Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation: The PrePARE Trial

Statistical Analysis Plan

Background

Severe complications are common during endotracheal intubation of critically ill patients. One of the most common complications, peri-procedural decrease in blood pressure, is associated with increased resource utilization and worsened clinical outcomes. Fluid loading, a rapid infusion of 500 milliliters of a intravenous crystalloid solution beginning prior to the start of the procedure, may prevent a decrease in blood pressure. However, effectiveness data are lacking. Currently, pre-intubation fluid loading occurs sporadically, with significant provider practice variation. We describe here the statistical analysis plan for a randomized trial comparing fluid loading versus none to prevent cardiovascular collapse after endotracheal intubation of critically ill adults.

Design: Multicenter, prospective, parallel-group, open-label, randomized trial comparing fluid loading versus no fluid loading with regard to the development of life-threatening cardiovascular collapse during endotracheal intubation of critically ill adults. The trial was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifier: NCT03026777).

Study Sites: LSU New Orleans/University Medical Center New Orleans ICUs, Ochsner Medical Center Jefferson Campus MICU, Vanderbilt Medical Center Nashville MICU, University of Washington Harborview Medical Center ICUs, University of Alabama Birmingham MICU, Lahey Medical Center MICU, Lincoln Medical Center Emergency Department

Patient Population

Adult patients undergoing endotracheal intubation in a participating intensive care unit.

Inclusion Criteria

1. Patient is admitted to a participating study unit
2. Planned procedure is endotracheal intubation and planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Administration of sedation (with or without neuromuscular blockade) is planned

Exclusion Criteria

1. Operator feels fluid loading is absolutely indicated or contraindicated
2. Urgency of intubation precludes safe performance of study procedures
3. Prisoners
4. Pregnant Patients
5. <18 years of age

Specific Hypothesis

Fluid loading will reduce the rate of cardiovascular collapse among critically ill adults undergoing endotracheal intubation

Study Interventions:

- **Fluid Loading:**
  - **Fluid Loading Group** – (1) an infusion of 500 milliliters of an intravenous crystalloid solution of the operator's choosing will be (2) initiated at any time after randomization and prior to the administration of procedural medications from (3) above the level of the central or peripheral intravenous or intraosseous access used and allowed to infuse by gravity and (4) stopped after 500 mL have infused. All intravenous infusions preceding the decision to perform endotracheal intubation will not be altered.
  - **No Fluid Loading Group** – No intravenous fluids are started after the decision is made to perform endotracheal intubation. All intravenous infusions preceding the decision to perform endotracheal intubation will not be altered.

Variable Definitions

Primary Outcome

- Cardiovascular collapse, defined as one or more of the following:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation

Secondary Outcomes

- Each component of the cardiovascular collapse composite:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation

Exploratory Outcomes

1. Cardiovascular collapse composite outcome with an alternate systolic blood pressure cutoff:
   i. Death within 1 hour of intubation
   ii. Cardiac arrest within 1 hour of intubation
   iii. New systolic blood pressure < 90 mmHg between induction and 2 minutes following intubation
   iv. New or increased vasopressor between induction and 2 minutes following intubation
2. Incidence of systolic blood pressure < 90 mmHg between induction and 2 minutes after intubation

3. Lowest systolic blood pressure between induction and 2 minutes after intubation
4. Change in systolic blood pressure from induction to lowest systolic blood pressure
5. Lowest arterial oxygen saturation between induction and 2 minutes after intubation
6. Incidence of hypoxemia (oxygen saturation <90%) between induction and 2 minutes after intubation
7. Incidence of severe hypoxemia (oxygen saturation <80%) between induction and 2 minutes after intubation
8. Incidence of desaturation (defined by decrease in oxygen saturation of >3%) between induction and 2 minutes after intubation
9. Change in saturation from induction to lowest oxygen saturation between induction and 2 minutes after intubation
10. Lowest SpO_2 in the 6-24 hours after intubation
11. Highest FiO_2 in the 6-24 hours after intubation
12. Highest positive end-expiratory pressure in the 6-24 hours after intubation
13. Cumulative diuretic dose (in furosemide equivalents) from enrollment through three days after intubation
14. Cumulative intravenous fluid administration from enrollment through three days after intubation
15. Vasopressor receipt in the 1 hour after intubation
16. Composite of new or worsening shock in the 1 hour after intubation
    - New mean arterial blood pressure < 65 mmHg
    - New vasopressor use
    - Increased dose of previous vasopressor
17. In-hospital mortality
18. Ventilator-free days (VFDs)
19. ICU-free days (ICUFDs)

Measures of Study Intervention Delivery

Measures of study intervention will be presented for each study group but are not study outcomes:

1. Estimated volume of intravenous fluids infused as part of fluid loading prior to induction drug administration

Co-interventions

Co-interventions are aspects of the endotracheal intubation procedure that will be presented for each study group but are not study outcomes:

1. Time from administering induction medications to successful endotracheal intubation
2. Cormack-Lehane grade of view on first attempt
3. Incidence of endotracheal intubation on first attempt
4. Number of attempts required for successful tube placement
5. Incidence of need for additional intubating equipment, second operator
6. Agreement between primary and secondary outcomes recorded by observers and study staff

ICU-free days to 28 days after enrollment will be defined as the number of midnights alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit before 28 days. If the patient is admitted to an intensive care unit service at day 28 or dies prior to day 28, ICU-free days will be 0. Censoring will occur at hospital discharge.

Ventilator-free days to day 28 will be defined as the number of midnights alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0. Censoring will occur at hospital discharge.

Data Collection and Follow Up

Given the pragmatic nature of this trial, data below will be collected when available in the medical record of the patient.

Baseline: Age, gender, height, weight, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, lowest systolic blood pressure and vasopressor use prior to intubation, noninvasive ventilator use, highest FiO_2 delivered in prior 6 hours, lowest oxygen saturation in the prior six hours, arterial pH, PaO_2, $PaCO_2$ in the prior six hours, indication for intubation, reintubation, preoxygenation technique, operator experience, baseline echocardiogram

Peri-procedural: Date and time of sedative and/or neuromuscular blocker administration, saturation at time of sedative and/or neuromuscular blocker administration, pre-oxygenation devices used, sedative, neuromuscular blocker, ventilation between induction and laryngoscopy, laryngoscope type and size, total number of attempts, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications (esophageal intubation, aspiration, airway trauma), volume of fluids infused as part of fluid loading, cardiac arrest, vasopressor use, and death. Lowest systolic blood pressure, lowest arterial oxygen saturation, vasopressor administration, fluid administration, time to intubation and other key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure.

0-1 hour after intubation: Post-intubation imaging, post intubation shock, vasopressor use or cardiac arrest, and range of SpO_2, FiO_2, PEEP, and SBO in the 0 to 1 hour after intubation

1-6 hour after intubation: Range of SpO_2, FiO_2, PEEP, and SBP in the 1 to 6 hours after intubation

6-24 hours: Range of SpO_2, FiO_2, PEEP, and SBO in the 6 to 24 hours after intubation

0-72 hours: cumulative intravenous fluid administration, cumulative diuretic administration (in furosemide equivalents)

In-Hospital Outcomes: Date of last extubation (ventilator-free days), date of last ICU discharge (ICU-free days), date of death

Treatment Allocation

Opaque randomization envelopes will be present in the ICUs and available to operators when it is determined endotracheal intubation will be performed. Randomization will be stratified by study site and in permuted blocks of two, four, or six. Study personnel along with the operators will be blinded to the group assignment prior to the opening of an envelope. Once it has been determined by the treating team that (1) intubation is required, and (2) the operator confirms the absence of exclusion criteria, the operator will open the envelope and follow the assignment of either fluid loading or no fluid loading.

Power and Sample Size

In a previous before-and-after observational study which incorporated preemptive intravenous fluid loading to prevent cardiovascular collapse during endotracheal intubation in critically ill adults, the rate of cardiovascular collapse was approximately 25% in the control arm and 15% in the preemptive intravenous fluid loading arm (an absolute risk reduction of 10% and a relative risk reduction of 40%). Randomization of a total of 500 patients (250 patients per group) will provide 80% power to detect the same 10% difference in cardiovascular collapse between groups with an alpha of 0.05.

During one scheduled interim analysis after 250 patients have been enrolled, the DSMB will have the ability to monitor the rate of the primary outcome overall in the study at the interim analysis and can ask that the study be re-powered to maintain an 80% power to show a 40% relative risk reduction.

Consent

Fluid loading or the absence of additional fluid administration are both commonly used approaches during endotracheal intubation of critically ill adults in current practice. In prior observational studies of critically ill adults undergoing endotracheal intubation, clinicians have opted to administer a fluid bolus prior to induction in approximately 50% of patients, with significant variability by provider and practice environment. Currently, there are no randomized trials or evidence-based guidelines to support the choice between fluid loading or none during endotracheal intubation of critically ill adults.

Because both approaches to peri-intubation fluid management being studied are (1) commonly used as a part of routine care, (2) are interventions the patient would arbitrarily be exposed to even if not participating in the study, and (3) are acceptable options from the perspective of the clinical provider (otherwise patient is excluded), we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Endotracheal intubation of acutely ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows for formal discussion of risks and benefits in less than 10% of airway management events in the ICU.

Because the study poses minimal risk, does not adversely affect the welfare or privacy rights of the participant, and consent is impracticable, the study is being conducted under a waiver of informed consent.

Statistical analysis

Analysis principles

- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Subgroup analyses will be performed irrespective of treatment efficacy.

Trial profile

We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline comparisons and assessment of randomization

To assess randomization success, we will summarize in a table the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for intubation; Active illnesses at the time of intubation; Severity of Illness (APACHE II score); Respiratory status pre-intubation; vasopressor use at the time of intubation; Airway management procedure (Preoxygenation technique, systolic blood pressure at time of induction, Induction medication, Neuromuscular blocker, Laryngoscope type).

Primary Analysis

Unadjusted test of treatment effect. The primary analysis will be an intention-to-treat, unadjusted comparison of the primary outcome between patients assigned to the fluid loading and no fluid loading groups. The primary endpoint will be the categorical variable of cardiovascular collapse. The difference between the two groups will be compared using the $\chi 2$ test.

Secondary Analyses

Analysis of Secondary and Exploratory Outcomes. We will conduct unadjusted analyses examining the treatment effect of fluid loading on each of the pre-specified secondary and exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the $\chi 2$ test. Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups.

Per-Protocol Analyses. In addition to the intention-to-treat analysis, we will conduct a per protocol analysis of the primary outcome comparing patients who received fluid loading prior to induction compared to patients who received no fluid loading prior to induction.

Effect Modification (Subgroup analyses). We will determine whether pre-specified baseline variables modify the effect of treatment group on the primary outcome. We will evaluate for effect modification by fitting a logistic regression model for the composite primary outcome of cardiovascular collapse; independent variables will include study group assignment, the potential modifier variable of interest, and the interaction between the two (e.g., study_group*vasopressors at enrollment). Significance will be determined by the *P* value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analyzed using restricted cubic splines with 3-5 knots and preferentially displayed as continuous variables with predicted probabilities of the categorical outcome. If the presentation of data requires it, dichotomization of continuous variables for inclusion in the forest plot will be performed.

Pre-specified subgroups that may modify the physiologic impact of fluid loading:

1. Vasopressor receipt at enrollment (Yes/No)
2. Baseline left ventricular ejection fraction (continuous variable)
3. Sepsis diagnosis in the ICU (Yes/No)
4. Congestive heart failure diagnosis at baseline (Yes/No)
5. Chronic kidney disease, including end-stage renal disease, diagnosis at baseline (Yes/No)
6. Cirrhosis diagnosis at baseline (Yes/No)
7. Non-invasive ventilation for preoxygenation (Yes/No)
8. Bag-valve-mask ventilation after induction (Yes/No)

Subgroups related to risk for the primary outcome:

1. APACHE II score at enrollment (continuous variable)
2. Reason for intubation (Hypoxic or Hypercarbic Respiratory Failure / Altered mental status or seizure / Procedure / Other)
3. Lowest systolic blood pressure in the 6 hours prior to the procedure
4. Lowest SpO2 in the 6 hours prior to the procedure and at induction
5. BMI
6. Re-intubation
7. Induction agent (Etomidate / Propofol / Other)

Modeling to Examine Potential Confounding Factors. We will develop a logistic regression model with the primary outcome as the dependent variable and study group and relevant confounders included as independent variables (age, APACHE II score, vasopressor receipt at induction, systolic blood pressure at induction).

Missing Data. In the initial analysis, missing data will not be imputed. As sensitivity analyses, the primary analysis will be repeated with missing data imputed by (1) assigning a value of "No, primary endpoint did not occur" to data missing from the fluid loading group and a value of "Yes, primary endpoint did occur" to data missing from the no fluid loading, and (2) assigning a value of "No" to data missing from the fluid loading group and a value of "Yes" to data missing from the no fluid loading group.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. All additional analyses will be considered hypothesis-generating, and no corrections for multiple comparisons will be performed.

Conclusion

We describe, before the conclusion of enrollment or data unblinding, our approach to analyzing the data from the PrePARE trial of fluid loading versus none to prevent life-threatening cardiovascular collapse. We anticipate that this pre-specified framework will enhance the utility of the reported result and allow readers to better judge the impact.