Comparison of mechanical ventilation with low and high tidal volumes in acute spinal cord injury: A pilot randomized comparative effectiveness trial

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STUDY PROTOCOL

PROTOCOL NUMBER:

PROTOCOL TITLE 1: Comparison of mechanical ventilation with low and high tidal volumes in acute spinal cord injury: A pilot randomized comparative effectiveness trial
PROTOCOL TITLE 2: "Effects of mechanical ventilation and tidal volumes on inflammatory biomarkers in people with spinal cord injury."

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GENERAL INFORMATION

Name and address of the sponsor of the study: KL2 Active and Craig. H Neilsen Foundation grant: pending

-Centre for Clinical and Translational Sciences KL2 funding, The University of Texas Health Science Centre

-Craig. H Neilsen Foundation, 16830 Ventura Blvd, Encino, CA 91436

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If your study does not have a monitoring plan, state that here.

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1. BACKGROUND AND RATIONALE

The annual incidence of SCI in the United States is about 17,810 new cases; cervical lesions resulting in complete or incomplete tetraplegia account for 55% of new cases.[1 2] In the acute phase after SCI up to 74-84% of people will experience respiratory complications such as pneumonia, atelectasis and ventilatory failure necessitating mechanical ventilation (MV).[1 3-9]

Pneumonia is the leading cause of death after acute spinal cord injury (SCI) and is associated with poor neurologic recovery, increased length of stay, and increased mortality.[1 10-13] The impact of infection can be seen with decreased functional gains during acute rehabilitation.[14] Therefore, strategies to mitigate the risk of pneumonia and facilitate early ventilator weaning **are of primary importance** to decrease morbidity and mortality and improve lifelong functional outcomes in people with SCI.

Optimal ventilator settings have been shown to reduce pneumonia and facilitate early weaning in people without SCI.[15-23] The ventilator settings of interest are tidal volume (Vt) and positive end-expiratory pressure (PEEP). Vt is the volume of air the ventilator provides with each "breath" in volume control modes. PEEP is the alveolar pressure above atmospheric pressure that is applied at the end of expiration to prevent cyclic opening and closing of alveoli to maintain adequate oxygenation.[24]

Acute Respiratory Distress Syndrome (ARDS) Network protocol recommends smaller tidal volume ≤6 ml/kg predicted body weight (pbw) and positive end-expiratory pressure (PEEP) to prevent secondary respiratory complications and decrease mortality in people with ARDS, based on robust evidence from multicentre clinical trials.[15 16 23] Following the ARDS Network trial, there have been several randomized clinical trials (RCTs) conducted in other diagnoses (non-ARDS and non-SCI population) in which Vt of greater than 8-12 ml/ kg pbw and less than 6-8 ml/kg pbw were compared.[17-22] Results from these trials revealed a decreased risk of acute lung injury (ALI) and pneumonia in low Vt groups compared to high Vt groups.[17-22]

However, current SCI clinical practice guidelines recommend starting Vt of 15 ml/kg pbw with an incremental increase in Vt up to 25 ml/kg pbw and weaning off PEEP.[4] Unlike the needs for MV with pulmonary disease, respiratory function after SCI is limited by low lung volumes due to hypoventilation secondary to weakness or paralysis of inspiratory muscles. Therefore, bigger "breaths" (high Vt) are recommended to prevent atelectasis and improve lung capacity. In preparation for ventilator weaning, Vt is further increased. [4 25] However, in studies comparing high vs. low Vt in non-SCI population, low Vt was not associated with a higher risk of atelectasis.[17 20 21] Importantly, in our cohort study of people with acute SCI, we did not find any difference in improvement in breathing capacity or vital capacity with high Vt and moderate Vt MV.[26] Furthermore, emerging evidence in people with and without SCI suggests that low Vt leads to improved respiratory outcomes.[17-22 26 27]

The presumed mechanism for worsening morbidity with increased Vt ventilation has been called ***volutrauma***- overstretched alveoli leading to disruption of pulmonary epithelium and endothelium, lung inflammation, hypoxemia, and the release of inflammatory mediators which play a role in the development of pneumonia, lung injury, and sepsis.[28 29] These changes result in poor pulmonary outcomes such as the prolonged need for mechanical ventilation, and increased risk for pneumonia.[15 17-20 30] In human RCTs with and without ARDS, lower tidal volume ventilation resulted in a greater reduction of inflammatory markers, e.g., tumor necrosis factor (TNF) α, IL-6 compared to the higher tidal volume group.[15 30-33]

Current evidence in SCI supporting high Vt practice has several limitations.[25 34] Current guidelines were written based on a small (n=42) retrospective study[34] in which vast range of Vts of 11.6 to 19.4 ml/kg ideal body weight (IBW) versus 20.3 to 32.2 ml/kg IBW were compared. The groups were different at baseline, with the low Vt group having a lower vital capacity at

admission and other factors suggesting a higher severity of SCI and respiratory impairment. This was not taken into consideration during the analysis. Further support for high Vt ventilation in SCI comes from a small randomized control trial (n=33) in subacute SCI comparing Vts of 10 and 20 ml/kg PBW, which did not find a difference in the rate of ventilator-associated pneumonia (VAP) and ventilator weaning days between 2 groups.[25] This study was limited by an underpowered sample size.[25] Therefore, the results of this study should be interpreted with caution.

Besides, preliminary results from our cohort studies and survey suggest:

- HVt in the ICU setting with increased probability of ventilator associate pneumonia (VAP).[27]
- HVt in acute rehab is associated with a higher risk of pneumonia and pulmonary adverse event compared to moderate Vt.[26]
- Variation in ventilator settings used for patients with acute SCI in acute care hospital at the time of discharge to a rehabilitation facility (Unpublished data).
- Variation in ventilator settings used in acute care hospital and rehabilitation facilities across the globe for patients with acute SCI (in press).

This clinically important controversy in acute SCI should be addressed in a large RCT with robust power analysis. However, prior to initiating a full-scale randomized clinical trial, a pilot comparative effectiveness randomized clinical trial is required to evaluate the outcomes and feasibility of recruitment, randomization, retention, and protocol adherence to demonstrate that the methods and procedures can work in a large-scale study. This pilot study will also help us identify inflammatory markers pertaining to lung injury in people with SCI.

2. HYPOTHESIS AND OBJECTIVES

We propose a pilot randomized comparative effectiveness trial comparing respiratory complications and inflammatory markers based on MV settings of 8-10 ml/kg pbw and higher Vt of 14-16 ml/kg pbw in people with acute cervical SCI in an acute inpatient rehabilitation hospital. Our **long-term goal** is to study optimal ventilator settings and treatment approaches in acute SCI to reduce infections and improve lifelong outcomes.

Objectives:

***Objective 1*: To compare MV outcomes of high vs. low Vt on the relative risk of pneumonia in the acute rehabilitation hospital.

***Objective 2*: To generate the feasibility data to inform the future RCT design.** To achieve this objective, we will obtain the following data: a) Recruitment rate**:** the proportion of eligible people who provide consent (b) Adherence rate: the proportion of participants in each group who receive assigned intervention per protocol; (c) Retention rate: the proportion of participants in each group who complete all study procedures prior to discharge from our hospital; d) Missing data: Percentage of missing data in each group.

Objective 3: To analyze MV related lung injury inflammatory biomarkers in relation to tidal volume and outcomes.

Hypothesis:

Hypothesis 1: We hypothesize that Bayesian analysis will indicate a>70% probability of lower risk of pneumonia in people with acute cervical SCI receiving lower Vt MV than higher Vt.

Hypothesis 2: We hypothesize that we will be able to recruit **at least** 80% of eligible people each year and among recruited subjects, adherence and retention rate will be 80%, with less than 10% missing data on outcome measures.

Hypothesis 3.1: We hypothesize that MV-related lung injury inflammatory biomarkers (IL-1, IL6, IL-8, and tissue necrosis factor α levels) in serum and tracheal aspirate would be lower in the low Vt MV group compared to high Vt).

Hypothesis 3.2: People with acute cervical SCI receiving MV will have higher inflammatory markers levels than people with acute cervical SCI who do not require mechanical ventilation.

Hypothesis 3.3: People with acute cervical SCI independent of mechanical ventilation status who have higher inflammatory marker levels are more likely to develop pneumonia and other respiratory complications.

Potential Risks and Benefits:

The overall risk of pulmonary complications in people with acute SCI ranges from 74-84%. The proposed study is comparing tidal volume parameters used within current clinical practice. Our objective is to find optimal ventilator settings within the current clinical range to lower the current risk of pneumonia. Based on current evidence, pneumonia is associated with poor neurological recovery. Therefore, any decrease in the incidence of pneumonia can contribute to improved neurological recovery. There are no known risks of pulmonary complications due to participation in this study.

Risks of a blood draw and tracheal aspirate sample collection: The risks and discomfort of drawing blood include temporary discomfort from the needle stick, the possibility of pain or bruising at the blood draw site. Similarly, tracheal sample collection can also result in temporary discomfort.
Other Risks: There is a risk that confidentiality will be inadvertently compromised.

3. STUDY POPULATION

Sample Size: We plan to recruit 45 subjects (15 in low Vt, 15 in high Vt, and 15 in the control group). We will recruit 30 adults with acute cervical SCI admitted on mechanical ventilation from TIRR MHH and Craig Hospital and an additional 15 people with acute cervical SCI not dependent on mechanical ventilation at admission to serve as controls from TIRR MHH.

Criteria for Recruitment: All consecutive patients with SCI admitted to TIRR MHH and Craig Hospital will be screened for eligibility based on inclusion and exclusion criteria during the study period. The screening will involve the review of history from the patient or primary admitting clinician. If a patient meets eligibility criteria, the research coordinator will provide further information on the study, answer any questions, and recruit if they are willing to participate and provide consent.

Inclusion Criteria**:** Subjects must meet all of the inclusion criteria listed below to participate in this study.

- Adult patients ≥ 18 years (Lung volumes and ventilator settings are different for ages <18 years).
- Acute SCI of duration ≤ four months
- Mechanical ventilation subjects: traumatic or non-traumatic cervical SCI with neurological level C1-C5 admitted to our acute inpatient rehabilitation facility (AIR) on mechanical ventilation.
- Control subjects: traumatic cervical SCI admitted to our acute inpatient rehabilitation facility (AIR) who are not dependent on mechanical ventilation.

Exclusion Criteria: All subjects meeting any of the exclusion criteria listed below at baseline will be excluded from participation.

- Severe dysphagia due to concomitant brain stem injury, which increases the risk of pneumonia
- Severe brain injury resulting in dysphagia and inability to follow instructions to perform vital capacity measurements
- ARDS or severe lung disease (required supplemental oxygen or ventilator prior to SCI) at the time of admission (these conditions will not allow patients to randomize because target Vt may below)
- Prolonged antibiotics for > 3 weeks at the time of admission due to infection (e.g., osteomyelitis, epidural abscess, etc.),
- Presence of diaphragmatic pacemaker.

Withdrawal Criteria: Possible reasons for discontinuation of study intervention: Intolerance to proposed ventilator settings.

Subject Replacement: Subjects who drop out will be replaced by screening the inpatient unit. Subjects that drop out will be followed for secondary outcomes collected via the EMR while they remain at TIRR.

4. TRIAL SCHEDULE:

Participants will be enrolled in the study upon consent within 48-72 hrs of admission to TIRR MHH or Craig Hospital, and participation will end on discharge from respective hospital. The trial will start upon IRB and respective hospital approval on July 1, 2021, and end on June 30, 2024.

5. STUDY DESIGN

We propose a randomized comparative effectiveness trial to study systematically current Vt ranges to determine optimal settings to improve outcomes. Study participants will be randomly assigned to high tidal volume (14-16 ml/kg pbw) or low tidal volume of 8 to 10 ml/kg pbw within 48 hrs of admission. Subjects will be stratified based vital capacity at admission (≥5.8 cc/kg pbw) to ensure equal allocation of those with the most severe respiratory impairment and unlikely to wean from the vent. In our experience, vital capacity ≥5.8 cc/kg pbw was associated with higher odds of weaning. We will screen and recruit an additional 15 people with acute SCI not dependent on mechanical ventilation at admission to serve as controls. We anticipate 3 years to complete study recruitment. A 1:1 allocation ratio will be applied to the mechanical ventilation groups. Participants, principal investigator, outcome assessors, and statistician will be blinded to tidal volume assignment.

6. METHODS AND ASSESSMENTS

Intervention: Lower Vt group will be kept 8- 10 ml/kg pbw with PEEP, and in the high Vt group, the participant will receive a tidal volume of 14-16 ml/kg pbw with PEEP. The PEEP will be adjusted based on atelectasis on X-ray findings and patient tolerance within 5-10 cm H_2O range. These thresholds are used based on our cohort study[26] and survey data, which suggest the current median minimum to maximum Vt range used in rehabilitation hospital setting ranges from 8-16 ml/kg pbw. Tidal volumes will be increased per our institutional protocol at a rate of 50-100 ml per day until the target range is achieved. All participants at admission will be switched to Assist Control (AC) Mode or synchronized intermittent mandatory ventilation which is the current standard of practice in our free-standing acute inpatient rehabilitation unit. We will monitor peak and plateau pressures. All study participants will receive standard respiratory care, including secretion management using sub-glottic suction, mechanical insufflator-exsufflator, albuterol-ipratropium nebulization as-needed medications for thick secretions (e.g., N-acetylcysteine, guaifenesin).

Ventilator weaning Protocol is managed by board-certified SCI medicine rehabilitation physicians in our institution. Internal Medicine physicians are consulted on all our mechanically ventilated patients, and pulmonologists are available for consultation as needed. The ventilator

weaning protocol begins once the patient is determined to be medically stable by the attending physician and satisfies the following institutional criteria: lung auscultation with clear or relatively clear breath sounds, vital capacity >10-12 ml/kg pbw measured by Wright's spirometer via mouth or tracheostomy, chest X-ray clear or stable, arterial blood gas analysis on room air within normal limits, no active infection, hemoglobin >10 gm/deciliter and should be tolerating tracheostomy cuff deflation. The institutional weaning protocol consists of 12-19 days of progressive ventilator-free spontaneous breathing. The weaning schedule is adjusted sometimes due to respiratory complications, anxiety, and inability to tolerate protocol.

Control group: Both controls and people in mechanical ventilation groups will receive standard comprehensive inpatient rehabilitation services, including physical therapy, occupational therapy, speech, and respiratory therapy if needed.

Outcomes: The **primary outcome is pneumonia episodes** with evidence of new or progressive and persistent infiltrate on chest radiograph plus 2 of the following abnormal white blood cell count, presence of fever or hyperthermia, purulent sputum, and deterioration in gas exchange. [21] Any new pneumonia episodes which meet the above criteria and developed 48 hrs after achieving target Vt will be recorded. New pneumonia events can only be recorded after 14 days from the onset of the first event.

The *secondary outcomes* include feasibility outcomes. We will obtain the following data: a) Recruitment rate**:** the proportion of eligible people who provide consent (b) Adherence rate: the proportion of participants in each group who receive assigned intervention per protocol; (c) Retention rate: the proportion of participants in each group who complete all study procedures and d) Missing data: Percentage of missing data in each group. Based on only one RCT[25] performed in SCI comparing high vs. low Vt, we anticipate a total recruitment rate of 80% (i.e., that 80% of the eligible would consent for the study), and of those who are enrolled in the study, 80% adherence and retention rate will be observed. We anticipate <10% missing data.

Additional outcomes: This data will be collected from the time of admission to our rehabilitation hospital until discharge. a) b) Other respiratory complications: The following ventilator-associated events will be reported: transfer to acute care hospital due to respiratory complications, weaning failure, new pneumothorax, ARDS, pleural effusion, pulmonary embolism, atelectasis, and pulmonary edema, and c) total ventilator days, weaning days and hospital length of stay.

We will perform an analysis of MV-related lung injury biomarkers**.** Blood and tracheal aspirate samples will be collected at 3-time points; at baseline within 48 hrs of admission to AIR facility, 48- 72 hrs after achieving target Vt, and 3rd sample post- weaning or 2 weeks from target Vt. Samples will be processed and stored at −80 ° C until use in Dr. Doursout's laboratory located at the Medical School, University of Texas in Houston, TX. We will focus on IL-1, IL-6, IL-8, and TNF-α levels. For controls we will obtain blood samples within 48 hrs of admission and 2 weeks from baseline.

Additional data: Additional data collection will include age, sex, weight, height, date of injury, date of admission to AIR, time since injury, mechanism of injury, American Spinal Injury Association (ASIA) impairment scale (AIS), vital capacity at admission, maximum vital capacity achieved during AIR stay, ventilator settings including Vt, peak and plateau pressure, hospital length of stay and discharge location. We will also collect information on any other ongoing or new infectious events other than pneumonia.

Randomization: Each subject will be randomized to either a tidal volume of 8-10 ml/kg pbw or 14-16 ml/kg pbw within 48 hrs of admission after obtaining consent. A 1:1 allocation ratio will be applied with permuted block size to maintain blindness and balance. Subjects will be stratified based on C1-C3 AIS A to ensure equal allocation of those with the most severe respiratory impairment and unlikely to wean from the vent. In our experience, C1-C3, AIS A was associated with lower vital capacity at admission. The study research assistant will randomize subjects in the redcap database, and he/she will not be involved in data analysis.

Blinding: The principal investigator (PI), statistician, outcome assessors, and participants will be blinded to tidal volume assignment.

Study Visits and Procedures:

Screening: Patients will be screened at the time of admission to TIRR Memorial Hermann. Respiratory therapist and SCI attendings will notify PI or research assistant (RA) regarding admits of an SCI patient dependent on mechanical ventilation or cervical SCI patients wo are not dependent on MV (controls). PI or RA will discuss eligibility with respiratory therapists or attending physicians. PI may review discharge summary from acute care hospital or history and physical performed at TIRR admission to determine eligibility. If a person doesn't meet eligibility criteria, we will not save any identified data other than deidentified information on the reason for screening failure.
The screening will require information on age, past medical and surgical history, the duration of SCI, etiology of SCI, the dependence on a ventilator, neurological level and current medications.

Consent: If a subject agrees to participate, then they will be given an IRB-approved consent form to review and sign. There will be separate consent forms for MV group and controls due to different risks and procedures involved for participation in respective group. Those with tetraplegia will unlikely have the ability to sign and we will have a third-party attest to the consent. Because of the study's time constraints, they will have 1 day to decide upon whether they will participate.

Study procedures for MV group:

Day 0-1: screen, approach for informed consent
Day 1-2: obtain consent and randomization
Day 1-2: Baseline blood and tracheal specimen for inflammatory marker analysis
Day 1-4: Titrate tidal volume to achieve respective targets in each group
Day 4-6: 2nd blood and tracheal specimen (within 48 hrs after achieving target Vt)
Days 14-18: 3rd sample (post-weaning or 2-week sample)
Day 0- Discharge: Adverse events monitoring and outcome data collection

Study procedures for control group:

Day 0-1: screen, approach for informed consent
Day 1-2: obtain consent
Day 1-2: Baseline blood specimen for inflammatory marker analysis
Days 14-18: 2nd sample (2-weeks from baseline)
Day 0- Discharge: Adverse events monitoring and outcome data collection

We will collect demographics, outcome data, and adverse events from electronic medical records during their stay at TIRR (day 0- discharge).

7. TRIAL MATERIALS

The intervention proposed in this study doesn't need new equipment. Study intervention involves adjusting their current ventilator settings. Clinical outcome measures will be collected from electronic medical records in respective hospitals.

Inflammatory markers will be analyzed from blood and tracheal samples of participants. ELISA assays to assess markers of inflammation. A Millipore Multiplex MAP® 37-plex human cytokine panel (EMD Millipore, Billerica, MA, USA) will be used. Laboratory supply will include pipettes, tubes, reagents, chemicals, and gauze. The majority of the equipment required is provided by the institution and/or is part of the standard of care at TIRR Memorial Hermann or available at UTHealth for research use. E.g., Office space, computers, and access to MS office software for creating data collection report forms. RA or PI will transport samples after collection for storage and analysis to Dr. Doursout's lab.

Storage of blood and tracheal specimens: *Samples will be processed and stored at −80 ° C until use in Dr. Doursout's laboratory located at the Medical School, University of Texas in Houston, TX and Craig Hospital Biorepository laboratory located at Craig Hospital, Englewood, CO.*

8. TREATMENT

The current clinical practice guidelines recommend a higher tidal volume starting at 15 ml.kg predicted body weight (pbw) and upto 25 ml/kg pbw. These guidelines were written based on a small retrospective study and biological plausibility. People with SCI suffer hypoventilation due to paralysis of the muscle of inspiration. However, current data in people with and without ARDs suggests that lower tidal volume lowers the risk of morbidity and mortality and improves respiratory outcomes. Cohort study performed at TIRR also suggests that lower tidal volumes may lower the risk of pneumonia.

Our cohort study and a recent survey of physicians managing mechanical ventilators for people with SCI suggest practice variation in ventilator settings used for people with SCI.

Data from our center and international survey:

Variation in ventilator settings used for patients with acute SCI in acute care hospital at the time of discharge to a rehabilitation facility (Unpublished data): We collected data on 91 patients who required mechanical ventilation at the time of admission to acute inpatient rehabilitation (AIR) facility from 2015-2019. We noted variation (Figure 1.) in ventilator modes and settings used at acute care hospitals at the time of discharge. Median (interquartile range) tidal volumes were 7.5 (6.7-8.5) ml/kg pbw on admission to AIR facility or at the time of transfer from acute care hospital. 84% of patients were receiving PEEP on admission. After admission to the AIR facility, all patients were weaned off PEEP within the next 1-2 days and switched to assist control mode. Patients' tidal volumes were gradually increased to prevent atelectasis per SCI clinical practice guidelines.[4] As a result, the median (IQR) tidal volumes received in rehabilitation hospital were 14 (13-16) ml/kg pbw. Our data suggest that ventilator settings used in acute care hospital and rehabilitation vary.

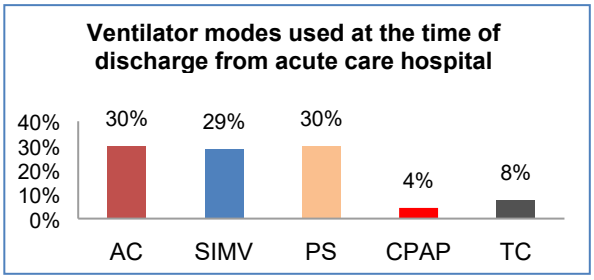

Figure 1: Ventilator modes at the time of discharge from acute care hospital
Abbreviations: Assist control; **SIMV**: Synchronized intermittent mandatory ventilation; **PS**: pressure support; **CPAP**: Continuous positive airway

Variation in ventilator settings used in acute care hospital and rehabilitation facilities across the globe for patients with acute SCI (manuscript under review): We conducted an international online survey of providers from acute care and rehabilitation hospitals to identify practice variations in the management and weaning of mechanical ventilation in patients with acute SCI. We received 137 responses from 33 countries. The highest Vt [median (interquartile range)] reported by acute care was 10 (8-10) ml/kg pbw compared to 13 (10-15) ml/kg pbw (p=0.001) in the rehabilitation setting. Application of PEEP and keeping the tracheostomy cuff inflated are commonly reported practices in acute care, whereas there is inconsistency with these practices in the rehabilitation setting. Regarding factors to initiate weaning, physicians in acute care mostly relied on arterial blood gas (70%) findings, whereas in the rehabilitation setting, physicians relied on vital capacity (73%). We found important differences in practices between "acute care and rehabilitation setting" and "within a rehabilitation setting."

The proposed ventilator settings are within the currently used ventilator settings across the globe and in our institution. Our proposed study compares tidal volume ranges of 8-10 ml/kg pbw and 14-16 ml/kg pbw. After reviewing our institute's data, current practice (survey results), and current literature in the non-SCI population, these settings were proposed. Tidal volumes are delivered via a mechanical ventilator used routinely in clinical practice.

Concomitant therapy: Patients in MV group will undergo ventilator weaning and respiratory care for secretion management per institution standard protocol. We will collect information on all medications taken by the participant during the study period. Controls will receive medical and rehabilitation therapies per current institution standard protocol.

Blinding: A panel of SCI attendings and a pulmonologist will determine the primary outcome. Deidentified data on respiratory events will be discussed with the team to determine if that event meets our diagnostic criteria for pneumonia and other ventilator-associated events. Data will be collected and presented by RA trained by PI. Inflammatory markers data from MV group and controls will be analysed by a blinded assessor.

9. SAFETY MEASUREMENTS

Collecting, Recording and Reporting of Adverse Events

An adverse event is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

Outcomes of this comparative effectiveness trial include data collection of adverse events. Adverse events include pneumonia and other ventilator-associated events, including acute care transfers due to respiratory complications, pneumothorax, transfer to acute care hospital due to respiratory complications, weaning failure, new pneumothorax, acute respiratory distress syndrome, pleural effusion, pulmonary embolism, atelectasis, and pulmonary edema.

The Investigators/ RA will be responsible for collecting and reporting adverse events during the trial. The investigators/ RA will collect adverse events related to the randomized control trial.

The PI will report problems according to the UTHSC-Houston IRB policy, specifically in the event which in the opinion of the PI is both unexpected and related and places subjects or others at risk of harm.

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AEs and Reportable Events will be recorded. AE will be recorded on the appropriate case report form (CRF) page from the time written informed consent is obtained until completion of the study or until resolution of the reportable event. Information to be collected includes the description of the AE, date and time of onset, severity, duration, causality, outcome, and relationship to the study procedure. If an AE is assessed by the I r as not reasonably

attributable to study intervention, its occurrence must also be recorded in the source documents and reported on the CRF.

Safety Monitoring Plan

The Data Safety Monitoring Plan (DSMP) for the research study includes statistical analysis on rates of morbidity of study participants compared to controls by the PI and the statistician at 50% recruitment stage. If preliminary results suggest the risk of pneumonia is <25% in one group compared to another group, we will stop the study.

We will follow standard clinical procedures in the event of a desaturation episode. The most common cause of desaturation is a mucus plug in people with spinal cord injury in the rehabilitation setting. We will first suction the patient. If a patient is still not improving with suctioning, we will adjust ventilator settings, including tidal volume, to address clinical needs. Given that we have a range of VT in each group, we will first adjust within that range if Vt has to be adjusted. If a person requires further adjustment in Vt, we will allow the changes in ventilator settings to meet the patient's needs. We will not remove any patient from the study. We will include this data for intent to treat analysis. However, this event will be considered a treatment failure, and data will be included to calculate feasibility metrics for a larger study.

10. DATA ANALYSIS

Data Quality Assurance

The PI will be solely responsible for the accuracy of the data. Single data entry will be performed with plans to check 10% of primary variables as a quality control. Single data entry error rates are slightly higher than 0.5% when performed by trained staff and the minimally improved error rate through double data entry is outweighed by substantial cost savings for single data entry. Data anomalies will be reviewed by the PI and clarification and/or correction will be performed. Incomplete entries will be reviewed and corrected if information is available.

Data Entry and Storage

Data will be entered in redcap database accessed through desktop computer of the PI located in a locked office in TIRR Memorial Hermann and Craig Hospital. Any paper documents will be filed in a study binder in a locked drawer in the office of the PI with HIPPA information removed. 5 years after manuscript publication, the paper reports will be placed into the shredder bins for destruction.

11. SAMPLE SIZE AND STATISTICAL METHODS

Determination of Sample Size:

The purpose of the proposed pilot trial is to test the feasibility of conducting a randomized control trial comparing high vs. low Vt MV. Given the complexity of this study and practice variation, it is essential to evaluate recruitment and study procedures. Our cohort study data suggest that approximately 19 patients per year will meet eligibility. Based on Fenton et al. study comparing high vs. low Vt MV in SCI, we anticipate a total recruitment rate of 80% (i.e., that 80% of the eligible would consent for the study), i.e., on average, we are expecting to enroll at least 10-12 participants with SCI who are on mechanical ventilation per year for mechanical ventilation group and total of 30 subjects for 3 years.

For the control group, we will recruit cervical SCI (neurological level C1-C5) who are not dependent on mechanical ventilation at admission to our acute inpatients rehabilitation facility. We plan to recruit a total of 15 subjects in 2 years. This is a pilot study based on feasibility of completing study within the above time frame this sample size was determined. We will have atleast 15 subjects in each group for the analysis.

Statistical and Analytical Plans:

Baseline data and unadjusted analysis of outcome variables will be presented as mean with standard deviation (SD) for a continuous variable with normal distribution otherwise as median with interquartile range (IQR). Categorical and ordinal data will be reported as totals and frequencies for baseline data and unadjusted analysis of outcome variables.

Aim 1: Respiratory outcomes: We will report relative risk with credible interval and posterior probability. We will use neutral prior, and for binary outcomes, this will be centered at RR of 1 with 95% credible interval of 0.3 to 3. Bayesian inference combines a prior or an estimated effect distribution based on previous studies and likelihood, which summarizes findings from the present study. [35] All Bayesian analyses will use similar models as the frequentist analyses. We will report risk ratios with 95% credible intervals and posterior probability of benefit or harm associated with the intervention.

Aim 2: The number of patients contacted and recruited per month will be presented, and we will use the CONSORT diagram to summarize the numbers and reasons related to recruitment, follow-up, and dropout. The main feasibility outcomes include recruitment rate, adherence rate, and retention rate.
We will summarize these outcomes by arm using frequency and percentage. We will inspect these percentages relative to our feasibility targets.

Aim 3: Individual inflammatory marker levels will be presented as mean with standard deviation. A linear mixed model will be constructed on cytokine levels, adding time and randomization group as factors in the model. In this model, the interaction between time and group will be used to study differences over time between groups. A random intercept for the patient will be included to account for within-patient correlation. If the residuals are not normally distributed in linear mixed model analyses, the data will be transformed (e.g., natural logarithm), or an alternative distribution will be used. The relation between cytokine levels and the development of pneumonia or pulmonary adverse events will be studied with a multivariate logistic regression analysis. A risk ratio with 95% confidence interval (95% CI) will be presented

12. ETHICAL CONSIDERATIONS

Informed Consent

Subjects will be recruited upon admission, meeting the established I/E criteria, and consenting to participation. Informed consent will be obtained by the PI and/or the research assistant, and they will have one day to decide. All procedures will be fully disclosed, and we will give the subjects as much information as possible about the intervention and the data analysis. The subjects will be given the opportunity to ask questions. They will be reassured that their participation in this study is voluntary, and they have the right to withdraw at any time from the study. Any new findings developed during the course of this research that may affect their willingness to continue will be provided to subjects. Choosing not to participate or withdrawing from this study will not negatively affect subjects' right to any present or future medical treatment or employment to which the subjects are otherwise entitled. Although the PI and collaborators may have admitting privileges, they do not have an inpatient service, minimizing unperceived coercion, which may be possible if the admitting physicians were directly involved in the study. Besides, the subjects will be asked to sign a Research Subject Authorization Confidentiality and Privacy Rights form to comply with HIPAA regulations.

IRB review

This protocol and the associated informed consent documents have been submitted to the IRB for review and approval.

Confidentiality of Data and Patient Records

All patient records will remain confidential. Data with Protected Health Information (PHI) will be de-identified and given a subject ID found on the Linking Log. The Linking Log is a separate file in a separate folder found on the PI's desktop computer.

13. PUBLICATIONS

We anticipate publication in a peer-reviewed journal within 1 year of completing this study describing the effects of high vs. low tidal volume people with acute SCI.

14. RETENTION OF TRIAL DOCUMENTS

All records for all participants, including case report forms (CRFs) and source documentation, will be retained by the PI in a binder locked in his office and on his desktop computer locked in his office. IRB and
regulatory records will be placed in a binder along with the mentioned documents and will be retained by the PI in his office at TIRR Memorial Hermann, locked in a cabinet.

15. BIOBANKING

In the case of participants from Craig Hospital with a SCI, we will undergo a separate and optional consent for participant to authorize the collection and storage leftover blood, urine, or tissue clinical samples that may be obtained related to either the primary study or in the future as part of the participant's regular medical care at Craig Hospital. The consent contains separate YES/NO Questions to specify consent for collection and storage of leftover research and clinically related samples, future permission to contact, and wishes related to incidental (unexpected) findings. The participant's choice will be recorded in a separate biorepository database.

References:

1. National Spinal Cord Injury Statistical Center. Spinal Cord Injury Facts and Figures at a Glance. University of Alabama at Birmingham: Birmingham, Alabama., 2019.
2. Jain NB, Ayers GD, Peterson EN, et al. Traumatic spinal cord injury in the United States, 1993-2012. *JAMA* 2015;313(22):2236-43. doi: 10.1001/jama.2015.6250
3. Berlowitz DJ, Wadsworth B, Ross J. Respiratory problems and management in people with spinal cord injury. *Breathe (Sheff)* 2016;12(4):328-40. doi: 10.1183/20734735.012616
4. Cosortium for Spinal Cord M. Respiratory management following spinal cord injury: a clinical practice guideline for health-care professionals. *J Spinal Cord Med* 2005;28(3):259-93. doi: 10.1080/10790268.2005.11753821
5. Cardozo CP. Respiratory complications of spinal cord injury. *J Spinal Cord Med* 2007;30(4):307-8. doi: 10.1080/10790268.2007.11753945
6. Tollefsen E, Fondenes O. Respiratory complications associated with spinal cord injury. *Tidsskr Nor Laegeforen* 2012;132(9):1111-4. doi: 10.4045/tidsskr.10.0922
7. Lemons VR, Wagner FC, Jr. Respiratory complications after cervical spinal cord injury. *Spine (Phila Pa 1976)* 1994;19(20):2315-20. doi: 10.1097/00007632-199410150-00011
8. Reines HD, Harris RC. Pulmonary complications of acute spinal cord injuries. *Neurosurgery* 1987;21(2):193-6. doi: 10.1227/00006123-198708000-00010
9. van den Berg ME, Castellote JM, de Pedro-Cuesta J, et al. Survival after spinal cord injury: a systematic review. *J Neurotrauma* 2010;27(8):1517-28. doi: 10.1089/neu.2009.1138
10. DeVivo MJ, Black KJ, Stover SL. Causes of death during the first 12 years after spinal cord injury. *Archives of physical medicine and rehabilitation* 1993;74(3):248-54.
11. Jaja B, Jiang F, Badhiwala JH, et al. Association of pneumonia, wound infection and sepsis with clinical outcomes after acute traumatic spinal cord injury. *Journal of neurotrauma* 2019 doi: 10.1089/neu.2018.6245
12. Failli V, Kopp MA, Gericke C, et al. Functional neurological recovery after spinal cord injury is impaired in patients with infections. *Brain* 2012;135(Pt 11):3238-50. doi: 10.1093/brain/aws267
13. Kopp MA, Watzlawick R, Martus P, et al. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. *Neurology* 2017;88(9):892-900. doi: 10.1212/WNL.0000000000003652
14. Stampas A, Dominick E, Zhu L. Evaluation of functional outcomes in traumatic spinal cord injury with rehabilitation-acquired urinary tract infections: A retrospective study. *J Spinal Cord Med* 2019;42(5):579-85. doi: 10.1080/10790268.2018.1452389
15. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-8. doi: 10.1056/NEJM200005043421801
16. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347-54. doi: 10.1056/NEJM199802053380602
17. Gu WJ, Wang F, Liu JC. Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials. *CMAJ* 2015;187(3):E101-E09. doi: 10.1503/cmaj.141005
18. Guay J, Ochroch EA. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. *Cochrane Database Syst Rev* 2015(12):CD011151. doi: 10.1002/14651858.CD011151.pub2
19. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA* 2012;308(16):1651-9. doi: 10.1001/jama.2012.13730

20. Yang D, Grant MC, Stone A, et al. A Meta-analysis of Intraoperative Ventilation Strategies to Prevent Pulmonary Complications: Is Low Tidal Volume Alone Sufficient to Protect Healthy Lungs? *Ann Surg* 2016;263(5):881-7. doi: 10.1097/SLA.0000000000001443
21. Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. *Crit Care* 2014;18(2):211. doi: 10.1186/cc13778
22. Zhang Z, Hu X, Zhang X, et al. Lung protective ventilation in patients undergoing major surgery: a systematic review incorporating a Bayesian approach. *BMJ Open* 2015;5(9):e007473. doi: 10.1136/bmjopen-2014-007473
23. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017;195(9):1253-63. doi: 10.1164/rccm.201703-0548ST
24. Chen Y, Luo C, He B, et al. [Effect of positive end-expiratory pressure on the incidence of acute respiratory distress syndrome in non-acute lung injury/acute respiratory distress syndrome patients in ICU: a Meta-analysis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020;32(2):155-60. doi: 10.3760/cma.j.cn121430-20191010-00029
25. Fenton JJ, Warner ML, Lammertse D, et al. A comparison of high vs standard tidal volumes in ventilator weaning for individuals with sub-acute spinal cord injuries: a site-specific randomized clinical trial. *Spinal Cord* 2016;54(3):245. doi: 10.1038/sc.2015.222
26. Korupolu R, Stampas A, Uhlig-Reche H, et al. Comparing outcomes of mechanical ventilation with high vs. moderate tidal volumes in tracheostomized patients with spinal cord injury in acute inpatient rehabilitation setting: a retrospective cohort study. *Spinal Cord* 2020 doi: 10.1038/s41393-020-0517-4
27. Hatton GE, Mollett PJ, Du RE, et al. High tidal volume ventilation is associated with ventilator-associated pneumonia in acute cervical spinal cord injury. *J Spinal Cord Med* 2020:1-7. doi: 10.1080/10790268.2020.1722936
28. Tremblay L, Valenza F, Ribeiro SP, et al. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997;99(5):944-52. doi: 10.1172/JCI119259
29. Halbertsma FJ, Vaneker M, Scheffer GJ, et al. Cytokines and biotrauma in ventilator-induced lung injury: a critical review of the literature. *Neth J Med* 2005;63(10):382-92.
30. Wolthuis EK, Choi G, Dessing MC, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. *Anesthesiology* 2008;108(1):46-54. doi: 10.1097/01.anes.0000296068.80921.10
31. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;282(1):54-61. doi: 10.1001/jama.282.1.54
32. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care* 2010;14(1):R1. doi: 10.1186/cc8230
33. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, et al. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. *Crit Care* 2010;14(2):R39. doi: 10.1186/cc8919
34. Peterson WP, Barbalata L, Brooks CA, et al. The effect of tidal volumes on the time to wean persons with high tetraplegia from ventilators. *Spinal Cord* 1999;37(4):284-8. doi: 10.1038/sj.sc.3100818
35. Wijeysundera DN, Austin PC, Hux JE, et al. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiol* 2009;62(1):13-21 e5. doi: 10.1016/j.jclinepi.2008.07.006