

# Efficacy of ketamine gargle 40 mg and benzydamine HCl 0.075% in reducing post intubation sore throat

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## ABSTRACT

Sore throat is a frequent complication in postoperative patients under general anesthesia which is performed with endotracheal tube intubation. This effect occurs because of mucosal irritation and damage and airways inflammation due to a lubricant gel on laryngoscopy or an emphasis of endotracheal tube cuff. This study was conducted to compare the efficacy of ketamine 40 mg gargle with benzydamine HCl 0.075% gargle in reducing post intubation of sore throat prior to the insertion of endotracheal tube. A prospective randomized double blind controlled clinical trial enrolled patients aged 18-50 years with physical status of ASA I and II who underwent elective surgery with general anesthesia in Dr. Sardjito General Hospital, Yogyakarta. Subjects were divided into 2 groups. 50 patients of group A were given 30 mL ketamine gargle 40 mg and 51 patients of group B were given 30mL benzydamine HCl gargle 0.075%. The sore throat was measured whenever the patients were fully awake, 2 hours and 4 hours post-extubation with Canbay score (no pain, mild pain, moderate pain and severe pain). There was a significant difference ( $p < 0.01$ ) in sore throat incidence of both groups especially at fully awake and 2 hours post-extubation; 20% in group A versus 66.7% in group B at fully awake and 16% in group A versus 58,8% in group B at 2 hours of post-extubation. However, there was not any significant difference in sore throat incidence of both groups at 4 hours post-extubation ( $p = 0.394$ ). In conclusion, giving ketamine gargle 40 mg 5 minutes before intubation is more efficient in reducing sore throat after endotracheal tube-general anesthesia compared with benzydamine HCl 0.075% at fully awake and 2 hours post-extubation.

## ABSTRAK

Nyeri tenggorok merupakan komplikasi yang sering terjadi pada pasien pascaoperasi dengan anestesi umum menggunakan intubasi pipa endotrakeal. Efek ini terjadi karena iritasi, kerusakan mukosa dan peradangan jalan napas akibat lubrikan gel pada laringoskopi atau penekanan dari balon pipa endotrakeal. Penelitian ini bertujuan membandingkan daya guna obat ketamin kumur 40 mg dan obat kumur benzydamine HCl 0,075 % untuk mengurangi nyeri tenggorok pascaintubasi sebelum pemasangan pipa endotrakeal. Penelitian ini merupakan uji klinis tersamar ganda dengan melibatkan pasien berusia 18-50 tahun dengan status fisik ASA I dan II yang menjalani operasi elektif dengan anestesi umum di Rumah Sakit Umum Dr. Sardjito Yogyakarta. Subyek dibagi menjadi 2 kelompok, 50 pasien kelompok A diberi 30 mL ketamin kumur 40 mg dan 51 pasien kelompok B diberi 30mL benzydamine HCl kumur 0,075%. Nyeri tenggorok diukur setelah pasien sadar penuh, 2 jam dan 4 jam pasca operasi dengan skor Canbay (tidak ada nyeri, nyeri ringan, nyeri sedang dan nyeri berat). Hasil penelitian menunjukkan adanya perbedaan kejadian nyeri tenggorok yang bermakna ( $p < 0,01$ ) pada kedua kelompok yaitu pada saat pasien mulai sadar penuh (20% pada kelompok A dan 66,7% pada kelompok B), dan 2 jam pasca ekstubasi (16% pada kelompok A dan 58,8% pada kelompok B). Tidak ada perbedaan yang bermakna ( $p = 0,394$ ) mengenai kejadian nyeri tenggorok antara grup A dan B pada 4 jam pasca ekstubasi.

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Sebagai kesimpulan, pemberian ketamin obat kumur 40 mg 5 menit sebelum intubasi lebih berdayaguna dalam mengurangi nyeri tenggorok pasca anestesi umum dengan pipa endotrakeal dibandingkan dengan obat kumur benzydamine HCl 0,075% pada saat sadar penuh dan 2 jam pasca ekstubasi.

**Keywords** : endotracheal tube - sore throat - ketamine gargle - benzydamine HCl gargle

## INTRODUCTION

Incidence of sore throat is a frequent complaint by the patients after undergoing surgery with general anesthesia using an endotracheal tube, which causes the patients to feel uncomfortable in the throat area. This effect occurs because there are mucosal irritation and damage and inflammation in the airway which are caused either by the gel as a lubricant and the emphasis of laryngoscopy or endotracheal tube balloon.<sup>1,2</sup> The mechanism of this incidence of sore throat is due to trauma to the tonsils, pharynx, larynx and trachea that causes a local inflammatory response and pain.<sup>3</sup>

An endotracheal intubation action in the general anesthesia is necessary to ensure airway patency and ensure that inhalation agents run and maintain the anesthesia. However, the action to secure airway with endotracheal tube will give some side effects with postoperative sore throat. An anesthesiologist is responsible to minimize side effects of sore throat caused by the use of endotracheal tube. Eventhough the complications are rare, postoperative sore throat can lead to morbidity and dissatisfaction for the postoperative patients.<sup>4</sup>

Some actions have been conducted to reduce the incidence of postoperative sore throat complications with general anesthesia using an endotracheal tube both through non-pharmacological and pharmacological actions. The non-pharmacological actions can be performed partly by using an endotracheal tube with smaller size, providing a lubricant gel dissolved in water of the endotracheal tube

balloon, inserting an endotracheal tube after the patients have been completely relaxed with their condition after induction of a jaw thrust predictor is conducted without motoric responses and reflexes of the airway, inserting endotracheal pipes after the vocal cords completely opened, suctioning the oropharynx area with caution, reducing the pressure on the endotracheal tube balloon and performing extubation after endotracheal tube balloon is completely deflated.<sup>3,4</sup>

The pharmacological actions to reduce the sore throat can be conducted by providing beclomethasone inhalation, intravenous and topical steroids, giving medication with intravenous non-steroid anti-inflammatory drug (NSAID), intravenous ketamine, gargling with azulenesulphonate, benzydamine HCl, oral ketamine and oral aspirin.<sup>5</sup>

The use of mouthwash before endotracheal intubation treatment is reported to reduce the incidence of sore throat. Canbay *et al.*<sup>4</sup> and Rudra *et al.*<sup>6</sup> reported that ketamine gargle significantly attenuates postoperative sore throat (POST) with no drug-related side effects. Ketamine is a rapidly acting anesthetic and analgesic agent that has been used as general anesthesia for more than 30 years. Now ketamine has been used as new analgesic for peripheral pain. The existing ionotropic glutamate receptor, such as N-methyl-D-aspartate (NMDA) receptor, on peripheral sensory axons can be the basis of ketamine-induced analgesia at peripheral.<sup>7,8</sup>

Agarwal *et al.*<sup>9</sup> reported that benzydamine hydrochloride gargles significantly reduces the

incidence and severity of POST. In addition, a review of clinical trials concluded that benzydamine HCl can be used as a treatment option for the oropharynx disorders and the pharynx, especially during post-intubation.<sup>10</sup> Benzydamine HCl is included into the group of topical NSAIDs that are widely used as the anti-inflammatory drugs for the mouth. Benzydamine HCl reduces the prostaglandin (PGE<sub>2</sub> and PGI<sub>2</sub>) synthesis in gingival fibroblasts, partly at the level of phospholipase A2, by diminishing the liberation of arachidonic acid (AA) from phospholipids, and partly at the level of cyclooxygenase.<sup>11</sup>

This study was conducted to compare the efficacy of ketamine 40 mg gargle with benzydamine HCl 0.075% gargle in reducing post intubation sore throat prior to the insertion of endotracheal tube.

## **MATERIALS AND METHODS**

### **Subjects**

One hundred and one patients who underwent elective surgery with general anesthesia in Dr. Sardjito General Hospital, Yogyakarta were enrolled in this prospective randomized double blind controlled clinical study. Patients were divided into 2 groups. 50 patients of group A were given 30 mL ketamine gargle 40 mg and 51 patients of group B were given 30 mL benzydamine HCl gargle 0.075%.

The inclusion criteria were men or women between the age 18-64 years old, with the Body Mass Index (BMI) <30 kg/m<sup>2</sup>, physical status ASA I-II, elective surgical procedures with the supine position to be performed under general anesthesia with endotracheal intubation, duration of operation not more than 2 hours, no prediction for the intubation difficulty, and agreed to participate in the study. The exclusion criteria in this study were the patients with

hypertension history and heart disease, surgery on the airway, abdomen with the nasogastric tube which is required to install, patients with pain history of sore throat, hyperactive history on the airway such as asthma, common cold, respiratory tract infection, history of allergy to drugs used in this study. While the criteria of drop-out was an attempt of intubation more than 60 seconds, allergy medications used during surgery.

### **Study protocol**

After the patients arrival in the operating room, the infusion of crystalloid at ½ fluid as replacement of 1 hour fasting was administered intravenously with the catheter IV no. 18 in a large peripheral vein. Furthermore, patients were randomly allocated to one of two groups. Group A received ketamine gargle 40 mg and group B received benzydamine HCl 0.075% 15 mL. All medications were made into 30 mL with distilled water which was placed into an opaque bottle. The investigators and patients were blinded to the medications given to the patients. The patients were taught how to gargle for 30 seconds, therefore patients could gargle properly and the mouthwash wet the hypopharynx and nosopharynx areas. Standards for patient monitoring during anesthesia i.e. electrocardiogram, blood pressure, mean arterial blood pressure (MAP), heart rate (HR) and oxygen saturation (SpO<sub>2</sub>) were initiated.

Five minutes after gargling with the mouthwash, the patients were premedicated with midazolam 0.05 mg/kgBW IV co-induction. This was followed by IV induction with propofol 2 mg/kg BW at a constant rate infusion 1.5 mg/kg/minute three minutes later until the negative reflect of eyelash, gave the ventilation for oxygen 100% with facemask. Endotracheal intubation was facilitated by injection of rocuronium 0.6 mg/kg BB and then blood

pressure, MAP, HR and SpO<sub>2</sub> were monitored 90 seconds later.

Endotracheal intubation was performed after ensuring that the patient was completely relaxed, when just thrust predictor showed no motoric response and airways reflect. The endotracheal was intubated with the high volume low pressure plastic pipe no 7 for females and no 7.5 for males. The cuff was inflated with air and cuff pressure was maintained around 22 cm of water with intracuff pressure manometer. The blood pressure, MAP, HR and SpO<sub>2</sub> were monitored again one minute later.

Anesthesia was maintained using 50% N<sub>2</sub>O in 50% O<sub>2</sub> and isoflurane. Ondansetron 4 mg IV and ketorolac 30 mg were administered 30 minutes before the surgery was finished. At the end of surgery, N<sub>2</sub>O was stopped. Before the patients were conscious as indicated with no airway reflexes but showed free of the muscle paralyzing, adequate breathing, stable hemodynamics, endotracheal extubation was performed followed with the 100% oxygenation by facemask until the patients opened their eyes with mild stimuli. The patients were then transferred to the postanesthesia care unit.

After the patients were fully conscious as indicated with the Ramsay score of 2, the patients were interviewed by a blinded observer to assess POST. Kappa ( $\hat{\epsilon}$ ) agreement test was conducted between interobservers before being involved in this study. The POST was assessed at 0, 2 and 4 hours after at patients arrival in the postanesthesia care unit. The POST was graded on a four-point scale (0-3) as described by Canbay *et al.*<sup>4</sup> as follows: 0 as no sore throat, 1 as mild sore throat (complains of sore throat only on asking), 2 as moderate sore throat (complains of sore throat on his/her own) and

3 as severe sore throat (change of voice or hoarseness, associated with throat pain). The side effects due to the the medications ingestion were also monitored.

This research protocol has been approved by Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

### **Statistical analysis**

Demographic data were presented as mean  $\pm$  standard deviation (SD) and analyzed with one t-test for continuous variables and Mann-Whitney U test for categorical variables. The incidence of postoperative symptoms was analyzed by Chi-square test, whereas the severity of symptoms was analyzed by the Mann-Whitney U test. All statistical analysis were performed with SPSS. Probability value (p) <0.05 was considered significant.

### **RESULTS**

This study involved 101 patients consisting of 50 patients who gargled with ketamine 40 mg and 51 patients who gargled with benzydamine HCl 0.075 %. The characteristics of patients of both group are presented in TABLE 1. Weight, height, BMI, anesthetic duration, recovery conscious, sex and type of surgery were similar among the two groups, except the patients' age and ASA physical status. The age of patients receiving ketamine was younger than those receiving benzydamine HCl. The ASA physical status I of patients receiving ketamine was higher than those receiving benzydamine HCl. Conversely, the ASA physical status II of patients receiving ketamine was lower than those receiving benzydamine HCl.

TABLE 1. Characteristics of patients of ketamine and benzydamine groups

Variables	Ketamine (n=50)	Benzydamine HCl (n=51)	p
Age (years)	36.24±12.67	42.86±16.57	0.026*
Weight (kg)	54.54±10.94	53.51±10.38	0.628
Height (cm)	156.58±6.28	156.20±7.29	0.777
BMI (kg/m <sup>2</sup> )	22.00±3.92	21.60±3.21	0.576
Anesthetic duration (minute)	92.90±21.48	85.98±22.23	0.115
Recovery conscious (minute)	18.16±11.99	19.41±16.75	0.667
Sex (n/%)			
• Male	19 (38%)	22 (43.1%)	0.599
• Female	31 (62%)	29 (56.9%)	
ASA physical status (n/%)			
• I	37 (74%)	28 (54.9%)	0.045*
• II	13 (26%)	23 (45.1%)	
Type of surgey (n/%)			
• Digestive	8 (16%)	4 (7.8%)	0.071
• Orthopedic	11 (22%)	6 (11.8%)	
• Oncologic	2 (4%)	4 (7.8%)	
• Urologic	3 (6%)	3 (5.9%)	
• Obstretic and gynecologic	14 (28%)	10 (19.6%)	
• Ear nose and throat	5 (10%)	3 (5.9%)	
• Eye	7 (14%)	21 (41.2%)	

\*significantly different

The incidence of POST at 0, 2, and 4 hours post-extubation on ketamine and benzydamine HCl groups is presented in FIGURE 1. The incidence of POST on ketamine group at 0 and 2 hours post-extubation was significantly lower

than benzydamine HCl group (p=0.001). However, at 4 hours post-extubation no significant difference in the incidence of POST of both groups was observed (p=0.394).

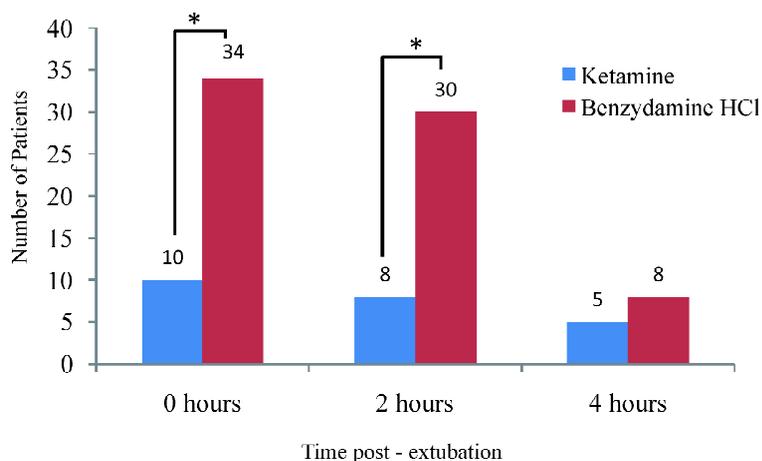


FIGURE 1. The incidence of POST at 0, 2, and 4 hours post-extubation on ketamine and benzydamine HCl groups; \* significantly different p<0.05

The severity of POST at 0, 2, and 4 hours post-extubation on ketamine and benzydamine HCl groups is presented in TABLE 2. Significantly, more patients suffered severe POST on ketamine group at 0 and 2 hours post-

extubation compared with benzydamine HCl group. However, the severity of POST was similar between ketamine group and benzydamine HCl group.

TABLE 2. The severity of POST at 0, 2, and 4 hours post-extubation on ketamine and benzydamine HCl groups

Incidence of POST	Ketamine		Benzydamine HCl		p
	N	%	N	%	
0 hours post-extubation					
• No sore throat	40	80.0	17	33.3	0.001*
• Mil sore throat	10	20.0	31	60.0	
• Moderate sore throat	0	0	3	5.9	
• Severe sore throat	0	0	0	0	
2 hours post-extubation					
• No sore throat	42	84.0	21	41.2	0.001*
• Mil sore throat	8	16.0	26	51.0	
• Moderate sore throat	0	0	4	7.8	
• Severe sore throat	0	0	0	0	
4 hours post-extubation					
• No sore throat	45	90.0	43	84.3	0.394
• Mil sore throat	5	10.0	8	15.7	
• Moderate sore throat	0	0	0	0	
• Severe sore throat	0	0	0	0	

*POST: postoperative sore throat; \*significantly different*

Changes in blood pressure, diastolic blood pressure, MAP, HR and SpO<sub>2</sub> of the patients after entering operating room, at pre intubation and 1 min post intubation are presented in TABLE 3. No significant changes of patients hemodynamic were observed in between both

ketamine and benzydamine HCl groups (p>0.05), except the MAP at pre intubation that showed the MAP of patients ketamine group were lower than those receiving benzydamine HCl.

TABLE 3. Changes in blood pressure, diastolic blood pressure, MAP, HR and SpO<sub>2</sub> of the patient at entered operating room, pre intubation and 1 min post intubation on ketamine and benzydamine HCl

Variables	Ketamine (n=50)	Benzydamine HCl (n=51)	p
Entered operating room			
• SBP (mmHg)	128.74±11.52	129.61± 13.88	0.73
• DBP (mmHg)	74.40±9.45	76.90± 10.71	0.46
• MAP (mmHg)	94.50±8.80	96.76± 10.94	0.26
• HR (beats/minute)	86.58±16.36	87.33± 13.04	0.80
• SPO <sub>2</sub> (%)	99.34±1.14	99.24± 0.89	0.61
Pre intubation			
• SBP (mmHg)	109.52±14.04	129.61±13.88	0.10
• DBP (mmHg)	66.16±10.60	17.90±10.71	0.24
• MAP (mmHg)	82.36±10.51	96.76±10.94	0.02*
• HR (beats/minute)	83.06±13.00	87.33±13.04	0.73
• SPO <sub>2</sub> (%)	99.64±0.60	99.24±0.89	0.36
One minute post intubation			
• SBP (mmHg)	119.06±13.36	118.88±14.18	0.95
• DBP (mmHg)	72.54±14.11	72.27±12.09	0.92
• MAP (mmHg)	89.90±12.90	91.49±12.38	0.53
• HR (beats/minute)	86.58±14.98	87.98±11.60	0.60
• SPO <sub>2</sub> (%)	99.70±0.54	99.67±0.52	0.75

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; HR: heart rate; SPO<sub>2</sub>: oxygen saturation; \*significantly different

## DISCUSSION

Postoperative sore throat (POST) is a common occurrence after surgery under general anesthesia using endotracheal tube. The POST may disappear after a few hours, but can occur again for two days or more.<sup>12</sup> Despite being a minor complication, POST contributes to post-operative morbidity and patient dissatisfaction. Some nonpharmacological and pharmacological intervention have been used for attenuating POST with variable success. In pharmacological intervention, beclomethasone inhalation, azulene sulfonate gargle and some NSAID such

as tenoxicam and aspirin have been used to reduce POST.<sup>4,9</sup> In this study, the efficacy of ketamine 40 mg and benzyldamine HCl 0.075% that administered prior to the endotracheal intubation for attenuating POST have been investigated. The findings of this study may be used as an alternative pharmacological intervention to reduce POST in general anesthesia with endotracheal intubation.

The contributing factors influencing the incidence and severity of POST have been controlled in this study. The weight, height, BMI, anesthetic duration, recovery conscious, sex and

type of surgery between ketamine group and benzydamine HCl group were similar ( $p>0.05$ ), except the patients age and ASA physical status ( $p<0.05$ ). Although the patients age were different, it was not correlated with POST as reported by Canbay *et al.*<sup>4</sup> while the ASA physical status has never been correlated with POST in some studies.<sup>4,9</sup> In addition, the suction of mucus from the patients' oropharynx was conducted one time carefully using the same type of endotracheal tube with size and high volume low pressure no 7 for female and no 7.5 for male. The intracuff pressure was measured on the initial endotracheal intubation and maintained around 22 cm of water with intracuff pressure manometer.

To avoid the presence of *bias* between observers, kappa ( $\kappa$ ) agreement test was conducted three weeks before study was started. Five residents who would be observers were involved in this test. The kappa agreement test result showed that the  $\kappa$  value interobserver was  $\geq 0.75$  and  $0.4 \leq \kappa \leq 0.75$ . It was indicated that the moderate and substantial agreement between interobserver were obtained in this test and can be involved in this study.

The incidence of POST on patients receiving ketamine 40 mg gargle at 0 and 2 hours post-extubation (20% and 16%) was significantly lower than those receiving benzydamine HCl 0.075% gargle (66.7% and 58.8%) (FIGURE 1). It was indicated that ketamine 40 mg gargle was more effective for attenuating POST compared with benzydamine HCl 0.075% in patients undergoing anesthesia with endotracheal intubation. However, the incidence of POST for 4 hours post-extubation was not significantly different on patients receiving ketamine 40 mg gargle (10%) compared to those receiving benzydamine HCl 0.075% gargle (15.7%).

The incidence of POST on both patients receiving ketamine 40 mg and benzydamine HCl

0.075% were reduced in time-dependent manner. It can be explained that noxious stimuli intensity (painful stimuli) derived from anesthetic procedure such as laryngoscopy and endotracheal tube cuff pressure would be compensated by the body after several hours. In addition, administration of postoperative analgesic could reduce painful stimuli. In this study, ketorolac 30 mg as postoperative analgesic was given 30 minutes before the operation was completed.

The incidence of POST in patients undergoing anesthesia with tracheal intubation has been reported by some authors. Canbay *et al.*<sup>4</sup> reported that the incidence of POST in Turkey was 30-40%, while in India the incidence of POST was 40%. In this study the incidence of POST was lower (16-20%) than those previous studies. Some contributing factors for the incidence of POST have been reported, including race, age, sex, type of surgery, large tracheal tube, cuff design, intra cuff pressure, postoperative analgesic administration, installation of naso gastric tube (NGT), and suctioning procedures.<sup>13,14</sup>

Ketamine is initially developed as anesthetic agent, however in low (subanesthetic) doses, ketamine is widely used as an analgesic in the treatment of both acute and chronic pain. The analgesic effect of ketamine is primarily based on the antagonism of NMDA receptor.<sup>15,16</sup> Besides acting on the NMDA receptor, ketamine also acts on nicotinic, muscarinic and opioid receptors.<sup>17</sup> Meanwhile the benzydamine HCl is a topical NSAID that has analgesic, local anesthetic, antiinflammatory and antimicrobial properties.<sup>18</sup> These mechanism of actions of benzydamine HCl may be mediated by the prostaglandin system.<sup>19</sup> Both of ketamine and benzydamine HCl have been used in reducing the incidence and severity of POST. Differences in their pharmacodynamics and pharmacokinetics may contribute in the

efficacy of these drugs to reduce POST in general anesthesia with endotracheal intubation.

The hemodynamic changes of patients after entering the operating room, at pre-intubation and one minute post intubation were monitored. No significant hemodynamic changes of patients were observed on both ketamine and benzydamine HCl groups ( $p>0.05$ ), except the MAP at pre intubation where the MAP of patients in ketamine group were lower than those receiving benzydamine HCl. However, this MAP value was still in normal range (70-110 mmHg). The stability of the patients' hemodynamic changes might be a consequence of the smooth insertion conducted, and complete relaxation in patients as indicated by the absence of motoric response and air ways after a jaw thrust.

## CONCLUSION

It can be concluded that ketamine 40 mg gargle is more effective for attenuating the incidence and severity of POST compared with benzydamine HCl 0.075% in patients undergoing anesthesia with endotracheal intubation.

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