Original Article

The effects of propofol, ketamine and combination of them in prevention of coughing and laryngospasm in patients awakening from general anesthesia: A randomized, placebo-controlled, double blind clinical trial

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Abstract

Background: Coughing and laryngospasm are undesirable outcomes occurring during emergence from general anesthesia. We compared the effect of small doses of propofol, ketamine and a combination of them on the occurrence and severity of coughing and laryngospasm in patients awakening from general anesthesia.

Materials and Methods: 160 patients who were scheduled to undergo operations under general anesthesia were randomly assigned to one of the following groups, 40 in each group: propofol group (0.25 mg/kg intravenous (IV) propofol), ketamine group (0.25 mg/kg IV ketamine), combination group (0.25 mg/kg IV propofol, and 0.25 mg/kg IV ketamine) and control (0.1 ml/kg IV saline). Drugs were administered before extubation at previously defined time. Presence and severity of coughing and laryngospasm were recorded within twominutes after extubation.

Results: The presence of coughing in the combination group (27.5%) was less than that in other groups; also it was less frequent in the propofol group (57.5%) than the control (82.5%) (all $P < 0.05$). But the incidence did not differ between the propofol and the ketamine (70%) group; nor did it differ between the ketamine and control groups ($P = 0.356$ and $P = 0.121$, respectively). The cases with severe coughing (grade 3) in the combination group (none) were significantly less than in the propofol (four) and the control groups (seven) ($P = 0.040$ and $P = 0.006$ respectively). There was no significant difference between the groups in frequency of laryngospasm.

Conclusion: Administration of propofol or combination of propofol and ketamine decreases the incidence of post extubation coughing. This combination can also decrease severe cases.

Key Words: Cough, general anesthesia, ketamine, laryngospasm, propofol

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INTRODUCTION

Coughing and laryngospasm are undesirable outcomes occurring during emergence from general anesthesia. Cough is a protective reflex that befalls because of airway irritation at extubation time.[1] It causes

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heavy discomfort to the patient and constitutes complications like hypotension, arrhythmias, herniations, diaphragmatic rupture, rib fractures, headache, pulmonary interstitial emphysema, disruption of surgical wounds and elevation of intracranial, intraocular, and abdominal pressure.[2] In several studies various methods and medications have been used to prevent or mitigate coughing during emergence from anesthesia, such as the use of the laryngeal mask during emergence,[3], administration of alfentanil and remifentanil,[4] and topical or intravenous lidocaine.[5,6] Airway irritation can also cause laryngospasm. In the majority of cases, laryngospasm is self-limiting but it can result in complications such as pulmonary aspiration, pulmonary edema, arrhythmia and cardiac arrest.[7,8] There are controversies about the role of anesthetized extubation (as opposed to awake extubation) in the prevention of laryngospasm.[8] Oral benzodiazepines,[9] intravenous lidocaine,[10] magnesium,[11] 5% carbon dioxide (in an animal experimentation) have been studied and some benefits have been reported.[12] Propofol is a common drug in routine general anesthesia, which is known as a strong depressant of airway reflexes at the anesthetic doses.[13] Protective effects of high dose ketamine against constriction of airways have been reported.[14] Several studies have demonstrated the efficacy of propofol and ketamine in the prevention of fentanil/remifentanil- induced cough.[15-18] Pak *et al*. assessed the effect of small doses of propofol and ketamine in the prevention of post extubation coughing and laryngospasm in children, reporting that propofol and ketamine have a significant effect on severity of coughing and that propofol has a significant effect on the presence of coughing as well.[1] We designed this study to compare the effect of small doses of propofol, ketamine and a combination of both in preventing coughing and laryngospasm in adult patients awakening from general anesthesia.

MATERIALS AND METHODS

This randomized double-blind clinical trial was conducted between November 2011 and September 2012 in Ayatollah Kashani Hospital of Isfahan University of Medical sciences. After receiving approval from ethical committee of Isfahan University of Medical sciences, 160 patients with American Society of Anesthesiologists (ASA) class I or II, aged between 17 and 75 years old from both sexes who were scheduled to undergo operations under general anesthesia were recruited in the study. All subjects provided informed consent in accordance with the procedures of the ethical committee. Patients with a history of sleep apnea syndrome, developmental mental disorders, airway or facial abnormalities, bronchial asthma, allergic disorders, upper respiratory infection symptom during the surgery, smoking, medication with angiotensin-converting-enzyme (ACE) inhibitors or those who did not show necessary cooperation or satisfaction to participate in the study were excluded. No premedication was allowed and the anesthetic technique was the same for all patients. All patients were NPO since about 6 hours before surgery. In the operating room heart rate, blood pressure, SpO_2 and end tidal carbon dioxide were continuously monitored. Anesthesia was induced with propofol (2 mg/kg) and fentanyl (1 μg/kg). Atracurium (0.6 mg/kg) was IV administered to neuromuscular relaxation and endotracheal intubation was performed. Intubation time was defined as the time between insertion of laryngoscope into a patient's mouth and tracheal tube cuff inflation. Anesthesia was maintained with isoflurane 1.2% in 66% nitrous oxide in oxygen using mechanical ventilation and controlled respiration was performed using capnogram maintained at 30-35 mmHg. At the end of the operation, return of neuromuscular function was evaluated using train-of-four. Residual neuromuscular block was reversed by neostigmine (0.4 mg/kg IV) as well as atropine (to prevent bradycardia). Afterwards, isoflurane and N_2O administration was discontinued and 100% oxygen was administered manually. Then the patients were assigned to the propofol, ketamine, combination and control group randomly. 0.1 ml/kg intravenous (IV) normal saline was administered in the control group, 0.25 mg/kg IV propofol (Provive 1%, Claris Lifescience Ltd, India) in the propofol group, and 0.25 mg/kg IV ketamine (Rotexmedica, Trittau, Germany mg/kg) in the ketamine group. In the combination group a combination of propofol (0.25 mg/kg) and ketamine (0.25 mg/kg) was used. The administration time of the drugs upon emergence was defined based on Batra *et al*.,[19] which was either when the patient's breathing returned to the regular spontaneous pattern, or when the patient opened his eyes or made purposeful movements such as trying to extubate himself. One minute after administration of the drugs, clearance of endotracheal secretions was performed with suctioning, and then, the patient was extubated. Extubation time was the time between discontinuing anesthetic drugs and the time patient was extubated. After extubation, patients were transferred to post anesthesia care unit and occurrence and severity of laryngospasm and coughing within 2 minutes after extubation were recorded by another blinded person who did not know what drug had been administrated to each patient. Laryngospasm was graded according to the following criteria:[20]

- Grade 0 no symptoms
- Grade 1: Stridor

- Grade 2: Total occlusion of the cords (respiratory efforts with no air movement)
- Grade 3: Cyanosis with evidence for airway obstruction at the level of vocal cords.

The severity of coughing was determined using the following criteria:[5]

- Grade 0: No incidence of coughing
- Grade 1: Only one cough
- Grade 2: Two coughs to slight coughing
- Grade 3: Severe or repetitive coughing.

The patients who developed laryngospasm after extubation were ventilated with positive pressure ventilation with 100% oxygen via a facemask. If the spasm continued or SpO_2 fell to 85%, 0.8 mg/kg propofol was administered with continuation of positive pressure ventilation. If this management was ineffective and spasm continued the succinylcholine was administered, the patient was intubated, and ventilated with 100% oxygen. Anesthesia time was defined as the time between the intubation and extubation. All statistical analyses were performed using the Statistical Package of Social Sciences (SPSS) version 19.0 (SPSS, Chicago, IL, USA). Categorical data was analyzed using the $\chi 2$ test. Parametric data was analyzed using one-way analysis of variance (ANOVA). Descriptive statistics were expressed as mean ± standard deviation or number (percentage in parenthesis). A P value less than 0.05 was considered statistically significant. SPSS software (version 19) was used for data analysis. The significance level was set at $P < 0.05$.

RESULTS

A total of 160 patients with a mean age of 33.3 ± 15.5 years (range 17-75 years) participated in this study, 40 in each group. No patients were excluded from analysis [Figure 1]. There were no significant differences in age, weight, height, sex, ASA physical status, indications of surgery and extubation, intubation and anesthesia times between the groups [Tables 1 and 2].

Total incidence and distribution of severity of coughing and laryngospasm in each group have been presented in Figures 2 and 3.

The occurrence of coughing in groups was as follows: Propofol group 23 cases (57.5%), ketamine 28 (70%), propofol-ketamine 11 (27.5%) and control 33 (82.5%). This presence in the combination group was less than that in the propofol, ketamine and control groups ($P = 0.007$, $P < 0.001$ and $P < 0.001$, respectively), and in the propofol group is less than that in the control group ($P = 0.015$), which are statistically significant. But the incidence did not differ between the propofol group and the ketamine group; nor did it differ between the ketamine and the control groups ($P = 0.356$ and $P = 0.121$, respectively).

Concerning severity, we compared the number of patients with severe coughing (grade three) across the groups. There were four cases with severe coughing in the propofol group, three in the ketamine group, none in the combination group and seven cases in the control. The difference between the combination group and the propofol group and between the combination and control groups was significant ($P = 0.040$ and $P = 0.006$, respectively). There was no other significant difference between other groups with respect to the presence of severe coughing ($P > 0.05$).

There was no significant difference between the groups in terms of frequency of laryngospasm ($P > 0.05$). No case of severe laryngospasm and one case of grade 2 (in the control group) was observed.

DISCUSSION

This study showed that a combination of propofol and ketamine might prevent coughing in patients awakening from general anesthesia and decrease its severity. Also, the results showed that this combination was more effective than administration of propofol or ketamine separately. In our study the effect of ketamine was not significant. As to laryngospasm, none of our drugs could reduce the presence of this unwanted outcome.

Table 1: Patient characteristic, intubation, operation, and anesthesia time in four groups

Variable	Propofol	Ketamine	Propofol-ketamine	Control	*P*
Age (years)	33.7±16.9	38.3±11.9	40.5±18.7	37.8±15	0.217
Weight (kg)	67.7±13.1	69.7±10.7	68.6±12.4	69.2±8.5	0.873
Sex (Male/female)	28/12	31/9	30/10	32/8	0.756
Height (cm)	165.7±7.7	167±14.2	166.2±9.5	168.1±6.2	0.725
ASA (grade 1/grade 2)*	31/9	33/7	30/10	29/11	0.746
Intubation time (second)	15.7±4.2	16.3±2.9	17.2±3.9	16.6±3	0.318
Extubation time (minutes)	26.6±7	28.5±4.4	27.8±6.1	29.6±2	0.083
Anesthesia time (minutes)	100.1±49.4	81±27.5	90.2±34.9	87.3±37.9	0.164

Data are expressed as mean±SD or number (proportion), *ASA=American Society of Anesthesiologists

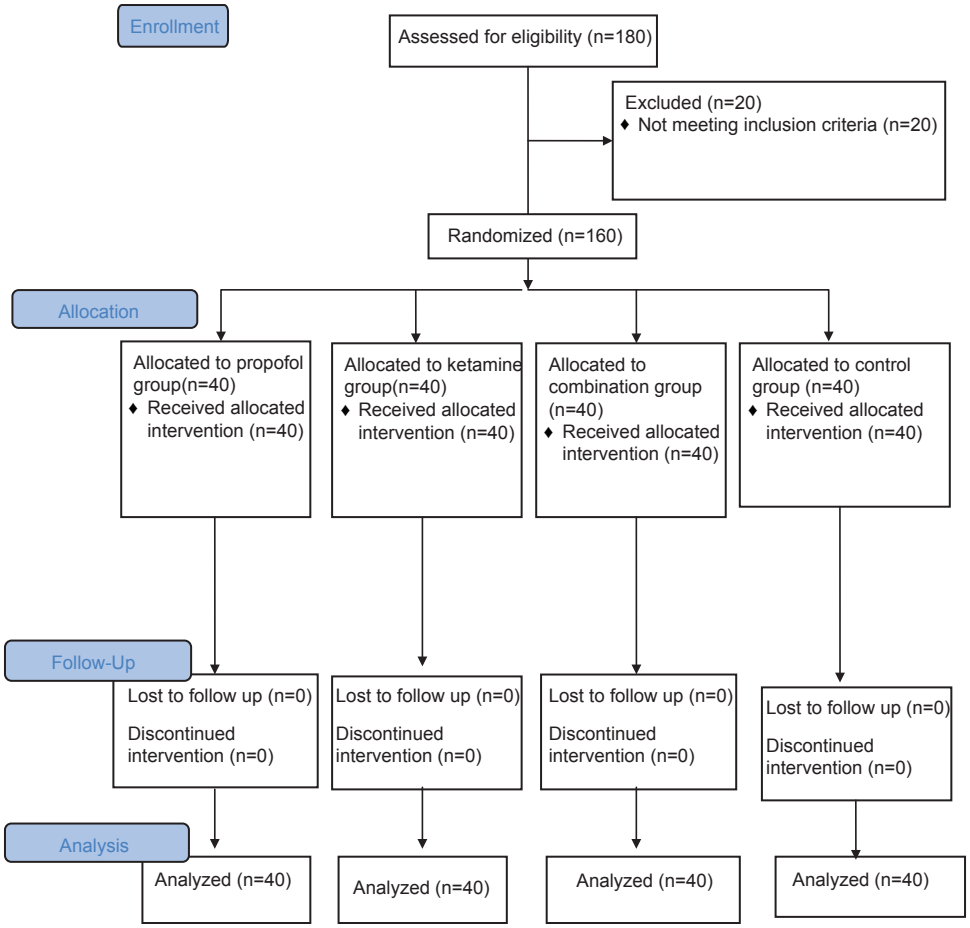

Figure 1: CONSORT flow diagram

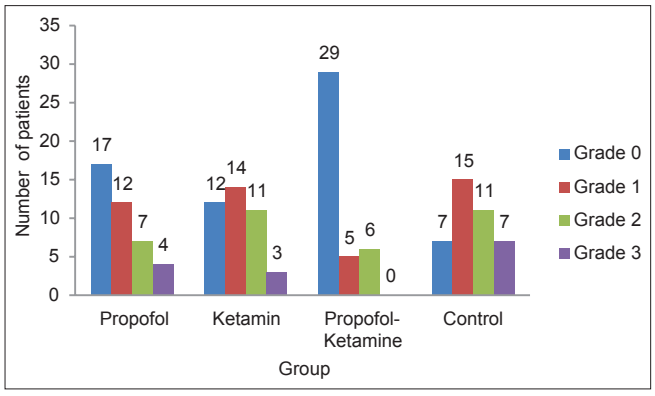

Figure 2: Incidence of cough and its severity in four groups

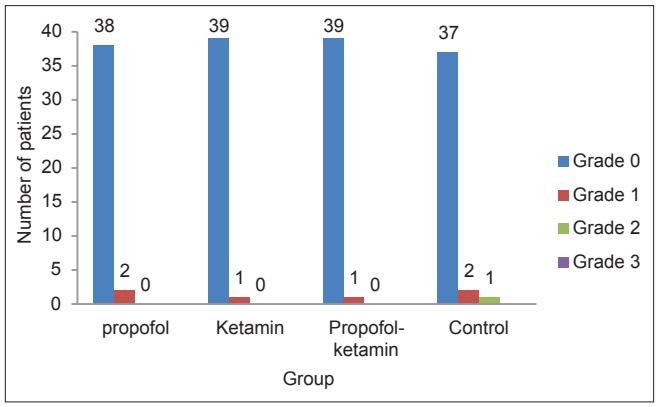

Figure 3: Incidence of laryngospasm and its severity in four groups

Table 2: Type of operations

Variable	Orthopedics-upper limb	Orthopedics-lower limb	Neurosurgery	Spinal disk herniation
Propofol	10*	8	14	12
Ketamine	8	11	10	10
Propofol-ketamine	14	13	9	14
Control	12	8	7	4

*Number P=0.833

The incidence of coughing on emergence from anesthesia is distressingly high (76% and 96% in some studies).[21,22] This incidence in our study was 46.8%. The presumed mechanism for cough in this setting is airway irritation by the endotracheal tube, noxious effects of the anesthetic gas or uncleared secretions.[22] It can be caused by irritant receptors in the larynx and airway rapidly adapting receptors (RARs) in the tracheobronchial tree.[23]

Laryngospasm is a rare but harmful unwanted complication of general anesthesia. This reflex is elicited by stimulation of the afferent fibers of the internal branch of the superior laryngeal nerve. It may occur secondary to loss of inhibition of the laryngeal closure reflex because of abnormal excitation.[24]

Anesthetic dose of propofol has been found to inhibit airway reflexes.[25] It has been shown to reduce post extubation cough and laryngospasm.[26] At subhypnotic doses, its preventive effect on laryngospasm has been reported.[19,27,28] Afshan *et al*.[27] used a small dose of propofol (0.8 mg/kg) for the management of laryngospasm on removal of the laryngeal mask airway and reported it as a useful drug with the success rate of 77%. Batra *et al*.[19] showed that IV administration of 0.5 mg/kg propofol during emergence from general anesthesia could reduce the likelihood of post extubation laryngospasm. We used 0.25 mg/kg propofol at the same time in adult patients and no significant effect was seen on the frequency and severity of laryngospasm. Regarding the findings of this study, it can be argued that higher doses of propofol might be effective.

Ketamine, as an induction agent has been reported to attenuate induced bronchoconstriction by its bronchodilator effect.[14] Low dose IV ketamine has been used as a premedication to prevent fentanyl-induced coughing and relief of bronchospasm in acute severe asthma.[18,29] In a study Pak *et al*.[1] administrated 0.25 mg/kg propofol and the same dose of ketamine to prevent post extubation coughing and laryngospasm. They reported that the incidence of coughing in the propofol group was lower than in the ketamine and control groups, whereas the incidence of severe coughing in the control group (17.14%,) was higher than that in the propofol (10.0%) and ketamine groups (6.98%). Regarding the effect of propofol, our results are consistent with Pak *et al*.'s study. We used the same dose of propofol, which turned out to be more effective than ketamine and placebo in reducing the frequency and severity of post extubation coughing.

The mechanism of action of propofol is not clear, but it has been suggested that it can suppress laryngeal reflexes.[25] Afferent signals from vocal cord and larynx activate N-methyl-D-aspartate (NMDA) receptors in the brain stem which in turn leads to an efferent vagal response resulting in vocal cord adduction (laryngospasm). It has been proposed that propofol may effectively inhibit NMDA receptors in brainstem and consequently suppress the vagal response.[19] Also, Propofol may relax airway smooth muscles directly or through the peripheral vagal pathway.[30]

The same effect on NMDA receptors has been shown for ketamine.[31] In addition, ketamine (like propofol) can reduce induced bronchoconstriction and make bronchiole muscle relax. The latter effect is mainly because of depression of neurally induced bronchoconstriction. But a minimal local effect has been suggested for them.[14]

There were some limitations in this study. First, we did not record the recovery times to compare between different groups. Second, we used the dose 0.25 mg/kg according to the previous studies but other doses (and also in small dose range) may bring about better results.

CONCLUSIONS

From this randomized double blind clinical trial we conclude that administration of propofol (0.25 mg/kg) or a combination of propofol and ketamine (propofol 0.25 mg/kg, and ketamine 0.25 mg/kg) in emergence phase decreases the incidence of post extubation coughing. This combination can decrease severe cases too.

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Conflicts of interest

There are no conflicts of interest.

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