

Diphenhydramine Definitely Suppresses Fentanyl-Induced Cough During General Anesthesia Induction: A Double-Blind, Randomized, and Placebo-Controlled Study

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Abstract- Fentanyl-induced cough (FIC) is a known complication, and many studies have been conducted to prevent it. The aim of this study was to evaluate the effectiveness of Diphenhydramine as an antihistamine in suppressing of FIC during induction of anesthesia. In a prospective, double-blind, randomized controlled trial, a total of 100 patients, ASA Class I and II, scheduled for elective laparoscopy surgery were randomly assigned into two equally sized groups ($n=50$). Diphenhydramine diluted with distilled water as 10 mg/ml. Then, patients in Group D, received diphenhydramine 30 mg (3 ml) through peripheral IV line within 1 min and Group C received the same volume normal saline 0.9% as placebo. Two min later, fentanyl 2 $\mu\text{g}/\text{kg}$ was administered through the peripheral IV line within 5 sec in all patients. The occurrence and intensity of cough within 2 min after the fentanyl injection were observed and recorded by a resident who was blinded to the study groups. The frequency of PONV, analgesic requirement in the recovery room and as a secondary outcome were recorded. The incidences of FIC were 47% in the control group, and there is no cough in the diphenhydramine group ($P=0.02$). The frequency of PONV was also reduced in diphenhydramine group (16% vs. 40%) and less number of patients in diphenhydramine group was needed to analgesia in the recovery room (60% vs. 82%). Our study determines that diphenhydramine (30 mg, IV) bolus injection 2 min before fentanyl injection can prevent FIC and PONV and also reduce analgesic requirement in the recovery room.

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Introduction

Fentanyl is an Opioids that is used as a component of balanced anesthesia during induction of general anesthesia every day. Coughing is the most common complication that is occurring in 30-65% of patients and raising concern among anesthesiologist (1-2-3).

Fentanyl-induced cough (FIC) usually occurs within early minutes after Fentanyl injection. Even though (FIC) is usually benign and brief, but in some circumstances, it needs immediate intervention to control subsequent complications (4-5). Repeated and severe explosive cough has been reported to cause intracranial, ocular and abdominal pressure and in some case report massive engorgement of the tongue and hypopharynx (6-7-8). The presence of FIC during induction of anesthesia and the occurrence of PONV

have been reported in some situation (9). The exact mechanism of FIC is still unclear. Therefore various interventions have been implemented to reduce its incidence during the induction of anesthesia with a varying success rate (10-11-12).

FIC may be attributable to histamine release, a pathway shared by PONV (13).

Diphenhydramine is an antihistamine, acts as an inverse agonist of the histamine H1 receptor. It is effective in the treatment of allergies, movement disorder, insomnia, nausea, and cough (14-15).

Hence we conducted this study to investigate the efficacy of diphenhydramine to suppress FIC during induction of anesthesia and nausea in the recovery room after laparoscopy surgery.

Materials and Methods

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After being approved by the Ethical Board Committee of Anaesthesiology Department of Tehran University of Medical Sciences (TUMS), this interventional, randomized clinical trial, was conducted on 64 elective patients American Society of Anesthesiologists Class I or II (20-60 years) candidate laparoscopy surgery under general anesthesia from June 22 2018 to November 31, 2018.

Exclusion criteria were any history of asthma, sleep apnea, 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, psychologic disorders, and antihistamine or antitussive drugs in the previous 2 weeks.

Patients who fulfilled the inclusion criteria were randomly allocated into Group D ($n=50$) and Group C ($n=50$) by sealed envelope technique. The patient allocation was performed by a nurse who was unaware of the study groups, according to numbers generated by the computer-generated list. After standard monitoring, venous access was obtained, and baseline systolic and diastolic blood pressure, mean arterial pressure, oxygen saturation, and heart rate were recorded. Diphenhydramine diluted with distilled water as 10 mg/ml. Then, patients in Group D, received diphenhydramine 30 mg (3 ml) through peripheral IV line within 1 min and Group C received the same volume normal saline 0.9% as placebo. Two min after the aforementioned treatment in each group, fentanyl 2 $\mu\text{g}/\text{kg}$ was administered through the peripheral IV line

within 5 s. The occurrence and intensity of cough within 2 min after the fentanyl injection were observed and recorded by a resident who was blinded to the study groups.

The intensity of cough as a primary outcome was arbitrarily graded as the following: No cough (None), 1-2 cough (Mild), 3-4 cough (Moderate) and 5 cough or more (Severe).

The frequency of PONV and analgesic requirement in recovery as a secondary outcome were recorded.

Statistical analysis

Considering the possibility of a 40% cough after fentanyl injection in patients, we defined a significant suppressive effect as decreasing the incidence of cough to half of the control. At a level of $\alpha=0.05$ with a power of 0.8, the sample size calculation was 50 in each group. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS), version 20 (SPSS Inc., Chicago, IL, USA), using the Student's *t*-test, paired *t*-test and Chi-square tests. Significance level was set at $P<0.05$.

Results

One hundred patients were enrolled in the study, 50 in each group. The median age of patients was the 43.5 ± 8.8 year (20-60 yr). Demographic variables of patients were demonstrated in Table 1.

Table 1. Characteristics of Included Patients and the Procedures

Variables	Diphenhydramine	Control	P
Age (mean \pm SD)	42.8 \pm 12.2	45.5 \pm 12.7	0.8
Sex (Male/Female)	23/27	21/29	0.13
Weight(kg)	65.7 \pm 11.2	63.4 \pm 15.2	0.78
Mean duration procedure, min	155.6 \pm 49.1	149.3 \pm 27.2	0.21

Fentanyl-induced coughing (FIC) on the induction of anesthesia presented in 23 (47%) patients of the control group, and there is no cough in the diphenhydramine

group (Table 2).

The frequency of PONV and analgesia requirement was also reduced in Diphenhydramine group (Table 2).

Table 2. Frequency and intensity of FIC, PONV and analgesia requirement in two groups

Variables	Control	Diphenhydramine	P
PONV n(%)	20(40%)	8(16%)	0.025
Analgesia requirement, n(%)	41(82%)	30(60%)	0.013
FIC n(%)	23(46%)	0	0
Severity	non	50(100%)	0.002
	mild	0	0
of cough N(%)	moderate	0	0
	sever	0	0

Discussion

Since the use of fentanyl and the identification of cough as one of the side effects of the drug, several pharmacological interventions were done to decrease this side-effect with varying success.

In a meta-analysis Kim *et al.*, found that lidocaine, NMDA receptor antagonists, propofol, α_2 agonists, β_2 agonists, and priming dose of fentanyl were effective in preventing FIC, but atropine and benzodiazepines were not (12).

The results of our study indicate definitely reduced incidence of FIC with the administration of Diphenhydramine prior to administration of fentanyl during induction of anesthesia.

Allergic mediators, such as histamine may play a role in the production of fentanyl-induced coughs.

In a study reported by Agarwal *et al.*, sodium cromoglycate, a mast cell stabilizer, led to a decrease in the incidence of fentanyl-induced cough (16). Ozgur Ozmen *et al.*, study shows that use of pheniramine maleate before induction reduces FIC rate from 20% in the control group to 2.5% (17).

Diphenhydramine as an antihistamine, peripherally reduce the intensity of allergic symptoms and centrally has sedative effects and by this mechanism may be reduced FIC before induction of anesthesia.

According to the results, 47% of control patients had a cough after fentanyl injection. There are discrepancies in the incidence of Fentanyl induced cough between 35% to 70% that may be related to doses, speed of injection, and route of administration (18). If Fentanyl injected at high doses in the central vein, less than five seconds can lead to a high incidence of FIC (19).

In our study, the incidence rate of PONV was more common in the control group, with a high incidence of FIC.

According to LI study, FIC has a predictive risk factor for the development of PONV (adjusted odds ratio 2.08, 95% confidence interval 1.41-3.07) and in his study, he showed that non-smoking women undergoing gynecological surgery who develop FIC during induction of anesthesia have a higher incidence of PONV. Histamine release can be associated with bouts of postoperative vomiting (9).

Histamine H1 receptor antagonists, including diphenhydramine, are more effective than placebo in preventing PONV (20). In different studies, antihistamine drug was as effective as serotonin 5HT-3 receptor antagonists in preventing PONV (21).

Diphenhydramine reduces the use of analgesia in the recovery room to 60% in comparison to control group 82%. Diphenhydramine has been shown to be a potentiator of analgesia induced by morphine in rats (22). The drug has also been found to act as an inhibitor of histamine N-methyltransferase (23).

Clinical analgesic efficacy of antihistamines was reported 30 years ago (24).

Since then, many controlled clinical trials have demonstrated that antihistamines have direct and adjuvant analgesic activity (25).

Diphenhydramine, as an analgesic adjuvant has been used in the treatment of postoperative pain, neuropathic, and nociceptive pain that has failed to respond to treatment with opioids (26).

Our study determines that diphenhydramine (30 mg, IV) bolus injection 2 min before fentanyl injection can prevent FIC and PONV and also reduce analgesic requirement in the recovery room.

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