Comparison Prophylactic Effects of Gargling Different Doses of Ketamine on Attenuating Postoperative Sore Throat: A Single-Blind Randomized Controlled Trial

Abstract
Context: Postoperative sore throat (POST) is a common annoying problem following endotracheal (ET) intubation. Aims: Comparing the impact of low and high doses of ketamine gargle on lowering POST incidence and severity. Settings and Design: 96 patients selected for septoplasty surgery under general anesthesia were investigated through a single-blind randomized controlled trial. Methods: This study was performed on three equal groups. Group K and G gargled 50 and 100 mg ketamine, respectively, solved in normal saline and group C gargled pure normal saline for 30 s at 5 min before tracheal intubation. POST severity measured immediately after the entrance to the postanesthetic care unit (PACU) and then 2 h, 4 h, 8 h, and 24 h after operation. Statistical Analysis Used: Collected data were analyzed by the Chi-square test, Mann-Whitney test, Kruskal-Wallis test, one-way analysis of variance (ANOVA) and Friedman test using SPSS version 20. Results: POST incidence and severity in group C were significantly higher than both K and G groups at all times. Although significant differences between low and high doses of ketamine were acknowledged at 8 h post-operation, 100 mg ketamine could attenuate POST severity further than 50 mg at all times. Conclusions: It seems that 100 mg outperformed 50 mg ketamine without rising complications and dissatisfaction for subjects. So, it gives us a powerful reason to suggest gargling 100 mg ketamine for lessening POST incidence and severity.

Keywords: Gargle, ketamine, pharyngitis

Introduction
Postoperative sore throat (POST) is a truly widespread issue following ET intubation. This complication was recently known as the 8th common clinical problem following general anesthesia.[1] POST incidence was reported 21–65%.2 The ET intubation procedure can cause airway mucosal injury and inflammation.

Different medical and nonmedical treatment strategies have various effects on POST incidence. Non-medication strategies include using a small size of endotracheal tube (ETT), lubricating the ETT with a water-soluble jelly, ET intubation only when the patient was completely paralyzed, oropharyngeal mild suction, direct intubation and laryngoscopy, use of size-adjusted ETT, use of minimum cuff pressure, and extubating patient when the ETT cuff is completely deflated.[3]

Medical treatments include beclomethasone inhalation, azilen sulfate and licorice gargle, rapid-sequence tracheal intubation with cisatracurium instead of succinylcholine and use of nonsteroidal anti-inflammatory drugs (NSAIDs), and local lidocaine.[4,5] Medical treatments were outstanding above nonmedical strategies.[3,4]

The impact of ketamine hydrochloride on reducing POST was recently appreciated via its anti-inflammatory and analgesic benefits. Ketamine antagonizes the N-methyl-D-aspartate (NMDA) receptors in both the central nervous system (CNS) and peripheral nervous system (PNS).[7,8] Previous findings have shown that NMDA receptors’ antagonists acting on peripheral receptors had anti-inflammatory and analgesic effects.[9] Studies recently claimed that preoperative gargling of ketamine in comparison to normal saline gargle in patients undergoing septoplasty surgery with general anesthesia reduced the frequency and severity of POST whilst the first 24

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h after operation. Doses of ketamine consumed for gargling in the previous studies were 40 mg and 50 mg. 50 mg ketamine decreased the incidence of POST from 85% in the control group to 40% during the first 4 h after operation. It has not been investigated if higher doses of ketamine (e.g., 100 mg) have more desirable effects on attenuating POST or not. Also, it has not been studied if higher doses of ketamine accompany more adverse effects or not. So, the present study has been designed to appreciate the effectiveness and complications of two different doses of ketamine (50 mg and 100 mg) gargling on POST severity and incidence.

Methods

Study design and participants

This study is a single blind randomized controlled trial that compared the prophylactic effects of gargling 50 mg and 100 mg ketamine on POST incidence and severity with each other and with control group as well. Ninety-six patients were selected who underwent septoplasty surgery with general anesthesia at Kashani University Hospital in Isfahan, Iran during the period of time from September 20, 2018 to November 20, 2018. Local ethics committee approval and informed written consent were taken from all subjects before enrolment in the study.

Inclusion criteria for the study considered as being the physical status classes I and II of American Society of Anaesthesiologists (ASA), the age range of 18–65 years old, patients undergoing elective septoplasty surgery with general anesthesia, lack of pre-OST, asthma, and allergy to consuming drugs. Patients who were at risk of prediction for difficult airway intubation or endured ET intubation try for more than one time were excluded from the study.

Ninety-nine patients were considered to take part in the study. However, three patients who didn’t meet inclusion criteria were excluded. After obtaining written informed consent, 96 patients were fallen into three equal groups by computer-based block design random assignment. Group K received 50 mg ketamine mixed in 29 mL saline, group G received 100 mg ketamine mixed in 28 mL saline, and group C received 30 mL normal saline as the control group. 30 mL of these prepared solutions are poured in the same opaque containers and then given to patients by a nurse to gargle for 30 s at 5 min before intubation. The nurse was blinded by the contents of the containers. The exclusive anesthesiologist who performed the ET intubation, as well as one who collected the data, were blinded about the study groups. Due to the fact that the solutions tasted differently, patients could not be blinded Diagram 1.

Procedures and variables assessment

Mean arterial pressure (MAP), heart rate (HR), percentage of oxygenated hemoglobin (SPO2) were recorded before anesthesia induction and then every 30 min during surgery. We used fentanyl 2 µg/kg and thiopental 5 mg/kg as anesthetic drugs. Tracheal intubation was facilitated by 0.6 mg/kg atracurium injection. ETT was a soft, sterile polymerizing vinyl chloride (PVC) tube with standard cuff. We didn’t use bougie or stylet for ET. An exclusive anesthesiologist utilized ETT with an internal diameter of 7.5 mm for women and 8 mm for men. The expert anesthesiologist with 12 years of experience performed the ET intubation after the neuromuscular receptors blockade.

Patients’ anesthesia was maintained with 33% oxygen-saturated operating room air and isoflurane inhalation. 0.1 mg/kg morphine was used as an analgesic during surgery. ET cuff was inflated with the maximum pressure of 20 cmH2O by the anesthesiologist. Cuff pressure was maintained in the range of 18–22 cmH2O by using a manual manometer (manual manometer is a device attached to tracheal tube cuff and measures its air pressure). Neuromuscular receptors’ blockade was removed by using 0.04 mg/kg neostigmine and 0.02 mg/kg atropine.

A physician who was not aware of the studied drugs collected our data. Data were obtained from the information checklist that had three sections: The first section was related to patients’ demographic information. The second section was related to POST severity and incidence. The POST incidence and severity were recorded at five times: 1) immediately after the entrance to the recovery room, 2) 2 h post-operation, 3) 4 h post-operation, 4) 8 h post-operation, and 5) 24 h after operation. POST severity was ranked from 0 to 3. Score 0 was defined as a lack of sore throat. Score 1 was defined as a mild sore throat which meant patients complained when they were asked about it. Score 2 was defined as a moderate sore throat which meant patients had complained about sore throat in the recovery room before they were asked whether they sustained sore throat or not. Score 3 was defined as severe sore throat that meant the presence of vocal changes or sore throat with hoarseness. The third section of the checklist was assigned to complications including cough, laryngospasm, headache, nausea, vomiting, and dizziness. (These complications are not related to ketamine but they are adverse consequences of ET intubation.)

The time from cessation of the anesthetic drug to pulling out the ETT defined as extubation time. The time from patients’ admission to the postanesthetic care unit (PACU) until his discharging from it (based on Modified Aldrete Score) was considered as recovery time. Both extubation and PACU times recorded in the three groups.

The laryngoscopy time (the time gap between insertion of the laryngoscope to the patient’s mouth and visibility of glottis) and intubation time (the time gap from inserting ETT into the glottis and inflating its cuff) were measured using a chronometer by an anesthesia assistant.
After the first 24 h post-operation, patients were asked whether they are satisfied or not and their answers were reported. The systemic adverse effects of ketamine including hallucination, confusion, delirium, agitation, and nausea were also recorded.

The study was registered in the Iranian clinical trial registration site before patients’ participation in this study (IRCT20101211005362N22).

**Statistical analysis**

In terms of estimating the sample size, it was shown that 32 patients per each group were necessary to achieving 80% power with a significant level of 0.05 to detect a 22% difference for the proportion of POST among three groups.

Differences concerning the Incidence of POST, complications, and patients’ satisfaction were compared by the Chi-square test among three groups, whereas the severity of POST between each pair of groups was analyzed by the Mann-Whitney test. The one-way analysis of variance (ANOVA) was used to analyze the demographic and clinical data among the three groups. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kruskal-Wallis test was applied for realizing any significant differences regarding POST severity, extubation time, recovery time, anesthesia time, laryngoscopy time, and intubation time among three groups. Friedman’s test was considered evaluating variables with the passage of time for each group separately. \( P \) value < 0.05 was considered significant.

**Results**

This study assessed 96 patients with ASA physical status classes I and II within three equal groups. Table 1 shows the demographic characteristics of all patients such as age, weight, gender. The Chi-square test showed no significant differences between patients in such variables in Table 1.

POST incidence in group C, group K, and group G were reported 50%, 13%, and 14%, respectively. Comparison of POST incidence between control group and intervention groups showed that it was significantly different at all the times (time 1 \([P < 0.001]\), time 2 \([P = 0.002]\), time 3 \([P < 0.001]\), time 4 \([P = 0.02]\), time 5 \([P = 0.002]\)). There were no significant differences between group K and group G concerning POST incidence at these times \((P = 0.20)\). As time passed by, POST incidence had a visible decline in all groups.
TABLE 2: Frequency distribution of postoperative sore throat (POST) various severity levels at different times in three groups

| POST severity | Group C (Normal saline) | Group K (50 mg ketamine mixed in normal saline) | Group G (100 mg ketamine in normal saline) | Chi-square test value | P |
|---------------|-------------------------|---------------------------------------------|-------------------------------------------|-----------------------|---|
|               | Number | %   | Number | %   | Number | %   |                     |          |
| Time 1        |         |     |         |     |         |     |                     |          |
| 0             | 8       | 25  | 29      | 90.6 | 26      | 81.25 | 85.58               | <0.001   |
| 1             | 5       | 15.6 | 2       | 6.25 | 5       | 15.6 |                     |          |
| 2             | 12      | 37.5 | 1       | 3.1  | 1       | 3.1  |                     |          |
| 3             | 7       | 21.8 | 0       | 0    | 0       | 0    |                     |          |
| Time 2        |         |     |         |     |         |     |                     |          |
| 0             | 12      | 37.5 | 18      | 56.2 | 21      | 65.6 | 44.58               | <0.001   |
| 1             | 2       | 6.2  | 10      | 31.2 | 10      | 31.2 |                     |          |
| 2             | 11      | 34.3 | 3       | 9.3  | 1       | 3.1  |                     |          |
| 3             | 7       | 21.8 | 1       | 3.1  | 0       | 0    |                     |          |
| Time 3        |         |     |         |     |         |     |                     |          |
| 0             | 9       | 28.1 | 17      | 53.1 | 21      | 65.6 | 34.16               | <0.001   |
| 1             | 6       | 18.7 | 11      | 34.3 | 8       | 25   |                     |          |
| 2             | 8       | 25   | 2       | 6.25 | 3       | 9.3  |                     |          |
| 3             | 9       | 28.1 | 2       | 6.25 | 0       | 0    |                     |          |
| Time 4        |         |     |         |     |         |     |                     |          |
| 0             | 16      | 50   | 17      | 53.1 | 25      | 78.1 |                     |          |
| 1             | 9       | 28.1 | 11      | 34.3 | 5       | 15.6 | 73.91               | <0.001   |
| 2             | 4       | 12.5 | 2       | 6.2  | 2       | 6.2  |                     |          |
| 3             | 3       | 9.3  | 2       | 6.2  | 0       | 0    |                     |          |
| Time 5*       |         |     |         |     |         |     |                     |          |
| 0             | 16      | 53.3 | 25      | 78.1 | 28      | 93.3 | 127.39              | <0.001   |
| 1             | 7       | 23.3 | 7       | 21.8 | 2       | 6.6  |                     |          |
| 2             | 5       | 16.6 | 0       | 0    | 0       | 0    |                     |          |
| 3             | 2       | 6.6  | 0       | 0    | 0       | 0    |                     |          |

†Score 0 was defined as a lack of sore throat. Score 1 was defined as a mild sore throat which means patients complained about sore throat only when they were asked about it. Score 2 was defined as a moderate sore throat which means that patients complained about sore throat in the recovery room before they were asked whether they had it or not. Score 3 was defined as a severe sore throat which means the presence of vocal changes or sore throat with hoarseness. *Data related to two subjects in group C and two others in group G were missed. ‡Time 1: immediately after the entrance to the recovery room, time 2: 2 h post-operation, time 3: 4 h post-operation, time 4: 8 h post-operation, and time 5: 24 h after operation

TABLE 3: Comparison of POST severity between three groups by pair at different times

| Times | Mann-Whitney Test (P) | Group C & K | Group C & G | Group K & G |
|-------|-----------------------|-------------|-------------|-------------|
| Time 1 | <0.001                | <0.001      | 0.301       |             |
| Time 2 | 0.007                 | 0.001       | 0.323       |             |
| Time 3 | 0.003                 | <0.001      | 0.307       |             |
| Time 4 | 0.601                 | 0.014       | 0.039       |             |
| Time 5 | 0.016                 | <0.001      | 0.092       |             |

*Group C gargled normal saline, †Group K gargled 50 mg ketamine mixed in normal saline, ‡Group G gargled 100 mg ketamine mixed in normal saline. †Time 1: immediately after the entrance to the recovery room, time 2: 2 h post-operation, time 3: 4 h post-operation, time 4: 8 h post-operation, and time 5: 24 h after operation

According to Table 2, the severity of POST recorded at certain five times for three groups. Chi-square test showed significant differences regarding the frequency distribution of various POST severities levels between three groups at all times (P < 0.05). Friedman’s test demonstrated a significant decrease in POST severity in studied groups as time passed by (P < 0.001) Table 2.

Kruskal-Wallis test showed that there were significant differences between three groups concerning POST severity at all times including time 1 (P < 0.001), time 2 (P = 0.001), time 3 (P < 0.001), time 4 (P = 0.036), and time 5 (P = 0.001).

According to Table 3, both groups G and K experienced significantly less severe POST than the control group at time 1, time 2, time 3, and time 5. There was no significant difference regarding POST severity between group C and group K at time 4. However, group G experienced more slight POST than group K at this time (P = 0.03). Findings illustrated that in all other times, 100 mg ketamine had superiorly lessen POST severity than 50 mg Table 3.

Comparison between three groups regarding intubation time, laryngoscopy time, extubation time, and recovery time didn’t show any significant differences between groups (P > 0.05) Table 4.

Patients did not suffer from complications like headache, nausea, vomiting, and dizziness. Although some subjects sustained cough and laryngospasm, three groups had no significant differences regarding these complications. No systemic adverse effects due to ketamine gargle (including hallucination, confusion, delirium, agitation, and nausea were observed in three groups.

According to Table 5, group C reported significantly much more dissatisfaction in comparison to intervention...
groups ($P < 0.001$). On the other hand, group G profited the most satisfaction rate in Table 5.

**Discussion**

Previous studies reported that POST incidence is influenced by many different variables such as age, gender, intubation time, ETT size, and use of succinylcholine.$^{10}$ This study did not find any relationship between POST incidence and severity with variables like age, gender, and intubation time.

This study showed that both 50 mg and 100 mg ketamine gargle at 5 min before intubation not only decreased POST incidence at all times but also significantly reduced POST severity in comparison with a control group without any more adverse effects. Consumption of 100 mg ketamine for gargling significantly subsided POST severity further than 50 mg of it at 8 h post-operation. Considering the excellence of 100 mg ketamine at various times concerning lessening POST severity and incidence, it would be found significant differences between gargling 50 mg and 100 mg ketamine if we had performed this study with more subjects.

Aigbedia *et al.*$^{11}$ showed that 40 mg of ketamine gargle decreased POST incidence more than lidocaine significantly. They found that POST severity was lower in the ketamine group as well. Most of the patients in the ketamine group experienced a low or moderate level of POST severity. But more patients in the lidocaine group experienced a severe sore throat. Their results were in accordance with our findings.

Aigbedia’s study found that POST incidence was higher in patients who were being intubated for more than 1 h. All of the patients in our study were being intubated for more than 1 h so POST incidence and severity were independent from intubation time.

Canbay *et al.*’s study$^{12}$ compared the effect of ketamine gargle on POST incidence and severity versus the control group at 0, 2, and 24 h after operation. It showed that the incidence and severity of POST in the ketamine group were lower than the control group, which was also in accordance with our findings.

Rudra *et al.*’s$^{13}$ study compared 50 mg of ketamine gargle effects on POST incidence with a control group. They found that the incidence reduced as time passed by in both groups that it was similar to our results. POST incidence was less in the ketamine group compared to the control group and no drug-induced complications were reported which were in accordance with our results as well.

Teimorian *et al.*$^{14}$ claimed that 0.5 mg/kg of ketamine gargle had fewer effects on reducing POST incidence and severity at 2,4, and 24 h following surgery compared to magnesium sulfate gargle which may be due to the use of a low dose of ketamine than other studies.

One of the POST causes is local trauma during ET intubation which makes aseptic inflammation of the laryngeal mucosa. Ketamine gargle decreased POST incidence and severity due to local anti-inflammatory effects of it. Another study claimed that a low dose of intravenous ketamine did not have any effects on POST incidence.$^{5,12}$

The POST incidence in the control group was 50%, which was similar to the previous studies.$^{13}$ This incidence depends on the method of sore throat evaluation. We used a questionnaire for patients to assess POST severity and incidence.

| Variable | Group C (Normal saline) | Group K (50 mg ketamine in normal saline) | Group G (100 mg ketamine in normal saline) | $P$ |
|----------|--------------------------|------------------------------------------|------------------------------------------|-----|
| Mean extubation* time (minutes) | 4.13±8.15 | 4.90±2.90 | 4.67±2.87 | 0.45 |
| Mean recovery† time (minutes) based on MAS** | 61.10±20.64 | 61.43±13.31 | 60.16±9.62 | 0.24 |
| Mean laryngoscopy‡ time (seconds) | 95.31±44.97 | 94.31±27.47 | 100±42.76 | 0.76 |
| Mean intubation‡ time (seconds) | 13.31±2.39 | 12.84±3.49 | 15.06±12.31 | 0.10 |
| Mean observation in the recovery room defined as recovery time. | 87.03±43.02 | 80.78±27.03 | 90.63±40.47 | 0.56 |
| $^*$The time from cessation of the anesthetic drug to ETT extraction considered as extubation time. $^†$The time spent on patients’ continuous observation in the recovery room defined as recovery time. $^‡$The laryngoscopy time was the interval between the insertion of the laryngoscope into the mouth and the visibility of the glottis. $^§$Intubation time defined as the time from inserting ETT into the glottis to inflating ETT cuff which was measured using a chronometer by an anesthesia assistant. **MAS: Modified Aldrete Score.
In a study performed by Chan et al.\textsuperscript{[14]}, it was shown that 30 s of gargling with ketamine 40 mg mixed in 20 mL normal saline at 5–10 minutes before anesthesia induction could attenuate POST in the early postoperative period.

Hadavi et al.\textsuperscript{[15]} compared POST severity and incidence followed by ketamine gargle, saline gargle, and no intervention. In spite of lacking significant differences between these two groups, subjects in the ketamine group experienced a lower level of POST severity and incidence. They didn’t realize significant differences between the saline group and the group without any intervention.

In our study, the doses of 50 mg and 100 mg ketamine consumed for gargling. Both two doses of ketamine attenuated POST severity and incidence significantly until 24 h after the operation. The current study showed that gargling a higher 100 mg dose of ketamine seems superior to attenuate POST severity than 50 mg ketamine.

\textbf{Limitations}

Age-limit, absence of patients with ASA physical status classes III and IV, and low sample size are considered to be the main limitations of this study.

Conclusion: gargling both 50 and 100 mg ketamine mixed with 30 mL normal saline at 5 min before tracheal intubation can reduce POST severity and incidence. Not only no more complications were accompanied by increasing the dose of ketamine to 100 mg but also the subjects’ satisfaction status significantly improved.

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\textbf{Conflicts of interest}

There are no conflicts of interest.

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