

ORIGINAL ARTICLE

A priming dose of intravenous ketamine-dexmedetomidine suppresses fentanyl-induced coughing: A double-blind, randomized, controlled study

AMIN J. SALEH, LIANGBIN ZHANG, SALLY M. HADI & WEN OUYANG

Department of Anesthesiology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China

Abstract

Objective. This study was designed to investigate whether a priming dose of ketamine-dexmedetomidine can effectively suppress fentanyl-induced coughing (FIC).

Methods. Altogether 400 patients of ASA I and II, aged 18–70 years, undergoing various elective surgical procedures, were randomly allocated into four groups of 100 patients each. Patients in the placebo group received volume-matched normal saline 0.15 mL/kg + normal saline 0.05 mL/kg. One group of patients was given ketamine 0.15 mg/kg + normal saline 0.05 mL/kg (KET), and another group dexmedetomidine 0.5 µg/kg + normal saline 0.05 mL/kg (DEX). Finally, one group of patients received ketamine 0.15 mg/kg + dexmedetomidine 0.5 µg/kg (KETODEX). After fentanyl administration, the onset time and severity of cough for 1 min were recorded. Cough severity was graded as mild (grade 1–2), moderate (grade 3–5), or severe (grade >5).

Result. The incidence of FIC was 53%, 34%, 20%, and 9% in the placebo, DEX, KET, and KETODEX groups, respectively. The incidence of cough was significantly lower in the KETODEX group. Likewise, the onset time of cough was significantly delayed in the KETODEX group. Only nine patients in the KETODEX group had either mild (6%) or moderate (3%) cough, with none suffering from severe cough.

Conclusion. A priming dose of KETODEX effectively suppressed the cough reflex induced by fentanyl and delayed the onset time of cough. Therefore, treatment with KETODEX may be a clinically useful method for preventing FIC.

Key words: Anesthesia, fentanyl-induced coughing, dexmedetomidine, ketamine

Introduction

During anesthesia induction and surgery, patients may experience some psychological and sympathetic adverse effects. Opioids are often used to allay anxiety and to decrease pain associated with surgery (1,2). Fentanyl, in particular, is often used as a premedicant agent during the induction of general anesthesia to prevent elevation of blood pressure during intubation in the operation room. The use of fentanyl is due to its rapid onset, short duration, intense analgesia, ease of titrability, reduced cardiovascular depression, and low histamine release (3). However, intravenous

bolus administration of fentanyl often elicits cough, and the frequency can reach 65% (4,5). Thus, fentanyl-induced coughing (FIC) is often observed after intravenous bolus administration of fentanyl during anesthesia induction. However, FIC is undesirable during anesthesia induction, especially in some patients suffering from coexisting diseases including increased intracranial pressure (ICP), cerebral aneurysm, brain trauma, brain hernia, dissecting aortic aneurysm, open eye injury, reactive airway disease, or pneumothorax (6). Furthermore, severe FIC at the induction time can cause multiple conjunctival and periorbital petechiae (7) and lead to upper airway

obstruction that might require immediate intervention (8). Therefore, effective ways to prevent FIC are clinically important.

The mechanism of FIC is still unclear. Previous studies with various pharmacological interventions have been conducted to reduce the incidence of fentanyl-induced cough using readily available anesthetic adjuncts (9) such as N-methyl-D-aspartate (NMDA) receptor antagonists, benzodiazepines, lidocaine, propofol, α_2 agonists, atropine, priming and slow injection of fentanyl, inhalation of selective β_2 -adrenergic bronchodilators, salbutamol, beclomethasone, or sodium chromoglycate (10-16). Several studies have been conducted on dexmedetomidine, alone, or in combination with other agents to reduce the incidence of fentanyl-induced cough (17,18). Because of its unique highly selective α_2 -adrenoceptor agonist mechanism, dexmedetomidine is regularly used in clinical practice to blunt the cardiovascular response to tracheal intubation (19-23). On the other hand, intravenously injected ketamine, an NMDA antagonist, has well-known potent analgesic and bronchodilatory effects (24-29). However, the suppression of FIC with priming doses of intravenous ketamine and dexmedetomidine (KETODEX) has not been studied. The aim of the present study was to investigate whether KETODEX could effectively prevent or suppress FIC.

Materials and methods

Patient selection

After the study had been approved by the ethical committee of Third Xiangya Medical Hospital of Central South University, Changsha, Hunan, P.R. China, written informed consent was obtained from all participants before they were enrolled into this randomized, prospective, double-blind, placebo-controlled study. Altogether 400 American Society of Anesthesiologists (ASA) physical status Grade I and II patients, aged between 18 and 70 years, undergoing general anesthesia for various elective surgeries, were recruited. The exclusion criteria were those older than 70 years or younger than 18 years, body weight exceeding 20% of the ideal body weight, impaired kidney or liver functions, a history of bronchial asthma and chronic obstructive pulmonary disease, a history of smoking, respiratory tract infection, hypersensitivity to local anesthetics, hyperactive patients on medication containing angiotensin-converting enzyme inhibitors, and patients on anesthetic premedication.

Procedures

None of the patients received any premedication before surgery. After the patient's arrival at the operating room, peripheral venous access was established on the right or left antecubital vein for fluid and drug administration with a 20-G intravenous cannula. Electrocardiography, non-invasive blood pressure, and pulse oxygen saturation were monitored. Dexmedetomidine (200 $\mu\text{g}/2\text{ mL}$) was diluted with normal saline to obtain a concentration of 4 $\mu\text{g}/\text{mL}$, and ketamine (100 mg/1 mL) was diluted with normal saline to obtain a concentration of 10 mg/mL. Patients were randomly assigned to four groups of 100 patients each, using computer-generated random numbers, to receive dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ + normal saline 0.05 mL/kg (DEX group), ketamine 0.15 mg/kg + normal saline 0.05 mL/kg (KET group), or ketamine 0.15 mg/kg + dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ (KETO-DEX group). The placebo group received normal saline 0.15 mL/kg + normal saline 0.05 mL/kg. The above-mentioned drugs were administered intravenously, in 10 mL isotonic saline. Dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ or its corresponding normal saline (0.05 mL/kg) for all groups was infused at a steady rate of 2 mL/min, over 5 min. Ketamine 0.15 mg/kg or its corresponding normal saline 0.05 mL/kg was administered over 10 s, 1 min before the fentanyl bolus injection (3.0 $\mu\text{g}/\text{kg}$ within 5 s).

After the fentanyl injection any episode of cough was classified as coughing. The onset time (from the end of bolus administration to the beginning of coughing), frequency, and severity of cough for 1 min were recorded, by a blinded observer, who was unaware of the type of medication given to the patients. Syringes for injection were labeled with specific numbers, keeping the identity of the group treatment concealed from all research staff until the end of the study. Recorded numbers of episodes of coughing were classified based on the number of coughs observed per min. Cough severity was graded as mild (grade 1-2), moderate (grade 3-5), or severe (grade >5). Later, general anesthesia was induced with a sleeping dose of propofol (1-2 mg/kg), and then anesthesia was maintained with infusion of propofol and/or inhalation agent and air/oxygen mixtures.

Statistical analyses

Statistical analyses were carried out using SPSS statistical package, version 13.0 (SPSS, Inc., Chicago, IL, USA) for Windows. Results are expressed as the mean \pm SD, number, proportion, or percentage. Frequencies of coughing and proportions of sex

Table I. Demographics of four patient groups ($n = 100$).

Group	Placebo	KET	DEX	KETODEX
Age (y)	39.1 ± 15.1	38.8 ± 17.3	40.2 ± 14.2	39.6 ± 15.6
Gender (M/F), n	61/39	58/42	66/34	63/37
Weight (kg)	58 ± 6	61 ± 6	60 ± 3	62 ± 1
ASA (I/II), n	94/6	93/7	98/2	96/4

Values are means ± standard deviation. No statistically significant differences were observed in this table.

ASA = American Society of Anesthesiologists physical status; KET = ketamine group; DEX = dexmedetomidine group; KETODEX = ketamine-dexmedetomidine group.

and ASA classes were compared using the chi-square test or Fisher's exact test with Bonferroni correction. One-way analysis of variance was used to compare age and weight among the four groups. A value of $P < 0.05$ was considered to be statistically significant.

Results

A total of 427 patients were assessed for eligibility, and 27 (6%) patients were excluded. Among them were 17 (4%) patients who did not meet the inclusion criteria, 8 (2%) other patients declined to participate, and 2 (0.5%) were excluded for other reasons. Those who withdrew did not differ significantly in any characteristics from those who continued the study. Therefore, a total of 400 (93%) patients were enrolled in the study, and there were 100 patients in each group. The demographic data were comparable for age, weight, gender, and ASA status in the four groups (Table I).

Following an intravenous fentanyl bolus, 53 patients had cough in the placebo group, 20 in the KET group,

34 in the DEX group, and only 9 of the patients in KETODEX group (Table II). The incidence of cough was significantly lower ($P < 0.05$) in the KETODEX group when compared with the other groups. The onset time of cough was significantly delayed in the KETODEX group. Only nine patients in the KETODEX group had either mild (6%) or moderate (3%) cough, with none suffering from severe cough (Table II). No patient in any of the groups suffered from hypoxemia, apnea, truncal rigidity, nausea, vomiting, or other adverse effects after the bolus injection of fentanyl.

Discussion

Cough reflexes commonly occur after fentanyl administration during induction of general anesthesia. Thus, FIC is then frequently observed but has so far received little attention, and therefore FIC may continue to be a troublesome factor in the delivery of safe and effective patient care (7). Multiple mechanisms have been proposed to be responsible for the occurrence of FIC at induction. Thus, fentanyl has been shown to inhibit central sympathetic outflow causing vagal predominance, inducing cough and reflex bronchoconstriction (6,30,31). Several recent studies have been conducted to investigate different pharmacological drugs with regard to their potency to reduce the adverse effects of FIC (3-5,8-12). In our study, the dose (3 µg/kg) of fentanyl was selected because it fitted to the common administration in our daily clinical practice. Interestingly, our study demonstrated that a priming dose of intravenous KETODEX reduced the incidence of FIC to 9% in compared to 53%, 34% and 20%, in the placebo, DEX and KET groups, respectively.

Of nine patients who had coughed in the KETODEX group, none of them experienced any degree of severe coughing 1 min after fentanyl administration. Patients in the placebo group showed a higher

Table II. Incidence of coughing and its severity after fentanyl injection.

Groups	Incidence (%)	Onset (s)	Severity of cough (%)				No cough (%)
			Mild	Moderate	Severe	Total	
Placebo	53/100 (53)	15.7 ± 3.9	25 (25)	17 (17)	11 (11)	53	47
KET	20/100 (20)	18.6 ± 3.3	10 (10)	6 (6)	4 (4)	20	80
DEX	34/100 (34)	18.2 ± 3.2	16 (16)	11 (11)	7 (7)	34	66
KETODEX	9/100 (9)	25.8 ± 3.8 ^b	6 (6) ^b	3 (3)	0 (0) ^a	9	91

The dose of fentanyl was 3 µg/kg for an injection duration of <5 s. Severity of coughing was graded as mild (grade 1-2), moderate (grade 3-5) and severe (grade >5) based on the number of coughs.

The onset time (mean ± SD) was the median value of patients who coughed.

^a $P < 0.01$, ^b $P < 0.05$.

incidence rate (53%) than patients in the KET (20%) or the DEX (34%) groups. There was a relative risk reduction for the KET group in the incidence of FIC (20%), but the difference did not attain statistical significance. In addition, the onset time of cough was delayed in the KETODEX group. The relatively slow time course for the fentanyl injection (5 s) may be considered to be a possible reason when compared with injection times (<2 s) used in previous studies (16,17,32-35). In our study, no patients received any premedication before surgery. This may be the reason why more of the patients in the placebo group experienced coughing (53%).

Yeh et al. demonstrated that ketamine (0.15 mg/kg) could suppress FIC (12). The activation of NMDA receptors in the larynx, lung, and airways can trigger airway constriction. Therefore, the direct bronchodilating and inhibitory effect of ketamine on bronchomotor tone may be attributed to its NMDA receptor antagonism to attenuate the fentanyl cough reflex (23,36). In another study, He et al. demonstrated that dexmedetomidine (0.5 µg/kg and, to a higher extent, 1.0 µg/kg) reduced the incidence of FIC (18). Dexmedetomidine is a highly selective α_2 -adrenergic agonist with sedative and analgesic properties. The combination of ketamine and an α_2 -adrenergic agonist has bronchodilatory effects on airway smooth muscles. The rapid response of the cough reflex after fentanyl injection suggests that a pulmonary chemoreflex is the likely mechanism, mediated by either irritant receptors or by vagal C-fiber receptors in close proximity to pulmonary vessels (5,12).

The relevant limitation of our study is that the priming dose of ketamine (0.15 mg/kg) in the KET and KETODEX groups was low, so perhaps the relatively high incidence rate in both groups could have been different if we had used a different dose.

In conclusion, the present study has shown that a priming dose of intravenous KETODEX could suppress FIC caused by fentanyl within 5 s during general anesthesia induction. Therefore, KETODEX could be a clinically effective choice for attenuating FIC.

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