COVER PAGE

Official Title:

The contribution of the combination of transthoracic and transcranial ultrasonography to the titration of positive end-expiratory pressure in patients with acute respiratory distress syndrome and acute brain injury

Brief Title:

The contribution of transthoracic and transcranial ultrasonography to the titration of PEEP in patients with ARDS and ABI

Sponsor/Responsible Party:

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Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

The primary research question evaluates the variation of optimal positive end-expiratory pressure (PEEP) for mechanical ventilation based on the combined use of lung and brain ultrasound. Four predefined PEEP levels (5, 8, 12, and 16 cmH_2O) will be assessed for both modalities.

Primary Analysis

In the first part of the study, patients will undergo transthoracic lung ultrasound to calculate the LUS (Lung Ultrasound Score) at each predefined PEEP level (independent ordinal categorical variable).

The mean LUS scores (dependent continuous variable) will be compared using repeated-measures analysis of variance (ANOVA).

This analysis will identify the optimal PEEP level for mechanical ventilation in patients with ARDS.

In the second part of the study, transcranial Doppler ultrasound (TCD) will be performed at each predefined PEEP level to measure the Pulsatility Index (PI) and Diastolic Flow Velocity (FVd) in the middle cerebral artery. These indices reflect cerebral blood flow and indirectly estimate intracranial pressure and brain ischemia.

If $PI > 1.2$ and $FVd < 0.2$ m/s, the corresponding PEEP level will be considered unsafe. If these values remain above the thresholds even at the lowest PEEP level, the patient will be excluded from the study (if $PI \geq 2.0$). PEEP levels maintaining PI and FVd within safe limits will be considered safe for cerebral protection.

In this part, PEEP level is the independent ordinal categorical variable, and the maintenance of PI and FVd within safe ranges is the dependent binary variable.

The Cochran's Q test for related samples ($k \geq 3$) will be used to assess the statistical significance of differences in the proportion of safe outcomes across the four PEEP levels. This test is an extension of McNemar's test for two related samples, which itself is a modification of the chi-square test for independent samples.

Secondary Analyses

Secondary analyses will evaluate the association between the difference in PEEP levels (optimal for respiratory mechanics vs. safe for cerebral protection) and clinical outcomes:

- Duration of mechanical ventilation (days)
- ICU length of stay (days)
- ICU mortality
- Hospital mortality

If the difference between the optimal and safe PEEP levels is large, it is hypothesized that patients may experience suboptimal ventilation, leading to prolonged mechanical ventilation, longer ICU stays, and higher mortality.

Association with duration outcomes

A multivariable linear regression model will be used to assess the relationship between PEEP variation and the duration of mechanical ventilation and ICU stay.

Independent variables will include:

- Significant PEEP difference (binary categorical variable, defined as a reduction by ≥2 PEEP levels)
- Admission Glasgow Coma Scale (GCS) score (continuous variable)

The dependent variables will be:

- Duration of mechanical ventilation (days)
- ICU length of stay (days)

Association with mortality

A multivariable logistic regression analysis will be applied to examine the relationship between PEEP variation and ICU mortality.

Independent variables:

- Significant PEEP difference
- Admission GCS score

The dependent variable:

- ICU mortality (binary variable: survived/died)

Descriptive and Additional Analyses

Quantitative variables will be presented as mean ± standard deviation (SD) or median (interquartile range), according to distributional characteristics, and illustrated with histograms or box plots.

Categorical variables will be presented as absolute and relative frequencies, and visualized with bar charts.

Comparisons between quantitative variables with normal distribution will use the Student's t-test, while non-normally distributed variables will be compared using the Mann–Whitney U test.

Comparisons between categorical variables will use the Chi-square test, or Fisher's exact test when appropriate.

The relationship between quantitative variables across different PEEP levels will be analyzed using repeated-measures ANOVA.

Associations between continuous variables will be explored using simple or multivariable linear regression, as appropriate.

Statistical Software and Significance

All statistical analyses will be performed using the R statistical software (version 3.5.2 or newer) (R Core Team, Vienna, Austria).

A two-tailed p-value < 0.05 will be considered statistically significant for all tests.