Original Article

Comparing the effect of ketamine and benzydamine gargling with placebo on post-operative sore throat: A randomized controlled trial

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Abstract

Background: Air way intubation for general anesthesia usually leads to sore throat after surgery. Ketamine plays an important role to block a number of receptors related to pain. Benzydamine hydrochloride is a non-steroidal anti-inflammatory drug that has been used to improve oropharyngeal disorders. In this study, it was intended to compare the effect of gargling different solutions before the surgery on post-operative sore throat (POST) in patients who underwent general anesthesia for hysterectomy.

Materials and Methods: A total of 60 patients who underwent the elective hysterectomy were entered to the randomized controlled trial regarding to the eligibility criteria. Patients were simply randomly allocated to three groups and received one code. Every code was representative for a specific drug: 20 cc normal saline (control group) or 1.5 mg benzydamine in 20 cc solution or 20 mg ketamine in 20 cc solutions. All the research teams were blinded to the received solutions. POST was evaluated with numerical rating scale. The data were entered to SPSS software and analysis of variance (ANOVA) and Kruskal-Wallis one-way analysis of variance test, were performed.

Results: The mean ages of ketamine, benzydamine, and normal saline recipients were not significantly different. The trend of the severity of sore throat during the first 24 h after the operation in ketamine recipients was significantly lower than the other two groups ($P < 0.001$).

Conclusion: The pain scale after surgery was reduced by using both ketamine and benzydamine, but the ketamine effect was more noticeable.

Key Words: Benzydamine, ketamine, post-operative sore throat, randomized controlled trial

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INTRODUCTION

Air way intubation within general anesthesia usually leads to sore throat. Although, the severity of sore throat is in association with lots of factors such as size and pressure of tracheal tube and also experience of the Anesthesiologist, the complication can be caused even by experts with slight trauma.[1-3] Sore throat can be accompanied by cough, laryngitis, tracheitis, dysphagia or hoarseness. It is assumed

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that the symptoms are in association with mucosal inflammation following trachea manipulation by means of laryngeal mask airway or oral airway.[4]

Previously, it was revealed that the damage was more frequent in womenfolk and was in correlation with gynecologic surgeries and succinylcholine administration.[5] To reduce the risk of this complication, lots of medical and practical methods have been studied. Among non-pharmaceutical methods, using the thinner tubes with slippery sheathes and doing intubation procedures after complete muscular relaxation were noticeable.[6] Gargling with sodium azulene sulfonate, fluticasone propionate oral inhalation, beclomethasone inhalation description, and intravenous dexamethasone injection and were all recommended as pharmaceutical prophylactic approaches to reduce post-operative sore throat (POST).[7-10]

Ketamine plays an important role to block a number of receptors related to pain. N-methyl-D-aspartate receptors in peripheral nerve synapses and the spine and 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors have been detected to be blocked by this drug. Furthermore, ketamine has been used in previous studies for POST control.[11,12]

Benzydamine hydrochloride is a local anti-inflammatory and analgesic agent produced initially by the Angelini laboratories in 1960s. Subsequently, topical productions have been advertised globally for the symptomatic healing of oropharyngeal disorders.[13,14]

Because, it was previously shown that POST complication was more common in female sex especially, after gynecologic surgeries[1,5] and with considering the palliative effects of ketamine and benzydamine hydrochloride in the other hand while as no study has compared formerly these two drugs effects on POST, this study was designed to find out if there was any symptomatic improvement by gargling these two drugs.

MATERIALS AND METHODS

Ethical approval

The protocol of this clinical trial was approved by the Iranian registry of clinical trials hosted by Tehran University of Medical Sciences (TUMS). The proposal was approved by the institutional review board of TUMS. The study was conducted in Rasool-Akram Hospital, and processes were followed by the official spectator informed about this study. Regarding to Helsinki declaration, the drugs and their adverse effects were explained to the patients prior to the study. The patients also were convinced that they would be blinded to drugs and could not ask about contain of the solution, but they were assured that it was one of the three studied drugs. The written consent including complete explanation of the study, all patients' and authors' rights and also the main purpose and future effect of this study was signed by the patients or their guardians.

Participants

From September 2011 to October 2012, patients who were candidated for elective hysterectomy at Rasool Akram Hospital were considered to be entered to the study. All women at the age of 15-60 years old were entered if they were convinced about the study. The included patients had to have an American Society of Anesthesiologists class of 1 or 2 and the patients who didn't underwent difficult intubation procedures such as no more than one time or the duration of intubation less 15 s. If the patient faced to any adverse effects of the drug or was not consent with the intervention during the study, the approach was changed, and she was excluded from the study. Furthermore, patients who were alcohol, opium or other drugs abuser, the ones with positive history of hypertension, diabetes mellitus, and chronic liver or renal failure, any previous sensitization to anesthetics, and sore throat due to cold or infectious diseases within the last 2 weeks were all excluded from the study.

Interventions

In this study, it was intended to compare the effect of gargling three solutions before the surgery on POST in patients who underwent general anesthesia for elective hysterectomy.

To hydrate the patients, before induction of anesthesia all patients received 300 ml normal saline serum in the operation room. Then they were asked to gargle one of the three solutions (according to their codes) for 30 s, 5 min before anesthesia: 20 ml normal saline (control group, number = 20) or benzydamine 1.5 mg (benzydamine hydrochloride mouthwash, each 100 ml contains: Benzydamine HCl 0.15 g. Behvarzan company, Rasht, Iran) in 19 ml normal saline (number = 20) or ketamine 20 mg (ketamine hydrochloride 50 mg/ml, Rotex medica, trittau, Germany) in 19 ml normal saline (number = 20).

Standard non-invasive monitoring was performed throughout the anesthesia. Following pre-oxygenation, induction of anesthesia was initialed with fentanyl 2-3 μg/kg, midazolam 0.02 mg/kg, propofol 1-2 mg/kg and atracurium 0.5 mg/kg. Maintenance of anesthesia was provided with oxygen and propofol 100 μg/kg/min. Furthermore every 30 min, 10 mg of atracurium

was used. The patients were intubated by a single lumen cuffed low-pressure and high volume polyvinyl chloride (PVC) tracheal tube number 7.5 (tracheal tube, oral/nasal-Well Lead Medical Company, Hamburg, Germany). The tracheal tube cuff was inflated with room air until no air leakage could be haired at a peak airway pressure of 20 cm H_2O. Then the cuff pressure was adjusted to 20 cm H_2O using a handheld pressure gauge. After the surgery, In order to reverse neuromuscular block at the end of the surgery, 0.02 mg/kg atropine and 0.04 mg/kg neostigmine were injected intravenously.

Objectives and outcomes

The primary goal of the study is to compare the effects of gargling ketamine and benzydamine on POST control. The secondary goals are hemodynamic changes and any side effects while using the above mentioned drugs. Demographic data's were recorded. To observe hemodynamic situations, systolic and diastolic blood pressure and pulse rate were all measured before, and after gargling. Furthermore, all vital signs were recorded before and after intubation. To define the efficacy of the intervention, sore throat was assessed after the operation according to a numerical rating scale (NRS) from 0 to 10.[15] Pain assessment was achieved by a trained technician using NRS at 0 (on arrival at the past anesthesia care unit), 2 h and 24 h of the operation. To reduce ascertainment biases, every patient was asked about scaling her pain within different times by a same person. Furthermore, because intubation skill could influence on the predicted sore throat, all the patients were intubated by the same expert anesthesiologist. The patients were evaluated for presenting any possible side effects such as hallucination, confusion, nausea, and vomiting. Prior to the study, it was hypothesized that NRS was not statistically different in the three groups.

Sample size

Regarding efficiency, ethics, cost-effectiveness and the research duration, the sample size in this study was calculated by the formula for clinical superiority design.[16] The α error (type one error) and power were considered 0.05 and 0.80 respectively.

Randomization and blinding

Patients' names were coded to numerical arrangement by the secretary with no other involvement in the trial. The patients were all explained and convinced that they would be placed in one of the three groups, but they could not choose or find their group. Patients were simply randomly allocated to three groups by means of a computer generated list (GraphPad Software®, Inc., La Jolla, California, USA) according to their numbers. A total of 60 envelopes including the code of the drug were prepared for the study, by a secretary of the operation room. Every patient received an envelope with one of the codes: A, B or C. The mean of the codes was representative just for the secretary who was responsible to provide the solution for the patients according to their codes inside their own envelopes. All the surgeons, anesthesiologists, and statistical analyzer were blinded to the means of the codes and the received solutions.

Statistical analysis

The data were entered to the SPSS software version 18. Mean and percentage were representative for quantitative and qualitative variables, respectively. To check the parametric situations, one sample-Kolmogorov-Smirnov test was performed for continuous variables.

If the data were distributed normally, analysis of variance (ANOVA) and if the distribution was not normal Kruskal-Wallis one-way analysis of variance test were performed. If there was a significant difference in three groups, to figure out where the differences lie, *post hoc* tests were checked (Tukey or Scheffe). To detect any overall differences between related means repeated measures ANOVA was used. The level of significance was considered less than 0.05.

RESULTS

This study was performed on 60 patients who underwent elective hysterectomy with general anesthesia and were allocated to three groups randomly (20 patients in each group). The mean ages of ketamine, benzydamine and normal saline recipients were 36.85 ± 10.69, 34.45 ± 12.25 and 35.00 ± 12.48 respectively ($P = 0.79$). The mean heights of ketamine, benzydamine, and normal saline recipients were 162.7 ± 6.0, 161.6 ± 6.3 and 163.0 ± 5.9 ($P = 0.7$) the mean weights of ketamine, benzydamine and normal saline recipients were 66.8 ± 8.8, 64.6 ± 11.5, and 65.1 ± 10.1 respectively ($P = 0.433$).

The mean NRS results for each group within different intervals after surgery are illustrated in Table 1.

The trend of the severity of sore throat during the first 24 h after the operation in ketamine recipients was significantly lower than the other two groups ($P < 0.001$). The trend of sore throat presentation by using different solutions is shown in Figure 1.

Comparing pulse rate before and after gargling revealed no significant differences. The comparison between patients' pulse rates before and after

intubation and also systolic and diastolic blood pressures was not statistically and clinically different. Furthermore, the mentioned variable changes were not significantly different by comparing means between the three groups [Tables 2-4]. No side-effects observed between groups. All of the intubations times were less than 15 s. The Consort flowchart of this study has shown in Figure 2.

DISCUSSION

In this study, we compared the effect of preoperative ketamine or benzydamine gargling with placebo on patients with POST. Furthermore, the effect of ketamine and benzydamine were compared with each other. Considering our results, the pain scale after surgery was reduced by using both ketamine and benzydamine, but the ketamine effect was more noticeable.

Tracheal damage and POST following general anesthesia and intratracheal intubation can be influenced by lots of factors including, sex, gender, size, and pressure of tracheal tube, the duration of intubation, patient position, and the Anesthesiologist's experience[5,17-20] To avoid the effect of these confounding factors on our results, all the patients were selected

Table 1: The mean NRS results for each group within different intervals after surgery

Used compounds	NRS (just after the surgery) mean±SD	NRS (after 2 h) mean±SD	NRS (after 24 h) mean±SD
Normal saline recipients (CR)	1/35±0.98	2/40±0.94	2/30±1.08
Ketamine recipients	0/00±0.00	0/35±0.67	0/25±0.55
Benzydamine recipients	0/55±1.31	1/35±1.26	0/90±0.91
P value	<0/001	<0/001	<0/001

NRS: Numerical rating scale, CR: Control group, SD: Standard deviation

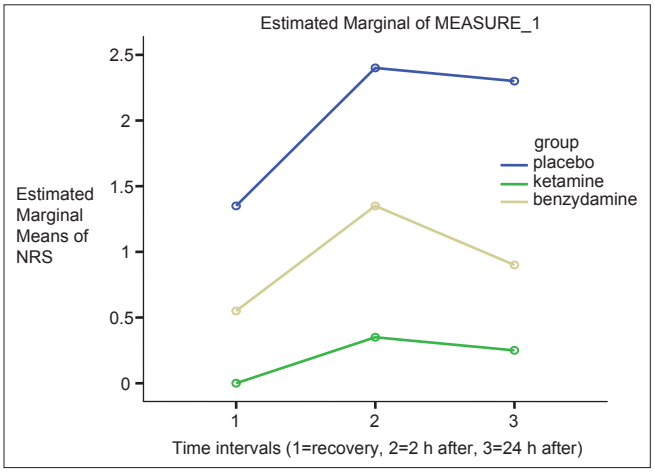

Figure 1: Comparing means of numerical rating scale between the three groups of study in 24 h interval after surgery

Table 2: Mean and SD of systolic and diastolic blood pressures before and after intubation in three groups

Used compounds	Systolic pressure mean (SD)		Diastolic pressure mean (SD)	
	Before intubation	After intubation	Before intubation	After intubation
Normal saline group	107.65 (13.89)	130.05 (10.97)	70.40 (11.45)	85.25 (11.70)
Ketamine group	101.30 (12.62)	128.15 (20.11)	63.10 (12.4)	84.20 (16.26)
Benzydamine group	102.30 (12.05)	130.00 (17.37)	65.35 (9.65)	88.10 (16.39)
P value	0.328	00.932	0.120	0.696

SD: Standard deviation

Table 3: Mean and SD of systolic and diastolic blood pressures before and after gargling in three groups

Used compounds	Systolic pressure mean (SD)		Diastolic pressure mean (SD)	
	Before gargling	After gargling	Before gargling	After gargling
Normal saline group	125.30 (17.54)	130.60 (17.05)	80.25 (8.78)	83.80 (10.90)
Ketamine group	127.40 (14.27)	134.70 (14.06)	83.70 (10.94)	89.65 (11.30)
Benzydamine group	129.60 (16.75)	131.15 (17.09)	84.20 (12.02)	83.65 (11.33)
P value	0.706	0.685	0.448	0.953

SD: Standard deviation

Table 4: Mean and SD of pulse rate before and after gargling and intubation in three groups

Used compounds	Pulse rate before gargling mean (SD)	Pulse rate after gargling mean (SD)	Pulse rate before intubation mean (SD)	Pulse rate after intubation mean (SD)
Normal saline group	78.20 (15.29)	81.90 (14.64)	69.35 (14.51)	82.50 (14.28)
Katamine group	86.20 (13.30)	92.65 (14.67)	79.10 (12.73)	89.75 (11.01)
Benzydamine group	84.10 (12.8)	84.95 (12.51)	73.70 (8.92)	86.85 (8.15)
P value	0.174	0.071	0.051	0.154

SD: Standard deviation

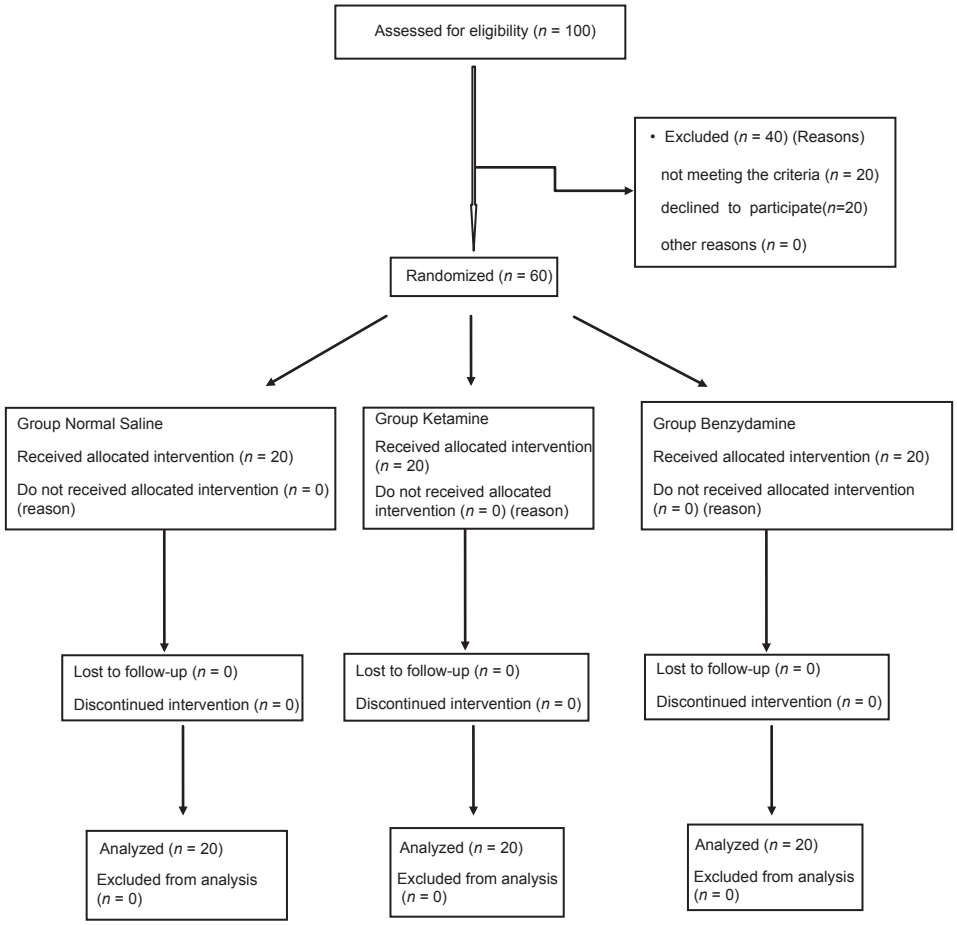

Figure 2: Consort flowchart of this study

from womenfolk (following hysterectomy surgery) and the mean ages of the three groups were not significantly different. Furthermore, the mean time of the operation was 2 h for all patients. Moreover, all the patients were intubated by a similar expert anesthesiologist with a high volume low pressure tube (size of 7.5).

To reduce post-intubation complications especially sore throat lots of studies have been performed. In 2008, a study[21] found that gargling ketamine prior to surgery could improve sore throat during the first 24 h after the operation. Following that to figure out the probable systemic effect of the drug, in 2010,[22] Park *et al*. designed a study and revealed that ketamine intravenous administration did not reduce POST. Although, we did not consider ketamine intravenous level in this study, the absence of any significant results between pre and post-operative pulse rate and blood pressure of the patients suggested that the favorable results achieved from NRS were not influenced by systemic effects of the drug.

In a clinical trial study, performed by Chan *et al*.[23] pain improvement in patients who gargled ketamine solution before surgery was scored approximately same as the control group in the 24th h although its effect was significantly more than placebo within first 2 h after surgery. In our study, although both studied drugs were effective, but gargling benzydamine hydrochloride was less effective than ketamine [Figure 1]. In a study, in 2006 it was proved that benzydamine could reduce POST within the first 24 h after surgery.[24] Furthermore, other studies during the next years showed the same results as we achieved in this study.[25]

There were some noteworthy limitations of the present study: Although systemic absorption of ketamine could effect on pain conception, we did not measure the plasma levels of the drug. In the other hand, inappropriate patients' compliance due to the severity of pain and sometimes delayed consciousness after surgery caused some unreliable scores evaluated by NRS.

In the present study, no side-effect was verified by gargling the low concentrations of the two drugs that could be suggestive for future usages of both ketamine and benzydamine hydrochloride although

the ketamine effect was more remarkable. Hereby, we suggest more studies to compare the systemic effects of these drugs on POST improvement.

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