Statistical Analysis Plan (SAP)

Study Title

Distinct Physiological Effects of High-Flow Nasal Cannula, Helmet CPAP, and Their Combination in Acute Hypoxemic Respiratory Failure

1. Study Overview

This study was designed as a short-term physiological crossover investigation aimed at characterizing the physiological effects of three non-invasive respiratory support strategies in patients with acute hypoxemic respiratory failure (AHRF):

- High-flow nasal cannula (HFNC)
- Helmet continuous positive airway pressure (H-CPAP)
- Combined HFNC plus Helmet CPAP (HFNC+CPAP)

The primary focus of the study is physiological and mechanistic, specifically evaluating inspiratory effort, respiratory mechanics, ventilatory demand, and gas exchange.

The study was not designed or powered to evaluate clinical outcomes.

2. Study Design

- Single-center
- Physiological crossover study
- Randomized intervention order
- Three sequential intervention phases:
  - HFNC
  - H-CPAP
  - HFNC+CPAP
- Duration of each intervention: 30 minutes
- Randomization sequence generated using a computer-based randomization tool (Random.org)

Each patient served as their own control.

3. Study Population

Inclusion Criteria

Patients were eligible if all the following criteria were met:

1. Acute hypoxemic respiratory failure
2. Need for supplemental oxygen to maintain:
    - $PaO_2 > 60$ mmHg OR
    - $SpO_2 > 90\%$
3. Respiratory rate > 25 breaths/min
4. $PaCO_2 < 45$ mmHg
5. Acute onset within 7 days
6. Age ≥18 years

Exclusion Criteria

- Asthma exacerbation
- COPD exacerbation
- Cardiogenic pulmonary edema
- Neuromuscular disease
- Pulmonary embolism
- Pregnancy

4. Objectives

Primary Objective

To characterize the effects of HFNC, H-CPAP, and HFNC+CPAP on inspiratory effort assessed by:

- Esophageal pressure swing (ΔPes)
- Simplified esophageal pressure-time product per minute (sPTPes/min)

Secondary Objectives

Respiratory Mechanics and Pattern

To characterize the effects of the different interfaces on:

- Respiratory rate (RR)
- Minute ventilation (Ve)
- Corrected minute ventilation
- Tidal volume (Vt)
- Vt/kg predicted body weight
- Dynamic transpulmonary driving pressure (ΔPL)
- Dynamic lung compliance (Vt/ΔPL)
- Transdiaphragmatic pressure (Pdi)

Gas Exchange

To characterize physiological effects on gas exchange through assessment of:

- PaO_2/FiO_2 ratio
- Venous admixture
- $PaCO_2$
- $ScvO_2$

Pneumatic Performance

To explore the physiological impact of:

- Flow-dependent PEEP valves
- Flow-independent PEEP valves

on:

- airway pressure stability
- inspiratory effort

during:

- H-CPAP
- HFNC+CPAP

Exploratory Analyses

To exploratorily assess:

- Associations between physiological variables and NIV failure
- Inter-individual variability in physiological response patterns

These analyses are exploratory and hypothesis-generating.

5. Outcomes

Primary Outcomes

- ΔPes
- sPTPes/min

measured during each intervention phase.

Secondary Outcomes

Respiratory Mechanics

- RR
- Ve
- Corrected Ve
- Vt
- Vt/kg PBW
- ΔPL
- Vt/ΔPL
- Pdi

Gas Exchange

- PaO_2/FiO_2
- Venous admixture
- $PaCO_2$
- $ScvO_2$

Pneumatic Performance

- ΔPaw
- Correlation between ΔPaw and ΔPes

6. Exploratory Outcomes

The following analyses were considered exploratory and were not strictly prespecified:

- NIV failure
- Need for endotracheal intubation within 48 hours
- Pneumatic performance subgroup analyses
- Inter-individual response heterogeneity analyses

These analyses should be interpreted cautiously and considered hypothesis-generating only.

7. Rescue Criteria and Clinical Safety

Predefined rescue criteria included:

- Worsening respiratory distress
- Severe hypoxemia
- Hemodynamic instability
- Intolerance to the interface
- Clinician judgment of clinical deterioration

In such cases:

- the protocol was interrupted,
- and standard clinical management resumed.

Decisions regarding escalation of respiratory support and endotracheal intubation were left to treating clinicians and were not protocolized.

8. Sample Size

Consistent with prior physiological crossover investigations, a convenience sample of 18 patients was planned.

No formal power calculation for clinical outcomes was performed because the study was mechanistic and physiological in nature.

9. Statistical Principles

- Two-sided hypothesis testing
- Statistical significance threshold:
  - $p < 0.05$
- No adjustment for multiplicity beyond post-hoc pairwise correction
- Exploratory analyses interpreted descriptively

10. Data Presentation

Continuous Variables

Presented as:

- median
- interquartile range (IQR)

Categorical Variables

Presented as:

- counts
- percentages

11. Primary Analysis

Because of the crossover design and repeated within-subject measurements:

Main Analysis

Within-subject comparisons across intervention arms were performed using:

- Friedman test

for non-parametric repeated measures.

Post-hoc Analysis

When overall significance was detected:

- Wilcoxon signed-rank tests
- Bonferroni correction

were applied for pairwise comparisons.

12. Mixed-Effects Models

To account for repeated measurements and nested data structure, linear mixed-effects models were additionally performed for:

- ΔPes
- sPTPes
- Vt

Fixed Effects

- Trial/interface
- PEEP valve type
- Baseline PaO_2/FiO_2

Random Effects

- Random intercept for patient ID

Estimation

- Maximum likelihood estimation
- Satterthwaite approximation for degrees of freedom

These analyses were considered supportive to the primary physiological analyses.

13. Correlation Analyses

Pearson correlation coefficients were used to evaluate the relationship between:

- ΔPaw
- ΔPes

stratified by:

- interface
- valve type

14. Missing Data

Missing data were not imputed.

Missing values were reported descriptively and considered missing not at random when appropriate.

Analyses were conducted on available data.

15. Software

All analyses were conducted using:

- RStudio
- Version 2023.06.0+421

16. Interpretation

The study was designed as a mechanistic physiological investigation.

Accordingly:

- findings should primarily be interpreted in physiological terms,
- not as evidence of clinical superiority of one interface over another.

The study was not powered to assess:

- mortality,
- intubation,
- or other patient-centered clinical outcomes.

Exploratory analyses should therefore be interpreted cautiously and considered hypothesis-generating.