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NEBULIZED MAGNESIUM VERSUS KETAMINE FOR PREVENTION OF POST-OPERATIVE SORE THROAT IN PATIENTS FOR GENERAL ANAESTHESIA

M.O. Orji[1], B.B. Osinaike[1], S.D. Amanor-Boadu[1], and A. Ugheoke[2]

1. Department of Anaesthesia, College of Medicine, University of Ibadan, Ibadan, Nigeria.
2. Department of Anaesthesia, University College Hospital, Ibadan, Nigeria.

Correspondence:
Dr. M.O. Orji
Department of Anaesthesia,
College of Medicine,
University of Ibadan,
Ibadan, Nigeria
E-mail: drmat02@yahoo.com

ABSTRACT

Background: **Sore throat is a common post-operative complaint which can cause significant distress and morbidity. We tested and compared the efficacy of nebulized Magnesium and Ketamine on the incidence and severity of sore throat within the first 24 hours after general anaesthesia.**

Objective: **To compare the incidence and severity of post-operative sore throat at 2, 4, 8, 12 and 24 hours after extubation following pre-induction administration of nebulized Magnesium and Ketamine.**

Method: **In this randomized controlled trial, 99 adult ASA I and II patients between the ages of 16 – 65 years were administered nebulized Ketamine 50 mg, Magnesium Sulphate 250 mg or saline for ten minutes prior to induction of general anaesthesia and orotracheal intubation. Incidence and severity of post-operative sore throat were assessed at 2, 4, 8, 12 and 24 hours post extubation.**

Result: **The incidence of sore throat at 4, 8, 12 and 24 hours post tracheal extubation were significantly lower in the Magnesium (18.2%, 12.1%, 0, 0; p = 0.009, 0.006, ≤0.0001, 0.003) and Ketamine group (24.2%, 12.1%, 6.1%, 0; p = 0.041, 0.006, 0.001, 0.003) compared with the saline group (48.5%, 42.4%, 39.4%, 24.2%). Patients also had significantly less severe sore throat at 4 and 8 hours post extubation in both Magnesium and Ketamine groups (p = 0.0 11, 0.041).**

Conclusion: **Pre-induction nebulization of Ketamine or Magnesium can decrease the incidence and severity of sore throat in the first 24 hours after anaesthesia.**

Keywords: Nebulize, Sore throat, Magnesium, Ketamine.

INTRODUCTION

Post-operative sore throat (POST) is a common phenomenon after general anaesthesia with endotracheal intubation. It is considered as the second leading minor adverse event after post-operative nausea and vomiting.[1] The incidence vary widely but reportedly as high as 49 and 69.6% in two separate studies in our sub-region.[2,3] Notable risk factors for developing POST include female sex, airway instrumentation and airway surgeries.[4] Mucosal injury during airway instrumentation is a recognizable pathophysiological mechanism in the literature. Endotracheal anaesthesia incorporate many manoeuvres that can cause these injuries including laryngoscopy, suctioning, endotracheal intubation and sometimes oro-/nasogastric tube passage.

Gentle airway manipulation at anaesthetic induction can minimize mucosal injury and prevent occurrence of POST. Pre-induction administration of topical/ local anti-nociceptive and anti-inflammatory agents attenuate POST by counteracting the inflammation or nociception induced by mucosal injury.[5–7]

The peripheral nerves in the airway subserving nociception contain N-methyl D-Aspartate receptors (NMDAR).[8] Antagonists to NMDAR are considered anti-nociceptive and have been investigated for POST in the forms of gargle, lozenge and nebulization with varied outcomes.[9–11] Nebulization however offers the unique advantage of even distribution over all areas exposed to instrumentation and mucosal damage while the gargle and lozenge forms are restricted to the supraglottic region with considerable inter-patient variability during administration.

Magnesium and Ketamine are commonly available NMDAR antagonists with anti-inflammatory properties. Previous studies compared these agents with placebo using varied doses and application patterns. We decided to undertake this study to test and compare the efficacies of pre-induction nebulized Magnesium and Ketamine for POST attenuation within 24 hours following general anaesthesia with endotracheal intubation.

METHOD

We conducted a double blind randomized controlled trial at the University College Hospital, Ibadan over a 6 month period. Ninety-nine eligible ASA I and II patients scheduled for elective surgical procedures in supine position under general anaesthesia were recruited. Patients with recent sore throat, chronic airway disease, anticipated difficult airway or undergoing head and neck procedures were excluded. Our sample size was calculated from the presumption that the incidence of POST in our environment is 69.6%.[3] To show a 50% reduction in incidence using a power of 80% with a 95% confidence interval, power analysis generated 30 patients per group.[12] We added 10% of the calculated sample size to account for attrition. Following institutional ethics approval, a block randomisation using computer generated table of random numbers divided the prospective patients into equal groups of 33. Written informed consent was obtained from each patient at the preoperative review. Patients were allocated according to group to receive one of three nebulized medications: Magnesium sulphate 250mg (Group M); Ketamine 50mg (Group K) and saline. The medications were made up to 5ml volume with sterile water and delivered with a compressor nebulizer (Omron Healthcare Co. Ltd., Japan) for 10 minutes. The drugs were indistinguishable in colour and to ensure blinding, an assistant carried out the nebulization. During nebulization, patients were inclined at 45^0 and encouraged to simultaneously breathe through the mouth and nose.

Induction was done with Propofol 2mg/kg and Fentanyl 2mcg/kg. Laryngoscopy was performed by a single anaesthetist after neuromuscular block with Pancuronium 0.1mg/kg was confirmed with ulnar nerve stimulation (MS-IVA, Life-Tech Inc, USA). Male subjects were intubated with lubricated size 7.5mm ID while females had 7.0mm ID high volume low pressure cuffs (Smiths Medical Int. Ltd, UK). The cuff pressures were monitored and kept at 25 cmH_2O with a manual manometer (NS60-TRS-CP, Tri-anim Health Services, Ireland). Anaesthesia was maintained with Isoflurane 1 – 2% in oxygen and morphine titrated to effect. Patients were monitored throughout surgery as per protocol.

At the end of surgery, Paracetamol 0.6g was administered while residual neuromuscular block was reversed with Neostigmine 2.5mg and Atropine 1.2mg. Gentle blind oropharyngeal suctioning was done prior to awake extubation. Patients were interviewed for POST at 2, 4, 8, 12 and 24 hours after tracheal extubation. Severity of POST was graded according to NRS 0 – 10. Strepsil® lozenges was prescribed for those with severe POST.

Our primary outcome was the incidence of POST at 4 hours post extubation while secondary outcomes were incidences and severities observed at 2, 8, 12 and 24 hours as well as correlation between POST and gender, external laryngeal manipulation and laryngoscopy grade. Statistical analysis were performed with IBM SPSS 21 (Chicago, IL., USA). Tests of association for continuous variables were done with independent t-test and one-way analysis of variance (ANOVA) while categorical variables were analysed with chi square test. Fisher exact was used for cell count <5. Level of significance was set at $P < 0.05$.

RESULT

We recruited 107 patients between July and December 2016: two patients declined consent, one patient had intraoperative surgical complications that necessitated post-operative ICU care while five patients dropped out for multiple attempts at laryngoscopy. Ninety-nine patients completed the study comprising 47 males and 52 females. The mean age and weight were 43.8 years

Table 1: Demographic characteristics of patients

Variable	Saline	Ketamine	Magnesium	f- test (p-value)
Age in years (means ± SD)	41.2 ± 13.3	45.5 ± 12.1	44.6 ± 13.3	0.366
Weight in kg (means ± SD)	66.6 ± 9.3	71.6 ± 10.2	68.6 ± 8.9	0.109
				χ^2 (p-value)
Sex (male/female) (%)	14/19 (42.4/57.6)	13/20 (39.4/60.6)	20/13 (60.6/39.4)	0.175

SD: Standard Deviation

and 68.9 kg respectively. Age, sex and weight were not significantly different among the three groups. Table 1 shows the demographic characteristics. The characteristics of the three groups as it relates to surgery and anaesthesia (including laryngoscope blade size, laryngoscopy grade, use of external laryngeal manipulation, durations of intubation, surgery and anaesthesia) are also comparable (Table 2).

POST at 4, 8, 12 and 24 hours between Magnesium and saline (p = 0.009, 0.006, d"0.001, 0.003) and Ketamine and saline (p = 0.041, 0.001, 0.003) as shown in Table 3. No significant difference was found when Ketamine was compared with Magnesium at all observation times (Table 4). Significantly more patients suffered severe POST at 4 and 8 hours in group S compared with group M and K (Table 5). No

Table 2: Comparison of factors related to anaesthesia and surgery (N = 33 in each group).

Variable	Saline	Ketamine	Magnesium	f-test (*P* value
Duration of intubation (sec) (mean ± SD)	17.3 ± 4.4	17.0 ± 5.2	16.1 ± 4.6	0.529
Duration of surgery (min) (mean ± SD)	118.7 ± 44.9	118.6 ± 42.3	126.6 ± 36.9	0.668
Duration of anaesthesia (min) (mean ± SD)	153.0 ± 43.3	156.2 ± 43.6	164.1 ± 37.6	0.537
				χ^2 (*p*-value
Laryngoscope blade size (n: 3/4) (%)	22/11 (66.7/33.3)	25/8 (75.8/24.2)	24/9 (72.7/27.3)	0.706
Frequency of ELM {n (%)}	13 (46.4)	8 (28.6)	7 (25.0)	0.214
Cormack & Lehane score (n:1/2/3) (%)	20/10/3 (60.0/30.3/9.1)	19/13/1 (57.6/39.4/3.0)	23/8/2 (69.7/24.2/6.1)	0.619

SD: Standard Deviation
ELM: External Laryngeal Manipulation
Sec: Second
Min: Minute

The overall incidence of POST at 4 hours was 30.3%. The incidence was highest in group S (48.5) and lowest in group M (18.2%) compared with group K (24.2%). There were significant differences in incidence of

correlation was found between POST at 4 hours and gender, external laryngeal manipulation at intubation and laryngoscopic grade in the three groups (Table 6).

Table 3: Comparison of incidence of POST (N = 33 in each group)

Time (Hours)	Saline n(%)	Ketamine n(%)	p-value	Magnesium n(%)	p-value
2	10 (30.3)	8 (24.2)	0.580	2 (6.1)	0.011*
4	16 (48.5)	8 (24.2)	0.041*	6 (18.2)	0.009*
8	14 (42.4)	4 (12.1)	0.006*	4 (12.1)	0.006*
12	13 (39.4)	2 (6.1)	0.001*	0 (0.0)	≤0.0001*
24	8 (24.2)	0 (0.0)	0.003*	0 (0.0)	0.003*

n: Number of patients with POST per group

Table 4: Comparison of incidence of POST [Ketamine vs Magnesium (N = 33 in each group)

Time (Hours)	Ketamine n (%)	Magnesium n (%)	χ^2	p-value
2	8 (24.2)	2 (6.1)	4.243	0 .082
4	8 (24.2)	6 (18.2)	0.363	0 .764
8	4 (12.1)	4 (12.1)	0.000	1.000
12	2 (6.1)	0 (0.0)	2.063	0.492
24	0 (0.0)	0 (0.0)	NA	NA

n: Number of patients with POST per group
NA: Not Available

Table 5: Comparison of severity of POST (N = 33 in each group).

Time (Hours)	Severity	Saline n(%)	Ketamine n(%)	Magnesium n(%)	P-value
2	**Mild**	6 (60.0)	6 (75.0)	1 (50.0)	0.719
	Moderate	4 (40.0)	2 (25.0)	1 (50.0)	
4	**Mild**	2 (12.5)	4 (50.0)	4 (66.7)	0.011*
	Moderate	5 (31.3)	4 (50.0)	2 (33.3)	
	Severe	9 (56.2)	0 (0.0)	0 (0.0)	
8	**Mild**	3 (21.4)	2 (50.0)	4 (100)	0.041*
	Moderate	5 (35.7)	2 (50.0)	0 (0.0)	
	Severe	6 (42.9)	0 (0.0)	0 (0.0)	
12	**Mild**	5 (38.5)	2 (100)	0 (0.0)	0.104
	Moderate	8 (61.5)	0 (0.0)	0 (0.0)	
24	**Mild**	4 (50.0)	0 (0.0)	0 (0.0)	N/A
	Moderate	4 (50.0)	0 (0.0)	0 (0.0)	

n: Number of patients with POST per group.
NA: Not Available.

Table 6: Analysis of risk factors for POST at 4 hours (N = 33 in each group).

	Patients with POST (n)/Sub-group (n^1)				
Variable	**Saline**	**Ketamine**	**Magnesium**	**Total**	**p-value**
Sex					
Male	5/14	3/13	3/20	11/47	0.115
Female	11/19	5/20	3/13	19/52	
ELM					
Yes	9/13	1/8	1/7	11/28	0.164
No	7/20	7/25	5/26	19/71	
LG					
1	7/20	3/19	4/23	14/62	0.089
2	6/10	5/13	2/8	13/31	
3	3/3	0/1	0/2	3/6	

n: Number of patients with POST per sub group
n': Number of patients with each variable per group
ELM: External Laryngeal manipulation
LG: Laryngoscopy grade (Cormack and Lehane)

DISCUSSION

The major finding of this study is that prophylactic administration of nebulized Magnesium or Ketamine can decrease incidence and severity of POST within the first 24 hours following endotracheal anaesthesia. The suggested mechanism for the attenuation is the anti-nociceptive and anti-inflammatory properties of NMDAR antagonists.[8] Typically, POST occurs following noxious stimulation provoked by inflammation that results from mucosal injuries.[4,10] Excitatory amino acids such as glutamate and inflammatory mediators are released after such mucosal injuries or following stretch of pharyngeal muscles by instrumentation.[13] Prior occupation of NMDAR by Ketamine or Magnesium molecules prevents glutamate mediated central sensitization and sensation of POST.[8]

In our study, Magnesium significantly attenuated POST at 2 hours post extubation when compared with saline. Teymourian *et al* [14] also demonstrated significant attenuation of POST at 2 hours following Magnesium gargles. On the contrary, we did not find a significant attenuation of POST at 2 hours post extubation when Ketamine was compared with saline. This may likely be due to manifestations of new mucosal injuries at emergence in the Ketamine group since we recorded twice as many blood stained suction tubes at emergence in the Ketamine group when compared with Magnesium.

The highest incidence of POST observed across the groups at 4 hours correlates with the incidence found in similar studies.[15,16] It may be indicative of the peak of noxious stimulation or release of inflammatory

mediators. This is also the period where the severest of POST was observed across the groups although no patient in the test groups had severe POST at any time during our study. We observed an increase in incidence in the Magnesium group between 2 and 4 hours. This could be due to a more gradual developing inflammation not evident at earlier post-operative period. We utilized the numerical rating scale for assessment of severity of POST because of its simplicity which makes it easily understood by our patient population. This also makes it easy to use in the early post-operative period where the residual effect of anaesthesia may still be present.

The decrease in incidence and severity from the 8th to the 24th hour period in all the groups may reflect resolution of inflammation and decreased nociception. This assumption is reinforced by decrease in severe POST in the non-tested (control) group by 12 hours and beyond. At 24 hours, the absence of any case of POST in both test groups coupled with an incidence of 24.2% in the control group suggest that the effect of the NMDAR antagonists extend to this period. Since the supposed mechanism is local anti-inflammatory and anti-nociceptive actions, continuous absorption from the mucous surface should diminish their effect over time. The rate of absorption may also account for the difference in incidence between the two NMDAR antagonists at different times. Many randomized controlled studies on NMDAR antagonism and POST report decreasing incidence over a 24 hour period.[9,15,16] In contrast, observational studies conducted after 24 hours of anaesthesia report high incidences of POST.[1,2,17]

We optimised the nebulization process to ensure maximum delivery of the active agent. Previous studies did not address the nebulization process which can significantly affect the amount of drug molecules delivered to the active sites. The recommended fill volume for nebulization is 4 – 5 ml.[18] The volume we administered was made up to 5 ml for this reason. The nebulization was carried out for 10 minutes because the nebulizer utilized for this study delivers 0.5 ml/min and would require 10 minutes to completely nebulize a 5 ml solution. Compressor nebulizer was our preferred form of nebulization because of the advantages of convenience, ease of operation, short inhalation times, efficient lung deposition and cost. We also encouraged subjects to simultaneously breathe through the mouth and nose to maximise delivery and reduce filtration of droplets that would otherwise occur with nasal breathing alone. This study demonstrated an insignificant higher incidence in females; previous studies had shown a greater predisposition to POST by females.[19–21] This outcome is possibly due to our sample size as well as the unequal representation of the sexes in the study groups. The female sex is adjudged to be more predisposed to POST because of the relative small larynx in relation to the ETT size applied.[22] We chose ETT sizes of 7.0 and 7.5 mm ID for women and men respectively because it was shown in a previous study that incidences of POST in women intubated with these sizes were not significantly different.[3]

All recruited patients were subjected to a single laryngoscopy attempt. Laryngeal exposure and visualisation were aided by external laryngeal manipulation (ELM) in some patients. Application of ELM may suggest initial poor laryngeal view and not necessarily a difficult laryngoscopy/intubation. The factors that can affect laryngeal view at laryngoscopy include operator technique, inadequate muscle relaxation, improper positioning and patient unique anatomical features. Operator guided ELM is known to be superior to both basic laryngoscopy and assistant's ELM in Cormack and Lehane score and percentage of glottic opening.[23] We found a greater predisposition in patients who had ELM with an absolute risk reduction of 12%. It is likely that the mucosa of the anterior larynx becomes more vulnerable to injury by the curved tip of the ETT when displaced.

The grade of laryngeal views obtained in this study were largely a function of patients' unique anatomical attribute since a single anaesthetist performed all laryngoscopies. All of the six patients who had Cormack and Lehane grade 3 view at laryngoscopy were assisted by ELM and had durations of intubation more than 15 seconds. The incidence of POST at 4 hours in this group indicates that not all difficult laryngoscopy eventually result in POST. No conclusion can however be drawn from this finding owing to the small number involved. The interaction between ELM, laryngoscopy grade and POST is also not clearly defined.

The evidence required to recommend NMDAR antagonists as effective prophylaxis against POST can only be substantiated by larger trials or meta-analysis. Although, our study showed an absolute risk reduction of 25% and 31% at 4 hours for Ketamine and Magnesium respectively, the calculated number needed to treat were 4 and 3 respectively. These can be considered high for a common minor post-operative anaesthetic complication.

LIMITATIONS

We had some limitations during the study. Post-operative analgesia could not be standardised in timing

and dosage during the period of observation hence patients whose predominant POST symptom is throat pain may have altered perception after analgesic administration. We did not also measure plasma concentration of the test agents to ascertain the likelihood of systemic contribution to the outcome.

CONCLUSION

Pre-induction administration of nebulized Magnesium or Ketamine can attenuate POST within the first 24 hours after endotracheal anaesthesia. Proper nebulization technique and careful airway manipulation are required to achieve this outcome.

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