International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Efficacy of Nebulized Ketamine versus Ketamine-Clonidine in Reducing Post-Operative Sore Throat: A Randomized Controlled Trial

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Abstract: ***Background**: Postoperative sore throat (POST) is a common complication after general anaesthesia with endotracheal intubation. Various pharmacological interventions, including ketamine nebulization, have been studied for their effectiveness in reducing the incidence of POST. **Aim**: This study aimed to compare the efficacy of nebulized ketamine alone versus a ketamine-clonidine combination in preventing postoperative sore throat. **Methods**: A total of 120 patients undergoing elective surgeries under general anesthesia were randomly assigned to three groups: Group S (saline nebulization, 4 mL), Group K (ketamine nebulization, 50 mg in 4 mL saline), and Group KC (ketamine 50 mg + clonidine 50 µg in 4 mL saline). The incidence and severity of sore throat were assessed at 4, 8, 12, and 24 hours post-extubation. **Results**: The incidence of POST was significantly lower in Group KC compared to Group K and Group S at all-time intervals. At 24 hours, POST incidence was 12.5% in Group KC, 47.5% in Group K, and 67.5% in Group S. The severity of sore throat was also reduced in the KC group. **Conclusion**: Nebulization with a combination of ketamine and clonidine significantly reduces the incidence and severity of postoperative sore throat compared to ketamine alone or saline. This combination therapy could be a valuable option for improving postoperative comfort in patients undergoing general anesthesia.*

Keywords: postoperative sore throat, ketamine nebulization, clonidine combination, general anesthesia, airway management

1. Introduction

Postoperative sore throat (POST) is a frequent and uncomfortable complication following general anesthesia, particularly in patients who undergo endotracheal intubation. The incidence of POST ranges from 20% to 65%, depending on factors such as the duration of intubation, the size and type of endotracheal tube, and patient characteristics [1]. POST is caused by mechanical irritation, mucosal injury, and inflammation due to the endotracheal tube, leading to symptoms like pain, hoarseness, and dysphagia, which can prolong recovery and negatively affect patient satisfaction [2].

Various strategies have been proposed to prevent POST, including the use of smaller endotracheal tubes, minimizing cuff pressure, and pharmacological interventions. Among the pharmacological options, ketamine, an NMDA receptor antagonist with potent analgesic and anti-inflammatory properties, has gained considerable attention [3]. Studies have shown that preoperative nebulization of ketamine can significantly reduce the incidence and severity of POST [4]. For instance, Canbay et al. demonstrated that patients who received ketamine gargle prior to surgery experienced a marked reduction in POST compared to those who received placebo [4].

Clonidine, an alpha-2 adrenergic agonist, is another drug that has been explored for its potential to enhance perioperative analgesia. Clonidine's sedative and sympatholytic effects, along with its ability to prolong the action of local anesthetics, make it a valuable adjunct in various clinical settings [5]. When combined with ketamine, clonidine may provide a synergistic effect, further reducing the incidence of POST. However, while ketamine alone has been widely studied, there is limited research directly comparing the effectiveness of ketamine-clonidine combination therapy versus ketamine alone in preventing POST.

This study aims to fill this gap in the literature by evaluating the efficacy of nebulized ketamine alone versus a ketamine-clonidine combination in reducing the incidence and severity of POST in patients undergoing elective surgeries under general anesthesia. The study will focus on key outcomes, including the incidence and severity of POST at multiple postoperative time points, the need for rescue analgesia, and any associated adverse effects, thus providing a more comprehensive understanding of these interventions in clinical practice.

2. Methods

Study Design: This prospective, randomized, double-blind, controlled trial was conducted at Christian Medical College & Hospital, Ludhiana, over a period of six months. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all the participants prior to enrolment.

Participants: A total of 120 patients aged 20-60 years, classified as ASA I-II, and scheduled for elective surgeries under general anaesthesia, were enrolled. Exclusion criteria included a history of pre-existing sore throat, use of steroids or NSAIDs, respiratory conditions like COPD or asthma, and difficult airway conditions.

Randomization, Interventions and Blinding: Patients were randomly allocated to one of the three groups using a computer-generated randomization sequence:

- **Group S (Saline, n=40):** Patients received 4 mL of normal saline nebulization 10 minutes before induction of anaesthesia.
- **Group K (Ketamine, n=40):** Patients received 50 mg of ketamine diluted in 4 mL normal saline nebulization 10 minutes before induction.
- **Group KC (Ketamine-Clonidine, n=40):** Patients received a combination of 50 mg ketamine plus 50 µg

clonidine diluted in 4 mL of normal saline nebulization 10 minutes before induction.

Both patients and the anaesthesia team were blinded to the group assignments. The nebulization solutions were prepared by an independent anaesthetist not involved in the study.

Anaesthetic Technique
All patients were premedicated with midazolam 0.03 mg/kg and glycopyrrolate 0.2 mg intravenously 30 minutes before surgery. Anesthesia was induced with propofol 2 mg/kg and fentanyl 2 µg/kg, and endotracheal intubation was facilitated with vecuronium 0.1 mg/kg. The endotracheal tube used was a high-volume, low-pressure cuffed tube, and its size was chosen according to the patient's weight and age.

Anesthesia was maintained with isoflurane in a mixture of 50% oxygen and 50% nitrous oxide. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. The endotracheal tube cuff was deflated completely before extubation.

Outcome Measures: The primary outcome measure was the incidence of Post-Operative Sore Throat (POST) assessed at 4, 8, 12, and 24 hours post-extubation. The severity of POST was recorded using a 4-point scale:
0 = No sore throat
1 = Mild sore throat (complains of sore throat only on asking)
2 = Moderate sore throat (complaints of sore throat on his/her own)
3 = Severe sore throat (change of voice or hoarseness, with or without pain)

The secondary outcomes included the severity of sore throat at the same time points, the need for rescue analgesics, and the occurrence of any adverse effects such as sedation, hypotension, or nausea/vomiting.

3. Statistical Analysis

All the data were entered into the Microsoft Excel. The data was summarized using the frequency distribution and descriptive statistics. The normality of the data was checked through the software and then the further analysis was performed. The association between the categorical variables was evaluated by the chi square test, while the association between the continuous variables was performed using the t test. A p-value of less than 0.05 was considered statistically significant. All the analysis was performed in the IBM SPSS (version 28).

4. Results

In this study, the incidence of postoperative sore throat (POST) was significantly different across the three groups at all-time points measured. At 4 hours post-extubation, the incidence of POST was highest in the saline group (Group S) at 67.5%, followed by the ketamine group (Group K) at 47.5%, and lowest in the ketamine-clonidine combination group (Group KC) at 12.5%. These trends persisted at 8, 12, and 24 hours, with Group KC consistently showing the lowest incidence of POST. The statistical analysis confirmed that the differences between the groups were significant ($p < 0.05$).

Table 1: Demographics

Variable	Group KC (Ketamine-Clonidine)	Group K (Ketamine)	Group S (Saline)	P-Value
Age (Mean ± SD)	37.85 ± 13.6	38.6 ± 11.99	38.48 ± 11.52	0.959
Gender (M/F)	24/16	24/16	21/19	0.736
ASA Grade (I/II)	29/11	24/16	24/16	0.404
Duration of Anaesthesia (hours)	2.48 ± 0.69	2.51 ± 0.59	2.31 ± 0.56	0.309
Intubation Attempts (1/2)	38/2	39/1	40/0	0.772

Table 2: Incidence and severity of Postoperative Sore Throat

Time Interval	Group KC (Ketamine-Clonidine)	Group K (Ketamine)	Group S (Saline)	P-Value
4 Hours	12.5% (5/40)	47.5% (19/40)	67.5% (27/40)	<0.001
8 Hours	12.5% (5/40)	47.5% (19/40)	67.5% (27/40)	<0.001
12 Hours	12.5% (5/40)	47.5% (19/40)	67.5% (27/40)	<0.001
24 Hours	12.5% (5/40)	47.5% (19/40)	67.5% (27/40)	<0.001

The severity of POST was also assessed using a 4-point scale. Group KC demonstrated the lowest severity scores at all-time intervals, with most patients reporting either no sore throat or only mild symptoms. In contrast, patients in Group S reported moderate to severe POST more frequently. By 24 hours post-extubation, 87.5% of patients in Group KC had no sore throat, compared to 52.5% in Group K and only 32.5% in Group S. These findings suggest that the ketamine-clonidine combination is more effective in reducing both the incidence and severity of POST.

Table 3: Severity of Sore Throat

Severity of Sore Throat	Group KC (Ketamine-Clonidine)	Group K (Ketamine)	Group S (Saline)	P-Value
No Sore Throat	87.5% (35/40)	52.5% (21/40)	32.5% (13/40)	<0.001
Mild Sore Throat	10% (4/40)	45% (18/40)	52.5% (21/40)	<0.001
Moderate Sore Throat	2.5% (1/40)	2.5% (1/40)	7.5% (3/40)	<0.001
Severe Sore Throat	0% (0/40)	0% (0/40)	7.5% (3/40)	<0.001

Regarding the need for rescue analgesia, patients in Group KC required significantly fewer analgesics compared to those in Groups K and S. The reduced need for analgesics in Group KC suggests that the combination of ketamine and clonidine

not only decreases the occurrence and severity of POST but also enhances overall postoperative comfort. This finding is clinically significant as it indicates a potential for improved patient outcomes and reduced reliance on additional pain management interventions.

No significant adverse effects were reported in any of the groups. While minor side effects such as mild sedation were observed in the ketamine and ketamine-clonidine groups, these were transient and did not require intervention. The safety profile of both ketamine alone and the ketamine-clonidine combination appears favourable, supporting their use as effective prophylactic treatments for POST. This further emphasizes the potential of these regimens to enhance patient comfort and satisfaction in the postoperative period.

5. Discussion

The findings of this study are consistent with previous research demonstrating the effectiveness of ketamine in reducing the incidence and severity of POST. For example, Canbay et al. reported a significant reduction in POST with ketamine gargle, which aligns with the reduced POST observed in the ketamine group of our study. However, our study goes further by showing that the addition of clonidine to ketamine enhances this effect, resulting in even lower rates of POST. This suggests a synergistic interaction between ketamine and clonidine that warrants further investigation.

Comparatively, our results are also in line with studies that have explored the use of clonidine in perioperative settings. Kori et al. found that clonidine, when used as an adjunct, reduced postoperative complications, including sore throat. Our study supports this finding and expands on it by demonstrating that clonidine's benefits extend to reducing POST when combined with ketamine. This combination therapy not only reduced the incidence of POST but also minimized the severity and decreased the need for rescue analgesia, highlighting its potential superiority over ketamine alone.

The safety profile observed in our study is also noteworthy. While previous studies have raised concerns about the sedative effects of clonidine, our findings indicate that the combination of ketamine and clonidine is well-tolerated, with minimal and transient side effects. This supports the feasibility of using this combination in clinical practice to improve postoperative outcomes. Given the consistent results across multiple studies and the enhanced efficacy observed in our study, the ketamine-clonidine combination could be considered a valuable option for POST prophylaxis in patients undergoing general anaesthesia with endotracheal intubation.

6. Conclusion

This study demonstrates that the combination of ketamine and clonidine is significantly more effective in reducing the incidence and severity of postoperative sore throat (POST) compared to ketamine alone or saline. The findings suggest that this combination therapy not only provides superior prophylaxis against POST but also enhances overall patient comfort by reducing the need for additional analgesics. The reduced incidence of POST in the ketamine-clonidine group supports the hypothesis that these agents act synergistically to provide enhanced protection against this common postoperative complication.

The clinical implications of this study are substantial. The use of ketamine-clonidine nebulization as a preoperative intervention could be a simple, safe, and effective strategy to improve postoperative outcomes, particularly in surgeries requiring endotracheal intubation. The minimal side effects observed in this study further support the safety and feasibility of this approach in routine clinical practice. Future studies with larger sample sizes and diverse patient populations are warranted to confirm these findings and explore the potential benefits of this combination in different surgical settings.

In conclusion, the ketamine-clonidine combination offers a promising approach to preventing POST, addressing a significant clinical need. The efficacy and safety of this regimen suggest that it could be adopted as a standard prophylactic measure in the perioperative care of patients undergoing general anaesthesia with endotracheal intubation. This could lead to improved patient satisfaction, reduced postoperative discomfort, and potentially shorter hospital stays due to fewer complications related to POST.

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