# Dexmedetomidine For the Prevention of Fentanyl Induced Cough in Patients Undergoing General Anesthesia: A Double-Blind Randomized and Placebo Controlled Study

Aliya S. Dabbous[1]*, Mabelle M. Baissari[2], Mayyas M. Msheik[3], Patricia W. Nehme[4], Mohamad Y. El Ghoul[5], Samar K. Taha[6], and Mohamad I. Khatib[7]

## Abstract

**Background and objectives**: The incidence of fentanyl induced cough (FIC) during induction of general anesthesia is around 40% and can be undesirable. This prospective, randomized, double-blind, placebo-controlled study evaluated the efficacy of dexmedetomidine for the prevention of FIC.

**Methods:** 364 (ASA1 and 2) adult patients undergoing elective surgical procedures under general anesthesia were randomly allocated into four groups. Ten milliliters of dexmedetomidine: 1 mcg/kg (group 1), 0.5 mcg/kg (group 2) and 0.25 mcg/kg (group 3); in addition, ten milliliters of isotonic saline (group 4) were administered intravenously over 10 minutes, to be followed by fentanyl 2mcg/kg intravenously over 5 seconds. The incidence and severity of the cough were recorded for one minute after fentanyl administration.

**Results**: The incidence of FIC was 0%, 5.56%, 10.98%, and 46.15% in groups 1, 2, 3 and 4 respectively. Dexmedetomidine in the three doses: 1 mcg/kg, 0.5 mcg/kg and 0.25mcg/kg significantly decreased the incidence of FIC as compared to placebo ($p<0.05$). There were no cases of severe cough in treatment groups 1 and 2, and no cases of cough in group 1 with no significant hemodynamic differences among the 4 groups.

**Conclusion**: Intravenous dexmedetomidine in doses of 1 mcg/kg, 0.5 mcg/kg, 0.25 mcg/kg, significantly reduced the incidence of fentanyl induced cough. Dexmedetomidine, in the 1 mcg/kg and 0.5 mcg/kg doses, prevented the occurrence of severe cough and dexmedetomidine in a dose of 1 mcg/kg abolished the occurrence of cough.

[1]Department of Anesthesiology and Pain Management, American University of Beirut Medical Center, Beirut, Lebanon

[2]Fakih IVF Fertility Center, Doha, Qatar

[3]Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon

[4]Department of Anesthesia, Mount Lebanon Hospital/Balamand Medical Center, Mount Lebanon, Lebanon

[5]Department of Anesthesia, Burjeel Hospital for Advanced Surgery, Dubai, United Arab Emirates

***Mailing address of the corresponding author**

Aliya Dabbous, MD, Assistant Professor, Anesthesiology, Department of Anesthesiology and Pain Management, American University of Beirut Medical Center, Beirut, Lebanon. Mailing address: Cairo Street PO-Box: 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon. Telephone number: +9611350000, ext. 6380. Email address: ad00@aub.edu.lb

## Introduction

Fentanyl is a drug that is commonly used during induction of general anesthesia. It is characterized by its rapid onset, short duration of action, profound dose-dependent analgesia, and cardiovascular stability mainly during laryngoscopy and endotracheal intubation.[1, 2] However, fentanyl induced cough is an undesirable side effect and results in increases in intracranial, intra-abdominal and intra-ocular pressure.[1, 3]

The incidence of fentanyl induced cough during induction of general anesthesia ranges between 28 to 60%.[3, 4] Lidocaine,[4] huffing mechanism,[5] ketamine,[6] ephedrine,[4] propofol,[7] prolonged fentanyl injection time,[8] dexamethasone,[9] minimal dose of fentanyl,[10] terbutaline inhalation,[11] and Salbutamol or sodium chromoglycate[12] have been found to be effective in reducing the incidence of fentanyl induced cough. The alpha 2 adrenoreceptor agonists, clonidine and dexmedetomidine, have been shown to suppress fentanyl induced cough without significant hemodynamic changes.[3, 13]

Our study is a double-blind randomized and placebo-controlled study that aims to identify the optimal dose of dexmedetomidine that can prevent fentanyl induced cough without any significant hemodynamic changes after a fentanyl bolus dose of 2mcg/kg given over 5 seconds.

## Methods

The study was approved by the Institutional Review Board of the American University of Beirut, Lebanon. Following patients' written informed consent, 364 adult patients (18-70 years), classified as American Society of Anesthesiologists (ASA) physical status I or II and scheduled for elective surgery under general anesthesia were enrolled in the study. Exclusion criteria were patient refusal, age over 70 years, obesity (BMI>30 Kg/m$^2$), intake of beta blockers or angiotensin converting enzyme inhibitors, bronchodilators and steroids in the past 2 weeks, heart rate < 60 beats/minute or systolic blood pressure < 100 mmHg, history of chronic cough, asthma, smoking or upper respiratory tract infection.

The patients were randomly allocated to four groups including a control group using a computer-generated table of random numbers. Upon arrival to the operating room, a 20-gauge cannula, connected to a T-port, was inserted in the dorsum of the hand. Standard monitors including a pulse oximeter, electrocardiogram and non-invasive blood pressure were applied. Midazolam 1mg was administered intravenously to all patients and preoxygenation using an oxygen face mask of 5 L/min was initiated. Each group received an intravenous infusion of 10 ml of dexmedetomidine solution or placebo over 10 minutes. Group 1, group 2 and group 3 received dexmedetomidine 1 mcg/kg, 0.5 mcg/kg, and 0.25 mcg/kg respectively, mixed with normal saline solution to a total volume of 10 ml. Group 4 (placebo) received 10 ml of normal saline solution. The anesthesiologist who prepared the infusion was different from the one administering it, who in turn, was blinded to the group assignment.

Mean arterial pressure and heart rate were measured and recorded as follows atT0: before starting the dexmedetomidine or the saline infusion, T2: 2 minutes after starting the infusion, T5: 5

minutes after starting the infusion,
T10: 10 minutes after starting the infusion, and
T12: 12 minutes after starting the infusion.
A fentanyl bolus of 2 mcg/kg was then injected intravenously within 5 seconds after which the anesthesiologist noted the presence and severity of cough for 60 seconds following fentanyl administration. Severity of cough was classified as mild (one to two coughs), moderate (three to four coughs), or severe (5 or more coughs). Afterwards, induction of general anesthesia proceeded with propofol 2 mg/kg followed one minute later, by rocuronuim 0.6 mg/kg intravenously.

## Statistical Analysis

A recent study showed that the incidence of fentanyl induced cough at induction of general anesthesia was 40% in the control group.[3] We assumed that a 50% decrease in this incidence (down to 20%) with dexmedetomidine is considered clinically significant. With $\alpha = 0.05$ and $\beta = 0.2$, 90 patients were required in each group. Proportions, means and standard deviations were computed. Continuous data were analyzed using ANOVA and Bonferroni test for post-Hoc analysis, and categorical data were analyzed using the Chi-square test. Non-parametric data such as scores were analyzed using Mann Whitney U-test. Statistical significance was considered at $p < 0.05$.

## Results

The patients in all four groups were comparable with respect to demographics (Table 1). Hemodynamic data were comparable with no statistical differences in the systolic, diastolic blood pressures and heart rate among the four groups ($p>0.05$) (Table 2) at all respective times. The incidence of fentanyl induced cough in the placebo group was 46.15%. Dexmedetomidine 1 mcg/kg abolished the cough completely for patients in Group 1. Dexmedetomidine 0.5 mcg/kg remarkably decreased the cough to 5.56% with no cases of severe cough for patients in Group 2. Dexmedetomidine 0.25 mcg/kg decreased the cough to 10.56% with one case of severe cough for patients in Group 3 (Table 3). Dexmedetomidine in the three doses of 1 mcg/kg, 0.5 mcg/kg and 0.25 mcg/kg significantly decreased the incidence of fentanyl induced cough compared to placebo ($p<0.05$) (Table 3). Comparing inter group variability showed a significant P value less <0.05 (Table3).

## Discussion

In the current study, the incidence of fentanyl induced cough (FIC) in the placebo group was 46.15%. Dexmedetomidine in a loading dose of 1mcg/kg over 10 minutes abolished the occurrence of fentanyl induced cough completely (0%), whereas a loading dose of 0.5 mcg/kg over 10 minutes significantly reduced it to 5.6% and a loading dose of 0.25 mcg/Kg over 10 minutes significantly reduced it to 10.98% with no significant hemodynamic differences among the four groups. There were no cases of severe cough in patients who received either 1 mcg/kg or 0.5 mcg/kg while only one patient who received 0.25 mcg/kg of dexmedetomidine and four patients in the placebo group had severe coughs.
We postulate that the mechanism for the pre-

vention of FIC by dexmedetomidine is through the activation of the alpha 2 receptors. Clonidine and Tizanidine have already been shown to reduce cough, whether injected into the nucleus tractus solitarius (cNTS) and caudal ventral respiratory group (cVRG), or intravenously in the rabbit (14). In a previous study, dexmedetomidine in a dose of 1 mcg/kg or 0.5 mcg/kg reduced FIC from 61% to 18% and 40% respectively after injecting fentanyl 4 mcg/kg in less than 2 seconds[3]. Similar to our study, they did not report any significant hemodynamic changes or any respiratory depression. Although FIC after induction of general anesthesia is mild and self- limiting, few case reports have shown the cough to be explosive and life-threatening.[15, 16] Lidocaine and ephedrine have been shown to decrease the incidence of FIC from 65% to 14% and 21% respectively.[4] Huffing maneuver also decreased FIC from 32% to 4%.[5] Low intravenous dose of ketamine decreased FIC from 21.6% to 7.2%.[6] Propofol 2mg/kg decreased the incidence of FIC from 80% to 3.3%.[7] Dilution and prolonged intravenous injection of fentanyl over 30 sec. decreased the incidence of FIC from 32% to 2%.[8] Intravenous dexamethasone decreased the incidence of FIC from 26.5% to 6.5%.[9] Terbutaline decreased FIC from 43% to 3%.[11] Sodium chromoglycate decreased FIC from 28% to 4%.[12] In addition, clonidine decreased FIC from 38.7% to 17.3%.[13] Despite the significant reduction of FIC by the above-mentioned different drugs or maneuvers, none was shown to completely abolish the cough. In our study, dexmedetomidine in a dose of 1 mcg/kg abolished completely the occurrence of any degree of cough after a dose of fentanyl 2mcg/kg given over 5 seconds, and a dose of 0.5 mcg/kg suppressed the occurrence of severe cough.

Cough is an airway defensive reflex that involves several brainstem structures including the second-order neurons within the caudal aspect of the cNTS and the expiratory premotor neurons of the cVRG.[14] The cough reflex has both sensory (afferent) mostly via the vagus nerve and motor (efferent) components. The cough receptors, or rapidly adapting irritant receptors are located mainly on the posterior wall of the trachea, pharynx, and at the carina of the trachea. When triggered, impulses travel via the internal laryngeal nerve, a branch of the superior laryngeal nerve which stems from the vagus nerve, to the medulla of the brain. This is the afferent neural pathway. The efferent neural pathway then follows, with relevant signals transmitted back from the cerebral cortex and medulla via the vagus and superior laryngeal nerves to the glottis, external intercostals, diaphragm, and other major inspiratory and expiratory muscles.[17]

Kubin et al, in a review on central pathways of pulmonary and lower airway vagal afferents suggested that receptors commonly associated with presynaptic effect such as alpha 2 receptors may affect respiratory reflexes.[18] Pulmonary irritant receptors (cough receptors) in the epithelium of the respiratory tract are sensitive to both mechanical and chemical stimuli. Activation of alpha 2 adrenergic receptors by microinjections of clonidine and tizanidine into the cNTS and the cVRG, as well as the intravenous administration of both drugs have been shown to have suppressant effects of cough responses induced by mechanical stimulation of the tracheobronchial tree or by citric acid inhalation in the anesthetized rabbit.[14]

The alpha 2 adrenergic receptor agonist, clonidine, has been shown to inhibit citric acid induced cough responses in guinea pigs when administered by aerosol as early as 1994.[19] It can be reasonable to assume that the mechanism of preventing FIC is via the activation of alpha 2 receptors.

Several mechanisms have been previously implicated in the pathogenesis of FIC during the induction of general anesthesia. One proposed mechanism is inhibition of sympathetic outflow causing vagal predominance inducing cough and reflex bronchoconstriction. However, premedication with the anticholinergic atropine does not decrease its incidence.[20-22] Another speculated mechanism is the stimulation of C fibers known as J receptors present on smooth muscles of the trachea and bronchi. The speculated cause was the addition of citrate in the fentanyl, that can release neuropeptides such as bradykinin and tachykinin responsible for the cough.[23] Moreover, dexamethasone and beta 2 agonist such as terbutaline and salbutamol were effective in decreasing FIC via inhibition of tachykinin-mediated hyper-reactivity of airways.[9, 11, 12] Ketamine has been shown to decrease FIC.[6] A priming dose of ketodsex (ketamine and dexmedetomidine) effectively suppressed the cough reflex induced by fentanyl and delayed the onset time of cough; the authors speculated that the rapid response of cough after fentanyl, suggests that a pulmonary chemoreflex is the likely mechanism mediated by either irritant receptors or by vagal C fibers receptors in close proximity to pulmonary vessels.[24] Histamine release is another possible cause for FIC[25] that has been shown to be reduced by sodium chromoglycate.[12] The alpha 2 agonist, clonidine, decreased FIC by an unknown mechanism different from its sedative properties; however, it was associated by respiratory depression, drowsiness and severe hypotension.[13] Dexmedetomidine, decreased FIC by reversal of fentanyl induced muscular rigidity and not through sedation with no significant hemodynamic changes.[3]

Our study showed that dexmedetomidine in 1 mcg/kg, 0.5 mcg/kg and 0.25 mcg/kg suppressed FIC without any respiratory depression or hemodynamic changes similar to what was previously reported.[3] Dexmedetomidine in a dose of 1 mcg/kg abolished the occurrence of any type of cough (0% incidence), and a dose of 0.5 mcg/kg abolished the occurrence of severe cough. We believe that our proposed mechanism, that is the activation of the alpha 2 receptors, must be investigated in future animal studies by injecting dexmedetomidine into the caudal nucleus tractus solitarius (cNTS) and caudal ventral respiratory group (cVRG), following fentanyl administration for the prevention of FIC.

## Conclusion

In conclusion, this study proves that dexmedetomidine (1 mcg/kg, 0.5 mcg/kg and 0.25 mcg/kg) is effective for the prevention of fentanyl induced cough caused by fentanyl 2mcg/kg injected over 5 seconds during induction of general anesthesia and the dose of 1 mcg/kg abolishes the occurrence of fentanyl induced cough completely.

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**Conflicts of interest:** None.

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