Original Article

Can low dose of propofol effectively suppress fentanyl-induced cough during induction of anaesthesia? A double blind randomized controlled trial

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Abstract

Background and Aims: Fentanyl-induced cough (FIC) is often seen after intravenous (IV) administration of fentanyl during the induction of general anesthesia.The aim of this study was to evaluate the effectiveness of low dose of propofol in suppressing of FIC during induction of anesthesia.

Material and Methods: In a prospective double-blind randomized controlled trial, a total of 240 patients, American Society of Anesthesiologists physical status Class I and II, scheduled for elective surgery were randomly assigned into two equally sized groups (n = 120). Patients in Group A received low dose of propofol (10 mg) and patients in Group B received the same volume of normal saline (control group). Two minutes later, all patients were given fentanyl (2 μg/kg) over 2 s through the peripheral IV line in the forearm. The vital sign profiles and frequency and intensity of cough were recorded within 2 min after fentanyl bolus by a nurse blinded to study design. Data were analyzed using independent t-test, paired t-test and Chi-square test.

Results: The incidences of FIC were 9.2% and 40.8% in Group A (propofol) and Group B (placebo) respectively (P = 0.04). Furthermore, there was a significant difference in the intensity of cough between Groups A and B (P < 0.0001). The hemodynamic value (systolic blood pressure, diastolic blood pressure, heart rate, mean arterial pressure and saturation of oxygen) were similar, and there was no significant difference between two groups in the baseline value or after propofol or placebo injection.

Conclusions: Administration low dose of propofol (10 mg) may effectively reduce the FIC frequency and intensity during induction of anesthesia without hemodynamic disturbances.

Key words: Cough, fentanyl, general anesthesia, propofol

Introduction

Fentanyl, a synthetic opioid, is used during the induction of general anesthesia because of its rapid onset, short duration of action, intense analgesia, ease of titrability, cardiovascular stability and low histamine release.[1,2] Reflex coughing after intravenous (IV) fentanyl administration occurs in 28-80% of cases.[3-8] FIC is usually benign, transient and self-limited, but at times may be spasmodic or explosive requiring immediate therapeutic intervention.[9,10] Although the mechanism of FIC is still unclear, but various interventions have been implemented to reduce its incidence during the induction of anesthesia by using adjuncts and other maneuver, with varying success. These interventions include the use of β2 receptor agonist, ephedrine, lidocaine, ketamine, clonidine, dexamethasone, dexmedetomidine, a huffing maneuver prior to induction etc. However these approaches are not uniformly effective.[3-5,7,11-15] Propofol, a short acting nonopioid, nonbarbiturate, sedative-hypnotic agent with quick onset and short duration of action is one of the pharmacologic agents that have been used for suppressing of FIC, in varying doses by few researchers with conflicting results.[4,8,16,17]

Hence we conducted this study to investigate efficacy of 10 mg of propofol to suppress FIC during induction of anesthesia.

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Material and Methods

After obtaining an Institutional Ethics Committee approval and an informed patient consent, a continuous sample of 240 adults' patients of both sexes, American Society of Anesthesiologists Class I or II, aged 18-50 years, scheduled for various elective surgical procedures under general anesthesia were enrolled in this prospective double-blind randomized, placebo control study. Patients with a history of asthma, chronic cough, smoking or substance abuse, cardiac disease, upper respiratory tract infection in the previous 4 weeks, any disease or surgery of trachea or larynx, impaired kidney or liver functions, pregnancy, medication with angiotensin-converting enzyme inhibitors, steroids, antihistamine or antitussive drugs in the previous 4 weeks, were excluded from the study. No premedication was allowed. The study was performed between December 2012 and July 2013. Patients who fulfilled the inclusion criteria were randomly allocated into Group A (n = 120) and Group B (n = 120) by sealed envelope technique. Patient allocation was performed by a nurse who was unaware of the study groups, according to numbers generated by the computer generated list. A venous access was obtained and monitoring instituted in the form of electrocardiogram, noninvasive blood pressure, and pulse oximeter. Baseline systolic and diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2) and heart rate (HR) were recorded. Then, patients in Group A, received propofol 10 mg and Group B received same volume (1 ml) normal saline 0.9% as placebo. All syringes containing propofol or placebo were covered with masking tape to conceal any details of product. At 2 min after the aforementioned treatment in each group, fentanyl 2 μg/kg was administered through the peripheral IV line within 2 s. The occurrence and intensity of cough within 2 min after the fentanyl injection (since the cough generally happens within this period of time), were observed and recorded by a nurse who was blinded to the study groups. The intensity of cough was arbitrarily graded as the following: No cough (None), 1-2 cough (Mild), 3-4 cough (Moderate) and 5 cough or more (Severe) (5). Moreover, systolic and DBP, MAP, SpO_2 and pulse rate were measured and recorded. This study registered in the Iranian Registry of Clinical Trials Database (IRCT201305216803N4). Estimation of sample size was based on a pilot study using this protocol in 30 patients and observed that 43% (n = 13) of patients had cough. We defined a significant suppressive effect as decreasing the incidence of cough to half of control. At a level of α = 0.05 with a power of 0.8, the sample size calculation was 105 in each groups; we therefore, recruited 120 patients to account for any dropouts.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS), version 16 (SPSS Inc., Chicago, IL, USA), using the Chi-square tests, Student's t-test, and paired t-test. Significance level was set at $P < 0.05$.

Results

All patients completed the present study and data from all patients were analyzed.

Demographic profile of all patients in both groups was comparable [Table 1].

Fentanyl-induced coughing on induction of anesthesia presented in 60 (25%) patients. There was a statistically significant difference for FIC frequency and intensity between two groups [Table 2].

The hemodynamic value (SBP, DBP, HR, MAP and SpO_2) were also similar and there was no significant difference between two groups in the baseline value or after propofol or placebo injection [Table 3].

Discussion

The results of our study indicate significantly reduced incidence (frequency and intensity) of FIC with administration of 10 mg propofol prior to administration

Table 1: Demographic characteristics of patients in the two groups

Variables	Group A (propofol)	Group B (placebo)	*P* value
Sex			
Male (%)	58 (48.3)	63 (52.5)	0.51
Female (%)	62 (51.7)	57 (47.5)	
Age (year)	34.52±9.31	32.69±9.53	0.13
Weight (kg)	66.3±10.8 (range: 40-98)	68.5±12.1 (range: 38-101)	0.15
BMI (kg/m^2)	24.1±3.6 (range: 16.7-32.1)	24.8±4.1 (range: 16.2-34.4)	0.13

Data are expressed as the mean ± SD, or number (%) of cases (only sex), SD = Standard deviation, BMI = Body mass index

Table 2: Frequency and intensity of FIC in two groups

Group	Total (n)	Patients had cough (%)	Patients had no cough	Cough severity (%)		
				Mild	Moderate	Severe
Propofol	120	11 (9.2)	109	5	5	1
Placebo	120	49 (40.8)	71	25	17	7

P = 0.000 (propofol vs. placebo group), FIC = Fentanyl-induced cough

Table 3: Changes in vital signs after intervention in two groups

Group	SBP (mmHg)		DBP (mmHg)		HR (bpm)		SpO_2 (%)		MAP (mmHg)	
	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
Propofol	129.6	128.7	81.7	81.1	90.1	89.6	98.2	98	96.3	95.4
P value (paired *t*-test)	0.38		0.5		0.56		0.19		0.3	
Placebo	130	130.6	83.7	83.9	88.9	89.4	97.9	97.6	97.9	98.4
P value (paired *t*-test)	0.66		0.73		0.53		0.13		0.61	

No statistical difference was observed between the propofol and placebo groups, SBP = Systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SpO_2 = pulse oximeter oxygen saturation, MAP = mean arterial pressure, T0 = Time before administration of propofol or normal saline injection (base line), T1 = 2 min after fentanyl injection

of fentanyl during induction of anesthesia. In a study conducted by Böhrer *et al*. FIC was observed in 45% of patients when fentanyl was given through a central venous line.[6] Yu *et al*. observed FIC in 32% of patients when fentanyl was administered through a peripheral IV line.[22] In a study by Sedighinejad *et al*. the incidence of FIC was reported 74.4%.[17] The differences in the incidence of cough may be related to the different doses of fentanyl and speed of injection. The mechanisms of FIC are not well understood, but various theories have been proposed. Fentanyl may cause vagal predominance and provoke reflex bronchoconstriction and cough.[8] In addition, substances like histamine and neuropeptides, released by an action on prejunctional μ-opioid receptors after IV fentanyl administration, play an important role in contributing to this cough.[13,20] The study by Yu *et al*. showed that dilution of fentanyl combined with a prolonged injection time could eliminate FIC.[22] However, according to Schäpermeier and Hopf's study, FIC does not depend on injection speed.[18] Another strategy that was reported as a useful way to prevent FIC is huffing maneuver.[15] Although it has been shown that this maneuver can prevent FIC, but some patients who receive propofol or midazolam during induction of general anesthesia cannot use this maneuver. Tang *et al*., Zeidan and El Sayed observed effective suppression of FIC by a priming dose of >1 mg/Kg of propofol.[8, 23] One possible explanation for the effect of propofol in suppressing FIC may be its bronchodilatory effect.[23] Pizov *et al*. showed that the incidence of wheezing was significantly reduced in asthmatic patients receiving a propofol-based induction of anesthesia compared to a barbiturate-based induction.[24] Cigarini *et al*. demonstrated that propofol was able to prevent fentanyl-induced bronchoconstriction in surgical patients.[25] There are several potential targets for propofol-induced bronchodilatation. Propofol has been found to attenuate vagal and methacholine-induced bronchoconstriction, with possible direct actions on muscarinic receptors.[27,28] The result of a study that conducted by Kamei *et al*. have been shown that IV injection of fentanyl markedly increased the histamine levels and suggested that fentanyl enhances the excitability of rapidly adapting receptors to cause cough, and enhancement of histamine release in the airways may somehow be related to this change.[1] Also in a study related to the propofol-induced bronchodilatation, it has been shown that propofol decreased peak intracellular calcium responses to histamine.[29] In a study by Lin *et al*. although the lower frequency of cough was noted in patients' receiving propofol (0.6 mg/kg), but it was not statistically different from that of the placebo group. Ineffectiveness of propofol for reducing FIC in this study may be due to the small sample size (n = 30) and also the higher dose of fentanyl (2.5 μg/kg) that was administered for the patients.[4] However, our study demonstrates that propofol in doses of 10 mg (sub-hypnotic dose) can be safely used, with stable hemodynamic profile. A limitation of this study was that we did not estimate the peak plasma concentration of propofol required suppressing the FIC. Therefore, a further study needs to be conducted to determine the timing of administration and the peak plasma concentration of propofol required to suppress FIC.

Conclusion

Our study suggests that low dose of propofol (10 mg, IV) bolus injection 2 min before fentanyl injection seemed to be feasible, simple, and cost-effective method to prevent FIC.

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