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Suppressing Effect of Dextromethorphan or Clonidine on Fentanyl-Induced Coughing: A Double- Blind, Prospective, Randomized Placebo-Controlled Study

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Abstract

Background: Various medications have been examined to reduce fentanyl-induced cough. We studied the efficacy and safety of premedication with dextromethorphan or clonidine versus placebo prior to intravenous fentanyl injection on the cough reflex.

Methods and Materials: In a randomized double-blind placebo controlled trial, 360 adult patients of American Society of Anesthesiologists physical status I-II, scheduled for elective surgery under general anesthesia were randomly allocated into three groups receiving clonidine (0.2 mg tablet orally),dextromethorphan (15 mg orally), or placebo 60 minutes before induction of anesthesia. The incidence of cough was recorded for 1 minute after fentanyl injection and graded as none (0), mild (1–2), moderate (3–5), and severe (>5 cough). Seventy three (20.3%) exhibited vigorous cough attacks during intravenous fentanyl administration.

Results The overall incidence of coughing in clonidine group (15.0%) and dextromethorphan (11.7%) group was lower than the placebo group (34.2%). Also, 3.3% of cases in the clonidine group and none of the patients in the dextromethorphan suffered from severe coughing, while 8.3% of the cases in the placebo group considered to have severe cough. Pretreatment with clonidine or dextromethorphan was positively associated with reduced incidence of fentanyl-induced cough after adjustment for potential confounders. Vital signs were all significantly lower following clonidine administration compared to both pretreatment regimens including dextromethorphan and placebo before and after intravenous fentanyl injection.

Conclusion Administering dextromethorphan or clonidine reduces the incidence of fentanyl-induced cough with better haemodynamic stability following the use of clonidine than dextromethorphan.

Keywords: Anesthesia; Cough; Clonidine; Dextromethorphan

Introduction

During induction of anesthesia fentanyl is used to reduce the hyperdynamic response to tracheal intubation, which may be accompanied by undesirable cough. Fentanyl-induced cough is estimated to be as high as 65% following intravenous fentanyl bolus injection [1]. Though fentanyl-induced cough is usually considered benign, it may sometimes result in intracranial, intra-ocular or intra-abdominal pressures requiring therapeutic intervention [2-5]. Various mechanisms have been proposed to explain fentanyl-induced cough. This phenomenon may be caused by stimulation of a pulmonary chemoreflex, mediated by C-fiber receptors present on smooth muscles of the trachea and bronchi; resulting in muscle contraction triggering the cough reflex by fentanyl [6]. Fentanyl-induced cough could also be the result of a mechanical or chemical stimulation of sensory receptors within the respiratory tract; the afferent impulses from these receptors may activate a putative brainstem cough center [7]. Drugs such as ketamine, terbutaline, clonidine, dexamethasone, and lidocaine as well as performing some maneuvers such as a forced expiration against open glottis, dilution of fentanyl to 10 µg/ ml, and prolonged injection time have all been evaluated in reducing this fentanyl induced cough [8-13]. Dextromethorphan is an antitussive drug that is used for suppression of cough caused by minor throat and tracheo-bronchial irritation, especially after inhalation of any irritants. At therapeutic doses, dextromethorphan acts centrally on the brain as opposed to locally on the respiratory tract [14], and thus it might be an effective medication for reducing fentanyl-induced cough.

The aim of this study was to evaluate and compare the effectiveness of intravenous injection of dextromethorphan with clonidine and placebo prior to intravenous fentanyl injection on the fentanyl induced cough during induction of anesthesia.

Materials and Methods

After approval by the Ethics Committee of Tehran University of Medical Sciences and obtaining a written informed consent from the participants, 360 adult patients of American Society of Anesthesiologists (ASA) physical status I-II, aged between 18 and 65 years scheduled for elective surgery under general anesthesia were included in this randomized double-blind placebo controlled clinical trial. Exclusion criteria were history of asthma, chronic cough, cigarette smoking, and upper respiratory tract infection in the previous four weeks, a history of bronchodilator or steroid therapy, or treatment with angiotensin-converting enzyme inhibitors or anti-psychotic drugs during the last year. Based on previous reports, we assumed the expected the incidence of fentanyl-induced cough to be 40% following pre-medication with placebo. We also expected a 50% reduction in cough compared to placebo in the groups given clonidine or dextromethorphan. 'We estimated that 120 subjects would be required per group in order to detect 50% absolute reduction in the incidence of coughing with 80% power and 5% probability of Type I error.

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Patients were randomly allocated to either Group A (n=120), Group B (n=120), or Group C (n=120) using a computer-generated randomization list. Group A patients received clonidine (0.2mg tablet orally) 60 minutes before induction of anesthesia. Group B patients received dextromethorphan 15 mg orally, and Group C patients received placebo tablet 60 minutes before the anesthesia. All patients were monitored with standard monitoring tools including noninvasive blood pressure, Electrocardiogram (ECG), and pulse oximetry. All patients were oxygenated with face mask throughout the study period. Then, 3 ug/kg of fentanyl prepared as solutions of 50 ug per mL was injected at a rate of 1 mL per second intravenously at room temperature. Any episode of cough within 60 seconds of fentanyl administration was classified as fentanyl-induced cough, and its severity was graded based on the number of coughing spasms (none 0, mild 1–2, moderate 3–5, and severe >5 coughs). A trained anesthesiologist who was blinded to group assignment observed and documented the cough episode of the patients. The values of heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were also determined immediately before and also 60 seconds after the fentanyl injection.

Results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the one-way ANOVA test for the continuous variables and the chi-square test (or Fisher's exact test if required) for the categorical variables. Predictors exhibiting a statistically significant relation with cough were taken for multivariate logistic regression analysis to investigate their independence as predictors. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The demographic profiles of the three groups were compared. There were no significant differences in male to female ratio, and the mean age and weight. Of the 360 patients, 73 (20.3%) exhibited vigorous cough attacks during intravenous fentanyl administration (Table 1). The overall incidence of cough was similar in the clonidine and dextromethorphan groups, but significantly lower than placebo group (Table 2). Based on a cough severity scale, the three groups were significantly different. In clonidine pre-medicated group, eight cases out of eighteen (6.7%) and in dextromethorphan group, eight cases out of fourteen (6.7%) had mild cough in comparison to thirteen patients (10.8%) in the placebo group ($p<0.001$). Only 3.3% of the cases in the clonidine group and none of the patients in the dextromethorphan suffered severe coughing, while 8.3% of the cases in the placebo group had severe cough ($p<0.001$). Multivariable logistic regression analysis showed that pretreatment with clonidine was positively associated with reducing incidence of fentanyl-induced cough after adjustment for potential confounders including gender, age, weight, and baseline clinical signs (Table 2). This regression model also showed that individuals administered dextromethorphan exhibited significantly reduced odds of appearing fentanyl-induced cough (Table 3).

With respect to the changes in clinical signs immediately before and one minute after fentanyl injection (Table 4), heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were all significantly lower following clonidine administration compared to

Item	Clonidine group (n=120)	Dextromethorphan group (n=120)	Placebo group (n=120)	P-value
Cough appearance, n (%)	18 (15.0)	14 (11.7)	41 (34.2)	< 0.001
Cough severity, n (%)				< 0.001
Mild	8 (6.7)	8 (6.7)	13 (10.8)	
Moderate	6 (5.0)	6 (5.0)	18 (15.0)	
Severe	4 (3.3)	0 (0.0)	10 (8.3)	

Table 1: Cough appearance and its severity after fentanyl injection at the three intervention groups.

Variable	Multivariate p-value	Odds Ratio	95% Confidence Interval	
Intervention (placebo versus clonidine)	0.007	2.278	1.239	4.189
Gender (male versus female)	0.495	0.869	0.581	1.300
Advanced age	0.824	0.939	0.541	1.631
Weight	0.894	0.972	0.642	1.472
Baseline heart rate	0.007	1.800	1.173	2.763
Baseline mean arterial pressure	0.054	0.667	0.441	1.008

Table 2: Difference in cough appearance after fentanyl injection between the groups received clonidine and placebo in a multivariable logistic regression model.

Variable	Multivariate p-value	Odds Ratio	95% Confidence Interval	
Intervention (placebo versus dextromethorphan)	0.001	2.929	1.518	5.651
Gender (male versus female)	0.897	0.973	0.646	1.466
Advanced age	0.741	0.912	0.527	1.578
Weight	0.947	0.986	0.650	1.494
Baseline heart rate	0.522	1.143	0.760	1.720
Baseline mean arterial pressure	0.588	1.111	0.759	1.626

Table 3: Difference in cough appearance after fentanyl injection between the groups received dextromethorphan and placebo in a multivariable logistic regression model.

Clinical sign	Clonidine group (n=120)	Dextromethorphan group (n=120)	Placebo group (n=120)	P-value
Heart rate (/min)				
Before injection	79.08 ± 12.90	87.82 ± 19.29	88.56 ± 16.74	< 0.001
After injection	80.65 ± 15.33	87.97 ± 15.49	90.27 ± 16.10	< 0.001
Systolic blood pressure (mmHg)				
Before injection	124.05 ± 15.89	132.05 ± 17.05	132.52 ± 17.28	< 0.001
After injection	122.63 ± 15.78	127.87 ± 16.61	128.14 ± 16.33	0.013
Diastolic blood pressure (mmHg)				
Before injection	76.22 ± 10.37	81.73 ± 11.40	83.16 ± 11.60	< 0.001
After injection	75.55 ± 11.68	78.82 ± 10.83	80.03 ± 12.12	0.009
Mean arterial pressure (mmHg)				
Before injection	91.73 ± 12.13	99.18 ± 12.57	98.65 ± 13.04	< 0.001
After injection	91.27 ± 13.17	94.72 ± 12.63	95.24 ± 12.85	0.036

Data are presented as mean ± SD

Table 4: Clinical signs before and after fentanyl injection at the three intervention groups.

pretreatment with dextromethorphan or placebo before and also after intravenous fentanyl injection.

Discussion

In this study we studied the beneficial preventive effects of the two premedication regimens including dextromethorphan and clonidine on fentanyl induced cough and hemodynamic parameters and compared it with placebo. We showed that both oral dextromethorphan 15 mg and clonidine 0.2 mg orally decrease the incidence and severity of fentanyl induced cough compared to placebo. The incidence of fentanyl induced cough was lower in the dextromethorphan group (11.7%) and the clonidine group (15.0%) in comparison to placebo (34.2%). In the dextromethorphan and the clonidine group, 6.7% of patients developed mild and 5% moderate cough, while severe cough occurred in in none of the patients in dextromethorphan group and 3.3% patients in the clonidine group. In the control group, 10.8% of patients developed mild, 15.0% moderate, and 8.3% severe cough. Our finding with regard to the efficiency of dextromethorphan administration was similar to the study by Mukherjee et al. that revealed a significantly lower incidence of cough in dextromethorphan than the control group [15]. However they used higher doses of this drug [15]. High doses of dextromethorphan although effective in reducing cough but could cause adverse effects such as dizziness and agitation which supports the rational of the lowest feasible dose. In another study by Elmenesy et al. aimed to evaluate effects of dextromethorphan on cough, it was shown that premedication with dextromethorphan decreased the incidence and severity of fentanyl induced cough than in our study [16]. A number of pharmacological measures have been studied in an attempt to reduce this adverse phenomenon, with varying degrees of success. We tested dextromethorphan and clonidine. The effect of dextromethorphan is attributable to its structural similarity to codeine. The recommended oral dose of dextromethorphan varies from 0.5 mg/kg to 150 mg. We selected a dose of 15 mg that was notably low based on previous reports [17]. In accordance with our findings, Horng et al. showed that intravenous premedication with clonidine 2 mcg/kg significantly decreased the cough induced by fentanyl administration (17.3% in clonidine pretreated patients versus 38.7% in control group). This effect was associated with mild reduction in heart rate and blood pressure [9]. Similarly, in our study, vital signs were more stabled in the clonidine group than the dextromethorphan and the placebo group. However, in line with other studies, we showed that premedication with either of these drugs is safe and effective in reducing fentanyl-induced cough.

In the current study, the incidence of cough following fentanyl 3 mcg/kg injection in the group pretreated with placebo was 20.3%. Phua [18], and Agarwal [5] reported similar results with 28% incidence of of cough following a dose of injected fentanyl between 1.5-2 mcg/kg. However, Bohrer [19] observed a 45% incidence of cough when fentanyl 7 μg/kg was given through a central venous line and Lui [20] reported a 43% incidence of fentanyl-induced cough using a dose of 5 μg/kg. The differences in the incidence of cough may be ascribed to the doses and routes of administration. Furthermore, fentanyl-induced cough may also be influenced by other factors such as age, cigarette smoking, a prior epidural injection of lidocaine, and a priming dose of vecuronium. In our study, we did not include those with the history of smoking or pulmonary problems. Also, using multivariable regression analysis, we assessed our finding with adjustment to gender, age, and baseline hemodynamic variables. Oral Clonidine has a relatively slow onset compared to dextromethorphan and perhaps more efficacies could have been reached if a longer duration in time surpassed prior to fentanyl induction.

In conclusion, premedication with either 15 mg dextromethorphan or 0.2 mg clonidine orally can effectively reduce the incidence and severity of fentanyl-induced cough. Clonidine offers better hemodynamic stability than dextromethorphan in this setting. Large multicenter trials are, however, needed to determine the optimal doses of these drugs for the prevention of fentanyl-induced cough during induction of anesthesia.

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