EFFECT OF DIFFERENT PRIMING DOSES OF PROPOFOL ON THE INCIDENCE AND SEVERITY OF FENTANYL INDUCED COUGH IN PATIENTS WITH VARIOUS SMOKING STATUSES

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ABSTRACT

Background: Fentanyl-induced coughing (FIC) is not always benign and can be remarkably troublesome at the most critical moment of induction of anesthesia. Additionally, propofol has a significant sedative effect that may reduce the incidence of FIC.

Objectives: The aim of the study was to investigate the effect of different priming doses of propofol on the overall incidence and severity of FIC during induction of anesthesia. Also, to find the overall incidence and severity of FIC among patients with various smoking statuses.

Methods: This study was carried out on 100 ASA physical status I–II adult patients of both sexes who were scheduled for elective abdominal surgery under general anesthesia in Zagazig University Hospitals.
Patients were randomly classified according to propofol priming dose into 4 equal groups, (each one consisted of 25 patients) , Group I received 0.15 mL/kg intralipid (placebo) iv, group II received 1 mg/kg propofol iv, group III received 1.5 mg/kg propofol iv, and group IV received 2 mg/kg propofol iv . One minute later, iv bolus injection of 2.5 mg/kg fentanyl was given to all patients of the 4 tested groups . During the two minutes following iv fentanyl injection , Patients who developed cough , beside cough severity , were detected and recorded . The hundred patients were classified again according to their smoking status into current smokers, former smokers and non smokers.

Results: Statistically, the demographic data (age, sex ratio, body weight, ASA ps class I/II ratio, the ratio of patient with/without past history of surgical intervention and the distribution of patients according to smoking status) of the 4 tested groups were comparable. The overall incidence of fentanyl induced cough in group III and group IV was significantly less than that of group I and group II . The incidence of each of mild, moderate and severe cough was significantly higher in group I and II than in group III and group IV. The overall fentanyl induced cough incidence was significantly higher in the current smokers than non smokers and former smoker patients .

  Fentanyl induced cough incidence was 40% , 30%., 20% and 10% in non smoker patients of each of group I, II,III and IV respectively, 50% , 33.3%., 16.7 and 0% in the former smokers patients of each of group I, II,III and IV respectively and 40%, 30%., 15, and 15% in the current smokers patients of each of group I, II, III and IV respectively. Statistically, fentanyl induced cough incidence in non smoker patients of each of group III and group IV was significantly lower than that of each of group I & group II (P2 & P3< 0.05) Also, fentanyl induced cough incidence in the former smoker patients of group IV was significantly lower than that of each of group I & group II (P3 & P5< 0.05). Moreover, fentanyl induced cough incidence in the current smoker patients of each of group III and group IV was significantly lower than that of each of group I and group II (P2, P3, P4 and P5< 0.05) .

Conclusion: Priming dose of more than 1 mg/kg of propofol iv which was given 1 minute before fentanyl was effective in reducing the incidence and severity of fentanyl-induced cough in a dose-dependent manner in patients with various smoking statuses .

Key words: fentanyl, cough, propofol, smoking

INTRODUCTION

Cough after intravenous fentanyl for induction of anesthesia had been overestimated for many years . The question of whether fentanyl-induced cough is of clinically considerable importance was raised since several prophylactic measures have been proposed to suppress cough after injection of fentanyl, all with specific possible side effects.[1,2]

  Fentanyl-induced cough (FIC) is usually transient, benign, and self-limited for most patients, but at times may be spasmodic or explosive and life threatening requiring immediate intervention. It is noteworthy that the incidence of FIC could be as high as 65% after a low dose of i.v. fentanyl (2.5 µg /kg) bolus injection.[3]

       However, fentanyl-induced cough is not always benign and is undesirable in patients with some pre-existing diseases, including cerebral aneurysms, brain trauma, open eye injury, dissecting aortic aneurysms, pneumothorax, and hypersensitive airway disease.[4]

       A lower incidence of FIC had been observed in light smokers, and a postulated possible mechanism for FIC might be via C-fiber (also known as rapidly adapting J stretch receptors) activation.[5]

The aim of our study was to investigate the effect of different priming doses of propofol on the overall incidence and severity of FIC during induction of anesthesia. Also to find the overall incidence and severity of FIC among patients with various smoking statuses .

METHODS

  This prospective randomized double blind placebo controlled clinical trial was conducted at Zagazig University Hospitals during the period from April 2011 to December 2011.

It was carried out on 100 ASA physical status I–II adult patients of both sexes , who were scheduled for elective abdominal surgery under general anesthesia . This study was approved by the Local Ethics Committee of Zagazig University Hospitals. The approval was on March 2011 . A written informed consent was obtained from all enrolled patients.

Exclusion criteria:

 Patients with body weight exceeding 20% of ideal body-weight or BMI > 30, impaired kidney or liver function, gastric tube in place , history of asthma, upper respiratory tract infection in the previous 2 weeks, or treated with angiotensin-converting enzyme inhibitors, bronchodilators, or steroids in the previous 2 weeks were excluded from this study.

Sample size calculation and sampling technique : the sample was estimated by using Epi Info version 6.04, regarding the ratio of control to intervention group was 1:3, the % of cough among control and the intervention groups was assumed to be 64% and 30% respectively, at 95% confidence interval with 80% study power, so the total calculated sample = 100 patients. The study sample was divided into 4 equal groups .(each one consisted of 25 patients) .

Study procedures:

All patients were premedicated with atropine sulphate, (0.5 mg IM) 30 min. before induction of general anesthesia. In the operating room, venous access to the left median cubital vein was established with an 18-gauge cannula. Electrocardiogram electrodes, non-invasive arterial blood pressure cuff, and a pulse oximeter probe were applied for continuous monitoring of ECG, heart rate and rhythm, arterial blood pressure and SpO2 throughout surgery . Patients were left undisturbed for more than 1 minute, then, iv induction of anesthesia was started.

 According to selected propofol priming doses , studied patients were randomly classified into 4 equal groups. (each one consisted of 25 patients) .

. Group I received 0.15 ml/kg intralipid (placebo) iv , group II received 1 mg/kg propofol (10 mg/mL ; AstraZeneca Co., Italy) iv, group III received 1.5 mg/kg propofol iv , and group IV received 2 mg/kg propofol iv . One minute later, an iv bolus injection of 2.5 mg/kg fentanyl was given to all patients of the four groups.

 Two minutes after fentanyl administration, a sleep dose of propofol was given iv to group I patients (placebo group) , and a supplemental propofol dose was given to any tested group patient still in need to lose his lash reflex. This was followed by iv injection of 2 mg/kg succinylcholine.

 All patients were successfully intubated, and they underwent surgery under the classic inhalational anesthesia with controlled ventilation..

 During the two minutes immediately following iv bolus injection of fentanyl, Patients who developed cough , beside cough severity, were detected ,cough (dry or wet) was graded and recorded.

The severity of cough was graded according to the number of cough episodes as : none (0), mild (1–2), moderate (3–4), or severe (5 or more) . (6).

 All Patients enrolled in this study were again classified according to their smoking status into : current smokers (i.e. those who smoked till start time of the study or had stopped smoking within the previous 6 months of it), former smokers: (i.e. those who had stopped smoking > 6 months before the start of study) , and non smokers (i.e. those who had never smoked before).

Statistical analysis:

Data were expressed as mean ± SD, number, proportion, or percentage.

Statistical analysis was performed by Statistical Product for Social Sciences (SPSS) software 14.0. Sex ratio, smoking status, overall incidence and severity of cough and ASA ps class I/II ratio were compared using chi-square test. One-way analysis of variance was used to compare the continuous variables among the four groups. $P < 0.05$ was considered statistically significant.

RESULTS

 Statistically, the demographic data (age , sex ratio, body weight, ASA ps class I/II ratio, the ratio of patient with/without past history of surgical intervention and the distribution of patients according to smoking status of the 4 tested groups) were comparable . (Table 1).

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 The overall fentanyl induced cough incidence was significantly higher in group I when compared with group III and group IV (P2,P3 < 0.05). Moreover, fentanyl induced cough incidence was significantly higher in group II when compared with group III and group IV (P4,P5 < 0.05) . On the other hand, mild cough was significantly higher in group I, and group II when compared with groups III and group IV , (P2,P3, P4, P5< 0.05) . Moderate cough was significantly higher in group I when compared groups III and group IV (P3,P5 < 0.05). (Table 2).

Fentanyl induced cough incidence was 40%, 30%., 20% and 10% in non smoker patients of each of group I, II,III and IV respectively, 50% , 33.3%., 16.7 and 0% in the former smokers patients of each of group I, II,III and IV respectively and 40%, 30%., 15, and 15% in the current smokers patients of each of group I, II, III and IV respectively. Statistically, fentanyl induced cough incidence in non smoker patients of each of group III   and   group IV was significantly lower than of each of group I &

group II (P2 & P3< 0.05) Also, fentanyl induced cough incidence in the former smoker patients of group IV was significantly lower than of each of group I & group II (P3 & P5< 0.05). Moreover, fentanyl induced cough incidence in the current smoker patients of each of group III and group IV was significantly lower than that of each of group I and group II (P2, P3, P4 and P5< 0.05) (Table 3 & fig.1). .
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Table (1) : Demographic data of the four studied groups :

	Group I n=25	Group II n=25	Group III n=25	Group IV n=25	P
Age (years)	45 ± 12	45 ± 13	48 ± 12	47 ± 16	> 0.05
Body weight (kg)	72 ± 10	73 ±12	75 ±13	74 ±14	> 0.05
Sex (male/female)	20/5	19/6	18/7	19/6	> 0.05
Distribution of patients according to smoking status:					
Current smoker.	14 (56%)	12 (48%)	10 (40 %)	11 (44%)	> 0.05
Former smoker.	3 (12%)	4 (16%)	5 (20%)	6 (24%)	> 0.05
Non smoker.	8 (32%)	9 (36%)	10 (40%)	8 (32%)	> 0.05
ASA ps class (I/II) ratio.	15/10	13/12	14/11	15/10	> 0.05
The ratio of patient with/without past history of surgical intervention.	5/20	6/19	8/17	9/16	> 0.05

P>0.05 non significant, *<0.05 significant, **<0.001 highly significant
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Table (2): The overall incidence of fentanyl induced cough and distribution of patients according to cough severity in the four studied groups:

	Group I n=25		Group II n=25		Group III n=25		Group IV n=25		P
	No	%	No	%	No	%	No	%	
The overall fentanyl induced cough incidence (%) .	20	(80%)	18	(72%)	8	(32%)	3	(12%)	*P2< 0.05 *P3< 0.05 *P4< 0.05 *P5< 0.05
Distribution of patients according to their cough severity:									
Non	5	(20 %)	7	(28 %)	17	(68%)	22	(88 %)	*P2,P3,P4,P5 < 0.05
Mild	11	(44%)	10	(40 %)	5	(20 %)	3	(12 %)	* P2,P3,P4,P5 < 0.05
Moderate	6	(24%)	5	(20%)	2	(8 %)	0	(0.0%)	* P3,P5< 0.05
Severe	3	(12%)	3	(12%)	1	(4%)	0	(0.0 %)	P> 0.05

P1: difference between group I & group II. P2 difference between group I & group III.
P3: difference between group I & group IV. P4:difference between Group II & group III
P5: difference between group II & group IV. P6:difference between group III & group IV.

Table (3): The incidences of fentanyl induced cough among patients with various smoking statuses in each of the 4 studied groups:

	Group I		Group II		Group III		Group IV		P
	N	% 0f distribution	N	% 0f distribution	N	% 0f distribution	N	% 0f distribution	
Non -smokers	4 %	40	3	30%	2 20%		1	10%	*P2 < 0.05 *P3< 0.05
Former smokers	3 50%	33.3%	2	16.7%	1 0%		0		*P3< 0.05 *P5< 0.05
Current smokers	8 40%	30%		15%	3 15%				*P2< 0.05 *P3< 0.05 *P4< 0.05 *P5< 0.05

P1: difference between group I & group II. P2: difference between group I & group III.
P3: difference between group I & group IV. P4: difference between Group II & group III
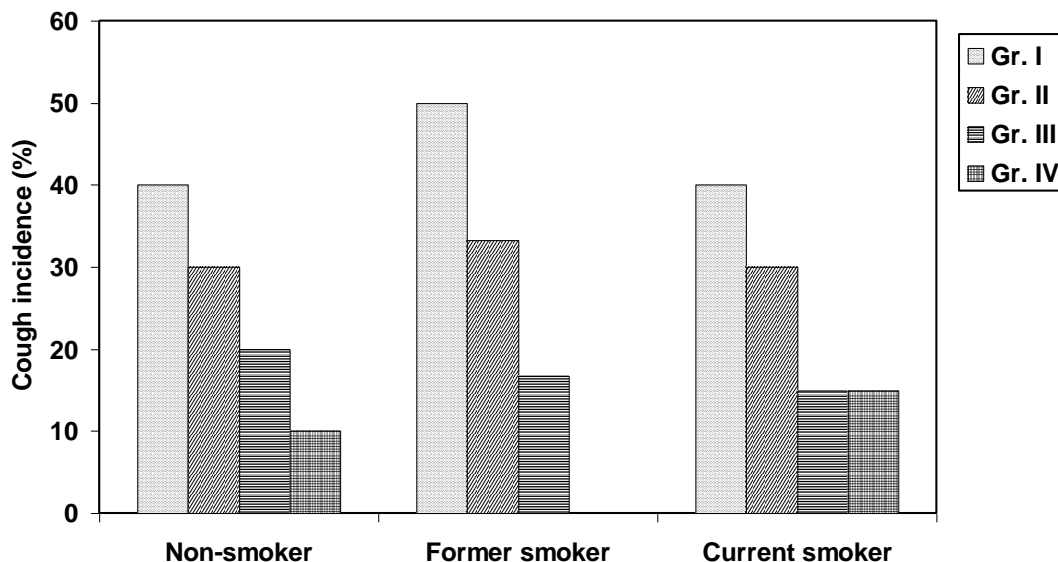P5: difference between group II & group IV. P6: difference between group III & group IV.

Figure (1): The incidences of fentanyl induced cough among patients with various smoking statuses in each of the 4 studied groups:

DISCUSSION

Fentanyl, a synthetic opioid, is widely used for general anesthesia and sometimes patients develop a cough after its injection. In Bohrer's report, up to 46% of patients had a reported fentanyl-induced cough after they were delivered 7 μg/kg of fentanyl through a central venous catheter , the vast majority of which are classified as benign, with rare occurrences of explosive and spasmodic coughing.[7]

On the other hand, Elcock stated his experience of using fentanyl clinically, (administering 30 mg of propofol when administering 100 ug of fentanyl before inducing anesthesia) did not induce a cough, and he was perplexed that research on fentanyl-induced cough continues, and that in actuality, it is not problematic except for pediatric patients.[8]

Moreover, Nishino et al and Tagaito et al reported that enflurane and propofol depress the cough reflex.

However, both studies addressed the effects of high, hypnotic concentrations of these drugs, that is 0.7 MAC enflurane and 3 mg/kg propofol concentrations.[9,10]

The present study revealed that, the overall incidences of FIC were 80%, 72%, 32% and 12% in groups I, II, III and IV respectively,

Burburan and colleagues have concluded that propofol inhibits bronchoconstriction and decreases the risk of bronchospasm during anesthesia induction.[11]

Previous studies showed that the incidence of fentanyl-induced cough

varies over a wide range (2.7–80%), and primarily depends on the doses of fentanyl

injected, the rates of injection, and the routes of injection.[12,13]

In this study, the demographic data of the studied groups (age, sex ratio, body

weight, ASA ps class I/II ratio and the ratio

of patients with/ without past history of surgical intervention) were comparable.

It is interesting that the incidence of cough after fentanyl administration appears to be higher in Asians compared to Europeans . For example, Schäpermeier and Hopf have observed that the incidence of cough following intravenous fentanyl 1.5 mg/kg over 2, 5, or 10 seconds is between 3% and 6% in European patients;[14] whereas Phua and co-authors have demonstrated that injection of the same dose of fentanyl (1.5 mg/kg) elicits cough in 28% of the Asian patients.[15]

A previous study performed by Lin et al proved that intravenous lidocaine 2 mg/kg or ephedrine 5 mg, but not propofol 0.6 mg/kg, was effective in preventing fentanyl-induced cough. The results provide a convenient method to decrease fentanyl-induced cough.[16]

On the other hand, a study of Ha et al suggested that a propofol-lidocaine mixture should be considered when patients require bronchodilation during induction of anesthesia. The incidence of cough reflex in patients receiving this mixture as propofol and lidocaine have been purported to attenuate bronchoconstriction induced by fentanyl administration during induction of anesthesia.[17]

Chronic tobacco exposure augments the substance P-evoked increase in activity of the rapidly adapting receptors and the irritant receptors and thus induces airway hyper-responsiveness. Smoking cessation clearly improves airway hyper-responsiveness, which is closely related to cough.[18]

In contrast, cough sensitivity is decreased in smokers, supporting the hypothesis that nicotine inhibits or blocks

C-fiber activity in the sensory nervous system of the lower respiratory tract . Taken together, nicotine can excite rapidly adapting receptors and inhibits C-fiber activity.[19,20]

A study performed by Lin et al., showed that fentanyl injection (2 ug/kg) induced cough in 18% of patients when the injection time was < 2 seconds, and the incidence of evoked cough decreased with injection time to 1.3% for an injection time of 30 seconds. Fentanyl-induced cough is a problem in some situations, such as ruptured eyeball or increased ICP; slow injection of fentanyl can almost obviate the problem and make the induction smoother. Also, smoking may have a protective effect against fentanyl-induced cough in light smokers but not in heavy smokers.[5]

Present study showed that the incidence of fentanyl induced cough did not markedly differ among patients with various smoking statuses in group I. Also priming administration of propofol reduced the incidence of fentanyl-induced cough in a dose dependant manner among the four studied patient groups with various smoking statuses .

This was in agreement with the study performed by Pokhis and Hopf in an European population which showed that the incidence of cough after intravenous injection of fentanyl was not different between smokers and nonsmokers and was unrelated to the speed of injection within the smoking and non-smoking group.[21]

A priming dose of fentanyl did not reduce the incidence or severity of FIC . Former smokers were found to cough more than current smokers after injection of fentanyl. [22]

In conclusion, Priming dose of more than 1 mg/kg of propofol iv which was given 1 minute before fentanyl was effective in reducing the incidence and severity of fentanyl-induced cough in a dose-dependent manner in patients with various smoking statuses .

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