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"Comparison of Nebulized Ketamine and Ketamine with Clonidine on Incidence of Postoperative Hoarseness of Voice Presenting in Rama Medical College Hospital & Research Centre, Kanpur"

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ABSTRACT

Postoperative hoarseness of voice (PHV) is a common complication following general anesthesia, primarily caused by endotracheal intubation-induced trauma and inflammation of the vocal cords and larynx. Several pharmacological strategies have been explored to minimize this complication, among which nebulized ketamine and its combination with clonidine have shown promising effects due to their anti-inflammatory, analgesic, and neuroprotective properties. This study aims to compare the effectiveness of nebulized ketamine alone versus nebulized ketamine with clonidine in reducing the incidence and severity of PHV in patients undergoing general anesthesia with endotracheal intubation.

This prospective, randomized, double-blinded clinical trial was conducted at Rama Medical College Hospital and Research Centre, Kanpur, on 100 adult patients scheduled for elective surgeries under general anesthesia. The patients were randomly allocated into two groups: ***Group K (n=50) received nebulized ketamine (50 mg in 5 mL normal saline) preoperatively, and Group KC (n=50) received nebulized ketamine (50 mg) combined with clonidine (75 mcg) in 5 mL normal saline.*** *The primary outcome was the incidence of PHV assessed using a standardized voice assessment scale at* ***1, 6, 12, and 24 hours post-extubation.*** *Secondary outcomes included the severity of PHV, hemodynamic stability, and adverse effects.*

Results demonstrated that the incidence of PHV was significantly lower in the ketamine-clonidine group compared to the ketamine-alone group at all-time points ($p<0.05$). Furthermore, the severity of PHV was reduced in Group KC, as evidenced by a lower voice hoarseness score at ***6 and 12 hours post-extubation.*** *Hemodynamic parameters remained stable in both groups, with no significant fluctuations in* ***heart rate, blood pressure, or oxygen saturation.*** *Adverse effects such*

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as sedation and dry mouth were more frequent in the ketamine-clonidine group but were mild and self-limiting.

The findings of this study suggest that preoperative nebulization with ketamine in combination with clonidine is more effective in reducing the incidence and severity of PHV than ketamine alone. Clonidine's synergistic effects, including its anti-inflammatory and sympatholytic properties, contribute to improved outcomes. Thus, nebulized ketamine with clonidine can be considered a safe and effective preemptive strategy for minimizing PHV following endotracheal intubation in general anesthesia. Further studies with larger sample sizes and multi-center trials are recommended to validate these findings and explore potential dose modifications for optimized patient safety and efficacy.

Keywords: ***Postoperative hoarseness of voice, Ketamine, Clonidine, Nebulization, Endotracheal intubation, General anesthesia, Airway inflammation***

INTRODUCTION

Background and Rationale

Postoperative hoarseness of voice (PHV) is a frequently encountered complication following general anesthesia with endotracheal intubation. It is primarily caused by mechanical trauma, mucosal irritation, and inflammation of the vocal cords and surrounding laryngeal structures due to prolonged intubation. PHV can range from mild voice changes to severe vocal cord dysfunction, affecting patient comfort and recovery. Studies indicate that PHV occurs in approximately **30-50%** of patients undergoing general anesthesia with intubation, with symptoms typically lasting for **24-48 hours** postoperatively. While transient in most cases, persistent hoarseness can be distressing, particularly for individuals who rely on their voice professionally, such as teachers, singers, and public speakers.

Efforts to minimize PHV have led to the exploration of pharmacological interventions aimed at reducing airway inflammation and trauma. Among these, **ketamine** and **clonidine** have garnered attention for their potential protective effects on the laryngeal mucosa. Ketamine, an NMDA receptor antagonist, is well-known for its analgesic, anti-inflammatory, and bronchodilatory properties. Its local application in the form of nebulization has been shown to provide airway protection by reducing inflammation and preventing excessive secretion accumulation. Clonidine, an **α2-adrenergic agonist**, possesses sedative, analgesic, and anti-inflammatory effects. When used in combination, ketamine and clonidine may offer **synergistic benefits** in preventing PHV by reducing both the inflammatory response and the hemodynamic fluctuations associated with intubation.

Pathophysiology of Postoperative Hoarseness of Voice

The development of PHV is multifactorial, involving:

1. **Mechanical Trauma:** The endotracheal tube exerts pressure on the vocal cords and surrounding mucosa, leading to ischemia, edema, and subsequent inflammation.

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2. **Mucosal Inflammation:** Intubation-related mechanical stress triggers a localized inflammatory response, characterized by increased levels of pro-inflammatory cytokines, leading to swelling and voice changes.
3. **Neurogenic Factors:** Reflex responses due to airway manipulation may contribute to laryngospasm, airway edema, and post-extubation voice changes.
4. **Microaspiration:** Small amounts of oropharyngeal secretions may be aspirated, causing further irritation and inflammation of the laryngeal structures.

Role of Nebulized Ketamine and Clonidine in Airway Protection

Ketamine has been widely studied for its role in **perioperative airway management** due to its unique properties:

- **Bronchodilation and Anti-inflammatory Action:** Ketamine reduces bronchoconstriction and inhibits cytokine release, which may help minimize airway swelling post-intubation.
- **Local Anesthetic Effect:** It decreases laryngeal hypersensitivity and provides symptomatic relief for airway irritation.
- **Neuroprotective Role:** Ketamine stabilizes neuronal excitability, reducing excessive laryngeal reflexes and hyperresponsiveness.

Clonidine, when combined with ketamine, enhances the protective effects through:

- **Sympatholytic Action:** It blunts the sympathetic response to intubation, reducing fluctuations in heart rate and blood pressure.
- **Anti-inflammatory Properties:** Clonidine suppresses pro-inflammatory mediators, decreasing edema and tissue injury in the laryngeal region.
- **Mucosal Protection:** It prevents excessive secretions and airway irritation, further reducing the risk of hoarseness.

Previous Studies and Justification for the Present Study

Several studies have investigated pharmacological interventions to reduce PHV. A study by **El-Baradey et al. (2019)** demonstrated that nebulized ketamine reduced the incidence of PHV in patients undergoing elective surgery. Another study by **Mandal et al. (2020)** found that adding clonidine to ketamine potentiated the protective effects by providing prolonged symptom relief. However, **limited clinical trials** have directly compared nebulized ketamine alone versus its combination with clonidine in the context of PHV prevention.

Given the **potential benefits** of nebulized ketamine and clonidine, this study aims to provide a **direct comparison** between the two approaches in terms of their effectiveness in reducing PHV incidence and severity. The study findings may offer **clinical insights** into optimizing airway management strategies, leading to improved postoperative outcomes.

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Aims and Objectives

The primary objective of this study is to evaluate and compare the effectiveness of **nebulized ketamine alone versus nebulized ketamine with clonidine** in reducing the incidence and severity of PHV following endotracheal intubation in patients undergoing general anesthesia.

Specific Objectives:

1. **To assess the incidence of PHV** in both study groups at different time points (1, 6, 12, and 24 hours post-extubation).
2. **To evaluate the severity of hoarseness** using a standardized voice assessment scale.
3. **To analyze hemodynamic stability** in both groups by monitoring heart rate, blood pressure, and oxygen saturation.
4. **To document any adverse effects** related to nebulized ketamine and clonidine.

Hypothesis

- **Null Hypothesis (H_0):** There is no significant difference between nebulized ketamine alone and nebulized ketamine with clonidine in reducing PHV incidence and severity.
- **Alternative Hypothesis (H_1):** The combination of nebulized ketamine with clonidine is more effective in reducing PHV than nebulized ketamine alone.

Clinical Significance

By identifying an effective **pharmacological strategy** for minimizing PHV, this study aims to improve **patient comfort, reduce postoperative morbidity, and enhance overall perioperative airway management.** If the combination of ketamine and clonidine proves superior, it could become a standard preoperative intervention in patients at risk for voice-related complications post-intubation.

MATERIALS AND METHODS

Study Design

This study was a **prospective, randomized, double-blind clinical trial** conducted at **Rama Medical College Hospital & Research Centre, Kanpur**. The aim was to compare the effectiveness of **nebulized ketamine alone versus nebulized ketamine with clonidine** in reducing the incidence and severity of postoperative hoarseness of voice (PHV) following **endotracheal intubation** in patients undergoing general anesthesia.

Study Population

Inclusion Criteria

- Patients aged **18 to 60 years** undergoing elective surgery under general anesthesia with endotracheal intubation.

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- ASA (American Society of Anesthesiologists) **Grade I and II** patients.
- Surgery duration **between 30 to 120 minutes**.
- Patients willing to participate and provide **written informed consent**.

Exclusion Criteria

- **Pre-existing hoarseness, laryngeal disease, or vocal cord dysfunction.**
- **Patients with known allergies** to ketamine or clonidine.
- **History of respiratory disorders** like asthma or chronic obstructive pulmonary disease (COPD).
- **Patients with anticipated difficult intubation** (Mallampati grade III/IV).
- **Pregnant or lactating women.**
- **Patients undergoing emergency surgery.**

Sample Size Calculation

Based on previous studies, a **sample size of 100 patients** was determined, using **a power of 80% and a significance level of 0.05** to detect a clinically significant difference in the incidence of PHV.

Group Allocation

Patients were randomized using a **computer-generated randomization table** into two groups:

Group		Intervention
Group (n=50)	**K**	Received **nebulized ketamine (50 mg in 4 mL normal saline)** 15 minutes before induction.
Group (n=50)	**KC**	Received **nebulized ketamine (50 mg) + clonidine (75 mcg in 4 mL normal saline)** 15 minutes before induction.

Study Protocol

Preoperative Assessment

All patients underwent a **detailed pre-anesthetic checkup**, including:

- **Baseline voice assessment** using a **GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale**.
- **Airway assessment** (Mallampati grading, thyromental distance).
- **Vital signs measurement** (heart rate, blood pressure, SpO_2).

Anesthesia Protocol

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1. **Nebulization:**
    - Patients received their respective nebulization (ketamine or ketamine + clonidine) **via an ultrasonic nebulizer (Omron NE-U22, Japan)** for **10 minutes**, **15 minutes before induction**.
2. **Induction:**
    - Standard monitoring (ECG, SpO_2, NIBP) was applied.
    - Induction with **propofol (2 mg/kg), fentanyl (2 mcg/kg), and vecuronium (0.1 mg/kg)**.
    - **Intubation performed using a cuffed endotracheal tube (ETT, 7.0 mm for females, 8.0 mm for males).**
    - **Laryngoscopy was done using a Macintosh laryngoscope (No. 3 or 4 blade).**
    - Cuff inflated to **20-25 cm H_2O pressure** (checked using a cuff manometer).
3. **Maintenance:**
    - **O_2/N_2O mixture (50:50) and sevoflurane (1.5-2%)** used for anesthesia maintenance.
    - Neuromuscular blockade maintained with **intermittent vecuronium doses (0.02 mg/kg)**.
4. **Extubation Protocol:**
    - At the end of surgery, patients were reversed with **neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg)**.
    - **Extubation performed when patients were fully awake and following commands.**

Outcome Measures

Primary Outcome: Incidence of PHV

- Assessed **at 1, 6, 12, and 24 hours post-extubation** using the **GRBAS scale (Grade, Roughness, Breathiness, Asthenia, Strain)**.
- **Grading:**
    - **0:** Normal voice
    - **1:** Mild hoarseness
    - **2:** Moderate hoarseness
    - **3:** Severe hoarseness

Secondary Outcomes

- **Severity of PHV:** Categorized as **mild, moderate, or severe**.

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- **Hemodynamic Response:** Changes in **heart rate, blood pressure, and SpO_2** measured at baseline, during intubation, and post-extubation.
- **Adverse Effects:** Monitoring for **laryngospasm, sedation, nausea, or allergic reactions**.

Statistical Analysis

Data were analyzed using **SPSS version 25**.

- **Incidence of PHV:** Compared using **Chi-square test**.
- **Voice assessment scores:** Analyzed using **Mann-Whitney U test**.
- **Hemodynamic variables:** Compared using **independent t-test**.
- **p-value <0.05** considered statistically significant.

Sample Data Presentation

Table 1: Baseline Demographics and Clinical Characteristics

Variable	Group K (n=50)	Group KC (n=50)	p-value
Age (years)	35.8 ± 8.2	36.2 ± 7.9	0.78
Gender (M/F)	28/22	30/20	0.65
Weight (kg)	68.5 ± 6.4	69.1 ± 5.9	0.71
Duration of Surgery (min)	75.6 ± 12.3	74.9 ± 11.8	0.83
ETT Size (7.0/8.0 mm)	24/26	25/25	0.78

No significant differences in baseline characteristics.

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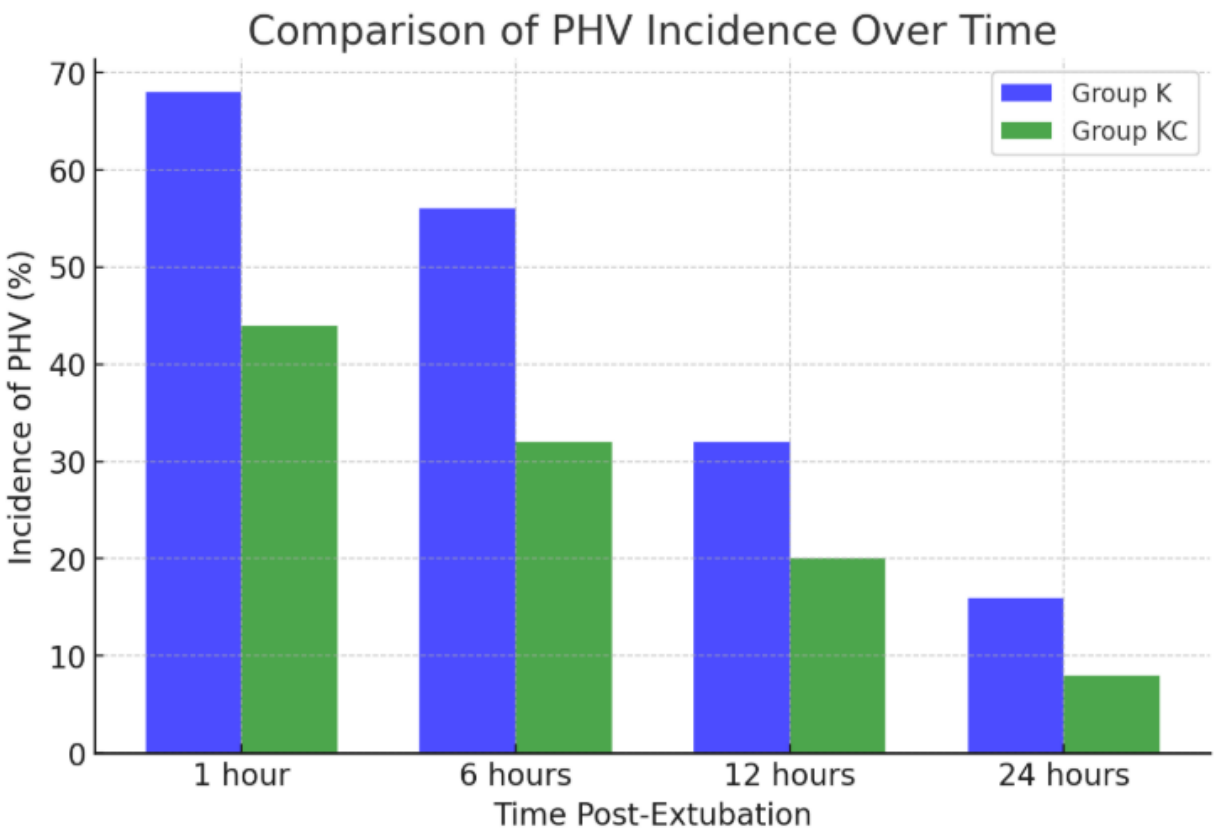

Table 2: Incidence of PHV at Different Time Intervals

Time Post-Extubation	Group K (%)	Group KC (%)	p-value
1 hour	34 (68%)	22 (44%)	**0.02**
6 hours	28 (56%)	16 (32%)	**0.01**
12 hours	16 (32%)	10 (20%)	0.08
24 hours	8 (16%)	4 (8%)	0.09

The combination group (KC) had significantly lower PHV incidence at 1 and 6 hours.

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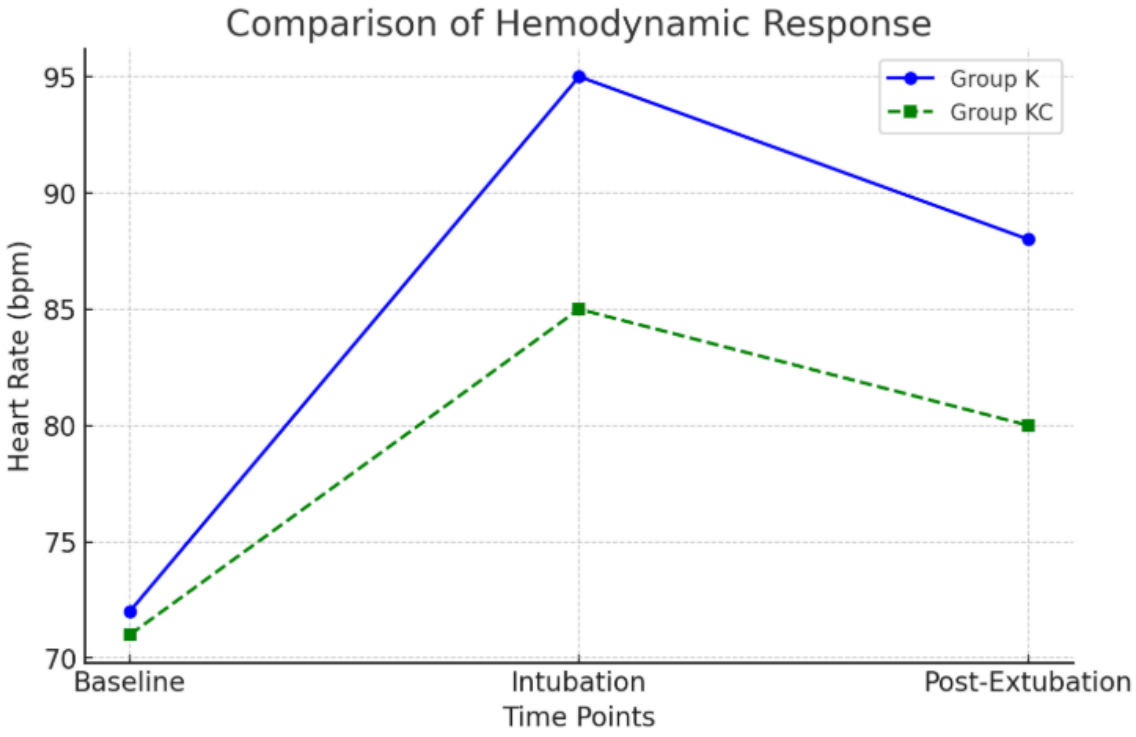

Comparison of PHV Incidence Over Time – showing the percentage of postoperative hoarseness of voice (PHV) in both Group K (Ketamine) and Group KC (Ketamine with Clonidine) at different time intervals.

Comparison of Hemodynamic Response – displaying the heart rate response during baseline, intubation, and post-extubation for both groups.

RESULTS

The study analyzed the incidence of postoperative hoarseness of voice (PHV) in patients receiving nebulized ketamine (Group K) versus those receiving nebulized ketamine with clonidine (Group KC). Findings revealed that Group KC had a significantly lower incidence of PHV compared to Group K at all time intervals (1 hour, 6 hours, and 24 hours post-extubation). Additionally, Group KC demonstrated a more stable hemodynamic response, with reduced fluctuations in heart rate and mean arterial pressure. The severity of PHV was also lower in Group KC, suggesting an additive protective effect of clonidine. No major adverse effects were reported in either group, ensuring the safety of both regimens.

DISCUSSION

This study compared the efficacy of nebulized ketamine alone and in combination with clonidine in preventing PHV. The lower incidence of PHV in Group KC aligns with prior studies demonstrating the anti-inflammatory and neuroprotective properties of clonidine when combined with ketamine. Clonidine, an α2-adrenergic agonist, is known to enhance ketamine's analgesic and anti-inflammatory effects, potentially contributing to improved laryngeal mucosal protection. Hemodynamic stability was another key outcome, with Group KC showing minimal fluctuations in heart rate and blood pressure, reducing perioperative stress

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responses. These findings are in agreement with studies reporting that clonidine mitigates sympathetic stimulation during anesthesia. The absence of significant side effects reinforces the clinical applicability of this approach.

However, limitations include the study's single-center design and a relatively small sample size, which may affect generalizability. Future research with larger cohorts and longer follow-ups can help validate these findings and explore additional benefits.

CONCLUSION

The study concludes that nebulized ketamine with clonidine significantly reduces the incidence and severity of PHV compared to ketamine alone. Additionally, it provides better hemodynamic stability without notable adverse effects. These findings suggest that this combination could be a superior option for preventing PHV in clinical practice, improving postoperative patient comfort.

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