A Comparative Evaluation Of Nebulized Ketamine Versus Nebulized Magnesium Sulfate On The Incidence And Intensity Of Post-Operative Sore Throat In Patients Undergoing Controlled General Anaesthesia - A Prospective Randomised Comparative Double-Blind Study

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DOI:10.47750/pnr.2023.14.S01.97

Abstract

Background and Aims: Tracheal intubation is associated with a greater incidence of sore throat ranging from 5.8% to 34%. The prophylactic management of Post-Operative Sore Throat (POST) is recommended to improve the quality of post- anaesthesia care, though the symptoms resolve spontaneously without any treatment in most of the cases. The aim of the study is to compare the effect of nebulisation of ketamine with nebulisation of magnesium sulphate on the incidence and intensity of postoperative sore throat following oral endotracheal intubation in patient undergoing general anaesthesia.

Patient and Methods: A prospective comparative double-blind randomized study was conducted on 124 patients after inclusion and exclusion criteria. Patients were divided into two groups: Group K (n=62) included patients who received nebulized ketamine (0.5 mg/ kg body weight) made upto to 5ml in normal saline and Group M (n=62) includes patients who received MgSO4 (20 mg/ kg body weight) made upto to 5ml in normal saline. Incidence and severity of post-operative sore throat were assessed at 0, 2, 4, 12 and 24 hours post extubation. Result: The overall incidence of sore throat was significantly higher in group M (50%) as compared to group K (27.42%) (p value=0.01). At 0 hour, none of the patients in both the groups complained of sore throat and the severity was significantly more in Group M as compared to Group K at 2,4 and 12hours (p value<0.05).

Conclusion: It can be concluded that ketamine nebulization significantly reduced severity and incidence of post-operative sore throat compared to magnesium sulfate nebulization after oral endotracheal intubation in patients undergoing general anesthesia.

INTRODUCTION:

Tracheal intubation is a commonly used technique in general anesthesia, but it can cause a few side effects, including sore throat and hoarseness. These symptoms, known as postoperative sore throat (POST), are relatively common, with reported incidence rates ranging from 5.8% to 34%. Although POST is generally a minor side effect that resolves on its own, it can cause significant patient dissatisfaction and prolong hospital stays. To improve the quality of post-anesthesia care, prophylactic measures to reduce the incidence and severity of POST are recommended. Magnesium and ketamine, both of which are NMDA receptor antagonists, have been used to reduce POST due to their anti-nociceptive and anti-inflammatory effects.[1,2] Although POST is a minor side effect and is self-limiting, it causes a great deal of patient dissatisfaction. So prophylactic management of POST is recommended to improve the quality of post-anaesthesia care, though the symptoms resolve spontaneously without any treatment in most of the cases.[1,3] Numerous pharmacological measures have been used for attenuating POST like the use of beclomethasone gel, gargling with azulene sulfonate, magnesium sulphate gargle, ketamine gargle, ketamine nebulization, magnesium sulphate nebulization, lidocaine spray, smaller size endotracheal tubes, minimizing cuff pressure to <20 cm of H_2O, and minimizing laryngoscopy attempts.[4,5] Magnesium and Ketamine are both N- methyl- D- aspartate (NMDA) receptor antagonists and have been used in the form of nebulization and gargle for reducing the incidence and severity of POST due to their anti-nociceptive and anti-inflammatory effects.[6,7] Nebulization has a few advantages over gargling: It spares the patient

from the bitter taste of the drug; much smaller volume is required as opposed to larger volumes required for gargling; hence better patient cooperation is likely.[8] The rationale of this study was to evaluate and compare the effect of nebulized ketamine with magnesium sulphate on the attenuation of POST, in patients undergoing surgeries under general anaesthesia with tracheal intubation.

METHOD

This Study was a Prospective and Interventional Randomized Controlled Comparative Double Blinded Study conducted after obtaining approval from ethical committee of institution (IEC/ECC-51/2020 dated on January 24, 2020); It was conducted in accordance with the declaration of Helinski. After written informed consent, 124 patients with American Society of Anesthesiologists(ASA) physical status I & II of both gender between the ages of 18-60 years, Mallampati grade 1 & 2 and surgery done under general anaesthesia with endotracheal intubation with duration greater than 1 hr and less than 3 hours and do not have any exclusion criteria such as patients with history of pre-operative sore throat / recent upper airwayinfection/bronchial asthma, history of allergies to study drug, who was already on inflammatory mediators, predictors of difficult laryngoscopy intubation and patients requiring ryle's tube were recruited for the study.
Patients were divided into 2 groups- Group K and M after computerized randomization.
Group M: Patients in this group received MgSO4 nebulisation 20 mg/ kg body weight made upto to 5ml in normal saline.
Group K: Patients in this group received Ketamine nebulisation 0.5 mg/ kg body weightmade upto to 5ml in normal saline.
In order to maintain double blind nature of the study, the study drug was prepared byanesthesiologist (not involved in the study) as per instructions in a sealed envelope. Procedure of nebulization was explained to the patient. Patients were shifted to the operation theatre on the day of the procedure, and 18G intravenous line and non-invasive standard monitoring were ensured before the procedure.

All patients nebulized with the study drug with a wall-mounted oxygen source at 10 L/min (50 psi pressure) for 15 minutes (Nebulizer manufacturer: Solitaire Canomed Corporation, Philippines). After nebulizing, patients were induced with midazolam 0.02 mg/kg IV, fentanyl 2 μg/kg IV, and propofol 2 mg/kg IV after preoxygenation with 100% oxygen for 3 min with face mask. Vecuronium 0.1 mg/kg IV was used as muscle relaxant. Portex polyvinyl chloride endotracheal tubes of size 8.0–8.5 mm ID was used for male patients and 7.0–7.5 mm ID for female patients. The tracheal cuff was inflated with air, and cuff pressure was maintained at 20-30 cm H2O by Portex cuff inflator (manufacturer: Smiths Medical International Ltd., UK). The duration of laryngoscopy and time taken to intubate was noted. More than one attempt for intubation, those taken more than 30 seconds and any traumatic intubation were excluded from the study. After confirmation of tracheal tube position, GA was maintained with 50% oxygen in 50% nitrous oxide, sevoflurane 1%–2%. At the completion of surgery, with the patient adequately anesthetized, the posterior pharynx was gently suctioned, and the sevoflurane and N2O turned off. Inspiratory oxygen concentration was increased to 100%. The neuromuscular block was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg. Patients were extubated when they were breathing spontaneously and obeying commands. As a rescue measure IV lignocaine 1.5 mg/kg was administered, if the patient has excessive bucking during extubation, and patient was excluded from the study.
After extubation, the incidence and severity of POST was assessed. Patient complaint of sore throat was recorded at baseline (0 hours) immediately after shifting the patient to recovery room and then at 2,4,12 and 24 hours after operation. All those variables were measured using positive or negative (yes/no) questions and were graded on a 4-point scale (0-3). If the scores were equal or greater than 3 at any time, Inj.Paracetamol 15mg/Kg I.V was administered.

Post-operative sore throat will be graded as: -

Grade	Severity
0	No sore throat
1	Minimal - Patient answered in the affirmative when asked about sore throat
2	Moderate - Patient complained of sore throat on his/her own
3	Severe – The patient is in obvious distress

Table 1- Grading of Post-operative sore throat (POST)[9]

STATISTICAL ANALYSIS

In reference with the previous study, the minimum required sample size with 80% power of study and 5% level of significance is 55 patients in each study group. So total sample size taken is 110 (55 patients per group). Taking to lost to follow up as 10%, sample size to be taken was 62 per group, so total sample size taken is 124 (62 per group).
The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and asmedian with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the results:

1. The comparison of the variables which were quantitative in nature were analysed using Independent t test.
2. The comparison of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was donewith the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).
For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS

The Study was successfully conducted with 124 patients, allocated to one of the two study groups (Group M and K) after computerized randomization and there were no excluded cases. Demographic details are in Table 2.

Table 2: -Comparison of demographic characteristics between group M and K.

Demographic Characteristics	Group M(n=62)	Group K(n=62)	Total	P value
Age				
Mean ± SD	40.87 ± 11.32	40.71 ± 11.51	40.79 ± 11.37	0.937*
Median(25th-75th percentile)	40(32.25-50)	39.5(31-50.25)	40(32-50)	
Range	20-60	20-60	20-60	
Gender				
Female	32 (51.61%)	35 (56.45%)	67 (54.03%)	0.589‡
Male	30 (48.39%)	27 (43.55%)	57 (45.97%)	
Body mass index(kg/m²)				
Mean ± SD	24.67 ± 2.21	24.17 ± 2.52	24.42 ± 2.37	0.245*
Median(25th-75th percentile)	24.43(23.142-25.868)	24.34(22.702-25.48)	24.38(23.108-25.542)	
Range	18.02-28.89	18.02-32.03	18.02-32.03	
ASA grade				
1	40 (64.52%)	47 (75.81%)	87 (70.16%)	0.169‡
2	22 (35.48%)	15 (24.19%)	37 (29.84%)	

* Independent t test, † Fisher's exact test, ‡ Chi square test

Table 3:-Comparison of incidence of sore throat between group M and K.

Incidence of sore throat	Group M(n=62)	Group K(n=62)	Total	P value
At 0 hour	0 (0%)	0 (0%)	0 (0%)	No p value
At 2 hours	13 (20.97%)	4 (6.45%)	17 (13.71%)	0.034†
At 4 hours	16 (25.81%)	6 (9.68%)	22 (17.74%)	0.019‡
At 12 hours	16 (25.81%)	7 (11.29%)	23 (18.55%)	0.038‡
At 24 hours	0 (0%)	0 (0%)	0 (0%)	No p value

† Fisher's exact test, ‡ Chi square test

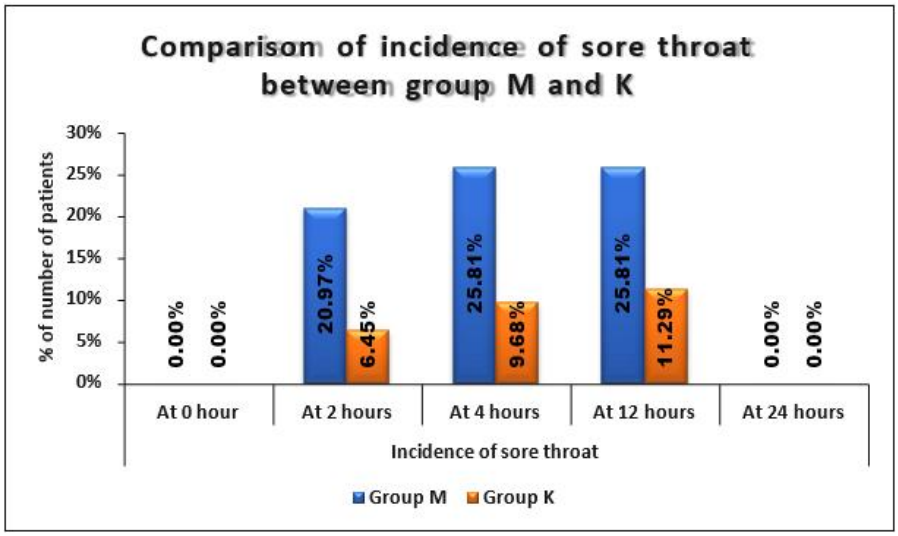

Figure 1:-Comparison of incidence of sore throat between group M and K.

Incidence of sore throat at 0 hour in group K was nil and in group M was nil. The proportion of sore throat at 2, 4, 12 and 24 hours was significantly higher in group M as compared to group K. (At 2 hours:- 20.97% vs 6.45% respectively (p value=0.034), At 4 hours:- 25.81% vs 9.68% respectively (p value:- 0.019) At 12 hours:- 25.81% vs 11.29% respectively (p value:- 0.038) and no incidence at 24hours in both the group.

It is shown in table 3, figure 1.

Table 4: - Comparison of overall incidence of sore throat between group M and K.

Overall incidence of sore throat	Group M(n=62)	Group K(n=62)	Total	P value
No sore throat	31 (50%)	45 (72.58%)	76 (61.29%)	0.01‡
Sore throat	31 (50%)	17 (27.42%)	48 (38.71%)	
Total	62 (100%)	62 (100%)	124 (100%)	

‡ **Chi square test**

The proportion of patients with incidence of Sore throat was significantly higher in M ascompared to K. (50% vs 27.42% respectively) (p value=0.01)
It is shown in table 4.

Table 5:-Comparison of sore throat grading between group M and K.

Sore throat Grading	Group M(n=62)	Group K(n=62)	Total	P value
At 0 hour				
No sore throat	62 (100%)	62 (100%)	124 (100%)	-
At 2 hours				
No sore throat	49 (79.03%)	58 (93.55%)	107 (86.29%)	0.029†
Minimal	10 (16.13%)	4 (6.45%)	14 (11.29%)	
Moderate	3 (4.84%)	0 (0%)	3 (2.42%)	
At 4 hours				
No sore throat	46 (74.19%)	56 (90.32%)	102 (82.26%)	0.067†
Minimal	12 (19.35%)	5 (8.06%)	17 (13.71%)	
Moderate	4 (6.45%)	1 (1.61%)	5 (4.03%)	
At 12 hours				
No sore throat	46 (74.19%)	55 (88.71%)	101 (81.45%)	0.107†
Minimal	13 (20.97%)	5 (8.06%)	18 (14.52%)	
Moderate	3 (4.84%)	2 (3.23%)	5 (4.03%)	
At 24 hours				
No sore throat	62 (100%)	62 (100%)	124 (100%)	-

† **Fisher's exact test**

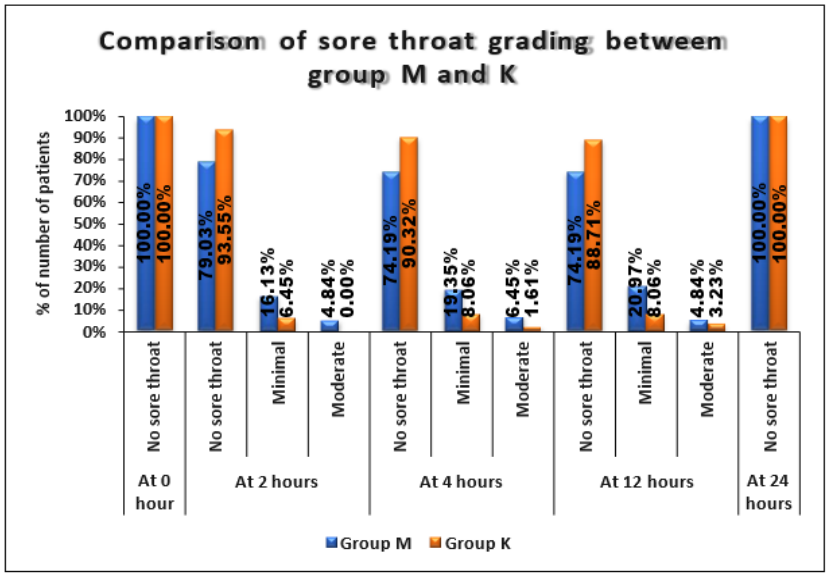

Figure 2:-Comparison of sore throat grading between group M and K.

Statistically significant difference was seen in the distribution of sore throat grading at 2hour 4 hours between group K and M. (p value<.05). Non-significance was seen in the distribution of sore throat grading at 12 hours between group K and M. (p value>.05)
At 0 hour and 24 hour, no patients had sore throat.(Table 5, Figure 2)

DISCUSSION

Airway instrumentation is a required component of general anaesthesia. Postoperative sore throat (POST) may be

perceived as a minor side effect of airway instrumentation; however, for most patients, it can be a disconcerting focal point that can detract from an otherwise positive surgical experience.
When compared to MgSO4 nebulization, Ketamine nebulization 15 minutes prior to induction of general anaesthesia significantly reduced the incidence and severity of POST at 2, 4, and 12 hours. Because 17/62 patients in the Ketamine group and 31/62 patients in the MgSO4 group had varying degrees of sore throat, it can be concluded that neither drug is completely effective in preventing POST.
Other studies, such as Segaran et al[9], support our findings where the incidence and severity of sore throat was significantly lower in Group B (Ketamine) as compared to that in Group A (MgSO4) at different intervals (4 hour, 6 hours) ($p < 0.05$). Similarly, Rajan S et al[10] concluded that nebulization with ketamine and magnesium sulfate, 15 min before the intubation, effectively reduces the incidence, and severity of POST and postoperative hoarseness of voice. And found out that statistically ketamine is more effective than MgSO4 in reduced the incidence of POST at 0, 2, and 4 hours.

Interestingly, at an individual level, as compared to controls, both ketamine nebulization and MgSO4 have shown decreased POST. For Example, Jain et al[11] found that incidence of sorethroat after nebulization of ketamine is 22% which is significantly less as compared to MgSo4 30% and Normal saline, which is 60%. It was observed in the study that there was a significant reduction in POST overall incidence and attenuation at 2 hrs and 4 hrs in post- operative period on nebulisation with ketamine and MgSO4 in comparison to Normal saline.

Interestingly, at an individual level, as compared to controls, both ketamine nebulization and MgSO4 have shown decreased POST. For Example, Ahuja V et al[8], Aditya AK et al[12] reported that ketamine nebulization decreases the incidence of POST following endotracheal intubation, but on increasing the ketamine dose, increased incidences of ketamine adverse effects were reported.

Similarly, Borazan H[13], Yadhav M et al[14], Gupta SK et al[15] found MgSO4 to be better in reducing POST. Considering together, it appears that both ketamine as well as magnesium sulphate act via local mechanisms and magnesium seems to be more effective as compared toketamine in reducing POST.
The proposed mechanism of POST could be attributed to the two drugs' different receptor effects:
1) Ketamine relaxes the tracheal muscle through a mechanism that is not dependent on NMDA receptors. Furthermore, the reduced Broncho motor tone caused by ketamine may be due to its interference with Calcium ions, which are required for contraction maintenance. Magnesium, on the other hand, may effectively block calcium entry into the tracheal muscle. After total intravenous anaesthesia with ketamine, there is sore throat and hoarseness, implying that the systemic effect is not significant in decreasing POST. [16]
2) MgSO4's anti-inflammatory and anti-nociceptive effect is thought to be due to a decrease in the release of inflammatory mediators such as leukotrienes, thromboxanes, and histamine. The effect of MgSO4 is due to direct contact of $Mg2+$ with the pharyngeal wall, whereas ketamine, along with its NMDA receptor antagonism, induces profound anti-nociceptive and anti-inflammatory action by acting on pharyngeal peripheral NMDA receptors. [11]
Yadav et al[14] and Blitz et al[17] reported no significant systemic effects of nebulized magnesium sulfate and explain that due to very low dose they used, in the form of nebulization and systemic absorption of which is 10% compared to the doses used in pre-eclampsia and eclampsia and this agreed with the current study as the same dose was investigated.

LIMITATIONS OF THE STUDY

These statements highlight several limitations of the study. Specifically, the scope of the study is limited to only one dose of the drug, and no control group was included. Additionally, the study did not measure the serum levels of magnesium and ketamine to monitor drug levels, and it was conducted at a single center, which limits the generalizability of the results. Finally, a cost-benefit analysis was not done. These limitations should be considered when interpreting the results of the study.

CONCLUSION

This study aimed to compare the effect of nebulizing ketamine and magnesium sulfate on the incidence and intensity of postoperative sore throat following oral endotracheal intubation in patients undergoing general anesthesia. The study was a prospective, comparative, double-blind, randomized study involving 124 patients. Patients were divided into two groups, one receiving nebulized ketamine and the other receiving nebulized magnesium sulfate. The results showed that the overall incidence of sore throat was significantly higher in the magnesium sulfate group (50%) compared to the ketamine group (27.42%). Additionally, the severity of sore throat was significantly higher in the magnesium sulfate group at 2, 4, and 12 hours post-extubation. The study concluded that nebulizing ketamine significantly reduced the severity and incidence of postoperative sore throat compared to nebulizing magnesium sulfate after oral endotracheal intubation in patients undergoing general anesthesia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Patient consent -Yes.

Ethical committee approval – yes

RS has done the data collection, concept, BS and VA have done the design and analyses, SPS has done the manuscript and communication.

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