

Official Title

**Nebulized Ketamine Plus Standard Care vs.
Standard Care Alone in Moderate to Severe
Asthma Exacerbations: A Randomized Clinical
Trial (KET-AIR Trial)**

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1 PROTOCOL SUMMARY

INTRODUCTION:

Asthma is a common and chronic respiratory condition characterized by airway inflammation and bronchial hyperresponsiveness. Exacerbations, particularly of moderate to severe intensity, are a frequent cause of emergency department visits and are associated with significant morbidity and healthcare burden. Standard treatment typically includes inhaled bronchodilators, systemic corticosteroids, and oxygen therapy. However, a subset of patients fail to respond adequately to these interventions. Ketamine, an NMDA receptor antagonist with bronchodilatory and anti-inflammatory properties, has shown promise in improving respiratory outcomes in severe asthma, particularly when administered intravenously. Nonetheless, evidence supporting the use of nebulized ketamine in this context remains limited. This study seeks to evaluate the effectiveness of nebulized ketamine, administered after standard asthma therapy, in improving pulmonary function in adults with moderate to severe asthma exacerbations. Through this randomized controlled trial, we aim to generate high-quality evidence that may support the inclusion of nebulized ketamine in acute asthma management protocols.

METHOD:

This double-blinded randomized controlled trial will enroll 100 adult patients presenting to the emergency department with moderate to severe asthma exacerbations. After receiving standard asthma care—which includes salbutamol and ipratropium nebulization every 20 minutes for the first hour and systemic corticosteroids—participants will be randomly allocated to one of two groups. The intervention group will receive a single dose of nebulized ketamine (0.5 mg/kg diluted in normal saline to a total volume of 5 mL), while the control group will receive a placebo nebulization (5 mL of normal saline). All patients, care providers, and outcome assessors will be blinded to group allocation. Peak Expiratory Flow Rate (PEFR) will be measured at baseline, 30 minutes, and 60 minutes following the intervention. Vital signs and adverse effects will be closely monitored and recorded at each time point.

AIM:

To evaluate the efficacy and safety of nebulized ketamine administered after standard care in the treatment of moderate to severe asthma exacerbations in the emergency department.

PRIMARY OBJECTIVE:

To determine the change in Peak Expiratory Flow Rate (PEFR) at 60 minutes post-intervention compared to baseline.

SECONDARY OBJECTIVES:

- Change in PEFR at 30 minutes
- Incidence of adverse effects
- Escalation of care (e.g., IV magnesium sulfate, ICU admission, intubation)
- Disposition plan (discharged, admitted, or transferred)
- Length of stay (if admitted)
- Type of admission bed (e.g., ward vs. ICU)

- Patient-reported symptom relief (Dyspnea Visual Analogue Scale - VAS) Visual Analogue Scale (VAS)

PATIENT POPULATION:

Adults (aged ≥ 18 years) presenting to Sultan Qaboos University Hospital with a clinical diagnosis of moderate to severe asthma exacerbation, defined as a PEFR between 33% and 75% of the predicted or patient's best value according to GINA/SIGN criteria.

INTERVENTION:

A single dose of nebulized ketamine at 0.5 mg/kg diluted in 5 mL normal saline, administered following standard asthma therapy (Nebulized Salbutamol, Nebulized Ipratropium, Systemic Corticosteroids, oxygen).

CLINICAL MEASUREMENT:

PEFR and vital signs will be recorded at baseline, 30 minutes, and 60 minutes post-intervention. Side effects and adverse events will be documented concurrently.

OUTCOME:

The primary efficacy outcome is the absolute change in PEFR at 60 minutes post-intervention. Secondary outcomes include the incidence of adverse effects, need for additional treatment, and symptom improvement as measured by VAS.

TRIAL REGISTRATION:

This study will be prospectively registered on ClinicalTrials.gov prior to the enrollment of participants. The registration number will be included in all future publications and presentations related to the trial.

2 Introduction

2.1 STUDY RATIONALE

Moderate to severe asthma exacerbations continue to pose treatment challenges in the emergency department, despite guideline-based therapies. Ketamine, known for its bronchodilatory and anti-inflammatory effects, presents a potential non-invasive adjunct when delivered via nebulization. While existing studies hint at its benefit, they are limited by small sample sizes and inconsistent methodologies. The KET-AIR trial aims to address this gap by evaluating the efficacy and safety of nebulized ketamine in a well-powered, randomized controlled trial, with the goal of improving patient outcomes and informing evidence-based emergency asthma care.

2.2 BACKGROUND

Asthma is a chronic, heterogeneous respiratory condition characterized by inflammation of the airways, leading to symptoms such as wheezing, shortness of breath, chest tightness, and coughing¹. These symptoms vary in frequency and severity and are often associated with expiratory airflow limitation. During an exacerbation, patients experience a worsening of these symptoms accompanied by a measurable decline in lung function¹. Exacerbations are classified based on severity into moderate, severe, life-threatening, and near-fatal categories. According to

the Scottish Intercollegiate Guidelines Network (SIGN), a moderate asthma exacerbation is defined by worsening respiratory symptoms with a peak expiratory flow (PEF) between 50% and 75% of the patient's best or predicted value, without features of severe asthma. A severe exacerbation is indicated by a PEF between 33% and 50%, a respiratory rate of 25 breaths per minute or more, a heart rate exceeding 110 beats per minute, and difficulty speaking in full sentences due to breathlessness².

In the emergency department (ED), the management of acute asthma exacerbations focuses on rapid relief of bronchospasm and reversal of airway inflammation. This involves administering supplemental oxygen to maintain oxygen saturation between 94% and 98%, repeated doses of nebulized beta-2 agonists such as salbutamol, often combined with ipratropium bromide, and systemic corticosteroids either orally (e.g., prednisolone) or intravenously (e.g., hydrocortisone)^{1,2}. For patients who do not respond to initial therapy, intravenous magnesium sulfate may be used for its bronchodilatory properties. If symptoms remain uncontrolled, escalation to advanced respiratory support, such as bilevel positive airway pressure (BiPAP) or mechanical ventilation, may be necessary^{1,2}. Continuous monitoring and frequent reassessment guide decisions regarding the intensity of care and disposition.

Measurement of PEF plays a vital role in assessing the severity of an asthma exacerbation and in monitoring treatment response^{1,2}. PEF and FEV₁ are both reliable indicators of airway caliber, but in acute settings, PEF is more practical due to its ease of use^{3,4}. Ideally, PEF should be interpreted as a percentage of the patient's best-known value⁵. If that is unavailable, reference to predicted values can offer a useful alternative. Consistent use of the same type of peak-flow meter is recommended to minimize variability in readings^{1,2}.

Ketamine has gained interest as a potential therapeutic adjunct in severe asthma exacerbations due to its unique pharmacological profile. It acts as a non-competitive antagonist at NMDA receptors, leading to bronchodilation by multiple mechanisms: it reduces bronchoconstriction, decreases nitric oxide production, and suppresses inflammatory cytokines by attenuating macrophage activity. Additionally, ketamine enhances endogenous catecholamine release and reduces cholinergic tone by lowering intracellular calcium levels in airway smooth muscle, further promoting bronchodilation^{6,7,8,9}. These properties make ketamine particularly useful in patients who are refractory to standard treatments.

Several clinical reviews and studies support ketamine's potential in this context. Goyal and Agrawal reviewed multiple reports involving 244 patients and found that ketamine improved clinical outcomes in the majority, often reducing the need for mechanical ventilation in cases of status asthmaticus⁷. However, the authors stressed the need for randomized controlled trials to better define its role. Epperson et al. also highlighted ketamine's bronchodilatory and anti-inflammatory benefits in severe asthma and emphasized the need for further evidence to confirm its routine clinical utility⁸. Ekong et al. compared nebulized ketamine with magnesium sulfate in managing status asthmaticus and found both agents improved respiratory parameters, but called for further standardization of dosing protocols and safety assessments⁹.

Esmailian et al. conducted a randomized trial administering intravenous ketamine at doses of 0.3 to 0.5 mg/kg and found significant improvements in PEF, particularly at the higher doses. The average PEF increased from 336.2 ± 101.5 L/min in the placebo group to 415.8 ± 76.2 L/min in the ketamine group, suggesting rapid efficacy without notable side effects¹⁰. A case report by Shlamovitz and Hawthorne showed that intravenous ketamine at a dissociative dose avoided the

need for intubation in a patient with a severe asthma crisis¹¹. Farshadfar et al. compared nebulized ketamine with intravenous magnesium sulfate in patients with corticosteroid-resistant asthma. PEFR improved by 29.4% in the ketamine group versus 15.2% in the magnesium group, although the difference was not statistically significant. Importantly, both treatments were well tolerated, suggesting a favorable safety profile¹².

Nebulized ketamine, in particular, presents a non-invasive and practical method for drug delivery in the ED setting. It maintains respiratory drive and provides therapeutic plasma concentrations with a bioavailability of 20–40%. The drug is rapidly absorbed, with a redistribution half-life of about 11 minutes and an elimination half-life of 2.5 hours^{13,14,15}. Although mild side effects like dizziness and increased secretions have been reported, serious adverse events are rare^{13,14}. Nguyen et al. conducted a randomized controlled trial comparing nebulized ketamine (0.75 mg/kg) to intravenous subdissociative ketamine (0.3 mg/kg) for pain control in the ED. Both routes showed similar efficacy in reducing pain scores with no significant side effects, suggesting that nebulization is a safe and effective alternative for short-term analgesia¹⁶. Dove et al. explored varying doses (0.75, 1, and 1.5 mg/kg) of nebulized ketamine and found comparable pain relief across all doses, with no significant increase in side effects at higher doses¹⁷. Ahuja et al. demonstrated that 50 mg of nebulized ketamine significantly reduced the incidence and severity of postoperative sore throat in patients undergoing general anesthesia, without causing sedation or psychomimetic effects¹⁸.

Given these findings, nebulized ketamine emerges as a viable adjunct in the treatment of acute asthma exacerbations, offering bronchodilation, anti-inflammatory effects, and a good safety profile. A dose of 0.5 mg/kg appears to be both effective and well-tolerated, particularly in the emergency setting where rapid, non-invasive interventions are critical. Nevertheless, current evidence is limited by small sample sizes and heterogeneity in study design. High-quality, adequately powered randomized controlled trials are needed to confirm these preliminary findings and establish standardized protocols for ketamine use in asthma care^{10,12,15-18}.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS²⁰

Ketamine Hydrochloride (Nebulized/Injection):

- **Cardiovascular Effects:** Transient elevations in blood pressure and heart rate; arrhythmias and cardiac decompensation have also been observed in susceptible individuals.
- **Neurologic Effects:** Emergence reactions (e.g., vivid dreams, hallucinations, confusion) in approximately 12% of patients.
- **Respiratory Effects:** Risk of respiratory depression, particularly with rapid or high-dose administration; laryngospasm and airway obstruction reported.
- **Gastrointestinal:** Nausea, vomiting, anorexia, and hepatobiliary dysfunction.
- **Urinary Tract Effects:** With recurrent use, lower urinary tract symptoms such as dysuria and hematuria have been reported.
- **Other Effects:** Increased salivation, diplopia, nystagmus, and injection site pain in parenteral use.

2.3.2 KNOWN POTENTIAL BENEFITS²⁰

- **Bronchodilation:** Ketamine has potent bronchodilatory properties, making it useful in severe asthma, especially in patients unresponsive to standard therapy.
- **Anti-inflammatory Effects:** NMDA antagonism contributes to reduced airway inflammation.
- **Maintenance of Respiratory Drive:** Unlike sedatives that cause respiratory depression, ketamine maintains airway reflexes and respiratory effort when used in subdissociative doses.
- **Rapid Onset:** The bronchodilatory effect is often noticeable within minutes of administration.
- **Non-invasive Delivery:** Nebulized ketamine avoids the risks of intravenous access and sedation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

- **Ethical Oversight:** The trial is conducted with full IRB approval and adheres to ethical standards that prioritize patient safety.
- **Informed Consent:** All participants receive comprehensive information about the risks and benefits before enrollment.
- **Close Monitoring:** Vital signs, PEFr, and potential side effects are closely monitored at predefined intervals.
- **Randomization and Blinding:** These procedures minimize bias and ensure fair comparisons between treatment groups.
- **Clinical Relevance:** Given the unmet need in patients unresponsive to first-line asthma therapy, the potential benefits of ketamine—in terms of improving respiratory outcomes—may outweigh its low incidence of adverse events when used appropriately.

3 Research Objectives and Hypothesis

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary	• Improvement in Peak Expiratory Flow Rate (PEFR) at 60 minutes post-intervention	PEFR is a validated and widely used measure of airflow limitation in acute asthma. The 60-minute mark was selected to capture the expected peak pharmacologic effect of nebulized ketamine.
Secondary	• Change in PEFR at 30 minutes • Incidence of adverse effects • Escalation of care (e.g., IV magnesium sulfate, ICU admission, intubation) • Disposition plan (discharged, admitted, or transferred) • Length of stay (if admitted) • Type of admission bed (e.g., ward vs. ICU)	These secondary endpoints offer a detailed assessment of clinical response, patient-centered outcomes, and healthcare resource use. Monitoring early PEFR response helps gauge onset of effect. Safety endpoints ensure risk profiling. Disposition planning, bed type, and length of stay capture real-world operational

	• Patient-reported symptom relief (Dyspnea Visual Analogue Scale - VAS)	implications. VAS adds patient-reported symptom data.
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Hypothesis:

Nebulized ketamine, when added to standard asthma care, will result in significantly greater improvement in PEFR at 60 minutes compared to standard care alone in adult patients with moderate to severe asthma exacerbations.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Statement of the Hypothesis:

Patients receiving nebulized ketamine in addition to standard asthma therapy will demonstrate a significantly greater improvement in peak expiratory flow rate (PEFR) at 60 minutes compared to those receiving standard therapy with placebo nebulization.

Type/Design of Trial:

This is a prospective, double-blinded, randomized controlled trial conducted at a single tertiary care emergency department.

Methods to Minimize Bias:

Several strategies will be employed to reduce bias and enhance the validity of the study results, including:

- Use of standardized treatment protocols for all participants
- Strict inclusion and exclusion criteria to ensure homogeneity
- Informed consent obtained ethically and in compliance with institutional guidelines
- Randomization to intervention and control arms
- Double blinding of participants, treating physicians, and outcome assessors
- Intention-to-treat analysis to account for all randomized patients

Number of Study Groups/Arms and Study Intervention Duration:

The study will consist of two groups:

Intervention group: Nebulized ketamine (0.5 mg/kg diluted in normal saline to a total volume of 5 mL)

Control group: Placebo nebulization (5 mL normal saline)

All patients will also receive standard asthma therapy. The primary assessment period is 60 minutes following intervention.

Single Site or Multi-Site:

This is a single-site study conducted at Sultan Qaboos University Hospital Emergency Department.

Name of Study Interventions:

Nebulized Ketamine versus Placebo, both given in addition to standard asthma management (inhaled salbutamol and ipratropium, systemic corticosteroids).

Interim Analysis:

An interim analysis is planned after 50% of the target sample size has been enrolled to assess both safety and preliminary efficacy of nebulized ketamine.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Reasoning for Control Group Selection and Study Design:

- **Control Group Selection:**

The control group will receive nebulized placebo (5 mL normal saline) following administration of standard asthma care, which includes inhaled salbutamol and ipratropium every 20 minutes for the first hour, along with systemic corticosteroids. This approach ensures that all patients receive the current best-practice management for moderate to severe asthma exacerbations, and the placebo allows for a fair and ethical comparison against the investigational treatment nebulized ketamine.

- **Study Design:**

This trial is designed as a double-blinded, randomized controlled trial (RCT), which is the gold standard for evaluating clinical interventions. Randomization reduces selection bias, and blinding of participants, physicians, and assessors minimizes detection and performance biases. Importantly, the study drug (nebulized ketamine or placebo) is administered *after* the full standard asthma treatment to isolate its additive effect. All clinical assessments including PEFR measurements, vital signs, and adverse effect monitoring will be conducted after administration of the study drug to accurately evaluate its impact.

Known or Potential Problems Associated with the Control Group Choice:

- **Generalizability:**

While the control group mirrors standard tertiary emergency department care, findings may have limited applicability in lower-resource or outpatient settings where such protocols are not standard.

- **Blinding:**

Although the trial is double-blinded, ketamine's potential side effects (e.g., dissociation or dizziness) could unintentionally reveal group allocation to patients or staff. Monitoring for this and minimizing suggestion or expectation bias will be critical.

- **Comparability:**
Ensuring that participants in both arms have comparable baseline PEFR, asthma severity, and clinical profiles is essential. Randomization will be strictly applied, and statistical adjustments may be used if necessary to address any baseline imbalances.

4.3 JUSTIFICATION FOR DOSE

Control Group Intervention: Placebo

- **Dose:** 5 mL of 0.9% normal saline
- **Maximum Dose:** Not applicable
- **Dilution:** Not applicable (administered as is)
- **Administration Route:** Nebulized via standard nebulizer device
- **Justification:** Normal saline serves as an inert placebo to allow blinding while maintaining equivalency in nebulized volume, ensuring that any observed effects can be attributed to ketamine.

Intervention Group: Nebulized Ketamine

- **Dose:** 0.5 mg/kg of ketamine hydrochloride
- **Maximum Dose:** Based on 0.5 mg/kg calculation (rounded to nearest measurable volume)
- **Dilution:** Diluted in 0.9% normal saline to a total volume of 5 mL
- **Administration Route:** Nebulized via standard nebulizer device over 10-20 minutes or until completion of medication
- **Justification:**

The selected dose of 0.5 mg/kg was chosen based on existing evidence demonstrating both efficacy and safety in emergency care settings. Nebulized ketamine achieves bioavailability of 20–40% and maintains respiratory drive—making it highly suitable for acute asthma management where sedation is undesirable.

Pharmacokinetically, ketamine offers rapid onset with a redistribution half-life of ~11 minutes and elimination half-life of ~2.5 hours, supporting its use in short-term, rapidly evolving clinical scenarios.

Multiple studies have explored the safety and analgesic efficacy of nebulized ketamine in doses ranging from 0.5 to 1.5 mg/kg, with no significant increase in adverse events at higher doses. Notably:

- Nguyen et al. found no difference in side effect profile between nebulized (0.75 mg/kg) and IV ketamine (0.3 mg/kg) in ED pain management¹⁶.
- Dove et al. demonstrated equivalent efficacy across nebulized doses of 0.75, 1, and 1.5 mg/kg without dose-dependent adverse reactions¹⁷.

- Ahuja et al. reported significant symptomatic benefit using 50 mg nebulized ketamine without sedation or psychomimetic effects¹⁸.

Given this, 0.5 mg/kg was selected as an effective and well-tolerated subdissociative dose appropriate for use in the emergency department. This dose balances clinical benefit, patient safety, and practicality, and aligns with preliminary findings while awaiting confirmation from larger-scale trials^{10,12,15-18}.

4.4 END OF STUDY DEFINITION

1. **Completion of Participant Monitoring and Data Collection:**

The study will be considered complete for each participant once the full assessment period is concluded—specifically, after 60 minutes of post-intervention monitoring. This includes recording of Peak Expiratory Flow Rate (PEFR), vital signs (heart rate, blood pressure, respiratory rate, SpO₂), and Visual Analogue Scale (VAS) scores at baseline, 30 minutes, and 60 minutes. All prescribed data points, including adverse event documentation and disposition outcomes, must be completed to consider a participant's involvement concluded.

2. **Safety Considerations:**

Participant safety is of primary importance. Should a participant experience a serious adverse event—such as respiratory failure, hemodynamic instability, or significant psychiatric effects—immediate clinical evaluation and potential withdrawal from the study will occur. The decision to continue the study as a whole will depend on the nature of the event, cumulative safety data, and input from the Data Safety Monitoring Board (DSMB) or ethical oversight committee. All such events will be formally reviewed to ensure ethical and clinical integrity.

5 STUDY POPULATION

5.1 Inclusion Criteria

Participants must meet **all** of the following criteria to be eligible for enrollment:

1. Adults aged 18 years or older presenting to the Emergency Department with a clinical diagnosis of moderate to severe asthma exacerbation based on SIGN (Scottish Intercollegiate Guidelines Network) criteria.
2. PEFR between 33% and 75% of predicted value or personal best, as measured using a peak flow meter.
3. Stable vital signs as deemed by the treating physician
4. Alert and oriented, able to understand the study purpose and provide informed consent.
5. Not requiring immediate advanced airway intervention, including intubation or emergency non-invasive ventilation.

5.2 Exclusion Criteria

Patients meeting **any** of the following will be excluded:

1. Known hypersensitivity or allergy to ketamine or any component of the nebulized solution.
2. History of psychosis, schizophrenia, or other severe uncontrolled psychiatric disorders.
3. Uncontrolled hypertension, defined as systolic BP > 180 mmHg or diastolic BP > 110 mmHg on two consecutive readings at least 5 minutes apart, despite initial ED management.
4. Hemodynamic instability, including persistent hypotension (SBP < 90 mmHg) or tachyarrhythmias requiring urgent treatment.
5. Significant chronic lung disease, including:
 - COPD with frequent exacerbations or baseline FEV₁ < 50% predicted
 - Interstitial lung disease (ILD)
 - Clinically significant bronchiectasis with baseline productive cough or infection
6. Pregnancy or currently breastfeeding.
7. Home BiPAP use or requirement for non-invasive ventilation (e.g., BiPAP/CPAP) during the ED visit (Note: isolated home CPAP for sleep apnea without daytime symptoms is acceptable).
8. Current intubation or imminent need for mechanical ventilation based on clinical judgment.
9. Severe cardiac disease, including decompensated heart failure, recent myocardial infarction (<6 weeks), or known severe valvular disease.
10. Any other medical, surgical, or psychiatric condition that in the opinion of the investigator would place the patient at undue risk from study participation or interfere with the interpretation of study results.

5.3 LIFESTYLE CONSIDERATIONS

No specific lifestyle restrictions apply. Eligibility must be confirmed by reviewing inclusion and exclusion criteria for each participant.

5.4 SCREEN FAILURES

Identification and Documentation

- Participants who do not meet the eligibility criteria during screening will be classified as screen failures.

Participant Support

- Appropriate clinical guidance or referrals will be provided if any medical issues are identified during screening that require follow-up.

Criteria for Re-screening

- Re-screening may be allowed under specific circumstances, such as:
 - Temporary clinical instability (e.g., fluctuating blood pressure or PEFr).
 - Correctable issues (e.g., reversible medication effects or transient contraindications).
- Any changes in eligibility status must be clearly documented before re-screening.

Re-screening Process

- Re-screening must follow the same standardized procedures as the initial assessment. All decisions must be guided by ethical considerations and prioritization of participant safety.

Data Handling

- Data from screen failures will be recorded and securely stored. If a participant is re-screened and enrolled, data will be integrated with care to maintain accuracy and transparency.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participant Recruitment Strategies:

- **Targeted Recruitment at Sultan Qaboos University Hospital (SQUH):**
 - Focus will be placed on adult patients presenting to the ED with moderate to severe asthma exacerbations who meet eligibility criteria.
- **Collaboration with ED Staff:**
 - Engage emergency physicians, respiratory therapists, and triage nurses to assist in identifying eligible participants.
 - Educate frontline staff on inclusion/exclusion criteria and study procedures.
- **Informational Materials:**
 - Develop accessible brochures, posters, and flyers summarizing the study purpose, eligibility, and consent process.
 - Materials will be displayed in high-traffic areas within the Emergency Department.

Participant Retention Strategies:

- Ensure patient comfort and clear communication during and after study procedures.
- Offer reassurance, regular updates, and availability of study staff for questions.

- Express appreciation for participation through verbal acknowledgment and follow-up contact if needed.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

- **Control Group:**
Participants will receive a placebo nebulization, consisting of 5 mL of 0.9% normal saline, administered after completion of standard asthma care.
- **Intervention Group:**
Participants will receive a single dose of nebulized ketamine at 0.5 mg/kg, diluted with normal saline to a total volume of 5 mL, administered after completion of standard asthma therapy

6.1.2 DOSING AND ADMINISTRATION

Control Group Drug Administration – Nebulized Normal Saline (Placebo):

1. Perform hand hygiene according to standard infection control protocols.
2. Put on clean gloves and verify the randomization allocation.
3. Prepare 5 mL of 0.9% normal saline in a sterile nebulizer chamber.
4. Connect the nebulizer to oxygen flow (6–8 L/min) and ensure mist generation.
5. Administer the placebo via face mask or mouthpiece, ensuring the patient is seated upright and breathing normally.
6. Observe the patient during and after nebulization for any adverse events.
7. After completion, dispose of used materials per hospital protocol and perform hand hygiene.

Intervention Group Drug Administration – Nebulized Ketamine:

1. Confirm **prescribed ketamine dose** at **0.5 mg/kg** based on actual body weight.
2. Using aseptic technique, draw the calculated ketamine dose (e.g., 50 mg from a 100 mg/mL vial = 0.5 mL for a 100 kg patient).
3. Dilute with 0.9% normal saline to a total of 5 mL in the nebulizer chamber.
4. Label the nebulizer cup according to blinded randomization code.

5. Connect the nebulizer to an oxygen source at 6–8 L/min and ensure fine mist generation.
6. Instruct the patient to sit upright and inhale deeply and evenly during nebulization (~15–20 minutes).
7. Monitor the patient for adverse reactions (e.g., dizziness, agitation, increased secretions).
8. Dispose of the nebulizer cup and any remaining drug safely. Remove gloves and perform hand hygiene.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Provision of Study Intervention and Control Product

- **Sourcing and Supply:**
A designated staff nurse will be responsible for sourcing and preparing the study intervention (nebulized ketamine) and control product (nebulized normal saline). These agents will be drawn from approved hospital stock and handled in accordance with institutional medication handling policies and manufacturer guidance.

Distribution of the Study Intervention

- **Role of Pharmacy or Drug Repository:**
The Emergency Department pharmacy unit at Sultan Qaboos University Hospital (SQUH) will oversee the storage, dispensing, and accountability of both ketamine and normal saline for this trial. Access will be limited to authorized personnel only.
- **Dispensing to Participants:**
Trained nurses or delegated study personnel will prepare and administer the intervention following protocol-specific blinding and dosing instructions. All drug preparation and administration steps will be documented, including lot numbers, dosing volume, and time of administration.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Control Group Drug: Nebulized Normal Saline (Placebo)

- **Formulation:** 0.9% sodium chloride solution for inhalation.
- **Appearance:** Clear, colorless, sterile solution.
- **Packaging:** Supplied in sealed ampoules or vials; each unit individually wrapped to maintain sterility.
- **Labeling:** Study-specific labeling includes the blinded group code, volume (5 mL), batch number, expiration date, and handling precautions.
- **Manufacturer:** Supplied by SQUH pharmacy using standard hospital saline sources.

Intervention Group Drug: Ketamine Hydrochloride for Nebulization

- **Formulation:** Ketamine Hydrochloride Injection USP (100 mg/mL), diluted to 0.5 mg/kg in 5 mL total volume with 0.9% normal saline.
- **Appearance:** Clear, colorless to slightly yellowish solution.
- **Packaging:** Vials containing 500 mg/5 mL or 500 mg/10 mL concentrations, in multi-dose format.
- **Labeling:** Original manufacturer label plus blinded trial label with dose, dilution instructions, patient code, batch number, expiration date, and warning: “*For investigational use only*”.

6.2.3 PRODUCT STORAGE AND STABILITY

Control Group Drug: Normal Saline (0.9%)

- **Storage Conditions:** Store at **controlled room temperature** (15°C to 30°C / 59°F to 86°F).
- **Stability:** Use immediately after opening. Discard unused contents according to hospital protocol.

Intervention Group Drug: Ketamine Hydrochloride

- **Storage Conditions:**
 - Store at **20°C to 25°C (68°F to 77°F)** with allowed excursions between 15°C and 30°C, per USP Controlled Room Temperature.
 - **Protect from light;** color may change slightly but this does not affect potency.
- **Handling:** Use aseptic technique during preparation. Must be used **immediately after dilution**.
- **Container Requirements:** Store in original vials or light-resistant containers.
- **Stability:** Do not use it if discolored or if particulate matter is visible. Do not freeze.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Study Population Identification:

Participants who meet all eligibility criteria and provide informed consent will be enrolled into the randomization pool for study allocation.

Sequence Generation:

An independent biostatistician will generate a computer-based randomization sequence using a random number generator. The statistician will remain blinded to all trial operations to preserve allocation integrity.

Block Randomization:

Participants will be randomized in a **1:1 ratio** to receive either:

- **Intervention group:** Nebulized ketamine at a dose of 0.5 mg/kg diluted in normal saline to a total volume of 5 mL, or
- **Control group:** Placebo nebulization with 5 mL of 0.9% normal saline. Block randomization with variable block sizes (e.g., 4 or 6) will be used to maintain balance and reduce predictability in group assignment.

Allocation Concealment:

The allocation sequence will be concealed from all study personnel involved in patient care, assessment, or analysis. A designated unblinded pharmacist or delegated nurse will be responsible for preparing and dispensing the study drug according to the randomization schedule.

Blinding:

This is a double-blinded study. The following parties will remain blinded to group assignment:

- Participants
- Treating physicians and nurses
- Outcome assessors
- Data entry personnel and statisticians

Both the intervention (ketamine 0.5 mg/kg diluted in normal saline to a total volume of 5 mL) and placebo (5 mL saline) will be identical in appearance, volume, and method of administration to preserve blinding. Study drug labels will include only the research ID, with no indication of group assignment. Any adverse events will be recorded carefully without compromising blinding.

Implementation:

- Site investigators will enroll participants after confirming eligibility and obtaining consent.
- Following enrollment, a designated unblinded staff member will assign the participant to a treatment arm and prepare the blinded medication.
- Nebulization will be administered after completion of standard asthma care, using a standard mask or mouthpiece.

Drug Prescription Protocol:

- A standardized study prescription form titled “**KET-AIR Trial**” will be used.
- Treating physicians will prescribe the intervention using this form, referencing only the research ID.
- The term “stat” will be used to indicate immediate administration following standard therapy.

Record Keeping:

- A confidential **randomization and drug accountability log** will be maintained by unblinded staff.

- The log will capture:
 - Participant research ID
 - Date and time of randomization
 - Assigned group
 - Dose, batch number, and preparer ID
- All records will comply with Good Clinical Practice (GCP) and institutional policies for audit readiness and data integrity.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of Study Intervention:

- The study intervention (either nebulized ketamine at 0.5 mg/kg in saline total volume of 5ml or 5 mL placebo saline) will be directly administered and observed by clinical staff following the completion of standard asthma care.
- The full nebulized dose must be delivered via standard nebulizer setup, with observation for tolerance and completion.

Use of Monitoring Devices:

- The hospital's electronic health record (EHR) system will be used to document vital signs, including PEFr, heart rate, respiratory rate, blood pressure, and oxygen saturation, at baseline, 30 minutes, and 60 minutes post-intervention.
- All values will be recorded to ensure accurate measurement of both efficacy (PEFR improvement) and safety (hemodynamic and respiratory stability).
- Visual Analog Scale (VAS) for dyspnea will also be recorded at each timepoint.

Mandatory Documents for Completion:

- All participants must provide signed informed consent before enrollment.
- Clinical staff will complete standardized documentation for study drug preparation and administration, including dose, time of administration, route, batch number, and any observed side effects.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICATION

- **Use of Rescue Medication:**
Rescue therapy is defined as any escalation of treatment beyond standard care and the assigned study drug, initiated at or after 60 minutes post-intervention due to lack of clinical improvement.
 - This includes the use of intravenous magnesium sulfate, non-invasive ventilation, ICU admission, or intubation.
- **Physician Discretion:**
The decision to initiate rescue therapy, including IV magnesium sulfate, will be at the

discretion of the attending emergency physician, based on the participant's clinical status and response to treatment.

- **Documentation:**

All rescue interventions must be clearly documented in the case report form, including time of administration, indication, and outcome.

6.6 EQUIPMENT SPECIFICATIONS AND HANDLING

6.6.1 Peak Expiratory Flow Measurement Device

Device Name and Manufacturer:

- Mini-Wright® Peak Flow Meter, manufactured by Clement Clarke International Ltd., United Kingdom.

Calibration and Certification:

- The Mini-Wright® peak flow meter is a mechanical, low-resistance device that comes pre-calibrated by the manufacturer.
- It complies with ISO 23747:2015 standards for peak expiratory flow measurement in clinical practice.
- Calibration will be checked regularly according to manufacturer recommendations, and devices will be replaced if found defective.

Measurement Range and Accuracy:

- Measurement range: 60 to 880 L/min
- Accuracy: $\pm 10\%$ or ± 20 L/min, whichever is greater
- Repeatability: $\pm 5\%$

Instructions for Use:

- **Patient Position:** The patient should be seated upright or standing during the measurement to ensure full lung expansion.
- **Procedure:**
 1. A new, single-use disposable mouthpiece must be attached for each patient to prevent cross-contamination.
 2. The participant is instructed to take a deep breath, seal their lips tightly around the mouthpiece, and exhale as hard and fast as possible into the device.
 3. The procedure is repeated three times. The highest of the three readings will be recorded as the patient's Peak Expiratory Flow Rate (PEFR).
 4. The mouthpiece will be disposed of after each patient use in accordance with hospital infection control policies.

Cleaning and Maintenance:

- The peak flow meter (excluding mouthpieces) will be cleaned with hospital-approved disinfectant wipes between uses and stored in a clean, dry area.
- Devices will be inspected weekly for wear or damage and replaced as necessary.

Standardization of Measurements:

- All measurements will be performed by trained study staff using standardized instructions and consistent technique.
- Readings will be performed at consistent time points: baseline (pre-intervention), 30 minutes, and 60 minutes post-intervention.
- The same model and brand of peak flow meter will be used throughout the study to reduce inter-device variability.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Criteria for Discontinuing Study Intervention:

- The study intervention (nebulized ketamine or placebo) will be discontinued immediately if the participant experiences serious adverse events, including but not limited to:
 - Severe agitation, hallucinations, or neuropsychiatric effects.
 - Hemodynamic instability, such as:
 - Heart rate > 140 bpm or < 50 bpm
 - Systolic BP < 90 mmHg or a drop of > 40 mmHg from baseline
 - Respiratory deterioration, including need for urgent intubation or oxygen saturation < 85% despite supplemental oxygen.
- If the treating physician determines that continuation of the intervention poses a clinical risk, administration will be stopped.
- Participants may voluntarily withdraw from the intervention at any point. Their choice will be fully respected and documented.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Criteria for Participant Discontinuation/Withdrawal:

- Participants may withdraw from the entire study at any time, for any reason, including discomfort, personal choice, or concerns about the study.
- Discontinuation will also occur if the participant develops:
 - Severe or intolerable adverse effects such as persistent dizziness, hallucinations, or significant elevation in blood pressure or intracranial pressure.
 - Worsening of underlying conditions (e.g., new diagnosis of pneumonia, decompensated heart failure, or psychiatric emergencies).
- Ethical concerns arising during the study (e.g., unanticipated risks) that jeopardize participant safety will lead to immediate review and possible withdrawal from the trial.
- The Withdrawal Case Log (Appendix IV, Section 12.4) must be completed for all discontinued participants, noting the reason and timing.

7.3 LOST TO FOLLOW-UP

- All participants will be monitored for 60 minutes post-intervention while in the ED.
- A follow-up call will be made at 48 hours post-discharge to assess clinical status and adverse events.
- If the participant is unreachable, follow-up will be attempted again at 72 hours and 7 days to ensure safety and document outcomes.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

- Data will be collected prospectively and include demographics, medical history, and baseline clinical parameters.
- Vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation) will be recorded at baseline (0 min), 30 min, and 60 min post-intervention.
- Peak Expiratory Flow Rate (PEFR) will be measured using a peak flow meter at baseline, 30 minutes, and 60 minutes to assess airway function improvement.
- Visual Analogue Scale (VAS) for dyspnea will be recorded at 0, 30, and 60 minutes.
- The primary efficacy outcome is the absolute change in PEFR at 60 minutes post-intervention.
- Secondary outcomes (PEFR at 30 min, VAS score change, and need for escalation of care) will also be documented.

8.2 SAFETY AND OTHER ASSESSMENTS

Screening Procedures:

- Review patient history to assess for contraindications to ketamine, including psychiatric illness, cardiovascular instability, or chronic respiratory failure.
- Evaluate current medications for potential interactions with ketamine.
- Perform a brief physical exam and mental status assessment to ensure patient stability.
- Measure baseline PEFr and vital signs to confirm eligibility.

Safety Monitoring During the Study:

- Participants will be monitored for 60 minutes post-intervention.
- Vital signs will be assessed at 0, 30, and 60 minutes.
- Clinical staff will assess for side effects such as hallucinations, agitation, dizziness, hypertension, increased secretions, or respiratory distress.

Intervention Administration:

- Either nebulized ketamine (0.5 mg/kg in NS total volume 5ml) or 5 mL of saline (placebo) will be administered after completion of standard asthma care.
- Nebulization will be directly observed by trained medical personnel.

Disposition Decision:

- Based on clinical response at 60 minutes, the treating team will determine if the patient can be safely discharged, requires further observation, or needs admission (ward or ICU).

Follow-up:

- Participants will receive follow-up calls at 24 and 48 hours post-intervention to monitor for adverse events and assess symptom resolution.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Definition of Adverse Events (AE):

Any unfavorable medical occurrence in a participant, whether or not considered related to the study intervention.

8.3.2 Definition of Serious Adverse Events (SAE):

An SAE includes any AE that results in:

- Death
- Life-threatening event
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly
- Any other medically significant event

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse Event Assessment:

- During the 60-minute ED observation period:
 - Monitor vital signs at baseline, 30, and 60 minutes.
 - Assess for any adverse reactions (e.g., agitation, hallucinations, increased secretions, hypertension, respiratory distress).
 - Document all AEs in the medical record and study-specific case report forms.

Post-ED Follow-up:

- Provide written instructions on identifying and reporting AEs.
- Participants will receive follow-up calls at 24 and 48 hours post-discharge.

8.3.5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

1. Immediate Assessment and Documentation:

- Record the date, time, severity, and clinical course of any AE or SAE.
- Update both the medical record and the AE/SAE log (Appendix II, Section 12.2).

2. Reporting to Principal Investigator (PI):

- SAEs must be reported within 24 hours of occurrence.
- Non-serious AEs should be reported within 48 hours to 7 days.

3. Patient Care and Follow-up:

- Ensure appropriate clinical management and monitoring of the patient.
- Continue to document the patient's recovery status or any ongoing issues.

8.4 UNANTICIPATED PROBLEMS

8.4.1 Definition of Unanticipated Problems (UP):

Any unexpected event that:

1. Differs in nature, severity, or frequency from what is described in the protocol.
2. Is possibly or definitely related to the research procedures.
3. Increases risk of harm to participants or others.

All UPs must be promptly reported to the PI and reviewed for potential impact on the study protocol or ethical approval.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The sample size for this study was determined using a two-sample t-test to compare the mean percentage change in peak expiratory flow rate (PEFR) between two groups: salbutamol alone vs. salbutamol + nebulized ketamine in adult patients with acute asthma exacerbations.

Minimal Clinically Important Difference (MCID) Selection

The Minimal Clinically Important Difference (MCID) for PEFR in acute asthma was set at 12%. This threshold aligns with prior studies that have assessed the effectiveness of bronchodilators in emergency asthma treatment and defined meaningful clinical improvements in airflow¹⁹.

Standard Deviation (SD) Estimation

To determine the SD of percentage change in PEFR, we reviewed previous randomized controlled trials (RCTs) that evaluated ketamine in acute asthma. The most relevant study, Esmailian et al. (2018), reported an absolute PEF increase of 111.3 ± 62.8 L/min in the ketamine-treated group, with a baseline PEF of 321 L/min¹⁰. From this, the SD of percentage change in PEFR was estimated as:

$$\begin{aligned} \text{SD}_{\% \text{change}} &= (\text{SD}_{\text{absolute change}} / \text{Baseline PEF}) \times 100 \\ &= (62.8 / 321) \times 100 \approx 19.6\% \end{aligned}$$

To ensure a conservative and reproducible calculation, we rounded this estimate to 20%, consistent with the variability observed in prior bronchodilator trials.

Sample Size Calculation

Using an MCID of 12%, an SD of 20%, and a Cohen's d effect size of:

$$d = \text{MCID} / \text{SD} = 12 / 20 = 0.6$$

we performed a power analysis for an independent two-sample t-test. Assuming:

- Two-tailed $\alpha = 0.05$ (5% significance level)
- Power = 80% ($\beta = 0.20$)
- Equal allocation between groups (1:1 ratio)

The required sample size per group was calculated using G*Power 3.1 and cross-validated with the Statsmodels package in Python. The estimated sample size per group was 45 patients, for a total of 90 patients.

Adjustment for Dropout

To account for potential dropouts and loss to follow-up, we plan to recruit an additional 10% of participants. Thus, the total planned sample size is 100 patients (50 per group).

9.2 STATISTICAL ANALYSES

9.2.1 GENERAL APPROACH

The general approach for analysis will involve a comprehensive assessment of both primary and secondary endpoints to evaluate the efficacy and safety of nebulized ketamine as an adjunct to standard care in the treatment of moderate to severe asthma exacerbations in the emergency department setting.

9.2.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is the absolute change in Peak Expiratory Flow Rate (PEFR) at 60 minutes post-intervention. This will be analyzed using:

- **Descriptive statistics:** mean, standard deviation, median, and interquartile range.
- **Inferential statistics:** Independent samples t-test or Mann-Whitney U test (if data is not normally distributed) to compare mean PEFR improvement between the ketamine and placebo groups.
- 95% confidence intervals will be calculated to estimate the precision of the effect size.

9.2.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints include:

- Change in PEFR at 30 minutes
- Improvement in Visual Analogue Scale (VAS) for dyspnea at 30 and 60 minutes
- Incidence of adverse events (e.g., dizziness, hallucinations, hypertension)
- Escalation of care: use of IV magnesium sulfate, ICU admission, intubation
- Disposition (discharge vs. admission), length of stay, and bed type

These will be analyzed using appropriate methods:

- **Categorical variables:** Chi-square or Fisher's exact test
- **Continuous variables:** t-tests or non-parametric equivalents
- **Logistic regression** may be used to adjust for potential confounders.

9.2.4 SAFETY ANALYSES

Safety endpoints will focus on the frequency and severity of adverse events post-intervention. Adverse events such as agitation, hallucinations, increased secretions, respiratory compromise, or cardiovascular instability will be tracked.

Comparisons between the ketamine and placebo groups will be conducted using:

- **Descriptive summaries**

- **Chi-square or Fisher's exact test** for categorical comparisons

9.2.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be presented for key baseline variables, including:

- Age, sex, weight, baseline PEFR
- Vital signs (HR, RR, BP, SpO₂)
- Comorbidities (e.g., history of asthma hospitalizations)

These summaries will ensure comparability between groups and contextualize outcome interpretation.

9.2.6 PLANNED INTERIM ANALYSES

An interim analysis will be conducted once **50% of the target sample size (n = 50)** is enrolled and followed up. The focus will be on:

- Assessing safety and early trends in efficacy
- Ensuring the trial does not pose undue risk to participants
Results will be reviewed by the Data and Safety Monitoring Board (DSMB) to determine if protocol modifications are warranted.

9.2.7 SUB-GROUP ANALYSES

Subgroup analyses may explore variations in treatment response by:

- Age (e.g., <40 vs ≥40 years)
- Gender
- Baseline asthma severity (PEFR 33–50% vs. 51–75%)

Interaction terms may be used to detect heterogeneity in treatment effects.

9.2.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual-level data will be tabulated, including:

- Demographics and baseline clinical values
- Serial PEFR and VAS measurements
- Intervention dose and timing
- Adverse events and escalation outcomes

These tables will support primary and secondary analyses and facilitate transparency.

9.2.9 EXPLORATORY ANALYSES

Exploratory analyses may be conducted to investigate:

- Time-to-clinical improvement

- Associations between initial response and final disposition
- Unexpected outcome trends or safety signals

These findings will inform future research directions and hypothesis generation.

9.2.10 MISSING DATA HANDLING

All randomized patients will be analyzed on an intention-to-treat basis. For missing primary outcome data (PEFR at 60 minutes), the last observation carried forward (LOCF) method will be used. Multiple imputation methods may be applied in sensitivity analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

Eligible participants will be identified by treating clinicians in the Emergency Department. Written informed consent will be obtained following a structured exchange of information using an IRB-approved Participant Information Sheet. Adequate time will be provided for participants to consider enrollment.

Consent will be obtained by trained site coordinators or research nurses, who will ensure that all patient questions are addressed prior to signing.

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

See **Appendix 12.5** for participant-facing materials.

10.1.2 Study Discontinuation and Closure

- Refer to Section 7.1 for criteria related to individual study intervention discontinuation.
- Study-wide closure may occur under the following conditions:
 1. Emergence of significant safety concerns
 2. Completion of all data collection per protocol
 3. Fulfillment of primary and secondary objectives
 4. Inadequate enrollment or lack of progress

10.1.3 Confidentiality and Privacy

Participant confidentiality will be strictly maintained. No personal identifiers will be disclosed to third parties without explicit written consent.

- Paper documents will be stored in a locked cabinet in the Emergency Department with access limited to study investigators.
- Electronic files will be secured using password-protected hospital or institutional computers.
- Data sharing will occur only via encrypted and password-protected platforms (e.g., secure Google Drive).
- No data will be transmitted via social media or unsecured communication platforms.
- Data will be retained for 3 years post-study and then securely deleted.

10.1.4 Quality Assurance and Quality Control

- Ethical approval will be obtained from the Sultan Qaboos University Hospital Review Board prior to study commencement.
- Required documents will be centrally maintained and include:
 - Investigator's Brochure
 - Signed Protocol
 - Informed Consent Form
 - Randomization Logs
 - Adverse Event Case Logs (Appendix II)
 - Protocol Deviation Logs (Appendix III)
 - Withdrawal Logs (Appendix IV)

Training of Staff (Physicians and Nurses):

- Informed consent procedures
- PEFr measurement using Mini-Wright device
- Timed data collection at 0, 30, and 60 minutes post-intervention
- Identification and documentation of side effects and adverse events

Routine Monitoring by PI Will Ensure:

- Informed consent forms are correctly and fully completed
- Participants meet all inclusion and exclusion criteria
- Randomization procedures are followed and blinding is preserved
- Protocol-specified assessments and drug administration are adhered to
- Source documents are accurate, timely, and complete
- All adverse events are recorded and reported appropriately

- Drug accountability and documentation are accurate
- Protocol deviations are identified and addressed
- Follow-up on any outstanding issues from previous visits
- Additional training is conducted as needed

10.1.5 Data Handling and Record Keeping

- Subject information will remain confidential and be accessed only with participant consent.
- Paper data will be stored in locked cabinets within the Emergency Department.
- Electronic data will be encrypted and password-protected.
- No data will be shared via social platforms like WhatsApp.
- Investigators may share de-identified data only via a secure Google Drive account.
- Data will be retained for three years following study completion and then permanently deleted.

10.1.6 Protocol Deviations

Definition:

Any departure from the approved study protocol or treatment plan.

Types of Deviations:

1. **Major Deviations** – May impact participant safety or study integrity
2. **Minor Deviations** – Less likely to have a significant impact

Steps in Reporting a Deviation:

1. **Assessment of Impact**
 - Document in the Subject Deviation/Unanticipated Problem Case Log (Appendix III)
2. **Notify the PI**
 - Report within 48 hours of identifying the deviation
3. **Corrective Measures**
 - Implement appropriate actions to resolve and prevent recurrence
4. **Study Record Documentation**
 - Log all deviations in official study logs
5. **Team Training**
 - Provide refresher training to study staff when appropriate

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12 APPENDICES

- **12.1 Appendix I:** Data Collection Sheet
- **12.2 Appendix II:** Serious Adverse Event (SAE) Case Log
- **12.3 Appendix III:** Deviation / Unanticipated Problem Case Log
- **12.4 Appendix IV:** Participant Withdrawal Form
- **12.5 Appendix V:** Informed Consent Form

AFFIX PATIENT STICKER HERE

KET-AIR Trial: Data Collection Sheet

Field	Information
Subject ID	
Date (DD/MM/YYYY)	
Medical Record Number (MRN)	
Age	
Gender	☐ Male ☐ Female
Weight (kg)	
Height (cm)	
Contact Number	

2. Eligibility Checklist****Inclusion Criteria: ****

- ☐ Age $\geq$ 18 years
- ☐ Clinical diagnosis of moderate to severe asthma exacerbation (SIGN criteria)
- ☐ PEF 33–75% of predicted/personal best
- ☐ Stable vitals
- ☐ Mentally competent and consents
- ☐ No need for immediate advanced airway

****Exclusion Criteria: ****

- ☐ Allergy to ketamine
- ☐ History of psychosis/schizophrenia
- ☐ Hemodynamic instability or uncontrolled hypertension (SBP >180 or DBP >110)
- ☐ ILD, bronchiectasis, or severe COPD ($FEV_1 < 50\%$)
- ☐ Pregnant or breastfeeding
- ☐ Requires BiPAP or is intubated
- ☐ Other contraindication to ketamine

12.1 Appendix I: Data Collection Sheet.

3. Serial Vital Signs Monitoring

Time	HR (bpm)	BP (mmHg)	RR (/min)	SpO ₂ (%)	Remarks
Baseline					
30 min					
60 min					

4. PEFR Measurement

Timepoint	PEFR (L/min)
Baseline (0 min)	
30 minutes	
60 minutes	

Measure 3 times per timepoint. Record the best value

5. Visual Analog Scale (VAS) for Dyspnea

(0 = No breathlessness, 10 = Worst imaginable)

Timepoint	VAS Score (0–10)
Baseline (0 min)	
30 minutes	
60 minutes	

6. Study Drug Administration

- Randomization Code: _____
- Allocation: ☐ Ketamine 0.5 mg/kg in 5 mL saline ☐ Placebo 5 mL saline
- Dose (mg): _____
- Time of Nebulization Start: ____:____
- Time of Clinical Improvement/Disposition: ____:____

12.1 Appendix I: Data Collection Sheet.

7. Adverse Events and Side Effects

☐ No adverse events observed

☐ Dizziness ☐ Nausea ☐ Hallucinations ☐ Agitation

☐ Increased secretions ☐ Tachycardia ☐ Hypertension ☐ Vomiting

☐ Other: -----

8. Escalation of Care

☐ No escalation required

☐ IV Magnesium Sulfate ☐ Non-invasive ventilation (BiPAP)

☐ ICU Admission ☐ Intubation ☐ Other: _____

9. Disposition Plan

☐ Discharged from Emergency Department

☐ Admitted to Hospital

****If admitted: ****

- Length of Stay (days): _____

- Type of Bed:

☐ General Medical Ward

☐ High Dependency Unit (HDU)

☐ Intensive Care Unit (ICU)

☐ Observation Unit

☐ Other: _____

10. Additional Notes / Observations

Adverse Event (AE) Case Log

AE Number	Adverse Event Description	SAE Classification (1–6)*	Event Start Date	Event End Date	Date Site Became Aware	Grade (1–5)**	Unexpected (Y/N)	Attribution (0–4)***	Outcome (0–4)****

If any of the serious adverse events criteria listed below observed (call hotline immediately)

SAE Classification	Grade	Attribution	Outcome	Description
1 – Fatal	1 – Mild	0 – Definite	0 – Fatal	Resulted in death
2 – Life-threatening occurrence	2 – Moderate	1 – Probable	1 – Not recovered/not resolved	Life-threatening occurrence
3 – Requires hospitalization	3 – Severe	2 – Possible	2 – Recovered with sequelae	Requires inpatient admission or prolongation of existing hospitalization
4 – Disability/incapacity	4 – Life-threatening	3 – Unlikely	3 – Recovered without sequelae	Results in persistent or significant disability/incapacity
5 – Congenital anomaly	5 – Death (Fatal)	4 – Unrelated	4 – Recovering/resolving	Results in a congenital anomaly or birth defect
6 – Medical risk (intervention)	—	—	—	Significant medical incident requiring intervention to prevent outcomes above

KET-AIR Trial: Subject Deviation/Unanticipated Problem Case Log

Principal Investigator: _____

IRB Number: _____ Protocol Number: _____

Subject ID #: _____

Short Protocol Title: KET-AIR Trial

#	Start Date	End Date	Description	Category	Impact Subject Safety* (Y/N/NA)	Affect Data Integrity* (Y/N/NA)	Affect Willingness to Participate* (Y/N/NA)	Reported to IRB (Y/N)

**If one or more is answered yes for any event, it must be reported to the IRB promptly (14 business days from notification of or becoming aware of the event).*

Category:

1. Consent Deviation
2. Drug/Device Administration/Accountability
3. Enrollment Deviation
4. Procedural Deviation
5. Loss of Confidentiality
6. Other (describe)

KET-AIR Trial: Subject Withdrawal Form

Subject ID: _____

Date: ____ / ____ / ____

Date Subject Went Off Study: ____ / ____ / ____

Reason for Withdrawal (Select One):

- ☐ Study activities completed
- ☐ Subject withdrawn – by Subject PRIOR to enrollment
- ☐ Subject withdrawn – by Subject AFTER enrollment
- ☐ Subject withdrawn – by PI PRIOR to enrollment
- ☐ Subject withdrawn – by PI AFTER enrollment
- ☐ Death
- ☐ Other (please specify): _____

Specific Reason(s) for Withdrawal (Select all that apply):

- ☐ Subject lost to follow-up
- ☐ Subject refused follow-up
- ☐ Due to adverse events or complications
- ☐ Other (please specify): _____

FORM COMPLETED BY: _____

Informed Consent Form

Comparing Nebulized Ketamine with Placebo in the Management of Moderate to Severe Asthma Exacerbations KET-AIR Trial

Introduction

We are a group of researchers at Sultan Qaboos University Hospital conducting a clinical study to explore the treatment of moderate to severe asthma exacerbations in adults. You are being invited to participate in this research. Before you decide, we will explain what the study involves. You are welcome to discuss this information with your family, friends, or anyone you trust before making a decision.

If at any point you do not understand something, feel free to ask questions or request clarification. You can also contact the study team later (contact details are provided below).

Purpose of the Research

Asthma is a chronic condition that sometimes flares up suddenly, causing shortness of breath, chest tightness, wheezing, and coughing. These exacerbations often require emergency care. Although most patients improve with standard treatments like inhaled bronchodilators and corticosteroids, some do not respond well. Ketamine is a medication that may help in such cases because it can relax the airway muscles and reduce inflammation.

Ketamine is usually given intravenously. However, in this study, we are investigating the effects of giving ketamine as a nebulized inhalation (breathing it in as a mist). This method is non-invasive, fast-acting, and easy to administer in the emergency department.

Type of Research Intervention

You will receive a single dose of either nebulized ketamine or a placebo (a harmless saltwater mist), in addition to standard asthma treatment. Neither you nor your doctor will know which treatment you are receiving. This is important to ensure the results of the study are unbiased.

Participant Selection

You are being invited to participate because you are an adult (18 years or older) presenting to the Emergency Department with moderate to severe asthma exacerbation. You meet the criteria required to take part in this study.

Voluntary Participation

Your participation in this study is entirely voluntary. You can choose not to participate or to withdraw from the study at any time. Your decision will not affect the quality of care you receive at this hospital.

Information About the Study Drug: Nebulized Ketamine

Ketamine is a well-known medication used for sedation, pain relief, and breathing support in emergencies. In this study, we are using a low dose of ketamine in the form of a nebulizer to see if it helps relieve symptoms of asthma exacerbation more quickly and effectively than standard treatment alone.

Studies in other emergency conditions have shown that nebulized ketamine can be safe and effective. All participants in the study will receive standard asthma care, and you may receive either nebulized ketamine or a placebo mist.

Procedures and Timeline

If you agree to participate, here is what will happen:

1. Your eligibility will be confirmed, and you will sign this consent form.
2. You will be randomly assigned to receive either nebulized ketamine or placebo.
3. You will continue to receive standard asthma treatment (salbutamol, ipratropium, corticosteroids).
4. Your breathing (measured as PEF – Peak Expiratory Flow Rate), symptoms, and vital signs will be recorded at baseline, 30 minutes, and 60 minutes.
5. After 60 minutes, your doctor will continue your treatment as needed.

Side Effects

Nebulized ketamine is considered safe, especially at low doses. However, some mild side effects may occur, such as:

- Dizziness or light-headedness
- Slight increase in heart rate or blood pressure
- Mild hallucinations or altered sensations
- Nausea

These effects are typically short-lived and resolve without treatment. Your doctor will monitor you closely and manage any side effects that arise.

Risks

Although rare, ketamine may cause side effects such as:

- Elevated blood pressure
- Increased salivation or airway secretions
- Anxiety or confusion
- Unpleasant dreams or restlessness

You will be carefully screened before enrollment to reduce these risks. If any complication arises during the study, it will be managed promptly and reported to the research ethics board.

Benefits

You may not directly benefit from participating. However, this study may help identify better ways to treat asthma in emergency settings, potentially benefiting other patients in the future.

Reimbursements

You will not be paid or receive any financial compensation for participating in this study.

Confidentiality

Your personal and medical information will be kept confidential. All study data will be anonymized using a unique code instead of your name. Only authorized researchers will have access to your information. No identifiable details will be published.

Sharing the Results

Once the study is complete, the results will be shared with the medical community through publications and presentations. You may request a summary of the results if you are interested.

Right to Refuse or Withdraw

Participation is voluntary. You may refuse to participate or withdraw at any point. This will not affect your access to treatment or the quality of care you receive.

Alternatives to Participation

If you choose not to participate, you will still receive all the standard treatments for asthma that are routinely offered in the Emergency Department.

Contact Information

If you have any questions or concerns at any time, please contact:

Dr. Almohanad Aljulandani

Phone: +968 93645233

Email: R24030@resident.omsb.org

Consent Statement

I have read (or have had read to me) the information provided above. I have had the opportunity to ask questions, and all my questions have been answered to my satisfaction. I understand that I can withdraw from the study at any time without affecting my care. I voluntarily agree to participate in this study.

Name of Participant: _____

Signature of Participant: _____

Date: ____ / ____ / ____

Appendix 12.5 Va: Informed Consent Form (English version)

Name of Physician: _____

Signature of Physician: _____

Date: ____ / ____ / _____