

# Ketamine Gargle Versus Tramadol Gargle for Attenuation of Post-Operative Sore Throat after Endotracheal Intubation: A Randomized Controlled Study

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## Abstract

**Aim:** The aim of the present study was to compare the difference between Ketamine gargle to Tramadol gargle given 5 minutes before induction on attenuating POST for 24 Post-operative hours.

**Methods:** The present study was conducted after obtaining ethical clearance from the Institutional Ethics Committee, Department of Anesthesiology and Critical care medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. The duration of the Double blind randomized, controlled study was of 2 years.

**Results:** The present study observed that maximum number of patients were in the Tramadol group (group T) of 20-30 years age group is 15 (30%) and Ketamine group (group K) has 40-50 years age group is 15 (30%). The mean age observed was  $40.700 \pm 12.813$  years in the Tramadol group (Group T) and  $43.720 \pm 12.641$  years in the Ketamine (Group K) group. While taking Gender into consideration, Tramadol group (T group) had 20 male patient (40%) & 30 female patient (60%), Ketamine group (K group) had 17 male patient (34%) & 33 female patients (66%), on comparing no significant difference observed (P -value= 0.534).

**Conclusion:** From the present study we can conclude that preoperative gargling with Tramadol attenuate the incidence and severity of postoperative sore throat more than Ketamine at 4, 8 and 12 hours along with lesser requirement of rescue analgesic than Ketamine that too without much adverse side effects.

**Keywords:** POST, Ketamine Gargle, Tramadol Gargle, Endotracheal Intubation, Sore Throat.

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## Introduction

Tracheal intubation is a foremost cause of trauma to the airway mucosa, resulting in postoperative sore throat (POST) with reported incidence of 21–65%. [1, 2] Even though a minor complication, POST

contributes to postoperative morbidity and patient dissatisfaction. POST had been rated by patients as the eighth most adverse effect in the postoperative period. [3] Various non-pharmacological and

pharmacological trials have been used for attenuating POST with variable success. Among the non-pharmacological methods, smaller-sized endotracheal tubes, lubricating the endotracheal tube with water-soluble jelly, careful airway instrumentation, intubation after full relaxation, gentle oropharyngeal suctioning, minimizing intra cuff pressure, and extubation when the tracheal tube cuff is fully deflated have been reported to decrease the incidence of POST. [4]

The inadequate relief of post-operative pain has adverse physiologic effects that can contribute to significant morbidity and mortality, resulting in the delay of patient recovery and return to daily activities. POST was recently ranked by American anaesthesiologists as the eighth most important problem of current clinical anaesthesiology. [3] POST following tracheal intubation is due to trauma to the airway mucosa. The reported incidence of POST varies from 21 to 65%. [1, 2, 5]

Ketamine a phencyclidine derivative is a noncompetitive antagonist of N-Methyl D Aspartic acid (NMDA) receptor. NMDA receptors are found not only in the central nervous system (CNS) but also in the peripheral nerves.[6] Experimental studies show that peripherally administered NMDA receptor antagonists are involved with antinociception and anti-inflammatory cascade, thus many studies been shown to preventing POST following ketamine gargle.[7-10]

Tramadol hydrochloride is a synthetic analogue of codeine. It is an opioid receptor agonist, it inhibits reuptake of monoamines (noradrenaline and serotonin), it is an NMDA receptor antagonist and has local anaesthetic effect. [11]

The high variability of occurrence is due to a large number of factors implicated in POST such as type and size of airway device, technique of insertion, use of lubricant, airway design, cuff pressure,

length of procedure, anaesthesia administered, evaluation techniques, and a multitude of patient features. Factors which contribute to development of POST include trauma to pharyngo-laryngeal mucosa from Laryngoscopy, placement of nasogastric tube or oral suctioning. The cuff design and pressure may affect tracheal mucocilliary perfusion.

The aim of the present study was to compare the difference between Ketamine gargle to Tramadol gargle given 5 minutes before induction on attenuating POST for 24 Post-operative hours.

### Materials and Methods

The present study was conducted after obtaining ethical clearance from the Institutional Ethics Committee, Department of Anesthesiology and Critical care medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India and registering the trial with Clinical Trials Registry - India ([www.ctri.nic.in](http://www.ctri.nic.in)) bearing registration number CTRI/2019/12/02255. The duration of the Double blind randomized, controlled study was of 2 years. Written informed consent in participant's own language was obtained from all the patients or their attendants before enrolling them in the study.

### Inclusion criteria:

- Age group 20-65 years,
- Either sex,
- Physical status ASA I-II,
- Surgery in supine position under GA lasting for up to 2 hours or more.

### Exclusion criteria:

- History of prior sore-throat,
- Patients using steroids or NSAIDS,
- Patients with COPD, Asthma, smokers,
- Mallampatti grade >2,
- Patients with >2 attempts of intubation
- Pregnant women
- Patient and/or his/her legally acceptable representative not willing to provide their voluntary written and

informed consent for participation in the study.

**Sample size with justification:** It was based on the assumption that the incidence of POST is 65%, and to show a 50% reduction in the incidence at  $\alpha=0.05$ , confidence interval of 95%, and a power 90%, we require a sample size of 46 patients per group. On adding 10% patients for possible loss to follow-up, the sample size required is 50 patients per group. The Randomized cluster sampling was done.

#### **Intervention & data collection methods:**

Patients were selected from different surgical departments, after enrolment in the study and pre-anesthetic checkup which included detailed physical examination, systemic examination and laboratory examination and then by use of computer generated random numbers, patients were allocated to one of two groups.

**Group 1 patients (K group)** received 1 mg/kg body wt. Ketamine in 30 cc of normal saline given 5 min before induction & to be gargled for 1 minute.

**Group 2 patients (T group)** received 1 mg/kg body wt. Tramadol in 30 cc of normal saline given 5 min before induction & to be gargled for 1 minute.

Patients were blinded to gargle solution and the solution was prepared by anesthesiologist not taking part in the study; thereby ensuring double blinding.

A suitable intravenous access was established after placing the routine ASA recommended monitors (i.e. ECG, non-

invasive blood pressure monitor, and pulse oximeter). Anaesthetic induction was done with Propofol 2mg/kg body weight after administering Fentanyl 2 $\mu$ g/kg body weight. Tracheal intubation was facilitated with Vecuronium 0.1mg/kg body weight. After tracheal intubation, anaesthesia was maintained with Isoflurane in oxygen with intermittent intravenous boluses of Vecuronium 0.01 mg/kg body weight every 30 minutes.

The anaesthesia technique remained same for all the patients. At the end of the procedure, the neuromuscular blockade was antagonized using a combination of Neostigmine 50 $\mu$ g/kg and Glycopyrrolate 10 $\mu$ g/kg.

As a rescue analgesic, Paracetamol 1 g IV (may be repeated 6 hourly) was administered for severe pain, or upon a request from the patient. If POST persisted after Paracetamol infusion then Nalbuphine 0.15 mg/kg IV (may be repeated 6 hourly) given.

#### **Parameters to be recorded:**

The following parameters were recorded by anesthesiologist / Nurse both blinded to the patients group:-

1.The incidence of POST (the number of patients developing sore throat), and the severity of postoperative sore throat using a Four point verbal rating scale (0-3): 0 = no sore throat, 1 = mild sore throat (complains of sore throat only on asking), 2 = moderate sore throat (complain of sore throat on his/her own), 3 = severe sore throat (change of voice or hoarseness, associated with throat pain) at 4,8,12 and 24 hours.

Pain Score	Degree of pain	Behavioral sign	Response
0	None	Negative response to questioning	
1	Mild	Pain reported in response to questioning only, without any behavioral sign.	
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported	

		simultaneously without questioning.	
3	Severe	Severe strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears.	

## 2. Postoperative side effects of the used drugs during the recovery time:

- Nausea and vomiting were assessed by a 3-point ordinal scale. (0= none, 1=Nausea, 2 = vomiting) & 4 mg IV Ondansetron was used for vomiting.
- Sedation (if any arises) was evaluated on a scale of 0-6 Inova sedation scale. (1= Alert, 2 = occasionally drowsy, easy to rouse, 3=Dozing intermittently, 4= Asleep, easy to awaken, 5= Difficult to awaken, 6= Unresponsive).

**Statistical Analysis:** T-test and ANOVA was performed to identify the statistical significance in the difference of the mean

value of the various responses among the two groups of patients. The Pearson's Chi-square test was used test for assessing difference in distribution of a categorical variable (Gender, ASA grade and MP grade) between two groups. All the statistical analysis was considered to be significant at p-value less than 0.05, highly significant at p-value <0.01 and considered non-significant when >0.05 and for all significant p-value, 95% confidence interval was considered. The statistical analyses were performed using SPSS version 26 software.

## Results

**Table 1: Age Group-wise distribution of patients**

Age group (years)	Tramadol		Ketamine	
	No.	Percentage (%)	No.	Percentage (%)
20–30	15	30.0%	8	16.0%
30–40	9	18.0%	11	22.0%
40–50	14	28.0%	15	30.0%
50–60	8	16.0%	12	24.0%
Above 60	4	8.0%	4	8.0%
<b>Total</b>	<b>50</b>	<b>100.0</b>	<b>50</b>	<b>100.0</b>
<b>Mean Age-wise distribution of patients</b>				
<b>Group</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>T</b>	<b>P-value*</b>
<b>Tramadol</b>	40.700	12.813	0.269	0.605
<b>Ketamine</b>	43.720	12.641		

The present study observed that maximum number of patients were in the Tramadol group (group T) of 20-30 years age group is 15 (30%) and Ketamine group (group K) has 40-50 years age group is 15 (30%). The mean age observed was 40.700±12.813 years in the Tramadol group (Group T) and 43.720±12.641 years

in the Ketamine (Group K) group. Analysis of the results of the present study showed that age distribution in both studied groups were matched with a P-value of 0.605. There were no significant difference between two groups in terms of Age distribution (P-value less than 0.05 considered significant).

**Table 2: The gender-wise distribution of all the patients and Mean Weight (Kg) of the study population**

Gender	Tramadol		Ketamine		P-value*
	No.	%	No.	%	
Male	20	40.0	17	34	0.534
Female	30	60.0	33	66	
<b>Total</b>	<b>50</b>	<b>100.0</b>	<b>50</b>	<b>100.0</b>	

Weight (Kg)	N	Mean	Std. Deviation	T	P-value*
Tramadol	50	59.70	11.586	1.29	0.257
Ketamine	50	59.46	9.867		

While taking Gender into consideration, Tramadol group (T group) had 20 male patient (40%) & 30 female patient (60%), Ketamine group (K group) had 17 male patient (34%) & 33 female patients (66%), on comparing no significant difference observed (P -value= 0.534). The mean

Weight (KG) was found  $59.70 \pm 11.586$  in the Tramadol group and  $59.46 \pm 9.867$  in the Ketamine group. No significant difference between two groups in terms of mean weight was observed (p -value 0.257).

**Table 3: ASA and MP Grade in Tramadol and Ketamine group**

ASA Grade	Tramadol		Ketamine		P-value*
	No.	(%)	No.	(%)	
I	25	50.0	18	36	0.157
II	25	50.0	32	64	
MP Grade					
I	28	56.0	28	56.0	1.00
II	22	44.0	22	44.0	

Among ASA group comparison, ASA I patient in T group was 25 (50%) & in K group was 18 (36%), ASA II patient in T group were 25 (50%) & in K group were 32 (64%). On comparison of both group no significant difference found (P -value= 0.157). Taking MPG Grade in

consideration, MP Grade I has 28 patients (56%) in T group & 28 patients (56%) in K group, MP Grade II has 22 patients (44%) in T group & 22 patients (44%) in K group. No significant difference found (P-value 1.00).

**Table 4: Mean Intubation Attempts in the two groups**

Intubation Attempts	Mean	Std. Deviation	T value	P-value*
Tramadol	1.16	0.370	1.32	0.253
Ketamine	1.12	0.328		

The mean Intubation attempts was  $1.16 \pm 0.370$  in the Tramadol group and  $1.12 \pm 0.328$  in the Ketamine group with a p-value of 0.253 and no significant difference found.

**Table 5: Mean duration of Anaesthesia in the two groups**

Duration of Anaesthesia	Mean	Std. Deviation	T value	P-value*
Tramadol	2 h 59 min	54.83	0.003	0.956
Ketamine	3 h 15 min	47.05		

The mean duration of anaesthesia in the two groups was 2 hours 59 minutes with SD  $\pm 54.83$  minutes in T Group & in K Group it was 3 hours 15 minutes  $\pm 47.05$ . On comparing no significant difference found as P-value was 0.956.

**Table 6: Distribution and evaluation of pain scores in the study groups**

Time	Pain Score	Group		P-value
		Tramadol (N=50)	Ketamine (N=50)	
4 h	No	21 (42%)	9 (18%)	0.012
	Mild	16 (32%)	13 (26%)	
	Moderate	10 (20%)	19 (38%)	

	Severe	3 (6%)	9 (18%)	
8 h	No	28 (56%)	18 (36%)	0.044
	Mild	13 (26%)	19 (38%)	
	Moderate	8 (16%)	6 (12%)	
	Severe	1 (2%)	7 (14%)	
12 h	No	37 (74%)	22 (44%)	0.008
	Mild	10 (20%)	19 (38%)	
	Moderate	3 (6%)	9 (18%)	
	Severe	-	-	
24 h	No	46 (92%)	43 (86%)	0.259
	Mild	3 (6%)	7 (14%)	
	Moderate	1 (2%)	0 (0%)	
	Severe	-	-	

In the Tramadol group the mild, moderate and severe pain at 4 hours was found 32.0%, 20.0%, and 6% respectively. In Ketamine group, the incidence of the mild, moderate and severe pain at 4 hours was 18.0%, 13.0%, and 9% respectively. The pain score at 4 hours in Ketamine group was comparatively high and statistically significant (p-value 0.012).

**Table 7: Adverse effect Post-operative Sedation in Tramadol and Ketamine group**

Postoperative Sedation		Tramadol (N=50)	Ketamine (N=50)
4 hrs	Alert	41 82.0%	25 50.0%
	Occasionally drowsy, easy to rouse	7 14.0%	25 50.0%
	Dozing intermittently	2 4.0%	0 0.0%
8 hrs	Alert	39 78.0%	40 80.0%
	Occasionally drowsy, easy to rouse	7 14.0%	2 4.0%
	Dozing intermittently	4 8.0%	8 16.0%
12 hrs	Alert	43 86.0%	40 80.0%
	Occasionally drowsy, easy to rouse	5 10.0%	6 12.0%
	Dozing intermittently	2 4.0%	4 8.0%
24 hrs	Alert	48 96.0%	46 92.0%
	Occasionally drowsy, easy to rouse	2 4.0%	4 8.0%

When comparing for post-operative sedation among both group, at 4 h period Tramadol group patient had less sedation score with patients occasionally drowsy and easy to rouse were only 14% while

same for Ketamine group was 50%. However this might be due slightly longer interval of anaesthesia among Ketamine group people. Nalbuphine an opioid causing sedation had been used in

Ketamine group as rescue analgesic at 8 h period however it increased number of patients dozing intermittently only 16% in comparison to Tramadol group patient which were dozing intermittently by 8% only. At 12 h and 24 h period there was not statistically significant difference in sedation score.

## Discussion

POST common complication of GA with overall incidence of 21% to 65% causing post-operative morbidity in the patients. [1,2] Many studies have shown gargling ketamine preoperatively is one of the effective means of reducing overall incidence & severity of POST due to its peripheral NMDA receptor antagonist action. [6-9] Few studies also have shown preoperative gargling with Tramadol reduced the incidence and severity of POST due to its NMDA receptor antagonist and local anaesthetic effect. [12] Our study is done to compare the effectiveness of preoperative oral ketamine gargle and tramadol gargle in reducing the incidence of postoperative sore throat following endotracheal intubation.

In this study we did a comparison between pre-induction gargle with Ketamine and Tramadol in dosing 1mg/kg body weight mixed with 30cc of normal saline for attenuation of POST among intubated patients for elective surgeries in ASA 1 or 2 cases aged between 20-65 years. In our study we did not find any significant difference between groups in terms of age, gender and weight. Intubation attempts were also taken into consideration in the study. In our study, no correlation was observed between age, gender, duration of surgery and intubation. So, the duration and difficulty of intubation had no effect in our study, a finding in agreement with Loeser EA et al, Winkel E and Knudsen J and Conway CM et al. [2, 13, 14]

Sore throat related to oro-tracheal tube might be consequence of localized trauma, leading to aseptic inflammation of

pharyngeal mucosa. It may also be associated with oedema, congestion, and pain. [2,15] Reduction of this inflammation by ketamine gargling may be the reason for decreased in POST in our study. However, a peripheral and central action following systemic absorption cannot be excluded. An improvement in quality of life is evident from the pain score difference at 4, 8, 12 and 24 hours. This difference though statistically not significant between the groups at 24 hours.

The anti-inflammatory properties of ketamine have been shown against lung injury. [16] Moreover, ketamine has been shown to diminish the expression of inducible nitric oxide synthase. [17]

Further, long term studies with ideal dosing are required to establish a clear and definite difference in terms of efficacy and tolerability of ketamine and Tramadol in prevention of POST. [18]

A limitation of this study was the absence of the measurements of plasma drug levels. The safety and dosage of the drugs used for gargle need further investigation, even though there was no finding of any adverse effects after their use, as the doses which were used in the study were quiet less when compared to that causing adverse effects. Though results of this study were conclusive but larger sample size would have been more beneficial and would have added more strength to findings. Some placebo could have been added. Effect of airway suction and endotracheal tube cuff pressure role in POST couldn't have been evaluated.

## Conclusion

From the present study we can conclude that preoperative gargling with Tramadol attenuate the incidence and severity of postoperative sore throat more than Ketamine at 4, 8 and 12 hours along with lesser requirement of rescue analgesic than Ketamine that too without much adverse side effects.

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