Original Article

Intravenous dexamethasone versus ketamine gargle versus intravenous dexamethasone combined with ketamine gargle for evaluation of post-operative sore throat and hoarseness: A randomized, placebo-controlled, double blind clinical trial

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Abstract

Background: Sore throat and hoarseness are the most frequent subjective complaints after tracheal intubation for general anesthesia. We conducted a prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intravenous (IV) dexamethasone plus ketamine gargle for reducing the incidence and severity of post-operative sore throat (POST) and hoarseness.

Materials and Methods: 140 patients (aged 16-65 year) scheduled for elective surgery were enrolled. Patients were randomly allocated into four groups of 35 subjects each: Group K, gargled 40 mg ketamine in 30 ml saline; Group D, were infused 0.2 mg/kg IV dexamethasone; Group KD, gargled 40 mg ketamine in 30 ml saline plus 0.2 mg/kg IV dexamethasone; Group P (placebo) that received saline (gargle and IV). POST was graded at 0, 2, 4, 8, 16 and 24 h after operation on a four-point scale (0-3).

Results: The incidence and severity of POST were significantly lower in Group KD, compared with the other groups at all times after tracheal extubation for up to 24 h ($P < 0.05$). Also the incidence and severity of hoarseness were significantly lower in each Groups of KD and K and D compared with group placebo ($P < 0.05$).

Conclusion: The prophylactic use of 0.2 mg/kg of IV dexamethasone plus ketamine gargle significantly reduced the incidence and severity of POST compared with using each of these drugs alone or using placebo.

Key Words: Dexamethasone, gargle, hoarseness, ketamine, sore throat, tracheal intubation

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INTRODUCTION

Post-operative sore throat (POST) and hoarseness as the result of trauma to the airway mucosa after tracheal intubation are common complications after general anesthesia. The incidence of POST has been reported about 21-65%.[1-7] It may leave the patient with an unpleasant memory of the operation after

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discharge from the hospital. It had been rated by patients as the eighth most adverse effect in the post-operative period.[5,8-11] Despite attempts to reduce its incidence and severity,[12-15] there are currently no effective therapies for the prevention of POST and hoarseness in patients. Various trials have been used for reducing POST with variable success. Like, smaller-sized endotracheal tubes, careful airway instrumentation, intubation after full relaxation, minimizing intracuff pressure, gentle oropharyngeal suctioning, and extubation when the tracheal tube cuff is fully deflated that have been reported to decrease the incidence of POST.[16] The pharmacological methods include, using azulene sulphate,[15,17] ketamine gargle,[18] steroid gels,[10] and steroid injections.[11,19,20] Experimental studies point out that peripherally administered N-methyl-D-aspartate (NMDA) receptor antagonists are involved with anti-nociception,[21] and anti-inflammatory cascade.[22] Ketamine is a potent antagonist of the NMDA receptor that currently available for use in humans.[23] Dexamethasone is a potent corticosteroid with analgesic and anti-inflammatory effects,[24-26] that has a prophylactic effect on post-operative nausea and vomiting,[25,27] and prescribed for the treatment of a sore throat resulting from tracheal mechanical irritation due to its modulating effects of tissue edema and pain.[24,28-30] Canbay *et al*.,[18] in one study showed that ketamine gargle significantly reduced the incidence and severity of POST but in this study, ketmaine couldn't reduce the incidence and severity of sore throat at all times up to 24 h after surgery. In the other hand, Park *et al*.,[11] in one study concluded that the prophylactic use of 0.2 mg/kg of dexamethasone significantly decreases the incidence and severity of sore throat and hoarseness 1 h and 24 h after tracheal extubation of a double-lumen tube (DLT). In this study the incidence of POST 24 h after tracheal extubation was 27%. There was no previous study that investigated the effect of using intravenous (IV) dexamethasone in combination with ketamine gargle on the incidence and severity of sore throat and hoarseness after tracheal extubation. So we designed present study to evaluate prophylactic effect of using dexamethasone – ketamine combination compared with using IV dexamethasone or ketamine gargle alone on the POST and hoarseness.

MATERIALS AND METHODS

After obtaining approval from the research committee of the Isfahan University, and individual written informed consent, 152 patients between 16 years and 65 years of age with American Society of Anesthesiologists (ASA) physical status I-II who were scheduled for elective surgery under general anesthesia in Kashani Hospital of Isfahan City, were enrolled in this study between October 2011 and October 2012. The study was conducted in a prospective, randomized, placebo-controlled, and double blind clinical trial. Inclusion criteria were patients undergoing elective surgical procedures requiring one-lung ventilation and patients with duration of surgery between 60 min and 300 min, mouth opening of >3.5 cm, a Cormack and Lehane score of lower than 4,[31] and patients without a history of POST and asthma, known allergies to study drugs, recent non-steroidal anti-inflammatory drug medication, known difficulty with tracheal intubation. Exclusion criteria were: Patients with the requirement of mechanical lung ventilation after surgery in the intensive care unit, and those who required more than one attempt for tracheal intubation. It took 12 months to complete this study. The sample size was estimated from lower frame and with consideration the assurance level of 95% and power test of 80%, presuming the incidence of POST to be 65%,[1-7] and the effect of dexamethasone in reducing 27% of POST,[11] obtained 60 person but with considering that the surveying are four groups, sample size enrolled 35 patients in each group. Finally the sample size estimated 31 people in each group, for raising the assurance level and to compensate for potential dropouts, we enrolled 35 patients in each group. Patients were randomized double blind clinical trial into the four groups with the help of a computer-generated table of random numbers. Group K, who gargled 40 mg ketamine in 30 ml normal saline for 30 s and received 2 mg/kg IV saline, 5 min before induction anesthesia. Group D, who gargled 30 ml normal saline for 30 s and received 0.2 mg/kg IV dexamethasone, 5 min before induction anesthesia. Group KD, who gargled 40 mg ketamine in 30 ml normal saline and received 0.2 mg/kg IV dexamethasone, 5 min before induction anesthesia. Group P who received a placebo of normal saline (gargled 30 ml normal saline for 30 s and received 0.2 mg/kg IV normal saline, 5 min before induction of anesthesia). The solutions were prepared by the researcher and then the anesthetic nurse without any information from the solution type asked patients to gargle with the preparation for 30 s after their arrival in the operation room and the another study drug (dexamethasone or normal saline) was injected IV 5 min before anesthesia induction. The same technique of anesthesia operated on all patients. Anesthesia was induced 5 min later. The randomized process and the identity of the study drugs were blinded from the patients, the participating Anesthesiologist during surgery, and the investigators who collected the post-operative data. Monitoring consisted of non-invasive arterial pressure, pulse oximetry, electrocardiography. Patients in the four

groups underwent a standardized anesthesia protocol which included induction with thiopental (5 mg/kg) and fentanyl (2 μg/kg). Atracurium was used as a muscle relaxant. The trachea was intubated with a soft seal cuffed sterile polyvinyl chloride endotracheal tube with a standard cuff (Supa incorporation, Iran) and an internal diameter of 7-8 mm. Tracheal intubation was performed by an experienced Anesthesiologist. After tracheal intubation, anesthesia was maintained with a 50% nitrous oxide/oxygen mixture along with isoflurane in a concentration of 0.8-1.2%. Ventilation was adjusted to produce normocapnia. All the patients received morphine 1 mg/Kg as an analgesic drug. The tracheal tube cuff was inflated until no air leakage could be heard with a peak airway pressure at 20 cm H_2O (and cuff pressure was maintained between 18 cm and 22 cm H_2O using handheld pressure gauge (Endotest; Rüsch, Kernen, Germany). Those patients who required more than one attempt for passage of the tube were excluded from the study. At the end of surgery, reversal of residual neuromuscular blockade was accomplished using IV atropine 20 μg/kg and neostigmine 40 μg/kg. Oropharyngeal suction was performed under direct vision to avoid trauma to the tissues before extubation and to confirm that the clearance of secretions was complete.[32] All patient's tracheas were carefully extubated when they were able to obey commands and lung ventilation was deemed adequate. The following variables regarding tracheal intubation were recorded: Glottis exposure as defined by Cormack and Lehane score;[31] laryngeal tube size; the time to achieve intubation defined as the time from the beginning of laryngoscopy until successful tracheal intubation; the duration of tracheal intubation; and the duration of tracheal extubation. The patients were interviewed in a standard fashion by a blinded investigator. Assessments of patients recovery were made by a blinded observer, including the times from discontinuation of anesthesia until the time to achieve a modified Aldrete score of 9.[33] On arrival in the post-anesthesia care unit (0 h), and at 2, 4, 8, 16 and 24 h thereafter, POST was graded on a four-point scale (0-3): 0, no sore throat; 1, mild sore throat (complains of sore throat only on asking); 2, moderate sore throat (complains of sore throat on his/her own); and 3, severe sore throat (change of voice or hoarseness, associated with throat pain). Hoarseness was defined as a change in voice quality and was graded on a four-point scale (0-3): 0: No hoarseness; 1: Hoarseness at the time of interview, but noted only by patient; 2: Hoarseness that is readily apparent, but mild; 3: Hoarseness that is readily apparent and severe. Sedation was assessed during interviewed the patients to investigate the POST using the four-point observer's assessment of alertness/sedation scale (where 0 = awake/alert and 3 = deep sleep).[34] Any complication (e.g. peptic ulcer, frequency of infections, and electrolyte imbalance) associated with a single use of dexamethasone was obtained from review of the medical record. Other side effects, if any, were also noted. Differences in the age and weight among the groups were compared by one-way analysis of variance. Differences in the incidence of POST among the groups were compared with the help of Mann-Whitney U-test. Severity of POST was analyzed by Fisher's exact test. SPSS 16 for windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P < 0.05$ was considered as significant.

RESULTS

Of the 152 enrolled patients, 12 patients were excluded from the analysis three patients in the Group D, 4 in the Group K, 3 in the Group KD and finally 2 in the Group P [Flow Diagram 1]; 11 patients required more than one attempt for intubation and one patient in Group D that required to mechanical lung ventilation after surgery in the intensive care unit. Demographic data for the remaining 140 patients are shown in Table 1. There were no significant differences among the four groups with respect to age, gender, weight, ASA status, duration of surgery, Duration of anesthesia and recovery ($P > 0.05$). Variables associated with tracheal intubation are listed in Table 2. Cormack and Lehane scores, the size of laryngeal tube, time to achieve intubation, duration of tracheal intubation, extubation time, did not differ among the four study groups. There were no significant differences in the incidence of sedation level during 24 h after the operation between the four groups ($P > 0.05$) [Table 3]. The incidence of post-operative laryngopharyngeal discomfort is listed in Table 4. The incidence and severity of POST were significantly lower in Group KD compared with the other groups at all times during 24 h after the operation as listed in Table 4 ($P < 0.05$). Also the incidence and severity of hoarseness were significantly lower in each Groups of KD and K and D compared with Group P at all times after tracheal extubation for up to 24 h ($P < 0.05$). But there were no significant differences between Groups KD with Group K and Group D in this regard ($P > 0.05$). No local or systemic side-effects were observed. Only one patient in Group P had vomiting.

DISCUSSIONS

The results of this study demonstrated that the incidence and severity of POST and hoarseness were decreased in each Groups of KD and K and D compared with Group P at all times during 24 h after tracheal extubation. Also gargling of 40 mg ketamine

Table 1: Demographic data and data related to the surgery

Group variable	Group D (*n*=35)	Group K (*n*=35)	Group KD (*n*=35)	Group P (*n*=35)	*P* value
Age (year)	29.7±12.3	31.1±13.6	33.5±13.4	34.5±13.4	0.41
Weight (kg)	69.3±9.8	69.9±7.6	71.2±8.8	71.5±6.1	0.64
Sex (male/female)	29/6	26/9	31/4	32/3	0.21
ASA (I–II)	25/10	22/13	23/12	20/15	0.65
Duration of operation (min)	70.3±19.9	67.2±20.4	76.6±26.8	77.5±24.3	0.18
Duration of anesthesia (min)	76.9±19.7	76.6±19	86.7±25.6	81.2±28.6	0.24
Recovery time (min)	31.6±2.3	32.1±2.3	31.5±2.1	33.1±4.8	0.13

Data are given as mean±SD or absolute number. No significant differences were found between the groups. Group D: Received IV dexamethasone 0.2 mg/kg and gargled 30 ml saline, Group K: Gargled 40 mg ketamine in 30 ml saline and received 2 mg/kg IV saline, Group KD: Gargled 40 mg ketamine in 30 ml normal saline and received IV dexamethasone 0.2 mg/kg, Group P: Received a placebo of normal saline (gargle and intravenously). ASA: American Society of Anesthesiologists, IV: Intravenous

Table 2: Variables associated with tracheal intubation

Group variables	Group D (*n*=35)	Group K (*n*=35)	Group KD (*n*=35)	Group P (*n*=35)	*P* value
Cormack and Lehane score (1/2/3)	26/6/3	21/9/5	28/5/2	25/8/2	0.61
Lt size (7,7.5,8)	1/5/29	1/8/26	2/3/30	0/4/31	0.51
Time to achieve intubation (s)	21±9.9	19.9±3.7	18.6±6.2	20.1±0.8	0.43
Duration of tracheal intubation (min)	101.1±22.9	95.3±26	103.8±30.9	106.4±29.9	0.38
Extubation time (s)	12.1±3	11.2±2.6	12.9±4.6	13.4±4.8	0.08

Data are given as mean±SD or number. Group D: Received IV dexamethasone 0.2 mg/kg and gargled 30 ml saline, Group K: Gargled 40 mg ketamine in 30 ml saline and received 2 mg/kg IV saline, Group KD: Gargled 40 mg ketamine in 30 ml normal saline and received IV dexamethasone 0.2 mg/kg, Group P: Received a placebo of normal saline (gargle and IV), Lt size: Laryngeal tube size. IV: Intravenous

Table 3: Sedation levels in patients undergoing of study

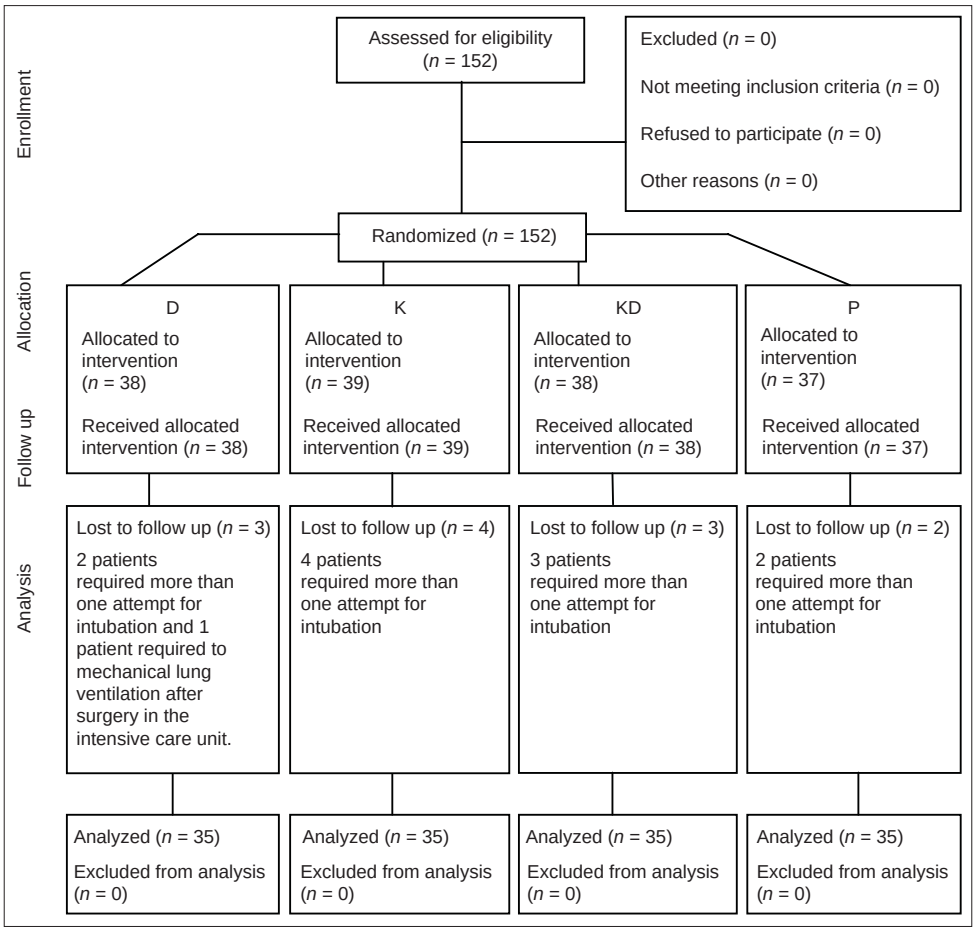
Group variables	Group D (*n*=35)	Group K (*n*=35)	Group KD (*n*=35)	Group P (*n*=35)
0 h after tracheal extubation (0/1/2/3)	17/13/5/0	17/12/6/0	17/11/7/0	15/12/8/0
2 h after tracheal extubation (0/1/2/3)	35/0/0/0	35/0/0/0	35/0/0/0	35/0/0/0
4 h after tracheal extubation (0/1/2/3)	35/0/0/0	35/0/0/0	35/0/0/0	35/0/0/0
8 h after tracheal extubation (0/1/2/3)	35/0/0/0	35/0/0/0	35/0/0/0	35/0/0/0
16 h after tracheal extubation (0/1/2/3)	35/0/0/0	35/0/0/0	35/0/0/0	35/0/0/0
24 h after tracheal extubation (0/1/2/3)	35/0/0/0	35/0/0/0	35/0/0/0	35/0/0/0

Values are number of patients. There were no significant differences between the groups. Group D: Received IV dexamethasone 0.2 mg/kg and gargled 30 ml saline, Group K: Gargled 40 mg ketamine in 30 ml saline and received 2 mg/kg IV saline, Group KD: Gargled 40 mg ketamine in 30 ml normal saline and received IV dexamethasone 0.2 mg/kg, Group P: Received a placebo of normal saline (gargle and IV). IV: Intravenous

Table 4: Severity scores of post-operative laryngopharyngeal complaints for each group

FQA1	Group D (*n*=35)	Group K (*n*=35)	Group KD (*n*=35)	Group P (*n*=35)	*P* value
0 h after tracheal extubation					
Sore throat (0/1/2/3)	28/7/0/0	25/10/0/0	34/1/0/0	15/14/3/3	0.0
Hoarseness (0/1/2/3)	33/1/1/0	33/1/1/0	34/1/0/0	25/7/2/1	0.042
2 h after tracheal extubation					
Sore throat (0/1/2/3)	27/8/0/0	24/11/0/0	34/1/0/0	17/12/4/2	0.0
Hoarseness (0/1/2/3)	32/2/1/0	32/1/2/0	34/1/0/0	24/7/3/1	0.045
4 h after tracheal extubation					
Sore throat (0/1/2/3)	28/7/0/0	25/10/0/0	35/0/0/0	18/11/4/2	0.0
Hoarseness (0/1/2/3)	31/3/1/0	31/2/2/0	34/1/0/0	22/9/3/1	0.022
8 h after tracheal extubation					
Sore throat (0/1/2/3)	29/6/0/0	26/9/0/0	35/0/0/0	17/11/6/1	0.0
Hoarseness (0/1/2/3)	32/2/1/0	31/2/2/0	32/3/0/0	22/9/3/1	0.045
16 h after tracheal extubation					
Sore throat (0/1/2/3)	28/7/0/0	25/10/0/0	35/0/0/0	18/12/5/0	0.0
Hoarseness (0/1/2/3)	31/4/0/0	29/4/2/0	32/3/0/0	22/9/4/0	0.031
24 h after tracheal extubation					
Sore throat (0/1/2/3)	27/8/0/0	24/11/0/0	35/0/0/0	16/15/4/0	0.0
Hoarseness (0/1/2/3)	31/4/0/0	29/5/1/0	31/4/0/0	22/9/4/0	0.034

Values are number of patients.*$P<0.05$ on between-group comparison. Group D: Received IV dexamethasone 0.2 mg/kg and gargled 30 ml saline, Group K: Gargled 40 mg ketamine in 30 ml saline and received 2 mg/kg IV saline, Group KD: Gargled 40 mg ketamine in 30 ml normal saline and received IV dexamethasone 0.2 mg/kg, Group P: Received a placebo of normal saline (gargle and IV). IV: Intravenous



Flow diagram 1: Flow diagram of the progress through the phases of a parallel randomized trial of four groups (that is, enrolment, intervention allocation, follow-up, and data analysis)

in 30 ml saline plus 2 mg/kg IV dexamethasone before induction general anesthesia significantly decreased the incidence and severity of POST compared with other groups at all times during 24 h after tracheal extubation. So ketamine gargle combined with 0.2 mg/kg of dexamethasone was more effective than using each drug alone for reducing sore throat and hoarseness at all times after tracheal extubation for up to 24 h. Several contributing factors for sore throat after surgery have been reported, including patient sex, age, large tracheal tube, cuff design, and intracuff pressure.[5,35,36] In this study, no correlation was observed between pain, age, gender, duration of surgery and intubation. Also the sedation scores recorded in our trial have clearly demonstrated that the patients in four study groups had similar scores. There is an increasing amount of experimental data showing that NMDA receptors are found not only in the central nervous system but also in the peripheral nerves.[37,38] Moreover, experimental studies point out that peripherally administered NMDA receptor antagonists are involved with antinociception,[21] and anti-inflammatory cascade.[22] Ketamine is a potent antagonist of the NMDA receptor that currently available for use in humans.[23] In the previous studies, Canbay *et al*.,[18] found that a ketamine gargle (40 mg ketamine in saline 30 ml; gargled for 30 s 5 min before induction) reduced the incidence and severity of POST in patients undergoing septorhinoplasty under general anesthesia with endotracheal intubation, potentially because of local anti-inflammatory and anti-hyperalgesic effect of ketamine (as a potent antagonist of the NMDA receptor). In the other hand Park *et al*.,[11] showed that the prophylactic use of 0.2 mg/kg of dexamethasone significantly decreases the incidence and severity of sore throat and hoarseness 1 h and 24 h after tracheal extubation of a DLT because of the potential mechanism of anti-inflammatory activity of dexamethasone, which includes inhibition of leukocyte migration, maintenance of cell membrane integrity, attenuation of lysosome release, and reduction of fibroblast proliferation.[39,40] With respect to these findings, we propose that ketamine gargle plus IV dexamethasone might be more effective than using each of these drugs alone in reducing the incidence and severity of POST and hoarseness, perhaps due to their synergistic effects. Finally we showed that, using this method decreased the incidence and severity of POST

and hoarseness without any complication or increasing recovery time and the level of sedation. Limitations of our study were as bellow:

1. The absence of the measurements of plasma ketamine levels. So we cannot rule out a systemic effect of ketamine
2. Our study did not have a large enough patient sample size; if the sample size was larger maybe decrease in the incidence and severity of hoarseness were significant between Group KD with each of Groups of K and D.

CONCLUSION

For reducing the incidence and severity of POST the administration of ketamine gargle combined with IV dexamethasone was more effective than using each of these drugs alone at all times after tracheal extubation. Also using this combination reduced the incidence and severity of hoarseness compared with placebo group at all times after tracheal extubation.

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