Study Protocol and Statistical Analysis Plan

Isoflurane Sedation Using AnaConDa® Device with Non-Invasive Ventilation for Acute Exacerbation of COPD

Protocol version 2.0
Dated 04.12.2022

1. Protocol Synopsis

Title	Isoflurane Sedation Using AnaConDa® Device with Non-Invasive Ventilation for Acute Exacerbation of COPD
Study Design	Prospective, single-arm, interventional pilot study
Study Population	Adult patients (≥18 years) with acute exacerbation of COPD requiring NIV
Sample Size	20 patients (interim analysis after 10 enrollees; final analysis planned on 20)
Intervention	Isoflurane sedation via AnaConDa® device during NIV
Primary Objective	Incidence of intervention failure (intubation or excessive sedation)
Secondary Objectives	Safety (vitals, ABG changes), sedation depth (RASS), patient comfort (VAS)
Duration	24 hours of sedation monitoring; follow-up until discharge or intubation
Ethics Approval	BREC 23/121 (20.03.2023), in accordance with ICH-GCP and Declaration of Helsinki

2. Background and Rationale

Acute exacerbations of COPD (AE-COPD) frequently lead to hypercapnic respiratory failure, where non-invasive ventilation (NIV) reduces intubation and mortality risks. However, NIV intolerance due to agitation or dyssynchrony often necessitates invasive ventilation, with attendant complications. Volatile anesthetics like isoflurane, delivered via AnaConDa®, offer rapid, titratable sedation with bronchodilatory effects and minimal accumulation. Preliminary ICU studies suggest improved hemodynamics and faster recovery with inhalational sedation, but data in the NIV setting are lacking. This pilot protocol aims to assess feasibility and safety of isoflurane sedation via AnaConDa® in AE-COPD on NIV.

3. Objectives

3.1 Primary Objective

- Evaluate the incidence of intervention failure, defined as either requirement for endotracheal intubation or occurrence of excessive sedation (RASS ≤ –3).

3.2 Secondary Objectives

- Monitor changes in vital signs and arterial blood gas (ABG) parameters at baseline, 2, 6, 12, and 24 hours.

- Assess sedation depth using the Richmond Agitation-Sedation Scale (RASS) at the same time points.
- Measure patient comfort during NIV via Visual Analogue Scale (VAS, 0–10).

4. Study Design

This single-center, prospective interventional pilot study will enroll consecutive AE-COPD patients requiring NIV. After informed consent, eligible patients receive isoflurane sedation via AnaConDa® integrated into a dual-limb NIV circuit. Continuous safety monitoring will guide dose titration. An interim analysis after 10 patients will inform potential early termination for futility or safety concerns.

5. Study Population

5.1 Inclusion Criteria

- Age ≥ 18 years
- Confirmed COPD exacerbation with hypercapnic respiratory failure
- Indication for NIV (BiPAP mode)

5.2 Exclusion Criteria

- Hypersensitivity to isoflurane or volatile anesthetics
- History of malignant hyperthermia
- Severe hepatic dysfunction
- Contraindications to NIV (e.g., facial trauma, uncontrolled secretions)
- GCS < 12 or inability to protect airway
- Hemodynamic instability unresponsive to fluids
- Pregnancy or recent upper airway surgery/tracheostomy

6. Intervention

Isoflurane infusion will be initiated at 1.5 mL/h via syringe pump (Infusia SP7s®, Fresenius Kabi). The AnaConDa® device is placed between mask and ventilator Y-piece, with scavenging on expiratory limb. Fresh gas flow (FGF) is set at patient minute ventilation plus 0.5 L/min. Target Fet% (end-tidal concentration) is 0.3–0.5 vol% for light sedation. NIV settings:

- Pressure support: 8–20 cm H_2O (titrated to 10 mL/kg IBW)
- PEEP: 4–6 cm H_2O
- RR: 12–16 breaths/min (I:E 1:3–1:4)
- FiO_2: 30–40% (titrate to SpO_2 88–94%)

Sedation depth will be adjusted based on RASS, targeting –1 to –2. Excessive sedation (RASS ≤ –3) prompts immediate cessation (failure event).

7. Study Assessments

Assessment	Baseline	2 h	6 h	12 h	24 h
Vital signs (HR, BP, RR)	✓	✓	✓	✓	✓
ABG parameters	✓	✓	✓	✓	✓
RASS	✓	✓	✓	✓	✓
VAS comfort score	✓	✓	✓	✓	✓
Intervention failure	—	✓	✓	✓	✓

8. Safety Monitoring

- Continuous pulse oximetry, ECG, non-invasive BP every 15 minutes for first hour, hourly thereafter.
- Monitor for hypotension (SBP < 90 mmHg), bradycardia (HR < 50 bpm), respiratory depression (RR < 10 breaths/min).
- ABG review for hypercapnia or hypoxemia.
- Report serious adverse events (SAEs) within 24 hours to DSMC.

9. Statistical Analysis Plan

9.1 Sample Size Justification

Assuming baseline NIV failure/intubation rate of 50%, a 30% absolute reduction requires 20 patients for 80% power at α=0.05 (two-sided). Interim analysis after 10 patients will assess safety and futility.

9.2 Analysis Populations

- **Intent-to-Treat (ITT):** All enrolled patients who received any study intervention.
- **Per-Protocol (PP):** Patients completing at least 2 hours of sedation without major protocol violations.

9.3 Primary Outcome Analysis

- Calculate proportion of intervention failures in ITT population.
- 95% confidence interval (CI) using Wilson’s method.

9.4 Secondary Outcomes

- Continuous variables (vitals, ABG, RASS, VAS):
  Summarize as mean ± SD or median (IQR) as appropriate.
  Paired t-test (or Wilcoxon signed-rank) comparing baseline vs. each time point.
- Categorical variables (intubation, excessive sedation):
  Chi-square or Fisher's exact test.
- Time-to-intubation: Kaplan–Meier curve with log-rank test.

9.5 Missing Data

- Use last observation carried forward (LOCF) for missing hourly RASS and VAS if < 10% missing.
- Conduct sensitivity analysis excluding patients with > 20% missing data.

9.6 Interim Analysis

- After 10 patients, DSMC reviews safety: if > 50% failure or SAE rate > 20%, consider early termination.

10. Data Management and Quality Assurance

- Case report forms (CRFs) will capture all assessments.
- Data entry into secure electronic database with audit trail.
- Regular monitoring visits by Clinical Research Associate (CRA).
- Query resolution within 72 hours.

11. Ethics and Informed Consent

- Approval by Institutional Ethics Committee.
- Conducted per ICH-GCP and Declaration of Helsinki.
- Written informed consent obtained prior to any study procedure.
- Confidentiality maintained; data anonymized.

Appendix A: Informed Consent Form

Title of Study: Isoflurane Sedation Using AnaConDa® with NIV for AE-COPD

Principal Investigator: Dr. Dhruva Chaudhry

Purpose: To assess safety and feasibility of inhaled isoflurane sedation in COPD exacerbations on NIV.

Procedures:

- Administration of isoflurane via AnaConDa® device while on NIV.
- Monitoring vitals, ABG, sedation, comfort for 24 hours.

Risks and Discomforts:

- Potential for excessive sedation, respiratory depression, hypotension.
- Standard safety monitoring and dose adjustments will minimize risks.

Benefits:

- May improve comfort and NIV tolerance; no guaranteed direct benefit.

Voluntary Participation:

- You may withdraw at any time without affecting your care.

Confidentiality:

- Personal data kept confidential; results published anonymously.

Contact Information:
Dr. Dhruva Chaudhry
Mobile: +91-999-110-1616
Email: dhruvachaudhry@yahoo.co.in

I have read and understood the information above. My questions have been answered. I voluntarily agree to participate.

Participant Name: _____
Signature: _____
Date: _____

Investigator Signature: _____
Date: _____