Comparison of the Effects of Ketamine or Lidocaine on Fentanyl-Induced Cough in Patients Undergoing Surgery: A Prospective, Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

BACKGROUND: Fentanyl-induced cough is common but has not been viewed as a serious anesthetic problem. However, the cough may be explosive at times, may require immediate intervention, and may be associated with undesirable increases in intracranial, intraocular, and intra-abdominal pressures. Prevention of fentanyl-induced cough in such situations is of paramount importance. Ketamine, at concentrations achieved with standard clinical doses, has a direct relaxant effect on airway smooth muscle.

OBJECTIVE: This study was designed to assess the effects of ketamine or lidocaine on fentanyl-induced cough.

METHODS: This double-blind, randomized, placebo-controlled study was conducted at the Erciyes University Medical School, Kayseri, Turkey. Consecutive adult patients aged 18 to 65 years and classified as American Society of Anesthesiologists physical status I or II who were undergoing elective surgery with general anesthesia were enrolled. Patients were randomly allocated equally into 3 groups to receive lidocaine 1 mg/kg, ketamine 0.5 mg/kg, or placebo intravenously 1 minute before fentanyl administration. Following intravenous fentanyl (1.5 µg/kg over 2 seconds) injection, an observer, unaware of the type of medication given to the patients, recorded the number of episodes of coughing, if any. Any episode of cough was classified as coughing and graded by investigators blinded to treatment as mild (1-2 coughs), moderate (3-4), or severe (≥5). Blood pressure, heart rate, pulse oximetry oxygen saturation (SpO₂), and adverse effects (AEs) were recorded.

RESULTS: A total of 368 patients were approached for inclusion; 300 patients met the inclusion criteria and were enrolled in the study. No patients in the ketamine group had cough. The frequency of cough was significantly lower in the lidocaine (11/100 [11%]; \( P = 0.024 \)) and ketamine (0/100; \( P = 0.001 \)) groups compared with the placebo group (23/100 [23%]). The intensity of cough was significantly lower in the lidocaine (mild, 7/100 [7%]; moderate, 4/100 [4%]; \( P = 0.037 \)) and ketamine (0/100; \( P < 0.001 \)) groups compared with the placebo group (mild, 10/100 [10%];
moderate, 12/100 [12%]; severe, 1/100 [1%]). Severe cough (≥5) was observed in 1 patient in the placebo group. Incidence and intensity of cough were significantly decreased in the ketamine group compared with the lidocaine group (incidence, \( P = 0.001 \); intensity, \( P = 0.003 \)). There were no significant differences between groups with respect to systolic blood pressure, diastolic blood pressure, heart rate, \( \mathrm{SpO}_2 \), and AEs.

**CONCLUSION:** Intravenous ketamine (0.5 mg/kg) significantly reduced the reflex cough induced by fentanyl compared with lidocaine and placebo, and was well tolerated. *(Curr Ther Res Clin Exp. 2010;71:289–297) © 2010 Elsevier HS Journals, Inc.*

**KEY WORDS:** fentanyl, coughing, ketamine, lidocaine.

**INTRODUCTION**

Fentanyl is often used as a preinduction adjunct to anesthesia because of its quick onset, short duration of action, intense analgesia, cardiovascular stability, and low histamine release properties; however, reflex cough is often observed after the administration of an intravenous bolus of fentanyl.

According to reports, the incidence of fentanyl-induced cough can reach 65%. It is usually transient and self-limiting in patients. However, fentanyl-induced coughing may not always be brief and benign. Tweed and Dakin found that an episode of explosive coughing after intravenous fentanyl in a boy aged 7 years led to multiple conjunctival and periorbital petechiae. Therefore, it is necessary to prevent fentanyl-induced cough in patients with some coexisting diseases including increased intracranial pressure, open eye injury, dissecting aortic aneurysm, pneumothorax, or reactive airway disease. Fentanyl-induced coughing may be more severe or occur at a higher incidence in patients with these coexisting conditions.

The mechanism of fentanyl-induced cough is still unknown. Various mechanisms proposed to explain fentanyl-induced cough are as follows: inhibition of central sympathetic outflow leading to vagal predominance, histamine release, and deformation of the tracheobronchial wall stimulating the irritant receptors, leading to reflex bronchoconstriction and cough. Various attempts have been made to reduce its incidence during the induction of anesthesia, with varying success. Agarwal et al. in a study of 200 American Society of Anesthesiologists (ASA) status I and II patients of either sex, aged 18 to 60 years, observed a 28% incidence of cough when fentanyl (2 μg/kg IV) was administered to the control group and reported that aerosol inhalation of salbutamol (6% incidence of cough), beclomethasone (0%), or sodium chromoglycate (4%) 15 minutes prior to entering the operating room was associated with a reduced incidence of cough. Horng et al. found that pretreatment with intravenous clonidine (2 μg/kg 2 minutes before the injection of a bolus intravenous fentanyl) suppressed the reflex cough induced by fentanyl in ASA status I and II patients, aged 18 to 80 years, but hemodynamic changes occurred. However, because these methods can be inconvenient and increase cost, their clinical acceptance is somewhat limited. There are conflicting studies on the effect of injection time on fentanyl-induced coughing.

One study found that prolongation of the injection time reduced the incidence of fentanyl-induced cough. A second study found that fentanyl-induced cough did not
depend on injection speed. In placebo-controlled clinical studies, it was found that pretreatment with intravenous lidocaine reduced fentanyl-induced cough. This method seems to be effective and convenient in clinical practice, but does not completely eliminate fentanyl-induced cough.

Ketamine is a versatile drug and the R(-)-enantiomer has an effect on airway smooth-muscle relaxation. Karnei et al reported that N-methyl-D-aspartate (NMDA) receptor antagonists are capable of modulating the cough reflex. Therefore, the present study was conducted in an attempt to find a simple method that might effectively attenuate fentanyl-induced cough while being convenient in a clinical setting.

PATIENTS AND METHODS

Approval was obtained from the ethics committee of the Erciyes University Medical School, Kayseri, Turkey. Written informed consent was obtained from all patients before they were enrolled into this prospective, double-blind, randomized, placebo-controlled study. Consecutive adult patients aged between 18 and 65 years were categorized as being a normal healthy patient (ASA status I) or a patient with mild systemic disease (status II). Patients were enrolled between October 2, 2007, and November 5, 2008. All eligible patients who were scheduled for various elective surgeries under general anesthesia in the Gevher Nesibe Hospital, Kayseri, Turkey, were enrolled into the study.

Exclusion criteria included a history of asthma, chronic cough, smoking, upper respiratory tract infection in the previous 2 weeks, impaired kidney or liver function, weight exceeding 20% of ideal, medication containing angiotensin-converting enzyme inhibitors, antidepressants, bronchodilators, and steroid or anesthetic premedication.

Patients were randomized using a computer-generated random number table; the group assignment was prepared by the enrolling anesthesiologist in sealed opaque envelopes. The enrolling anesthesiologist was not the same as the treating anesthesiologist. A total of 300 sealed envelopes containing the names of the groups (100 for each) were prepared before initiation of the study. The envelopes were opened before induction of anesthesia, and the drugs were prepared by an independent nurse who was not participating in any other part of the study.

In the operating room, venous access was established on the dorsum of the nondominant hand, and an intravenous cannula was connected to a T-connector for drug injection. All patients were monitored by ECG, noninvasive blood pressure measurement, and pulse oximetry. Patients received lidocaine* 1 mg/kg IV in 5 mL of normal saline, ketamine† 0.5 mg/kg IV in 5 mL of normal saline, or 5 mL of normal saline IV alone over 5 seconds, 1 minute prior to the intravenous administration of fentanyl (1.5 μg/kg over 2 seconds). Any episode of cough was classified as coughing. An observer, blinded to the type of medication administered to the patients, recorded the number of episodes of coughing, if any. There were 3 observers present for all 300 patients. The severity of cough was graded as mild (1–2 coughs), moderate (3–4), or

*Trademark: Arithmal 2% (Biosel, Istanbul, Turkey).
†Trademark: Keralar (Pfizer, Istanbul, Turkey).
severe (≥5), based on the number of coughs within 1 minute following fentanyl injection. Systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), and pulse oximetry oxygen saturation (SpO₂) were recorded before the administration of each drug (0) and 1 minute after fentanyl injection. All patients were given oxygen via a face mask. The adverse effects (AEs) associated with fentanyl, ketamine, or lidocaine, such as apnea, truncal rigidity, nausea, hypotension, respirator depression, bradycardia, or altered consciousness,¹⁷,¹⁸ were also recorded before induction for general anesthesia. General anesthesia was induced via intravenous propofol (2 mg/kg) and vecuronium (0.1 mg/kg).

**Statistical Analysis**

Considering the expected incidence of cough following peripherally administered intravenous fentanyl to be 25%, and assuming a reduction of ≤20% following any of the treatments and a power of 80%, the minimum sample size required in each group was 86. Anticipating some variability in reduction, we enrolled 100 patients in each group. Patients’ characteristics were compared using 1-way ANOVA. Comparison between the groups was performed for overall incidence of cough and severity of cough by χ² testing. P < 0.05 was considered statistically significant.

**RESULTS**

A total of 368 consecutive patients were approached for study inclusion; 68 were not included (45 patients were current smokers and 23 patients were receiving angiotensin-converting enzyme inhibitors, antidepressants, or bronchodilators) in the study based on the exclusion criteria. Three hundred patients completed the study.

There were no significant differences in the demographic data between the 3 groups, including age, gender, weight, and ASA physical status (Table I).

No patients in the ketamine group had cough (Table II). The frequency of cough was significantly lower in the lidocaine (11/100 [11%]; P = 0.024) and ketamine (0/100; P = 0.001) groups compared with the placebo group (23/100 [23%]). The mean intensity of cough was significantly lower in the lidocaine (mild, 7/100 [7%]; moderate, 4/100 [4%]; P = 0.057) and ketamine (0/100; P < 0.001) groups compared with the placebo group (mild, 10/100 [10%]; moderate, 12/100 [12%]; severe, 1/100 [1%]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lidocaine (n = 100)</th>
<th>Ketamine (n = 100)</th>
<th>Placebo (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>33.0 (9.8)</td>
<td>34.1 (12.2)</td>
<td>36.4 (9.8)</td>
</tr>
<tr>
<td>Male/female</td>
<td>51/49</td>
<td>55/45</td>
<td>48/52</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>68.8 (10.7)</td>
<td>70.2 (10.5)</td>
<td>71.5 (12.5)</td>
</tr>
<tr>
<td>ASA status I/II</td>
<td>84/16</td>
<td>81/19</td>
<td>82/18</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists.

*No significant between-group differences were observed.
Table II. Frequency and intensity of cough induced by fentanyl. Data are number (%) of patients (95% CI).

<table>
<thead>
<tr>
<th>Severity*</th>
<th>Lidocaine (n = 100)</th>
<th>Ketamine (n = 100)</th>
<th>Placebo (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cough</td>
<td>89 (89) (0.81–0.94)</td>
<td>100 (100) (0.97–1.00)</td>
<td>77 (77) (0.68–0.85)</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (7) (0.03–0.14)</td>
<td>0 (0.00–0.03)</td>
<td>10 (10) (0.05–0.18)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (4) (0.01–0.10)</td>
<td>0 (0.00–0.03)</td>
<td>12 (12) (0.06–0.20)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.00–0.03)</td>
<td>0 (0.00–0.03)</td>
<td>1 (1) (0.00–0.05)</td>
</tr>
<tr>
<td>Overall incidence</td>
<td>11 (11) (0.06–0.19)†</td>
<td>0 (0.00–0.03)§§</td>
<td>23 (23) (0.15–0.32)¶</td>
</tr>
</tbody>
</table>

*Severity: No cough (0 coughs), mild (1–2), moderate (3–4), severe (>5).
† P = 0.003 versus lidocaine.
‡ P = 0.024 versus placebo.
§ P = 0.001 versus placebo.
¶ P = 0.001 versus lidocaine.
† Intensity of cough was significantly higher in the placebo group compared with the lidocaine (P = 0.037) and ketamine (P < 0.001) groups.

Incidence and intensity of cough were significantly decreased in the ketamine group compared with the lidocaine group (incidence, P = 0.001; intensity, P = 0.003).

The baseline and 1 minute after fentanyl injection vital-sign profiles were not significantly different between the 3 groups. There were no significant differences among groups for the SBP, DBP, HR, and SpO₂ values (Table III).

No AEs associated with fentanyl, ketamine, or lidocaine were observed in any of the patients throughout the study.

DISCUSSION

This study suggests that pretreatment with ketamine 0.5 mg/kg IV 1 minute prior to fentanyl administration was associated with attenuating the coughing induced by fentanyl. This result is consistent with that from a study by Yeh et al.¹⁹ That study compared the effects of low-dose ketamine and placebo on fentanyl (1.5 μg/kg)–induced coughing in 360 ASA physical status I and II patients (aged 18–65 years; weight 40–80 kg) and reported that patients in the placebo group had a significantly higher frequency of cough than those in the ketamine pretreatment group (21.6% vs 7.2%; P < 0.05). In the present study, although a higher dose of ketamine was used than the dose that Yeh et al used in their study, the effect of ketamine on fentanyl-induced coughing increased without an increase in AEs.

In the present study, coughing occurred in 23% of patients in the placebo group. Phua et al¹ found that fentanyl 1.5 μg/kg, administered through a peripheral venous line elicited cough in 28% (14/50 patients) of the patients. A similar incidence of cough after fentanyl 2 μg/kg IV administered through the same route over a period of 5 seconds was observed by Agarwal et al.⁷ These results are not significantly different from the findings of the present study.
Table III. Comparison of the hemodynamic data and pulse oximetry oxygen saturation (SpO₂) of the 3 groups. Data are mean (SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lidocaine (n = 100)</th>
<th>Ketamine (n = 100)</th>
<th>Placebo (n = 100)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>133.5 (15)</td>
<td>130.4 (14)</td>
<td>134.8 (19)</td>
<td>0.245</td>
</tr>
<tr>
<td>One minute</td>
<td>120.5 (15)</td>
<td>120.6 (17)</td>
<td>122.5 (18)</td>
<td>0.763</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>82.6 (90)</td>
<td>84.6 (10)</td>
<td>83.4 (11)</td>
<td>0.432</td>
</tr>
<tr>
<td>One minute</td>
<td>75.4 (12)</td>
<td>77.7 (12)</td>
<td>75.1 (12)</td>
<td>0.275</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.8 (13)</td>
<td>84.7 (15)</td>
<td>85.2 (14)</td>
<td>0.309</td>
</tr>
<tr>
<td>One minute</td>
<td>84.7 (12)</td>
<td>86.8 (12)</td>
<td>82.6 (12)</td>
<td>0.087</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>98.7 (1.1)</td>
<td>98.6 (1.2)</td>
<td>98.6 (1.2)</td>
<td>0.635</td>
</tr>
<tr>
<td>One minute</td>
<td>98.7 (1.1)</td>
<td>98.8 (1.1)</td>
<td>98.8 (1.1)</td>
<td>0.598</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

*No statistically significant differences were observed between groups.

The exact mechanism of fentanyl-induced cough is still unclear. Some studies report that fentanyl inhibits central sympathetic outflow and therefore activates the vagus nerve, which induces cough and reflex bronchoconstriction. However, the involvement of a vagal-dependent pathway was not favored in previous studies because atropine, an antimuscarinic agent, failed to suppress cough. Another likely mechanism is pulmonary chemoreflex, which is mediated by either irritant receptors (rapidly adapting receptors) or by vagal C fiber receptors that are in proximity to pulmonary vessels (juxtacapillary receptors). However, experimental studies have found that juxtacapillary-receptor stimulation did not induce cough, although it did mediate pulmonary chemoreflexes. Histamine release in humans from lung mast cells is a possible mechanism of fentanyl-induced cough, though this appears very unlikely as fentanyl rarely causes histamine release. Suppression of cough with inhaled betamethasone (as it is known to reduce bronchial hyperirritability, mucosal edema, and also to suppress the inflammatory response to trigger stimuli) supports the trigger stimulus and bronchial hyperirritability theory. In addition to this, terbutaline and salbutamol (a selective β₂-adrenergic bronchodilator) inhalation and effective suppression of cough support the concept of bronchoconstriction. Constriction of the tracheal smooth muscles and the possible stimulation of irritant receptors after deformation of the tracheobronchial wall triggering the cough are other plausible explanations.

Although intravenous ketamine prevented fentanyl-induced cough in the present study, the actual mechanism is unknown. The presence of NMDA receptors has been reported in the larynx, lung, and airways, and activation of these receptors can trigger airway constriction. Therefore, the direct bronchodilation effect of ketamine may be attributed to its NMDA-receptor antagonism. However, Sato et al reported that ketamine relaxes the tracheal smooth muscle contracted by histamine through a
mechanism independent of NMDA receptors. In another study, Sato et al.\textsuperscript{25} investigated whether the relaxant effect of ketamine is dependent on any of the epithelium-derived relaxing factors and concluded that ketamine relaxes the airway smooth muscle by an epithelium-independent mechanism. However, Durieux\textsuperscript{26} reported that ketamine inhibited muscarinic acetylcholine receptor function. Postsynaptic acetylcholine receptors may have a major role in distal airway tone, and ketamine possibly acts as a bronchodilator in this way.

Gateau et al.\textsuperscript{27} found that ketamine antagonizes bronchoconstriction via histamine, acetylcholine, barium chloride, and potassium chloride. The investigators also theorized that, because ketamine exerts a nonspecific antagonism to multiple bronchoconstrictors, there might be inhibition of a common pathway leading to bronchorelaxation. Abdalla et al.\textsuperscript{28} hypothesized that ketamine inhibits the transmembrane influx of calcium (Ca\textsuperscript{2+}), because ketamine was able to bronchodilate airway smooth muscle contracted with potassium chloride, which is known to change membrane potential and allow a greater influx of Ca\textsuperscript{2+}.\textsuperscript{27} However, Yeh et al.\textsuperscript{19} speculated that ketamine counteracts the action of fentanyl by preserving the sympathetic–parasympathetic balance, which might affect the incidence of cough. These data have suggested that ketamine acts as a bronchodilator by a variety of mechanisms.

Although the bronchodilation effect of lidocaine has been questioned,\textsuperscript{29} intravenous lidocaine administration has been found to suppress both mechanically and chemically induced airway reflexes, including the cough reflex.\textsuperscript{30,31} The mechanisms by which lidocaine suppresses cough are not known, but it has been proposed that depression of brain-stem functions by lidocaine may be responsible for cough suppression. An alternative mechanism is that lidocaine may act by anesthetizing peripheral cough receptors in the trachea and hypopharynx.\textsuperscript{32}

**CONCLUSIONS**

Intravenously administered ketamine 0.5 mg/kg and lidocaine 1 mg/kg were associated with significantly reduced incidence of fentanyl-induced cough compared with placebo in these patients undergoing elective surgery with general anesthesia. The reduction was significantly greater in the ketamine group compared with the lidocaine group. Both treatments were well tolerated.

**ACKNOWLEDGMENTS**

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Dr. Guler designed and developed the study, oversaw study conduct, and assisted in writing the report. Dr. Aksu performed statistical analysis and acted as an observer. Drs. Bicer and Tosun conducted data collection. Dr. Boyaci assisted in writing the report and was responsible for the final content of the paper.

**REFERENCES**


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