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

Kimberley Lewis[1,2], Sarah Culgin[3], Roman Jaeschke[1,2,3,4], Dan Perri[1,4,5], Corry Marchildon[4], Kelly Hassall[4], Yousef Almubarak[6], Wojciech Szczeklik[7], Thomas Piraino[8], Lehana Thabane[2,3], Khaled M. Alqahtani[9], Abdulazez Alghamdi[10] Mohammed Alshahrani[6], Waleed Alhazzani[1,2,3,4]

[1] McMaster University, Department of Medicine, Hamilton, Canada; [2] McMaster University, Department of Health Research Methods, Evidence, and Impact, Hamilton, Canada; [3] St Joseph's Healthcare, St. Joseph's Health Research Institute, Hamilton, Canada; [4] St. Joseph's Healthcare, Hamilton, Canada; [5] McMaster University, Clinical Pharmacology and Toxicology, Hamilton, Canada; [6] Imam Abdulrahman Bin Faisal University, Department of Critical Care, Dammam, Saudi Arabia; [7] Jagiellonian University Medical College, Department of Intensive Care and Perioperative Medicine, Krakow, Poland; [8] St. Michael's Hospital, Toronto, Canada; [9] Prince Sattam Bin Abdulaziz University, Department of Mathematics, Al-Kharj, Saudi Arabia; [10] King Fahad Hospital of the University, Imam Abdul Rahman ben Faisal University Respiratory Therapy Department, Dammam, Saudi Arabia

INTRODUCTION

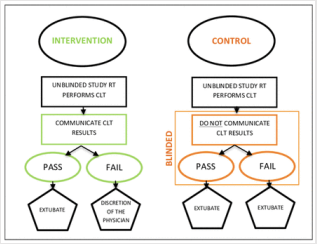
- Intubation and invasive mechanical ventilation can be lifesaving interventions
- However, one of the known complications of intubation is laryngeal edema[1]
- Up to 10.5% of patients with LE will fail extubation and require re-intubation[2]
- For multiple reasons, reintubation is associated with significant morbidity and mortality
- The cuff leak test is a non-invasive test that can be done at the bedside to detect laryngeal edema prior to extubation
- Unfortunately, the diagnostic accuracy of the CLT is questioned[3]

AIM

- To addressed the feasibility of conducting an adequately powered trial to ultimately investigate the clinical utility of the CLT and its impact on patient-important outcomes.

METHODS

- Studies protocol
  - Registered to ClinicalTrials.gov (Identifier: NCT03372707)
  - Full protocol published separately[4]
- Study design
  - International, multicentred, randomized, parallel-group trial
  - Ran in one Canadian, one Saudi Arabian, and one Polish centre
- Ethics
  - Local research ethics boars of participating centres approved of the study protocol
  - Canada and Saudi Arabia used a mixed consent model: *a priori* from next of kin when possible, otherwise deferred consent
  - Poland used waived consent
- Inclusion criteria
  - Mechanically ventilated adults >18yo admitted to the ICU and an order to extubate has been provided by the treating physician
- Exclusion criteria
  - 1)Palliative; 2)Pregnant; 3)Known airway injury (e.g. smoke inhalation, head and neck surgeries, admitted with airway edema, self extubation event); 4)Difficult or traumatic intubation; 5)Known pre-existing trachea-laryngeal abnormalities; 6)Mechanically ventilated through a tracheostomy; 7)Failed extubation within current ICU admission; 8)History of airway obstruction; 9)Failed CLT within 24hours prior to enrollment; 10)ICU physician declines enrollment
- Randomisation
  - 1:1 allocation by central computer of undisclosed variable block sizes
  - Randomisation stratified by: 1)ETT size <8mm or 8mm); 2)>7days vs ≤7 day duration of mechanical ventilation prior to randomization and; 3)Study site
- Outcomes
  - Primary: Feasibility
  - Secondary: Clinical
- Intervention
  - All patients undergo a CLT by an unblinded study RT (Figure 1)
  - In the intervention group, the results were communicated to the treating team. The team could elect to administer corticosteroids, diuretics, withhold extubation, any combination of the aforementioned options, or simply extubate
  - In the control arm, the results of the CLT were not communicated to the treating team (whether passed or failed) and the patient was extubated regardless of results



RESULTS

1. Patient characteristics

- From July 2018 to July 2019 we screened a total of 716 patients who were being treated in the three participating ICUs
- 507 were not eligible (Table 1)
- 109 eligible but not enrolled (Table 2)

Reason for ineligibility	Proportion of patients- no. (%)
Not Intubated	304 (60.0)
Palliative care plan or plan of care does not include reintubation	41 (8.1)
Known pregnancy	2 (0.4)
Mechanical ventilation via a tracheostomy	69 (13.6)
Difficult or traumatic intubation	42 (8.3)
Known pre-existing tracheolaryngeal abnormalities	10 (2.0)
Smoke inhalation/facial burns	1 (0.2)
History of post-extubation airway obstruction	4 (0.8)
Under 18 years of age	2 (0.4)
Failed extubation attempt in the current ICU admission	9 (1.8)
Admitted with laryngeal edema	17 (3.4)
Other	6 (1.8)
Total	507

Table 1: Reasons for ineligibility

Reason for eligible but not enrolled	Proportion of patients- no. (%)
Extubated outside screening schedule	56 (51.3)
Patient or SDM Declined enrollment	12 (11.0)
ICU physician declined enrollment	1 (0.9)
Family not approached due to stressful situations or language barriers	7 (6.4)
Already had a CLT performed prior to enrollment	11 (10.1)
Other (e.g. patient died, self extubated, transferred to another hospital, etc).	22 (20.2)
Total	109

Table 2: Reasons for eligible but not enrolled

- Of 100 eligible patients, 56 randomised to intervention arm and 44 to control arm (Figure 2, Table 3)

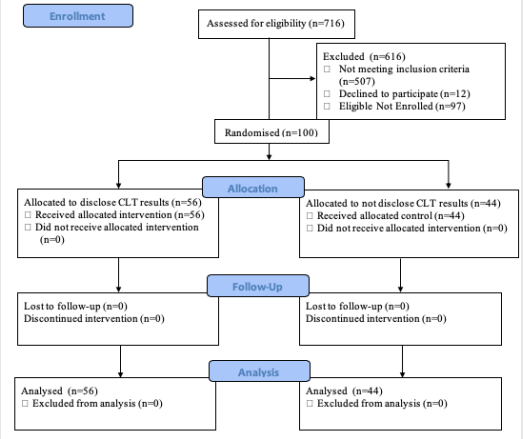


Figure 2: Consort diagram

Characteristic	Results of CLT communicated (n=56)	Results of CLT not communicated (n=44)
Age-Yr.	57.7±16.3	66.2±16.5
Female sex—no. (%)	23 (41.1)	21 (47.7)
BMI‖	28.9±8.3	28.0±9.1
Size of ETT-mm	7.7±0.5	7.6±0.4
APACHE II Score†	19.3±8.6	20.0±8.0
Patient type—no. (%)		
Medical	37 (66)	18 (40.9)
Surgical	19 (33.9)	26 (59.1)
Admitting diagnosis—no. (%)		
Cardiovascular	4 (7.1)	5 (11.4)
Respiratory	20 (35.7)	12 (27.3)
Gastrointestinal	11 (19.6)	13 (29.5)
Neurologic	4 (7.1)	4 (9.1)
Sepsis	8 (14.3)	4 (9.1)
Trauma	1 (1.8)	1 (2.3)
Renal	3 (5.4)	3 (6.8)
Other medical	3 (5.4)	1 (2.3)
Other surgical	2 (3.6)	1 (2.3)
Median time from intubation to randomisation- days (IQR)	2.7 IQR (1.5-5.1)	2.9 IQR (1-4.6)
Reason for mechanical ventilation-no. (%)		
Hypoxia	17 (30.4)	13 (29.5)
Inability to protect airway	25 (44.6)	23 (52.3)
Prophylactic intubation	8 (14.3)	3 (6.8)
Hypercapnia	6 (10.7)	5 (11.4)
Medications administered during admissions-no. (%)		
Propofol	37 (66.1)	33 (75.0)
Opioid	42 (75.0)	36 (81.8)
Benzodiazepines	27 (48.2)	22 (50.0)
Vasopressor	30 (53.6)	24 (54.5)
Paralytic	3 (5.4)	4 (9.1)
Inotrope	1 (1.8)	2 (4.6)
Physiologic parameters at the time of extubation		
PaO2-mmHg	86.3±23.6	98.0±41.5
Arterial pH	7.4±0.06	7.4±0.05
FiO2 (%)	30 IQR (30-39)	30 IQR (27.3-33.3)
PEEP-cm of water	6 IQR (5-6.25)	6 IQR (5-8)
HR-beats per minute	89.2±17.9	91.5±18.8
Mean arterial pressure-mmHg	90.5±17.4	90.3±15.1
Glasgow coma scale	12 IQR (11-15)	12.5 IQR (10-14)

Table 3: Enrolled patients' baseline characteristics

2. Primary outcome: Feasibility

- All feasibility criteria met pre-defined success thresholds (Table 4)

Feasibility Outcome	Criteria for Success of Outcome	Estimates (95% CI where applicable)
Consent rate	≥70% of SDMs or patients approached providing consent	88.3% (82.1 to 94.5%)
Recruitment rate	≥4 patients/month	7.6 patients/month
Protocol adherence	≥80% of patients assigned to the control arm being extubated immediately after the CLT	98% (95 to 100%)

Table 4: Feasibility criteria

3. Clinical Outcomes

- 93% of patients passed the CLT and 6% failed
- No significant difference between the groups in reintubation, duration of invasive mechanical ventilation, ICU length of stay, hospital length of stay, or 30 day mortality (Table 5)
- Reasons for reintubation are presented in Table 6

Outcome	Results of CLT communicated (n=56)	Results of CLT not communicated (n=44)	Odds ratio* or Mean Difference (95% CI)
Reintubation-no. (%)	4 (7.1)	4 (9.1)	0.77* (0.13-4.41)
Post-extubation stridor-no. (%)	2 (3.6)	0 (0.0)	--
Clinically significant post-extubation stridor-no. (%)	2 (3.6)	0 (0.0)	--
Mortality	2 (4.5)	10 (17.8)	0.22 (0.02 to 1.16)
Hospital LOS-days	22.77±13.01	24.74± 13.08	0.94 (-3.04 to 6.49)
ICU LOS-days	10.13±9.52	9.84±9.41	-0.16 (-2.28 to 1.90)
Duration MV-days	2.76 IQR (1.61-5.27)	3.29 IQR (1.24-4.81)	-0.05 (-1.04 to 1.04)

Table 5: Clinical outcomes

Outcome	Results of CLT communicated (n=4)	Results of CLT not communicated (n=4)
Reason for reintubation		
Inability to protect airway -no. (%)	0 (0.0)	2 (50.0)
Hypoxia -no. (%)	4 (100)	1 (25.0)
Hypercapnia -no. (%)	0 (0.0)	0 (0.0)
Airway obstruction -no. (%)	0 (0.0)	1 (25)
Time from extubation to reintubation-days	1.55±0.61	0.23±0.25

Table 6: Reason for reintubation

CONCLUSION

- Our results will likely support the feasibility of conducting a larger trial
- Although underpowered for clinical outcomes, there was no alarming increase in reintubations or surgical airway requirements
- Strengths of trial include: 1)This is the first RCT to identify that a powered trial will be feasible to determine; 2)This trial is international and multi-centered (including Poland which does not often order the CLT); 3)Mythological design to reduce bias with undisclosed variable block sizes and central allocation; 4)No loss to follow-up
- Limitations include: 1)Stratification with a small sample size resulted in imbalance; 2)Small event rate secondary to including some patients with no risk factors for laryngeal edema; 3)This was a pilot trial and therefore underpowered to detect any clinical outcomes
- A large RCT will help us to understand the risk and benefit of the CLT in critical illness and will impact practice around the world.

REFERENCES

1-Maury E et al. J Crit Care. 2004;19:23-8
2-Zhou T, et al. J Evid Based Med. 2007;4:242–54.
3-Girard TD, et al. Am J Respir Crit Care Med. 2017;195:120–33.
4-Lewis K, et al. BMJ Open. 2019;9:e029394.

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