11 parallel randomized controlled trials (RCTs) with a total of 2472 patients examined the effect of prophylactic corticosteroids prior to extubation on postextubation stridor and reintubation¹⁶. Prophylactic corticosteroids use reduced the risk of postextubation airway events when compared to placebo or no treatment (RR 0.43; 95% CI 0.29-0.66, P=0.002)¹⁶. A subgroup analysis demonstrates that this benefit is only significant in patients that are deemed “high risk” for LE. Prophylactically treating unspecified patients shows no reduction in postextubation events and exposes patients to high dose steroids¹⁶. Moreover, a false positive CLT can unnecessarily delay extubation, leading to a prolonged length of stay in the intensive care unit (ICU), barotraumas, and increased risk of ventilator associated pneumonias¹⁷, therefore, exposing patients unnecessarily to these undesirable outcomes. On the other hand, if a CLT is not performed, or if in case of a false negative test, some patients may fail the extubation attempt and require reintubation.



Recent clinical practice guidelines for using CLT reflect this uncertainty. The American Thoracic Society guidelines on liberation of mechanical ventilation issued a weak recommendation for performing CLT in mechanically ventilated adults who are at high risk for postextubation stridor (conditional recommendation, very low certainty)¹⁷. There is also significant clinical equipoise. A recent unpublished survey found that 42% (12/26) of Canadian intensive care unit (ICU) physicians either never or rarely request to know the results of a cuff leak test prior to extubating a patient that is at moderate risk of laryngeal edema while 23% will always or usually order the test. Therefore, a large RCT is necessary to investigate the diagnostic accuracy of the CLT and its impact on patients' outcomes. Herein, we report the protocol for the COMIC Pilot Trial to determine the feasibility of undertaking a powered RCT to examine the impact of CLT on postextubation stridor and reintubation. Subsequently, describing the diagnostic accuracy of this test.

METHODS

Design

The COMIC (Cuff leak and airway Obstruction in Mechanically ventilated ICU patients) pilot trial will be a multicenter, randomized, concealed, blinded, parallel-group, pragmatic pilot trial.

Population

Eligible patients will be mechanically ventilated adults (>18 years) who are admitted to the ICU and an order to extubate has been provided by the treating physician.

Exclusion criteria



The exclusion criteria are:

- 1) A palliative care, a one-way extubation, or a decision to withdraw advances life support order has been written.
- 2) Pregnancy.
- 3) Patients at high risk for LE: burn patients, smoke inhalation injuries (as defined as singed facial hair or nasal hair, carbonaceous secretions/sputum, and known to be in an enclosed fire), blunt or penetrating trauma involving the neck and airway, postoperative head and neck surgeries, and patients admitted with airway edema to the ICU (e.g; anaphylaxis)¹⁸⁻²⁰.
- 4) Patients with either a difficult or traumatic endotracheal intubation.
- 5) Patients receiving mechanical ventilation via tracheostomy.
- 6) Known preexisting tracheolaryngeal abnormalities such as: vocal cord paralysis, tracheolaryngeal neoplasm, tracehomalasia, tracheolaryngeal stenosis, or previous head and neck surgeries.
- 7) Patients receiving systemic corticosteroids of greater than 30 mg of PO prednisone or equivalent, within 4 days prior to the decision to extubate.
- 8) Patients who failed extubation attempt within the current ICU admission.
- 9) History of postextubation airway obstruction.
- 10) The ICU physician declined enrolling the patient.
- 11) Patient had a failed CLT in the previous 24 hours.

Eligible non-randomized patients



We will record all patients who were eligible but not randomized for any of the following reasons: 1) The patient or substitute decision maker (SDM) declined consent; 2) The ICU physician declined enrolling the patient; 3) Any other reason.

Ethics

We will apply and obtain research ethics board (REB) approval at the participating centres. As most patients will be incapable at the time of enrolment, the SDM will provide consent *a priori* whenever possible. If the patient is able to consent at the time of enrolment then we will get written consent from them. We will follow the 2-phase, 13-step informed consent process that we have used in prior international trials²¹.

If we are unable to locate the SDM for *a priori* consent, then patients may be enrolled using deferred consent until the SDM can be contacted as permitted by local REBs. The consent encounter will occur as soon as possible. If, when found, the SDM response could be permission to continue all trial proceedings, or decline further trial proceedings. In the latter situation, data collected will be used up to that point, unless the SDM requests otherwise. For the patient who has no identifiable family member, or power of attorney to provide consent, we propose to continue study protocols while we attempt (and the ICU team attempts) to locate a SDM and/or the patient recovers. In the event that such a patient subsequently recovers to the extent that an informed consent can be provided, we will ask the patient for their consent.

Deferred consent model is crucial to ensure the proper conduct of the COMIC Trial. To begin with, extubating patients is a daily routine in the ICU, and should not be delayed unless there is a valid reason to do so. Therefore, we will allow a one hour window for the study Research Coordinator (RC) to obtain *a priori* consent whenever possible, but mandating *a priori* consent



will make this study infeasible. Although CLT is commonly performed in the ICU prior to extubation, there is no clear evidence that this practice benefit patients⁵, in fact performing a CLT routinely could result in harm in some patients by delaying extubation unnecessarily and exposing them to high dose corticosteroids. The results of this trial will inform practice about an intervention that is being used for decades with lack of high quality evidence. We have successfully used deferred consent model in recent a RCT²². Several other large, multicenter, international RCTs have successfully used deferred consent model in acute settings²², and it would not have been possible to inform practice and conduct those trials without a deferred consent model.

Randomization and allocation concealment

The study RC will use the web-based system RANDOMIZE.NET (<http://www.randomize.net/>) to randomize eligible patients in a 1:1 allocation using undisclosed variable block sizes. Randomization will be stratified by: a) ETT size into three strata (6, 7, 8 mm ETTs), and b) duration of mechanical ventilation prior to randomization into two strata (>7 days and \leq 7days).

Intervention

The Respiratory Therapist (RT) will perform the CLT on all enrolled patients. The patients will first be switched to volume assist-control (V-AC) with a respiratory rate of 10 breaths/min (to allow patient assist), constant flow of 60 l/min, and tidal volume set to match the average tidal volume currently being delivered during supportive ventilation. The RT will document the average exhaled volume over 3-5 breaths after switching to V-AC. The test will be performed by deflating the ETT balloon cuff with a 10 cc syringe, and: a) auscultation with a stethoscope to identify audible air leak around the ETT, and b) measuring the difference between the average



exhaled volume prior to cuff deflation and the average exhaled volume over 3-5 breaths after cuff deflation.

We define a “failed CLT” as the RT being unable to identify air leak during auscultation.

Patients randomized to the intervention arm will have the results of the CLT (whether failed or passed CLT) communicated to the treating physician; the treating physician will decide whether to proceed with extubation or not based on the CLT results. It is at the discretion of the treating physician to provide corticosteroids (4-5 mg of intravenous dexamethasone every six hours for up to 24 hours, with the last dose given one hour preceding extubation) and/or delay extubation by 24 hours should the patient fail the CLT²³.

In the control arm of this trial; the treating physicians and healthcare workers will be blinded to the results of CLT; therefore, the RT will proceed with extubation without delay or administering systemic steroid, regardless to the CLT results.

Patients, physicians, RCs, study investigators, adjudicators, and data analysts will be blinded to the results of CLT in the control group.

OUTCOMES

Feasibility Outcomes

Although we will report all clinical outcomes relevant for the future COMIC RCT, the primary outcomes of the COMIC Pilot Trial will be the following feasibility outcomes:

- 1) Consent Rate: a successful consent rate will be defined as 70% of SDMs or patients approached to consent, choosing to participate in the trial. This will be calculated as the overall proportion of SDMs or patients consenting out of those approached (with 95% CI). As this is a Pilot Trial, the consent rate will be reviewed monthly and if applicable, barriers to informed



consent will be discussed and factors associated with improved consent as produced by the CCCTG Research Coordinators will be employed²¹.

2) Recruitment Rate: a successful recruitment rate will be defined as achieving enrolment of 40 patients, conventionally expressed as four patients per month over the duration of the trial. While the pilot trial is ongoing, recruitment will be reviewed weekly and the screening records will be reviewed monthly with the cases of missed eligible patients reviewed. If applicable, barriers to enrolment will be addressed to maximize recruitment. The recruitment metric will be measured and interpreted at the end of the pilot trial by calculating the mean number of recruited patients per active screening month.

3) Protocol Adherence: Successful adherence will be defined as $\geq 80\%$ of patients assigned to the intervention arm being treated as previously described. The adherence will be calculated as the proportion of patients that were assigned to the control arm being extubated after CLT being performed and the portion of people that assigned to the intervention arm who are given the prescribed steroids for a failed CLT. As this pilot trial is ongoing, we will review adherence monthly and investigate the reasons for compliance failure. All reasons for either failure to extubate after a failed CLT in the control arm will be investigated. The RC will review the Respiratory Therapists' notes, and the medication profile to determine actual compliance. All reasons for non-compliance will be recorded for both groups using distinguishing clinical reasons (eg. Palliation, death, consent withdrawal, errors).

Clinical Outcomes

The clinical outcomes are:



- 1) Postextubation stridor: defined as an audible high pitched inspiratory noise caused by turbulent airflow through the narrowed airway that is detectable with or without a stethoscope within 48 hours of extubation.
- 2) Clinically significant postextubation stridor: Defined as stridor (see definition above) that requires medical intervention such as the administration of systemic steroids, racemic epinephrine, or Heli-ox.
- 3) Reintubation: defined as reintubation within 72 hours of original extubation while in the ICU. Reasons for intubation will be recorded.
- 4) Emergency surgical airway: defined as performing urgent tracheostomy or cricothyroidotomy for a life-threatening airway obstruction.
- 5) In ICU mortality.
- 6) In hospital mortality truncated at 30 days.
- 7) Duration of mechanical ventilation: defined as time on the ventilator after randomization in days.
- 8) ICU length of stay in days.

Clinical outcome adjudication

The RC will enter data in a web-base and send relevant clinical information to staff at the methods centre who will validate data and prepare adjudication packages for all clinical outcomes. Two independent blinded physicians will adjudicate post extubation stridor and reintubation outcomes.

Data collection and follow-up



The RC will screen the ICU Monday to Friday to avoid incurring additional weekend on-call costs. RC will collect information including the patient baseline data (e.g., demographics, illness severity, advanced life support including duration of mechanical ventilation, daily data (e.g., CLT results, postextubation stridor, rate of reintubation, steroids administered), and source documentation that will help with adjudication of outcomes. RC will review patients daily in the ICU where the trial data including mortality, length of stay, and length of mechanical ventilation will be gathered. Once patients are discharged from the ICU they will no longer be followed daily, but incidence of in hospital mortality will be assessed at time of hospital discharge. Mortality, duration of ventilation, and ICU stay outcomes will be censored at 60 days.

Duration of the COMIC Pilot Trial

We anticipate that 10 months will be required to recruit 40 patients. A subsequent three months will be needed to validate the data, adjudicate the outcomes, analyze, interpret and present results. The total duration of the Pilot Trial may take up to 13 months to complete.

Analysis of the COMIC Pilot Trial

Calculation of consent and recruitment feasibility outcomes for the COMIC Pilot Trial will not require analysis by group, however compliance rates will have to be assessed for each group. Therefore, clinical outcomes will be analyzed as means or proportions in each arm. In addition, given the small sample size and short duration, we will not conduct any subgroup or interim analyses. An independent data safety and monitoring board will be created for the large COMIC RCT.

The proportion of patient in the two groups with the primary and secondary outcomes will be



analyzed using the Mantel-Haenszel χ^2 test or Fisher exact test. A t-test will be used for continuous outcomes and a statistical significance will be set at alpha=0.05. We will develop a full statistical analysis plan adherent to the intention to treat principle and some subgroup analysis (e.g., size of endotracheal tube).

DISCUSSION

Extubation can be a precarious step for patients admitted to the ICU. Therefore, critical care physicians undertake the utmost cautions prior to extubating patients. Moderate quality evidence supports the use of a spontaneous breathing trials with inspiration pressure augmentation as a method to predict a patient's capacity to breath upon liberation from the ventilator²⁰. CLT is the most commonly used test to detect LE in mechanically ventilated patients. However, the diagnostic accuracy and impact on clinical outcomes in average risk patients are unclear. Therefore, recent guidelines issued a weak recommendation to perform CLT prior to extubating high risk patients (i.e. traumatic intubation, a large endotracheal tube, or reintubated after an unplanned extubation)¹⁷. Patients who fail a CLT are often treated with high dose systemic corticosteroids and extubation may be delayed, both outcomes are likely not desirable by most patients.

To our knowledge, only observational studies showed that in subsets of patients; a CLT may help identify patients at higher risk of airway obstruction. We therefore, have presented a protocol for a pilot RCT to determine the feasibility of examining the effect of using CLT on postextubation complications, versus not using the test. Physician and public acceptance of performing such a



protocol is uncertain and it is integral that the recruitment rate, consent rate, and adherence rate are examined before a large scale RCT is pursued.

In conclusion, this protocol describe in detail the design and methodology of COMIC Pilot Trial. We believe that the results of this trial will help inform the design and the conduct of a large RCT examining the effect of bedside CLT on postextubation events in average risk mechanically ventilated patients.

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