

# Ketamine Gargle Peripheral Analgesic Effect on Sore Throat after Ear Surgery, a Randomized Clinical Trial

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**ABSTRACT---** *Background: Intubation could cause trauma to the airway mucosa which leads to postoperative sore throat with the incidence of 21-65%, which leads to other complications and patients' dissatisfaction. Postoperative sore throat leads to morbidity particularly after head and neck and ear surgery and patient dissatisfaction.*

*Aim: to determine the effect of ketamine gargle on sore throat after intubation and to measure serum ketamine level.*

*Materials and methods: A prospective, randomized and placebo-controlled double blind study was conducted on 78 patients who underwent ear surgery. The patients were randomized into three groups of 26 patients: The control group received 30ml normal saline as placebo and the experimental groups 40mg and 60 mg of ketamine in 30ml normal saline. Blood samples were obtained from the patients in order to measure serum ketamine level. Patients sore throat was assessed using visual analogue scale immediately after surgery, at arrival in the recovery unit, and at 2, 4 and 12 h after the surgery.*

*Results: The patients who received ketamine gargle (40 and 60 mg) had less sore throat at 0 and 2 h recovery than those who received placebo (<0.05). Sore throat was not significantly different in both groups received ketamine ( $p>0.05$ ) while the ketamine level in blood in ketamine group was less than analgesic dose in both 40 and 60 mg groups.*

*Conclusion: ketamine gargle reduces sore throat after surgery and such effect is not caused by the blood absorption of ketamine.*

**Keywords----** gargle, ketamine, postoperative sore throat, topical analgesia

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## 1. INTRODUCTION

Tracheal intubation is one of the most common causes of airway mucosa trauma, resulting in postoperative sore throat<sup>1</sup>. The incidence of sore throat varies between 21–65% dependent on the anesthesiologists' expertise and the techniques used<sup>2,3</sup>. The diagnosis and definition of sore throat is not exactly the same based on its subjective nature<sup>4</sup>. Postoperative sore throat leads to morbidity after surgery and patient dissatisfaction<sup>5</sup>. It had been rated by patients as the eighth unpleasant complication in the postoperative period<sup>6</sup>. Pharyngeal mucus trauma, edema of vocal cords and posterior pharynx wall, mucous dehydration and effect of cuff pressure on tracheal mucus can lead to postoperative sore throat which may reduce by steroid<sup>7</sup>. Inhalation spray of Beclomethason has been also attempted but none has been with conclusive success<sup>8</sup>.

Several pharmacological and non-pharmacological methods have been used to attenuate postoperative sore throat with variable success<sup>9,10</sup>. Non-pharmacological methods include using smaller-sized endotracheal tubes, lubricating the endotracheal tube with water-soluble jelly, careful airway instrumentation, intubation after full relaxation, gentle oropharyngeal suctioning, minimizing the cuff pressure, and extubation when the tracheal tube cuff is fully deflated are effective ways to decrease postoperative sore throat incidence<sup>11,12</sup>. The pharmacological methods include beclomethasone inhalation and gargling with azulenesulphonate both of which have decreased the postoperative sore throat<sup>13,14</sup>. Packing gas, Tenoxicem Hydrophilic and non-steroid anti-inflammatory drugs have been effective on

moderate or severe postoperative sore throat<sup>15</sup>. Local Bepizdomine hydrochloride has also caused the reduction of postoperative sore throat<sup>16</sup>.

Several studies have showed that N-methyl-D-aspartate receptor (NMDA) receptors are not only found in CNS for example the term CNS will likely not be repeated so this can be out in full but also in the peripheral nerves<sup>17</sup>. Therefore, administration of ketamine may actually contribute to relieve post-operative sore throat (POST) with no major systemic effects.

The aim of this study was to determine the effect of ketamine gargle on sore throat after intubation and distinguished whether ketamine caused such a result peripherally or through mucous absorption in the blood.

## 2. METHODS

The study was reviewed and approved by the University Review Board and hospital ethics committee and been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>). Information about trial was given comprehensively both orally and in written form. All patients gave their informed written consents prior to their inclusion in the study according to University Hospital Ethical Board Committee.

### **Participant selection:**

This study was a prospective, randomized, placebo-controlled and double-blind, clinical trial. Randomization was performed using stratified allocation (even and odd numbers). Patients were randomly assigned into two groups; odds number received Ketamine gargle and even numbers received normal saline as placebo (control group). Allocation concealment from those assigning participants to intervention groups, was performed holding up sealed envelopes until the moment of assignment. The drugs were administered in the same size and shape syringes to blind the physician to the drug and anesthesiologist administering drugs were blind to the one assessing outcomes.

Inclusion criteria were patients underwent ear surgery, adults (>16 years old (this is the legal age of consent for surgery and participation in research in Iran), and American Society of Anesthesiologist (ASA) class I and II. Exclusion criteria were any history of asthma and sore throat, history of allergy to ketamine, Mallampati score >2, having a troublesome intubation (more than 1 attempt at intubation), those who received an opioid drug other than 2 µg/kg fentanyl during the operation, having recently used non-steroid anti-inflammatory drugs, the surgery duration being <1 h and >3h (due to vocal cord edema of longer duration of surgery). If the intubation was performed with stylet in a or required more than one attempt for passage of the tube or patient had bucking during the intubation were excluded from the study. Patients were enrolled according to mentioned factors by the anesthetist in the anesthetic clinic or in the hospital at night before surgery.

### **Method of Anesthesia:**

The patients were randomly assigned into two experimental and one control group. The control group received 30ml normal saline and the experimental groups (k) received either 40mg or 60 mg of ketamine in 30ml normal saline.

Ketamine gargle solutions were prepared by dilution of ketamine (40mg or 60 mg) into 30 ml normal saline. Participants were given identical containers and the appearance, consistency and taste of the placebo and ketamine solutions was similar, ensuring that no differences between them could be detected. Participants were asked to gargle with the solutions twice (each time 15ml for 30 seconds) after their arrival in the operation room.

Anesthesia was induced 5 minutes later. Monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, and end-tidal carbon dioxide as per standard procedure. Anesthesia was induced with fentanyl 2 µg/kg and propofol 2 mg/kg. The intubation was performed after administration of 0.5 mg/kg atracurium. Sterile PVC endotracheal tube with a standard cuff and an internal diameter of 7–8 mm for women and 8-9 mm for men was used for all patients.

Tracheal intubation was performed by the same experienced anesthesiologist. Anesthesia was maintained with the mixture of nitrous oxide with oxygen 50% and isoflurane with concentration of 1.1%. Infusion of remifentanyl was started in all the patients at a dose of 0.1-0.2 µg/kg. Repeated administration of relaxing drug was permitted all along the surgery.

The tracheal tube cuff was inflated until no air leakage could be heard with a peak airway pressure at 20 cm H<sub>2</sub>O, and cuff pressure was maintained between 18 and 22 cm H<sub>2</sub>O using portable pressure gauge.

### **3. DATA COLLECTION AND SORE THROAT MEASURE**

Twenty to 30 minutes after anesthesia a blood sample of 2 ml was obtained from the patients and sent to the laboratory for ketamine analysis. The serum samples were centrifuged and frozen then ketamine level was measured through High Performance Liquid Chromatography (HPLC) (Hamilton, SW) with the precision of 3ng/ml.

At 2, 4 and 12h after surgery, a nurse unaware of the patients group, asked for sore throat. Postoperative sore throat was graded on a four point scale (0-3): as 0 to no sore throat, 1 to mild sore throat (complains of sore throat only on asking), 2 to moderate sore throat (complains of sore throat on patient's own), 3 to severe sore throat (change of voice and hoarseness, associated with throat pain).

### **4. STATISTICAL ANALYSIS**

Statistical calculations were conducted using SPSS 18. The parametric variables were presented as mean  $\pm$ SD and were analyzed by student t- test or ANOVA and Pearson correlation test as appropriate. Statistical analysis was performed using Chi-Square or Mann-Whitney U-test and Spearman correlation coefficients for non-parametric samples.  $P < 0.05$  was considered as statistically significant. Sample size was estimated using  $\alpha = 5\%$ , and power of 80% and 30% difference of outcome as 80 participants.

### **5. RESULTS**

Total of 78 patients assigned to one of three groups: 26 received 40 mg ketamine gargle, 26 cases received 60 mg ketamine gargle, and 26 control cases received placebo. Age, weight sex, and duration of anesthesia were not significantly different among three groups (Table1). Two patients were excluded due to difficult airway (difficult intubation).

The systemic effects of ketamine are demonstrated in Table 2. Blood pressure and pulse rate in ketamine group was not significantly higher than those of the control group. Patients' conciseness (measured by mini-mental state examination (MMSE)) was not also impacted by ketamine (Table2). Only one of the patients, who had received 40 mg of ketamine, got agitated. The mentioned patient had a severe sore throat (grade 3) at arrival in the recovery unit and asked for analgesia 1 hour later. Her plasma level of ketamine was 40 ng/ml. Other patients did not have such complication.

The Postoperative sore throat visual analogue scale (VAS) in control group was higher than that of both ketamine groups at 0 and 2 h ( $P < 0.05$ ) (chi-square analysis) (Figure1). At 4 and 12 h there were no significant differences between ketamine groups (40 and 60 mg) and control group in their sore throat.

The severity of postoperative sore throat in patients of ketamine groups (40 and 60 mg) and the average ketamine level is depicted in Table 3. Patients with ketamine gargle 40 and 60 mg had no significant difference in their NAS at any time points ( $p > 0.05$ ). There was no significant differences in NAS between patients with serum ketamine level higher and lower than 30 ng/ml ( $p > 0.05$ ).

Only 3 patients had a plasma level above or equal to 100 ng/ml. In two cases, the plasma level of ketamine was 100 ng/ml and the patient had no sore throat at all time points. In one other case, the plasma level of ketamine was 120 ng/ml and the patient had mild sore throat (NAS 2) just at 0 and 2h. In one case, the patient's plasma level of ketamine was 200 ng/ml and she had no sore throat at any time. In this study, coughing after surgery was also measured but the difference between the three groups was not statically significant.

### **6. DISCUSSION**

Sore throat is a common side effect of endotracheal intubation reported in many patients after tracheal intubation<sup>18</sup>. The growing amounts of experimental data show that NMDA receptors are present both in central nerve system (CNS) and in the peripheral nerves<sup>19</sup>. Moreover, experimental studies point out that NMDA receptor antagonists act with antinociception mechanism<sup>20,21</sup>. However, there is a paucity of systematically obtained clinical data to give a perspective to the actual magnitude of the benefit associated with ketamine in peripheral usage. We propose that ketamine gargle might be effective in reducing the incidence and severity of postoperative sore throat due to its anti-inflammatory effects.

Our results showed that ketamine gargle could effectively diminish post-operative pain in patients. It seems that ketamine gargle would be plausible method in preventing moderate to severe pain post-operative sore throat. However there is still debate that this effect is due to systemic absorption of ketamine or it is only local effect. The adequate plasma level of ketamine for analgesia is supposed to be at the lowest extent 100 ng/ml. Our results showed that ketamine levels was not associated with VAS scores; in fact patients with high blood level of ketamin and low levels had no significantly difference in sore throat. The reported ketamine level to relieve tourniquet pain after an intravenous (IV) bolus was 100 ng/ml<sup>22</sup>. But when ketamine was administrated orally, it was noted that a lower mean plasma concentration at 40 ng/ml had been analgesic, presumably due to the higher corresponding norketamine levels of 160 ng/ml<sup>23,24</sup>. Although mean plasma ketamine levels was lower than 30 ng/ml in both ketamine groups (40 and 60 mg) in our study, but systemic analgesic effects might not be excluded completely from the mechanisms. To support our conclusions that the effects of reducing POST by ketamine gargling is not caused by blood absorption, we administered ketamine at two different doses (40 and 60 mg) but the response and serum ketamine level was not significantly different showing that increase in gargle dose may not increase serum level. Therefore, analgesic effect is most probably due to peripheral receptor effect. A similar study by Chan L et al? had demonstrated lower ketamine and norketamine plasma levels (16.16 and 11.43 ng/ml, respectively), but with longer inhibition of POST (up to 2 hr after surgery). Although ketamine may actually appear to have both systemic and local analgesic effects, but the results of current study emphasizes on more local effect than systemic effects in relief of sore throat?. Ketamine level did not reach its analgesic level in many of our cases but still had the effect of pain relief. Systemic blood level of ketamine was measured in the present study by the precision of 3ng/ml. With respect to other similar studies<sup>25</sup>, our study actually confirmed that ketamine might actually harbor a local analgesic due to lack of significant systemic blood level.

Ketamine only reduces sore throat at 0 and 2 hour of arrival in the recovery unit compared to the control group. This could be due to short acting effect of ketamine in periphery. Apparently increasing dose of ketamine would not help to extend this local anesthetic phenomenon. Increase in dose also may not increase the blood level of ketamine or change the duration of analgesic effects. Besides, 24-h analgesic consumption was not significantly higher 60 mg ketamine gargle group compare to 40 mg ketamine and control group similar to others<sup>26</sup>.

In conclusion, Ketamine gargle before the ear surgery reduces the incidence of postoperative sore throat at arrival in the recovery unit. The anti-analgesic effect of ketamine was not due to its systemic effects.

**Table 1.** The age, weight, height, gender, duration of surgeries and total intubation time, total remifentanil consumption (mean±SD) of patients in Ketamine group versus control group.

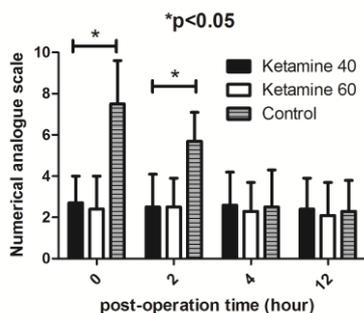
|                                 | Ketamine (40 mg) | Ketamine (60 mg) | Control (26)   | p-value |
|---------------------------------|------------------|------------------|----------------|---------|
| Age (year)                      | 33.70 ± 19.04    | 36.70 ± 16.14    | 31.46 ± 16.63  | >0.05   |
| Sex (Male/Female) (n)           | 10/16            | 12/14            | 9/17           | >0.05   |
| Weight (kg)                     | 70.51 ± 14.93    | 73.11 ± 14.45    | 70.50 ± 12.350 | >0.05   |
| Height (m)                      | 1.68 ± 0.35      | 1.71 ± 0.32      | 1.66 ± 0.21    | >0.05   |
| BMI                             | 24.76 ± 3.60     | 25.65 ± 3.22     | 25.23 ± 3.55   | >0.05   |
| duration of surgery (minutes)   | 166 ± 47.8       | 169 ± 53.24      | 172 ± 51.5     | >0.05   |
| Total intubation time (minutes) | 185.5 ± 62.7     | 191.23 ± 71.23   | 188.9 ± 69.4   | >0.05   |

BMI: body mass index

**Table 2.** Heart rate, blood pressure, and total 24 hours postoperative analgesia requirement in Ketamine and control group.

|                                       | Ketamine (40 mg) | Ketamine (60 mg) | control       | p-value |
|---------------------------------------|------------------|------------------|---------------|---------|
| Heart rate                            | 87.75 ± 15.39    | 91.25 ± 18.34    | 82.39 ± 17.79 | >0.05   |
| Systolic blood pressure (mmHg)        | 134.4 ± 28.53    | 129.55 ± 24.65   | 124.6 ± 21.31 | >0.05   |
| conscious status (MMSE)               | 26 ± 3.5         | 25.4 ± 2.5       | 26.5 ± 2.7    | >0.05   |
| Total remifentanil consumption µg/24h | 7.8 ± 4.3*       | 8.33 ± 4.2*      | *15.4 ± 3.7   | <0.05*  |

\*: significant (p<0.05) in post-hoc ANOVA test: Ketamin 40 and control p= 0.03, Ketamin 60 and control p=0.02  
MMSE:mini-mental state exam



**Figure 1.** Numerical analogue scale (NAS) to measure postoperative sore throat in patients within ketamine gargle groups (40, 60 mg) and control group.

**Table 3.** Serum ketamine level and post-operation numerical analogue scale (NAS) to measure post-operation sore throat in patients after ear surgery.

| Post-operation Time (hour) | Ketamine 40 mg         |                    | Ketamine 60 mg         |                    |
|----------------------------|------------------------|--------------------|------------------------|--------------------|
|                            | Serum ketamine (ng/ml) | Post-operation NAS | Serum ketamine (ng/ml) | Post-operation NAS |
| 0                          | 0                      | 2.6±1.7            | 0                      | 2.9±1.5            |
| 2                          | 15.3±6.3               | 2.7±1.5            | 18.32±7.3              | 2.3±1.6            |
| 4                          | 12.6±5.2               | 2.8±1.3            | 19.5±6.4               | 2.1±1.7            |
| 12                         | 8.7±6.3                | 2.3±1.4            | 9.4±7.2                | 1.8±1.2            |

VAS: Visual analogue scale

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