Original Article

# A comparison of the effect of pretreatment with intravenous dexamethasone, intravenous ketamine, and their combination, for suppression of remifentanil-induced cough: A randomized, double-blind, placebo-controlled clinical trial

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## Abstract

**Background:** The injection of remifentanil can cause cough during induction of anesthesia. This study was designed to examine the efficacy of ketamine, dexamethasone, and their combination on remifentanil-induced cough (RIC).

**Materials and Methods:** One hundred and twenty patients scheduled for elective surgery were randomly assigned into four groups: Group K received 10 mg ketamine; Group D received 10 mg dexamethasone; Group KD received 10 mg ketamine in combination with dexamethasone; and Group S received saline in a similar volume, five minutes prior to the injection of remifentanil. The incidence and severity of the cough was recorded in each person.

**Results:** The incidence of RIC was significantly lower in Group KD compared to Group K, Group D, and Group S (3.3 vs. 20%, 20%, and 46.7%, respectively, $P < 0.05$).The severity of RIC was significantly lower in Group KD compared to Group K, Group D, and Group S ($P < 0.05$). There was no significant difference between Group K and Group D in this regard ($P > 0.05$). There was no significant difference in the onset time of coughing among the four groups (19.8 ± 1.3, 20.8 ± 0.9, 19.0 ± 1.1, and 19.9 ± 2.2 in Group K, Group D, Group KD, and Group S, respectively, $P > 0.05$).

**Conclusion:** We found that pretreatment with 10 mg ketamine in combination with 10 mg dexamethasone five minutes prior to the injection of remifentanil could significantly reduce the incidence of RIC, and it was better than using each drug singly.

**Key Words:** Cough, dexamethasone, ketamin, remifentanil

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## INTRODUCTION

Remifentanil, a fentanyl derivative, is a specific mu-opioid receptor agonist with rapid onset and offset of action. Like other synthetic opioids, the injection of remifentanil can cause cough during induction of anesthesia. Studies have reported an incidence of about 25-34%.[1,2]



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Coughing during anesthetic induction is undesirable and has threatening complications for the patient, such as, increased cerebral, ocular or abdominal pressure and unstable hemodynamics. It is also associated with conjunctival and periorbital petechiae.[3] Therefore, it is very important to prevent remifentanil-induced cough.

Many attempts have been made to date, to reduce the incidence of opioid-induced cough. For example, studies have shown that selective B-2 agonists terbutaline and salbutamol or beclamethasone can reduce fentanyl-induced cough.[4,5] Intravenous lidocaine and low-dose ketamine and dexamethasone have suppressed both fentanyl and remifentanil-induced cough.[1,2,6-9]

However, there are no studies on the effect of the combination of ketamin and dexamethasone on remifentanil-induced cough. Also there is no study that compares the efficacy of ketamine and dexamethasone on reducing remifentanil-induced cough. Hence, we have designed this randomized, double-blind, placebo-controlled clinical trial study, to evaluate and compare the efficacy of low-dose ketamine, dexamethasone, and their combination in reducing remifentanil-induced cough (RIC).

## MATERIALS AND METHODS

After obtaining Institutional approval from the Ethics Committee of our university and taking written informed consent from the patients, the present study was performed on 120 ASA physical status I and II patients, of age 18 to 70 years, who were scheduled for elective surgery under general anesthesia.

The other inclusion criteria was patients with body weight less than 20% of the ideal body weight, with no history of smoking, chronic obstructive lung diseases, bronchial asthma, respiratory tract infection, or allergy to the study drugs. Also, patients treated with the angiotensin-converting enzyme inhibitor, bronchodilators, or steroids were excluded from the study. If there was any change in technique of anesthesia due to any problem, the patient was excluded from the study.

The patients were fasted for eight hours before operation. Prior to their arrival to the Operating Room, an 18 G cannula was inserted into the dorsal vein of the hand and a T-connector was connected to it for drug injection and infusion. No premedication was given to the patients.

After arrival to The Operating Room, patient monitoring was performed by an electrocardiogram (ECG), noninvasive blood pressure measurement, and pulse oximetry throughout the study.

The patients were randomly divided into four groups by using computer-generated, random numbers: Group K: Five minutes prior to the injection of remifentanil, 10 mg of ketamine (Rotexmedica TRITTAU.GERMANY) in a volume of 3 ml was injected; Group D: Five minutes prior to the injection of remifentanil (Iran Daru),10 mg of dexamethasone(Iran Hormone) in a volume of 3 ml was injected; Group KD: Five minutes prior to the injection of remifentanil, 10 mg ketamine in combination with 10 mg dexamethasone in a volume of 3 ml was injected; Group S: Five minutes prior to the injection of remifentanil, the same volume of saline was injected.

Remifentanil 1 μg/kg (diluted with normal saline to a concentration of 20 μg/ml) was administered at constant rate, over 10 seconds, by using an infusion pump. The preparation of study drugs and infusion of remifentanil was performed by an anesthesiologist who was not involved in data collection.

After starting remifentanil infusion, the onset time from the beginning of infusion of remifentanil to occurrence of cough and severity of cough were recorded for two minutes by a physician who was unaware of the study drug administered to the patients. The severity of coughing was recorded based on the number of episodes of cough as: Mild, 1-2; moderate, 3-4; severe, equal to or more than 5.

If arterial oxygen saturation (SpO2) was less than 90% during remifentanil infusion, assisted ventilation with a mask was performed. If there was apnea, muscle rigidity or neuropsychological symptoms after remifentanil infusion, it was recorded. If breathing stopped for more than 15 seconds, it was considered as apnea. If the tone of the trunk muscle was increased where mask ventilation was difficult or impossible, it was considered as muscle rigidity. If patients developed a feeling of dissociation (such as body floating), drowsiness or numbness it was considered as a neuropsychological symptom.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and oxygen saturation of the patients were recorded immediately after arrival to the Operation Room (T0), immediately after termination of remifentanil infusion (T1), and after the injection of propofol (T2). The time interval between T0 and T1 was 5-10 minutes, while the time interval between T1 and T2 was five minutes.

By using the statistical software, it was estimated that a minimal of 30 patients per group was needed to

obtain 80% statistical power, at the 95% significance level, for reducing 25% incidence of cough in comparison with the control group.

For analysis of data, we used the SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The continuous variables such as age, weight, height, remifentanil dosage, and onset time of cough were analyzed with one-way analysis of variance (ANOVA), with Bonferroni's correction. The categorical variables such as sex, ASA, incidence of cough, and frequency distribution of severity of cough were analyzed by the Chi-squared test. Repeated continuous variables such as SBP, DBP, and HR were analyzed by repeated measure analysis of variance. A *P* value less than 0.05 was considered statistically significant.

## RESULT

In this study, a total of 129 consecutive patients were evaluated during one year with ASA I and II, who were candidates for elective surgery, under general anesthesia. Out of these, nine patients were excluded from the study. Subsequently, nine patients in four groups were unable to cooperate and were, therefore, excluded from the study [Figure 1]. Therefore, 120 patients were included in the study and received study medication after randomization.

There was no significant difference in age, gender, weight, height, ASA class, or the total remifentanil dose between the four groups [Table 1]. The SBP, DBP, HR the, and SpO2 changes at T0, T1, and T2 time intervals were not different between the four groups [Table 2].

**Table 1: Patient demographic data and remifentanil dose**

| | Group K (*n* = 30) | Group D (*n* = 30) | Group KD (*n* = 30) | Group S (*n* = 30) |
|---|---|---|---|---|
| Age (years) | 34.2±14.5 | 35.1±12.1 | 34.9±15.2 | 35.3±15.5 |
| ASA status (I/II) | 29/1 | 25/5 | 27/3 | 26/4 |
| Gender (M/F) | 21/9 | 19/11 | 15/15 | 16/14 |
| Weight (kg) | 70.7±5.6 | 71.6±7.2 | 70.7±5.5 | 71.1±10.7 |
| Height (cm) | 1.69±0.1 | 1.68±0.05 | 1.68±0.1 | 1.67±0.2 |
| Remifentanil dose (μg) | 78.1±7.5 | 77.1±6.3 | 76.2±2.3 | 77.9±5.6 |

Values are presented as mean±SD or number. Group K: Received 10 mg ketamine intravenously five minutes before injection of remifentanil, Group D: Received 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group KD: Received 10 mg ketamine intravenously combined with 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group S: Received the same volume of saline five minutes before injection of remifentanil. There was no significant difference between the four groups

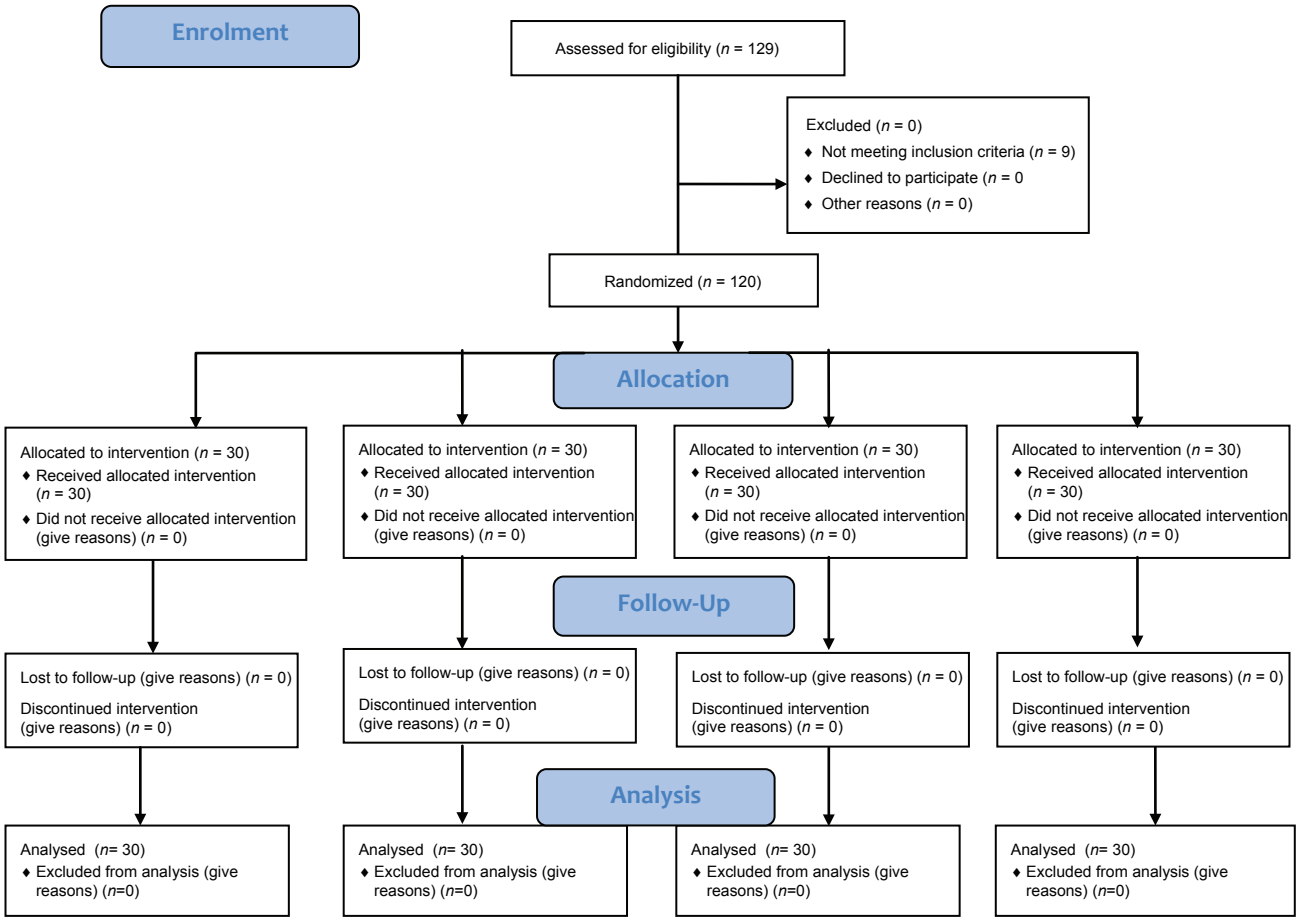


**Figure 1:** Consort flow diagram

The incidence and severity of remifentanil-induced cough (RIC) was significantly lower in Group KD when compared with Group K and Group D ($P < 0.05$) [Table 3]. These variables were also significantly less in Group K and Group D when compared with Group S ($P < 0.05$) [Table 3]. There was no significant difference between Group K and Group D in this regard ($P > 0.05$) [Table 3]. No significant difference was noted in the onset time of coughing among the four groups ($P > 0.05$) [Table 3]. No patient had apnea, stiffness, arrhythmias, or oxygen desaturation in any group.

**Table 2: Vital sign changes at different time intervals in the four groups**

| | Group K (*n*=30) | Group D (*n*=30) | Group KD (*n*=30) | Group S (*n*=30) |
|---|---|---|---|---|
| SBP (mmHg) | | | | |
| T0 | 120.4±9.3 | 124.1±11.9 | 125.9±10.9 | 125.7±13.8 |
| T1 | 115.2±7.7 | 116.1±9.1 | 116.6±5.0 | 115.8±12.5 |
| T2 | 111.9±7.1 | 112.2±9.4 | 114.7±18.4 | 113.6±10.6 |
| DBP (mmHg) | | | | |
| T0 | 76.9±10.5 | 78.4±11.4 | 81.4±9.5 | 78.0±9.2 |
| T1 | 70.6±7.5 | 71.9±9.1 | 73.9±6.8 | 72.9±10.1 |
| T2 | 67.8±8.3 | 68.0±7.2 | 66.9±8.7 | 70.2±9.2 |
| HR (bpm) | | | | |
| T0 | 90.0±9.8 | 87.1±12.4 | 92.1±10.4 | 89.0±11.5 |
| T1 | 78.8±6.6 | 82.8±11.0 | 84.3±9.4 | 83.4±16.7 |
| T2 | 76.6±5.2 | 79.0±10.8 | 78.1±10.6 | 78.2±10.2 |
| SpO2 (%) | | | | |
| T0 | 98.2±1.3 | 97.2±1.3 | 98.1±1.5 | 97.9±1.4 |
| T1 | 98.6±1.2 | 97.5±1.2 | 97.6±1.2 | 98.2±1.3 |
| T2 | 98.2±1.1 | 98.3±1.1 | 98.2±1.3 | 98.1±1.2 |

Data are presented as mean±SD. Group K: Received 10 mg ketamine intravenously five minutes before injection of remifentanil, Group D: Received 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group KD: Received 10 mg ketamine intravenously combined with 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group S: Received the same volume of saline five minutes before injection of remifentanil, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SpO2: Arterial oxygen saturation, T0: Immediately after arriving at Operation Room, T1: Immediately after injection of remifentanil, T2: Immediately after injection of propofol. No statistical difference was observed among the four groups

**Table 3: The incidence, onset time, and severity of coughing after remifentanil infusion**

| | Group K (*n*=30) | Group D (*n*=30) | Group KD (*n*=30) | Group S (*n*=30) |
|---|---|---|---|---|
| Incidence of cough (%) | 6 (20)* | 6 (20)* | 1 (3.3)*† | 17 (46.7) |
| Onset of coughing | 19.8±1.3 | 20.8±0.9 | 19.0±1.1 | 19.9±2.2 |
| Severity of cough | | | | |
| Mild | 4 (66.6)* | 5 (83.3)* | 1 (100)*† | 8 (47) |
| Moderate | 2 (33.3)* | 1 (16.6)* | 0 (0)*† | 8 (47) |
| Severe | 0 (0)* | 0 (0)* | 0 (0)* | 1 (5.8) |

The data are presented as mean±SD or numbers (%).Group K: Received 10 mg ketamine intravenously five minutes before injection of remifentanil, Group D: Received 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group KD: Received 10 mg ketamine intravenously combined with 10 mg dexamethasone intravenously five minutes before injection of remifentanil, Group S: Received the same volume of saline five minutes before injection of remifentanil. Severity of cough: Mild (1-2), moderate (3-5), severe (□ 5), *$P$<0.05 compared with Group S, †$P$<0.05 compared with Group K and Group D. There was no significant difference between Group K and Group D

## DISCUSSION

Our study showed that pretreatment with 10 mg ketamine in combination with dexamethasone 10 mg intravenously, five minutes prior to the infusion of remifentanil, could significantly reduce the incidence of remifentanil-induced cough from 46.7% in Group S to 3.3% in Group KD. In addition, the severity of cough in Group KD was significantly less in comparison to Group S.

Our data showed that using ketamine 10 mg or dexamethasone 10 mg intravenously, five minutes before remifentanil infusion, significantly reduced the incidence and severity of remifentanil-induced cough. No significant difference was noted between Group K and Group D with respect to this variable.

Several reports have been recently published using different drugs to prevent the opioid-induced cough.[1,2,4-6,9,10-13] Although several mechanisms responsible for opioid-induced cough have been explained, its exact mechanism is not yet known. Some studies have reported that opioids may block the central sympathetic nervous system, thus activating the parasympathetic nervous system, which can provoke cough and reflex bronchoconstriction.[4,5,8,10]

Another likely mechanism includes stimulation of the pulmonary chemoreflex, which is mediated by rapidly adapting irritant receptors or vagal C-fiber receptors that are in proximity to the pulmonary vessels (juxtacapillary receptors).[11,12]

Furthermore, opioid receptors have been identified in the trachea, bronchi, and alveolar walls. Another possible mechanism is that opioids constrict the bronchial smooth muscle and this causes remodeling of the bronchial wall. This stimulates the receptors, which trigger the cough reflex.[13,14]

The presence of N-methyl-D-aspartate (NMDA) receptors has been shown in the larynx, lung, and airways, and activation of these receptors can trigger airway constriction.[15-17] Ketamine is a noncompetitive NMDA receptor antagonist. Therefore, the direct or indirect effect of ketamine on the airway smooth muscle may be attributed to its NMDA receptor antagonism effect.[16,18,19]

Ketamine inhibits Ca2+ influx and consequently decreases the bronchomotor tone.[19] As Durieux *et al.*[20] shows, ketamine suppresses the muscarinic signaling that finally causes bronchodilation.

It has been reported that dexamethasone increases the activation of neutral endopeptidase, which reverses the enhanced airway reactivity of the airway epithelial cells.[21-23] It has been reported that corticosteroids increase the beta adrenergic receptors in the pulmonary cells.[24] Also it has been used as a mast cell stabilizer. Murlas *et al*.[25] have reported that in guinea pigs dexamethasone improves bronchoconstriction mediated by tachykinin, which induces contraction of the smooth muscle. It has been shown that tachykinin induces the release of histamine from the mast cell in the airway, which facilitates the excitation of the receptors. Dexamethasone inhibits the release of tachykinin and consequently the excitation of the receptors.[21,26]

Kim *et al*.[2] reported that administration of 0.1 mg/kg ketamine, one minute before injection of remifentanil, was effective in reducing remifentanil-induced cough. The incidence of RIC in their study was 27.6%, while in our study it was 46.7%. This difference in incidence of RIC was due to the difference in dose and timing of the remifentanil administered. The dosage of remifentanil used in our study was not based on target controlled infusion (TCI). This could be another cause of the difference between our results and those of the Kim *et al*. study.

Yu *et al*.[7] reported that administration of 10 mg of dexamethasone prior to the injection of remifentanil reduced the incidence and severity of remifentanil induced cough. Their results were similar to the findings in the Kim *et al.* study.[1]

The results of our study were in agreement with the Kim *et al*. and Yu *et al*. studies. We showed that administration of ketamine in combination with dexamethasone was significantly more effective than using each drug singly, for reducing the incidence and severity of remifentanil-induced cough. This could probably be attributed to the synergistic effect of ketamine with dexamethasone, and must be documented in future studies.

One limitation of our study was administration of 10 mg ketamine or 10 mg dexamethasone singly or in combination, regardless of the patients' body weight. We recommend conduting more studies with the exact dose of each drug, based on the patients' weight.

In conclusion, our study showed that the combined use of ketamine 10 mg with dexamethasone 10 mg reduced the incidence and severity of remifentanil-induced cough, without developing significant adverse effects, and it was better than using each drug singly. In addition, we found that there was no significant difference between using ketamine or dexamethasone for controling the cough following remifentanil infusion.

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