Original Article

Effect of a Priming Dose of Propofol Immediately before Induction on Fentanyl-induced Cough: A Prospective Clinical Study

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Abstract

Context: It is not uncommon for fentanyl to induce cough at the time of induction. **Aims:** To evaluate the effect of subhypnotic dose of propofol on the incidence of occurrence and intensity of fentanyl-induced cough (FIC). **Settings and Design:** This is a prospective, randomized controlled study. **Subjects and Methods:** A total of 150 patients of the American Society of Anesthesiologists Classes I and II were assigned to one of the two groups: Group A received normal saline as placebo and Group B received low dose propofol (20 mg) before fentanyl given at a dose of 1.5 μg/kg through a peripheral intravenous catheter. The incidence of occurrence and intensity of cough were observed for the two groups. **Statistical Analysis Used:** One-way ANOVA, Chi-square test, Fisher's exact test, and Mann–Whitney U-test were used for statistical analysis. P <0.05 was considered statistically significant. **Results:** The incidence of occurrence of FIC was 29.3% and 6.6%, respectively, for placebo and propofol groups (P = 0.0000). Further, there was statistically significant difference between the groups for different grades of intensity (P = 0.032). There were 21% of patients who suffered desaturation and 1.3% chest wall rigidity in placebo group while no such cases were recorded for the propofol group. **Conclusions:** Subhypnotic dose of propofol can effectively attenuate FIC. It reduces not only the incidence of occurrence but also the intensity of the cough.

Key words: Fentanyl-induced cough, propofol, sub hypnotic dose

Introduction

Although opioids are well-recognized for its antitussive property, potent synthetic opioids derived from phenylpiperidine such as fentanyl, on the contrary, induce cough when given at the time of induction.[1] The intensity of cough has a varying degree of severity from transitory, unremarkable to occasional unbearable, life-threatening explosive nature which may demand prompt intervention. Invariably, its occurrence during induction is associated with a sudden undesirable elevation in intracranial, intraocular, and intra-abdominal pressures.[2,3] Various strategies have been employed to prevent or reduce its incidence. These include pharmacological mediation with terbutaline, a β2 receptor agonist, ephedrine, lidocaine, ketamine, dexamethasone, and dexmedetomidine, an α_2 agonist.[4,5] Nothing conclusive can be drawn from these studies.

Since propofol is short-acting agent and can suppress airway reflex, we hypothesized a study designed to investigate if a small dose given just before fentanyl could suppress fentanyl-induced cough (FIC).

Subjects and Methods

It was a prospective, randomized controlled study initiated after obtaining approval from the Institutional Ethics Committee and written informed consent. A total of 150 adult patients of either sex belonging to the American Society of Anesthesiologists Classes I and II between 20 and 55 years scheduled for elective surgical procedures of various specialties under general anesthesia.

Those with recent upper respiratory tract infection, chronic obstructive pulmonary disease, asthma, and chronic

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smokers and on antihypertensive medications such as angiotensin-converting enzyme inhibitors, cough suppressants, antihistamines, steroids, and bronchodilators were excluded from the study.

Those who were included in the study were randomly separated into two groups of 75 patients each by computer-generated numbers by a person no more involved in the study.

- Group A: Received 0.9% normal saline 2 ml intravenously
- Group B: Received propofol 20 mg (2 ml) intravenously.

Premedication was not given before the study drug. Both groups received the study drug after securing an intravenous (iv) catheter. Patients were monitored for heart rate, rhythm on electrocardiogram, noninvasive blood pressure, and oxygen saturation (SpO_2). One minute after the administration of the study drug, iv fentanyl was given at a dose of 1.5 μg/kg injected within 10 s. The primary end-point was FIC and intensity of cough.

An observer who did not witness the administration of the study drugs recorded the occurrence of FIC if it ensued within 1 min of fentanyl administration. The intensity of cough was graded as:

- Mild: 1–2 cough
- Moderate: 3–4 cough
- Severe: ≥5 cough.

The secondary end-points were desaturation and chest wall rigidity. Desaturation was defined as SpO_2 <90% within 5 min of fentanyl.

All patients subsequently received full dose of propofol 2.0 μg/kg and vecuronium 0.1 mg/kg to facilitate intubation and maintained on isoflurane with oxygen: Air at 1:1 ratio.

Estimation of sample size was based on pilot study with 28% had cough, and with power of 90% and $\alpha = 0.05$, a minimum sample size calculation was estimated to be seventy in each group. On account of any dropout, the final sample was kept at 75 patients in each group.

Statistical analysis

One-way ANOVA test was used for continuous variables and Chi-square test for categorical variables. The occurrence of FIC was analyzed with Fisher's exact test and intensity by Mann–Whitney U-test; SPSS version 20.0 (IBM, Armonk, NY, USA) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

The demographic profile was found to be comparable with no statistically significant difference between the groups [Table 1].

FIC was observed in 27/150 (18%) patients in both groups. It was more common in Group A compared to Group B (29.3% vs. 6.6%) ($P = 0.0000$) [Table 2].

When comparing the two groups for the intensity of cough, Group A was observed to have more patients for all the grades of intensity which was statistically significant ($P = 0.032$). As far as Group B is concerned, no patient had severe cough [Table 3].

There was statistically significant difference for the desaturation and chest wall rigidity between the groups [Table 4].

Discussion

Cough brought about by fentanyl is a very common occurrence at the time of induction. Literature search suggests that different authors quote varying incidence in the occurrence of FIC. Sedighinejad *et al*.[6] and Böhrer *et al*.[7] reported the incidence of FIC as 74.4% and 45%, respectively. The incidence is higher because Sedighinejad *et al*. used 4 μg/kg fentanyl instead of conventional 2 μg/kg dose. A similar study by Lin *et al*. also revealed a very high incidence (65%) of cough.[8] This was due to rapid administration (within 2 s) of fentanyl at high dose of 2.5 μg/kg. Phua *et al*. have demonstrated that the injection of fentanyl 1.5 μg/kg via a peripheral venous line elicits cough in only 28% of the patients.[9] Thus, incidence can be correlated with dose and speed of injecting the drug.

The exact cause of FIC is still debatable although different mechanisms have been postulated. Inhibition of central sympathetic outflow, vagal predominance, and bronchospasm

Table 1: Demographic parameters of the two groups

Variables	Group A ($n=75$)	Group B ($n=75$)	*P*
Age (years)	29.6±8.7	28.4±8.2	0.23
Male/female	39/36	40/30	0.34
Weight (kg)	58.4±11.1	55.3±9.9	0.19
ASA I/II	38/37	39/36	0.37

Data as mean±SD, SD: Standard deviation, ASA: American Society of Anesthesiologists

Table 2: Incidence for occurrence of fentanyl-induced cough in two groups

	Group A (%)	Group B (%)	*P*
FIC occurred	22 (29.3)	5 (6.6)	0.0000
FIC did not occur	53 (70.6)	70 (93.3)	

FIC: Fentanyl-induced cough

Table 3: Intensity (frequency) of cough in the two groups

	Group A (%)	Group B (%)	*P*
Mild (1-2)	11 (14.6)	4 (5.3)	0.032
Moderate (3-4)	7 (9.3)	1 (1.3)	
Severe (5-6)	4 (5.3)	0	

Table 4: Desaturation and chest wall rigidity for the two groups

	Group A (%)	Group B	*P*
Desaturation	16 (21.3)	0	0.0000
Chest wall rigidity	1 (1.3)	0	0.0000

have been described.[10] Böhrer *et al*. have implicated J-receptors in lower respiratory tract for cough caused due to fentanyl.[7] These are nonmyelinated vagally mediated c afferent fibers. Further, fentanyl evokes bronchospasm and may stimulate irritant receptors present in the trachea.

Our study revealed that there is a decrease in the occurrence of FIC from 29.6% in Group A where normal saline was injected before fentanyl to 6.6% in Group B in which a small subhypnotic dose of propofol was given before fentanyl. Sedighinejad *et al*. observed a very high incidence of FIC (74%) with fentanyl and a drastic decrease to 25.6% with propofol.[6] Compared to our study, high incidence in this study was due to more dose of fentanyl (4 μg/kg). The incidence of cough observed by Tang *et al*. was 80%.[11] During this study, propofol was given at different doses: 1.0, 1.5, and 2.0 mg/kg with the incidence of cough was 40, 6.7, and 3.3%, respectively. Average fast bolus speed of fentanyl 2.5 μg/kg (bolus time: 1.5 ± 0.3 s) and the possible bias due to small sample size have been attributed for such high incidence. Such high dose of propofol before fentanyl makes patients hemodynamically unstable.

There are a good number of reasons why propofol has been so beneficial in suppressing FIC. Subhypnotic dose will produce only conscious sedation and amnesia but no hypnosis or anesthesia. Anesthetic-sparing effect is seen with blood concentration at <3.0 mcg/ml and will insure that patient remains responsive to verbal command; at the same time, it inhibits upper respiratory reflexes. Propofol also produces bronchodilation and may even be beneficial in asthmatics. Pizov observed that the incidence of wheezing was significantly reduced in asthmatic patients receiving a propofol-based induction of anesthesia compared to a barbiturate-based induction.[12] Lin *et al*. observed FIC incidence as 65% for placebo group and 14%, 37%, and 21% with lignocaine, propofol, and ephedrine.[13] This discrepancy with propofol compared to our study can be explained by high dose of fentanyl (2.5 μg/kg) and very rapid rate of administration (within 2 s). In our study, the incidence was lower because we chose fentanyl at a lower dose (1.5 μg/kg) and gave it in a longer time (10 s). Henceforth, both dose and rapidity with which it is given rule the incidence and intensity of cough.

Ambesh *et al*. used huffing immediately before the induction of anesthesia to prevent fentanyl-induced coughing.[14]

Huffing maneuver is a gentle voluntary cough or a forced expiration against open glottis which clears the secretions from upper airway, open closed alveoli, decreases atelectasis, and thereby increasing functional residual volume of the lung. The reported incidence of cough was 32% in the control group (patients breathed normally) and 4% in the huffing maneuver group (patients were asked to perform huffing maneuver just before the fentanyl injection). Huffing maneuver is sufficient to decrease the cross-sectional diameter of airways sufficient to increase linear velocities and aid secretion movement that might cause preconditioning of stretch receptors of trachea and bronchial tree and hence decreases incidence of FIC.

Several other pharmacological interventions have been tried to control FIC. Horng *et al*. have used clonidine (2 μg/kg over 2 s) and found successful in halving the incidence but was associated with hemodynamic instability.[15]

Schlimp and Wiedermann questioned the use of lidocaine which may cause arrhythmias.[16] Similarly, ephedrine seems promising for attenuating FIC but it is contraindicated in coronary artery disease.

Conclusions

To our knowledge, pretreatment with propofol appears to mitigate the cough-inducing quality of fentanyl. It is safe and an effective way to attenuate FIC when given as premedicant at subhypnotic dose.

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Conflicts of interest

There are no conflicts of interest.

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