Evaluating the Safety of Transpulmonary Pressure Guided Optimal PEEP in Neurocritical Care Patients

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Safety of Optimal PEEP in NSICU Patients: Master Protocol

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TABLE OF CONTENTS

Table of Contents **2**
Abbreviations and Definitions of Terms **3**
Protocol Synopsis **4**
1 BACKGROUND AND RATIONALE 7
2 STUDY OBJECTIVES 8
3 INVESTIGATIONAL PLAN 8
4 STUDY PROCEDURES 9
5 STUDY EVALUATIONS AND MEASUREMENTS 10
6 STATISTICAL CONSIDERATIONS 10
9 SAFETY MANAGEMENT 11
10 DATA COLLECTION AND MANAGEMENT 11
11 RECRUITMENT STRATEGY 11
12 CONSENT PROCESS 12
13 PUBLICATION 12
14 REFERENCES 13

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
PEEP	Positive end expiratory pressure
MV	Mechanical ventilation
VILI	Ventilator induced lung injury
ARDS	Acute respiratory distress syndrome
ICP	Intracranial pressure
CPP	Cerebral perfusion pressure
CT	Computed tomography
HR	Heart rate
BP	Blood pressure
FiO_2	Fraction of inspired oxygen
SpO_2	Peripheral oxygen saturation
P_{es}	Esophageal Pressure
P_{aw}	Airway pressure
P_{tp}	Transpulmonary pressure
NSICU	Neurosurgical intensive care unit
CVP	Central venous pressure
MAP	Mean arterial pressure

PROTOCOL SYNOPSIS

Study Title	Evaluating the Safety of Optimal PEEP in Neuro Critical Care Patients
Funder	Departmental funds
Study Rationale	The use of positive end expiratory pressure (PEEP) in mechanical ventilation (MV) is important to reduce the collapse of alveoli between breaths. This atelectasis increases the patient's work of breathing and impairs oxygenation. In addition, atelectrauma can lead to ventilator-induced lung injury (VILI) through repetitive shear injury. There is a patient-specific response to PEEP titration, but PEEP titration is frequently not guided by individual patient data. There is a growing body of evidence that titrating PEEP according to estimated transpulmonary pressure (P_{tp}) measurements obtained by an esophageal balloon can improve outcomes, including measurements of lung function and time to liberation from tracheostomy in obese patients requiring prolonged mechanical ventilation, but also with trends toward decreased mortality and less time on the ventilator in survivors of ARDS. Notably, these trials have excluded patients with elevated intracranial pressure (ICP) or conditions where hypercapnia-induced elevations in intracranial pressure should be avoided [including intracranial bleeding, cerebral contusion, cerebral edema, mass effect (midline shift on CT scan), flat EEG for ≥2 h] for theoretical concerns of increasing ICP and decreasing cerebral perfusion pressure (CPP). Contrary to these concerns, small studies have shown that cerebral autoregulation is improved or unchanged while increases in intracranial pressure are small or nonexistent with increases in PEEP. Additionally, one case cohort study showed improved hypercapnia with use of esophageal balloon to guide PEEP. This study seeks to evaluate the safety of titrating PEEP to "optimal PEEP" based on P_{tp} as measured by an esophageal balloon in patients requiring mechanical ventilation who have CPP or ICP monitoring in place to correlate titrated PEEP with changes in ICP.
Study Objective(s)	To evaluate the safety of PEEP titration using esophageal balloon guided estimates of P_{tp} in neuro critical care patients.
Study Design	Non-inferiority trial comparing the effects of titrated PEEP compared to standard PEEP management on ICP, CPP, and hemodynamics in neurocritical care patients. All enrolled patients will have esophageal balloons placed with measurement of P_{tp} before and after intervention as well as baseline measurements of ICP, CPP, and MAP. All patients will undergo titration of PEEP based on P_{tp} measurements to an "ideal PEEP" (defined as end expiratory P_{tp} of 0-2). Measurements of ICP, and CPP, and MAP will be taken 5

	minutes after the titration of PEEP to evaluate the effect of PEEP titration on ICP, CPP, and MAP.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria: Adults (age ≥ 18) admitted to the Neuro ICU of UNC Hospital requiring mechanical ventilation and with intracranial pressure monitoring in place. Exclusion Criteria: 1. Pneumothorax or pneumomediastinum 2. Life expectancy < 24 hours or expected to require mechanical ventilation for < 24 hours 3. Condition that precludes placement of an esophageal balloon (esophageal or nasopharyngeal pathology preventing insertion of the esophageal balloon catheter, severe thrombocytopenia or coagulopathy) 4. Pre-enrollment ICP > 20 mg Hg or refractory ICP elevation necessitating current pharmacological treatment 5. Pre-enrollment CPP < 60 mm Hg 6. Planned change in the external ventricular drain set point during the pre-intervention, intervention or post-intervention periods 7. Pregnancy 8. Incarceration 9. Variation in ICP > 2 cm H_2O in the 15 minutes prior to intervention.
Number Of Subjects	Approximately 25 subjects
Study Duration	Each subject's participation will last 1 hour. The entire study is expected to last 12 months.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: Screening for eligibility and obtaining consent (2) Pre-Intervention: Baseline data collected, including ICP monitoring every 5 minutes for 15 minutes prior to the intervention to insure patients are at a steady state as it pertains to cerebral pressures. Patients with minimal ICP variation will then have an esophageal balloon placed to measure transpulmonary pressure. (3) Intervention: PEEP titrated to "optimal PEEP" based on P_{tp} (4) Post-Intervention: Data collection five minutes after intervention. (5) Subject Completion/Withdrawal: Ventilator management will be returned to the primary critical care team to determine PEEP going forward. In patients who continue on the titrated level of PEEP, safety data will be collected for an additional 24 hours.
Efficacy/Safety Evaluations	This study is will use endpoints of ICP, CPP, and MAP to assess the safety of PEEP titration by P_{tp} measurements via

	esophageal balloon. Determination of safety will be made based on the lack of a clinically significant increase in ICP, decrease in CPP, or decrease in MAP. All patients will have continuous hemodynamic and oxygenation monitoring, in addition to ICP/CPP monitoring, per NSICU protocol to monitor patient safety. In patients who continue on the titrated level of PEEP after the intervention (decision made by the primary critical care team), ICP, CPP, hemodynamic, and oxygenation data will be recorded for 24 hours after the intervention to evaluate for any possible adverse events, and this data will also be reported.
Statistical and Analytic Plan	The trial is an interrupted time-series design non-inferiority trial evaluating "optimal PEEP" as determined by an esophageal balloon compared to baseline standard PEEP management. The primary outcome will be intracranial pressure with a non-inferiority limit of 4 mm Hg, analyzed with a non-inferiority design. CPP and MAP are secondary outcomes with non-inferiority margin of 10 mm Hg each.
DATA AND SAFETY MONITORING PLAN	The PI and Faculty Mentor will be responsible for maintaining patient data and ensuring accuracy of the data collected. All patient data will be collected using REDCap through the NC TraCS system. REDCap allows for immediate data validation and range setting to reduce the likelihood of erroneous data entry. Data created for analysis will be de-identified and secured on a password protected UNC School of Medicine network hard drive. All investigators will be trained on completing the electronic case report form. Patient safety will be monitored with continuous cardiovascular monitoring by the critical care team. At the conclusion of the intervention, PEEP management will be returned to the primary clinical team. In patients who remain on the titrated level of PEEP, clinical information will be reviewed for 24 hours to identify and report any possible adverse events.

1 BACKGROUND AND RATIONALE

1.1 Introduction

This is an interrupted time-series design, non-inferiority trial to evaluate the safety of "optimal PEEP" in mechanically ventilated neurocritical care patients at UNC Hospital.

1.2 Description of Intervention

Trial participants will have placement of an esophageal balloon with manometry capabilities. Baseline measurements of P_{tp}, ICP, CPP, and MAP will be made at their baseline PEEP measurement. All patients will then undergo titration of PEEP based on P_{tp} measurements to an "ideal PEEP" with end expiratory P_{tp} of 0-2. Measurements of ICP, CPP, and MAP will be taken 5 minutes after the intervention. Data will be compared before and after intervention. At the conclusion of the intervention, PEEP management will return to the primary team. In patients continued on the "optimal" level of PEEP, patient data will be monitored for an additional 24 hours in order to report any possible adverse events.

1.3 Background (Relevant Literature and Data)

The use of PEEP in mechanical ventilation (MV) is important to reduce the collapse of alveoli between breaths. This atelectasis increases the patient's work of breathing and impairs oxygenation. In addition, atelectrauma can lead to ventilator-induced lung injury (VILI) through repetitive shear injury (1). There is a patient-specific response to PEEP titration, but PEEP titration is frequently not guided by individual patient data. There is a growing body of evidence that titrating PEEP according to estimated transpulmonary pressure (P_{tp}) measurements obtained by an esophageal balloon can improve outcomes, including measurements of lung function and time to liberation from tracheostomy in obese patients requiring prolonged mechanical ventilation, but also with trends toward decreased mortality and less time on the ventilator in survivors of ARDS (2-4). These trials, as well as an ongoing multicenter trial using an esophageal balloon to titrate PEEP in patients with ARDS, have excluded patients with elevated intracranial pressure (ICP) or conditions where hypercapnia-induced elevations in intracranial pressure should be avoided [including intracranial bleeding, cerebral contusion, cerebral edema, mass effect (midline shift on CT scan), flat EEG for ≥ 2 h] for theoretical concerns of increasing ICP and decreasing cerebral perfusion pressure (CPP) (5). Contrary to these concerns, small studies evaluating use of PEEP in this patient population have shown that cerebral autoregulation is improved or unchanged while increases in ICP are small or nonexistent (6-10). Increases in PEEP without guidance of an esophageal balloon in one study caused a clinically insignificant rise in ICP in patients with normal ICP at baseline, however patients with elevated ICP (> 15 mm Hg) at baseline saw no increase in ICP as PEEP was increased (11). Additionally, one case cohort study showed improved hypercapnia with use of esophageal balloon to guide PEEP (3).

This protocol seeks to evaluate the safety of titrating PEEP to "optimal PEEP" based on P_{tp} as measured by and esophageal balloon in patients requiring MV who have CPP or ICP monitoring in place.

2 STUDY OBJECTIVE

The purpose of the study is to evaluate the safety of esophageal-pressure-guided PEEP management in neuro critical care patients.

2.1 Primary Objective

To determine that titration of PEEP to optimal PEEP does not result in clinically significant changes in ICP (defined as an increase in ICP > 4 mm Hg).

2.2 Secondary Objectives

a. To determine that titration of PEEP to "optimal PEEP" does not result in clinically significant changes in CPP (defined as an increase in CPP > 10 mm Hg.
b. To determine that titration of PEEP to "optimal PEEP" does not result in clinically significant changes in MAP (defined as a decrease in MAP > 10 mm Hg.
c. To report any possible adverse events after titration of PEEP.

3 INVESTIGATIONAL PLAN

3.1 Study Design

Noninferiority trial

3.2 Study Duration, Enrollment and Number of Subjects

Enrollment will continue until 18 subjects have been enrolled who require an increase in PEEP of at least 5 cm H_20 (based on P_{tp} at the time of enrollment). Based on a prior study which found 29% of participants were within 5 cm H_2O of optimal PEEP at the time of enrollment (2), we expect we will need to measure esophageal pressures on approximately 25 patients to find 18 patients who require titration of PEEP. Based on expected enrollment of 2-4 participants per month, the trial is expected to complete enrollment within 12 months. Each patient's participation will last 1 hour; for the few patients who remain on higher PEEP per the request of the team, safety monitoring will continue for an additional 24 hours.

3.3 Study Population

Inclusion Criteria: Adult patients (age ≥ 18) admitted to the Neuro ICU of UNC Hospital requiring mechanical ventilation and with ICP monitoring in place.

Exclusion Criteria:

1. Pneumothorax or pneumomediastinum
2. Life expectancy < 24 hours or expected to require mechanical ventilation for < 24 hours
3. Condition that precludes placement of an esophageal balloon (esophageal or nasopharyngeal pathology preventing insertion of the esophageal balloon catheter, severe thrombocytopenia or coagulopathy)
4. Pre-enrollment ICP > 20 mm Hg
5. Pre-enrollment CPP < 60 mm Hg
6. Planned change in the external ventricular drain set point during the pre-intervention, intervention or post-intervention periods
7. Pregnancy
8. Incarceration
9. Variation in ICP of > 2 cm H_2O in the 15 minutes prior to intervention.

4 STUDY PROCEDURES

4.1 Screening/Enrollment

Daily screening of all intubated patients in the Neurosurgery ICU will be conducted by the research team. Intubated patients will be evaluated for the presence of ICP monitors. For patients meeting these criteria, chart review will be performed to evaluate for exclusion criteria. The primary clinical team will then be approached for permission to enroll prior to approaching families of patients for enrollment.

4.2 Pre-Intervention

All patients will have an esophageal balloon catheter inserted into their nare while upright (head of bed > 30 degrees) to a depth slightly more than the estimated distance from the lower sternum to the back of the ear (typically around 60 cm). Gastric positioning will be confirmed with abdominal compression testing and the catheter then retracted 10 – 20 cm into the lower esophagus. Placement will be confirmed with the presence of cardiac oscillations on the esophageal probe. The probe will then be secured to the patient's nasal opening using tape.

Pressures [Esophageal Pressure (P_{es}), Airway Pressure (P_{aw}), and Transpulmonary Pressure (P_{tp})] are measured directly through the ventilator. The waveforms of P_{aw}, P_{es}, and P_{tp} will be visualized on the ventilator. P_{tp} is obtained from $P_{aw} – P_{es}$. All patients will have baseline measurements recorded of ICP, CPP, HR, and MAP.

4.3 Intervention

PEEP will be increased on the ventilator to achieve a P_{tp} between 0 and +2 cm H_2O ("Optimal PEEP").

4.4 Post-Intervention

Measurements of ICP, CPP, and MAP will be repeated 5 minutes after the change in PEEP.

4.5 Subject Completion/ Withdrawal

At the conclusion of the intervention, the trial will be completed. Ventilator management will be returned to the primary critical care team who will determine PEEP level going forward. In patients who are maintained thereafter on the "optimal PEEP", safety data will be collected for an additional 24 hours.

5 STUDY EVALUATIONS AND MEASUREMENTS

	Pre-Intervention	Post-Intervention	Hourly x 24 Hours*
ICP	x	x	x
CPP	x	x	x
MAP	x	x	x
HR	x	x	x
SpO_2	x	x	x
FiO_2	x	x	x
PEEP	x	x	x
P_{tp}	x	x	
P_{aw}	x	x	
P_{es}	x	x	
Age	x		
BMI	x		
Diagnosis	x		

*Hourly data collected in patients who are continued on "optimal PEEP at the discretion of the primary team.

6 STATISTICAL CONSIDERATION

6.1 Primary Endpoint

The primary endpoint is change in ICP 5 minutes after PEEP titration. the parameter representing mean increase during/after titration is > 4 (mm Hg) in the target population.

6.2 Secondary Endpoints

1. CPP before and after intervention.
2. MAP before and after intervention.
3. Adverse events will be evaluated by the frequency, type, and severity, and these data will be reported

6.3 Statistical Methods

All endpoints will be described in term of means and standard deviation, with associated 95% confidence intervals, and median [Q1-Q3]

The change in ICP will be analyzed with a non-inferiority study: the ICP value after intervention will be considered equivalent to the ICP before intervention if the 95% upper bound of the change is lower than the non-inferiority margin of 4 mm Hg.

In a similar manner, the CPP and MAP values before and after intervention will be considered equivalent if the 95% lower bounds of the respective changes are higher than -10 mm Hg.

Should the 95% upper bounds of ICP be higher than 4, the effect of the intervention would be considered inconclusive. Similarly if the equivalence of CPP and MAP cannot be observed, the intervention will be reported inconclusive for these endpoints.

Adverse events will be reported.

By study design, all patients will be monitored in the ICU for the duration of the study and missing values are not expected. However, in the unlikely event that missing values would be present, the subjects will not be excluded and statistics will be calculated on all available data. The dataset for analysis will consist of all subjects regardless of protocol deviation, as an Intent-to-treat population.

Additional data points from the table above will be collected and tabulated using mean and standard deviation.

6.4 Sample Size and Power

Based on a non-inferiority trial design using a one-sided 95% confidence interval, a power of 80%, a non-inferiority limit of 4 mm Hg for ICP, and a standard deviation of 4.4 mm Hg based on previously published data (11), the study will need 15 participants who require a change in PEEP based on esophageal balloon measurements. To evaluate our secondary goals, using a non-inferiority limit of 10 mm Hg for CPP and a standard deviation of 11.3, we would need 16 subjects, and using a non-inferiority limit of 10 mm Hg for MAP and a standard deviation of 11.8, we would need 18 subjects.

Since we estimate that 29% will not need a change in PEEP (2), we expect we will need to enroll 25 participants and obtain esophageal balloon pressure measurements in order to have 18 participants requiring changes in PEEP.

7 SAFETY MANAGEMENT

7.1 Risks to Human Subjects

The placement of the esophageal balloon catheter in carefully selected patients (see exclusion criteria above) confers minimal risk to the patient (such as trauma to the nasopharynx, esophageal irritation, stimulation of cough or vomiting). Adverse events possibly related to mechanical ventilation and PEEP titration will be defined as barotrauma, pneumothorax, and hypotension thought to be related to changes in mechanical ventilation. Despite these theoretical concerns, no adverse effects were seen in a small randomized trial using an esophageal balloon to titrate to optimal PEEP in patients with ARDS (2).

7.2 Safety Monitoring

Data will be collected 5 minutes after the intervention, giving time for pressure equilibration from the ventilator and its effect on ICP, CPP, and MAP. Significant changes in these metrics, as defined above, will be reported as adverse events. At the conclusion of the intervention, PEEP management will be returned to the primary team. In patients whom they continue the “optimal PEEP” level, we will continue to evaluate for possible adverse events for an additional 24 hours, and this data will be reported. In addition to clinically significant changes in ICP, CPP, and MAP as defined above, additional adverse events that will be reported will include evidence of new barotrauma, change in pressor requirement,or change in HR to > 120 or < 50.

7.3 Adverse Event Reporting

“Possible Adverse Event” will be defined as a patient meeting any of the above parameters. Each possible adverse event will be reviewed by a UNC critical care physician who is independent of the study within 72 hours. After independent review, events considered to be likely or definitely related to the intervention will be submitted to the IRB for review.

8 DATA COLLECTION AND MANAGMENT

All patient data will be collected using REDCap through the NC TraCS system. REDCap allows for immediate data validation and range setting to reduce the likelihood of erroneous data entry. Data created for analysis will be de-identified and secured on a password protected UNC School of Medicine network hard drive. All investigators will be trained on completing the electronic case report form.

9 RECRUITMENT STRATEGY

Potential participants will be identified from daily screening of intubated patients in the NSICU by the study team. After identification of potential participants, study team members will approach the critical care team for confirmation of appropriateness and permission to enroll participants. If the clinician is agreeable, a study team member will approach the family/next-of-kin for explanation of the study.

North Carolina General Statute 90-21.13 for surrogate medical decision making to establish next of kin is as follows:

a. Court-appointed legal guardian (except to the extent any appointed health care agent has authority, unless the health care agent's authority has been suspended by a court order).
b. A health care power of attorney (HCPOA) may provide surrogate consent for research participation to the extent this does not contradict the written HCPOA.
c. A durable general power of attorney, unless the research participation includes an activity expressly excluded from the power of attorney.
d. In the event that there is neither a court appointed guardian nor an agent under a durable general power of attorney or HCPOA, surrogate consent for research may be given, as long as there is no evidence to the contrary, by the other individuals listed below, in order of priority:
    1. The subject's spouse.
    2. A majority of the subject's reasonably available parents and adult children.
    3. A majority of the subject's reasonably available adult siblings.
    4. Another individual with an established relationship with the subject who is acting in good faith on behalf of the subject and can reliably convey the subject's wishes.

Protection of Human Subjects

The patients' decision-making surrogates will be primarily approached to consent for participation in this study as most mechanically ventilated patients are medically or clinically sedated and not able to have decision making capacity. The investigators and research coordinators will approach the surrogates individually after the patients are identified as being eligible for the study to provide an informed consent process. Full disclosure will be provided that enrollment in this study will be optional and not affect major treatment decisions.

10 CONSENT PROCESS

The recruitment team will approach the patient's legal next of kin. These conversations will occur in the patient care room of the intensive care unit or a private consultation room in/near the intensive care unit with a trained study team member. Study information will be reviewed with the patient's next of kin and a copy of the IRB approved consent form will be provided for review. After having the chance to consider the trial, a time will be scheduled for the consent process.

For patients whom no legal next of kin is physically present, the study team will make contact via telephone.

11 PLANS FOR PUBLICATION

At the conclusion of the study, the data will be analyzed and reported in manuscript form for submission to relevant critical care and neurology journals, including but not limited to *Chest*, *Critical Care*, *Neurocritical Care*, and *Journal of Critical Care*. Data will also be used for further grant applications.

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