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Research Article

Influence of Speed of Fentanyl Citrate Injection before Induction of Anesthesia on Fentanyl-Induced Cough: a Prospective, Randomized, Double Blinded Study

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Abstract

Background: Fentanyl Induced Coughing (FIC), with the incidence ranging from 18-65%; is not always benign and brief and can be remarkably troublesome, spasmodic, explosive at the most critical moment of induction of anesthesia when airway reflex is lost, attracting immediate emergency intervention. We designed this study to evaluate the effect of injection time on fentanyl induced cough.

Methods: 456 patients of ASA physical status I and II, aged between 18-60 years, undergoing elective surgical procedures were randomly allocated into 3 groups consisting of 152 patients each. Patients in Group F2 received Fentanyl (2 microgram/kg) over 2 seconds, Group F6 over 6 seconds whereas Group F10 over 10 seconds prior to induction of anesthesia. The incidence of cough was recorded for 1 minute before the induction of anesthesia and graded as mild (1-2 cough), moderate (3-5 cough) and severe (>5 cough). The number of cough episodes and other numerical variables were compared between the groups by ANOVA followed by Tukey's test for post-hoc comparison. Severity grading of the cough and categorical variables were compared between groups by Pearson's Chi-Square test.

Results: Baseline patient parameters were comparable. The incidence of cough was 59.9% in Group F2, 29.8% in Group F6, 10.5% in Group F10 which were statistically significant severity wise too.

Conclusion: In conclusion slow fentanyl citrate injection definitely reduces both the incidence and severity of fentanyl induced cough which is rather a simple, inexpensive, effective, very cost effective way of solving this issue. This method does not require patient cooperation neither does it require administration of any pharmacological agent. We recommend injection time of 10 seconds to get best results.

Introduction

Even in the era of ultra short acting opioid, fentanyl is a very popular and one of the most commonly used opioid in anaesthetic practice. The properties of fentanyl like profound analgesia, quick onset, short duration of action, reduced MAC of inhaled anaesthetics, reduced requirement of other anaesthetics without the cost of severe hemodynamic instability and alteration in cerebral perfusion made fentanyl an excellent choice for use as premedication, analgesic, in co-induction and in monitored anaesthesia care[1]. The main drawback of fentanyl use includes: cough, chest rigidity, awareness etc. Although other opioids possess anti-tussive activity, intravenous fentanyl is known to produce transient, benign and self limiting cough which at times may be spasmodic or explosive even life threatening [2-10]. Incidence of fentanyl induced cough (FIC) may range from 18 to 65% [11] and the associated rise of intraabdominal, intracranial and intraocular pressures may complicate an already compromised situation, therefore undesirable in situations like cerebral aneurysm, brain trauma, reactive airway disease, dissecting aortic aneurysm, pneumothorax, and open eye injury [4]. Several methods have been applied to control FIC with variable results. These include non-pharmacological methods like a huffing manoeuvre [12], prolonged injection time [4,13] , pre-emptive small dose [14] or pharmacological methods. Concepts behind the drugs used in FIC are bronchorelaxation (By ephedrine [3], β_2-receptor agonist [7,8,15], Sodium chromoglycate [7,8], ketamine [16], clonidine [17], priming dose of propofol [18] etc), reduction of bronchial hyperirritability (e.g., Betamethasone, dexamethasone [19]), depression at brain stem (e.g. Lignocaine [3,5,6] propofol [18]), suppression of peripheral cough receptors (Lignocaine [3,5,6] light smoking [11]) and attenuate sudden rise in fentanyl concentration (e.g., Preemptive use of Small Dose Fentanyl [11,14] Slow injection [4,13]) All these methods are quite cumbersome, uncomfortable and associated with some or other side-effects. Hence we designed this study to evaluate that whether a slower injection time reduces fentanyl induced coughing. Though only one study has been done where fentanyl citrate given over 15 seconds and 30 seconds at a constant rate has significantly reduced fentanyl induced coughing; this study further evaluates whether 10 seconds injection time stands statistically significant or not in comparison to 2 seconds group and 6 seconds group.

Methods

After obtaining institution Ethics committee permission and written informed consent from each of the patients this randomized double blind parallel group study was conducted on 455 adult patients, 18-60 years of age, ASA physical status I and II of either sex undergoing elective surgical procedure under general anesthesia. Obese patients (Body weight exceeding 20% of ideal for age), patients with history of smoking, asthma, chronic cough, upper respiratory tract infection in last two weeks, recent treatment with ACE inhibitor, steroids or bronchodilator and patients with impaired liver or kidney functions were excluded from our study. Sample size calculation was

based on incidence of Fentanyl induced cough reported in literature (18-65%) [11]. Assuming the expected incidence of fentanyl induced coughing as 40% it was estimated that 152 subjects would be required per group in order to detect 15% absolute reduction in the incidence of coughing with 80% power and 5% probability of Type I error. Patients were randomized to either Group F2/F6/F10 using computer generated randomization list generated by a statistician in a sealed envelope.

All patients received premedication with oral lorazepam (0.04 mg/kg) the evening before. Upon arrival in the operation theatre continuous ECG lead II, NIBP, pulse oxymetry were instituted. Venous access was established using an 18G cannula on the forearm of non-dominant hand. All patients received Fentanyl citrate 2 µg/kg via a 3 way connector through the peripheral venous line. Patients in Group F2 received Fentanyl over 2 seconds, Group F6 over 6 seconds, Group F10 over 10 seconds at a constant rate. After fentanyl injection, the incidence and severity of cough were recorded by another anesthesiologist who was blinded to the nature of study. The primary endpoint of our study was FIC (In terms of both incidence and severity) defined as any episode of cough within 60 seconds of fentanyl administration. Based on the number of coughs observed, cough severity was graded as mild (1–2), moderate (3–5), or severe (>5) [10,12]. Recorded secondary end point was heart rate, mean arterial pressure or occurrence of chest rigidity requiring intervention 60 seconds after fentanyl injection for patients who did not cough or immediately after cessation of cough in patients who had FIC. General anesthesia was induced with propofol 1% (2 mg/kg) 1 minute after administration of fentanyl.

Patient characteristic data (Age, Wt, Ht, MAP, HR) i.e. Continuous/ numerical variables were compared between groups by ANOVA whereas Pearson's Chi-Square test was used for comparing categorical variables between groups. The number of cough episodes within 1 minute was compared between the groups by ANOVA followed by Tukey's test for post-hoc comparison. Severity grading of the cough was compared between groups by Pearson's Chi-Square test. P value<0.05 was considered statistically significant. Softwares used were, Statistica version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001) and SPSS Statistics version 17 (Illinois, Chicago: SPSS Inc., 2008).

Results

Baseline patient characteristics, e.g., age, sex, height, weight and mean arterial pressure and heart rate prior to and after administration of Fentanyl were comparable between two groups. (Table1).

Parameters	Groups (mean ± standard deviation or count)			P Value
	F2	F6	F10	
Age (years)	39 ± 12.747	38.245 ± 13.585	38.809 ± 12.500	0.870
Sex (M/F)	74/78	74/77	74/78	0.99790
Height (cm)	164.171 ± 8.442	163.742 ± 7.057	164.171 ± 8.442	0.865
Weight (Kg)	62.316 ± 9.599	64.092 ± 10.260	62.382 ± 9.610	0.205
MAP_Pre (mm hg)	91.447 ± 6.311	91.457 ± 6.330	91.447 ± 6.311	1.000
MAP_Post (mm hg)	91.434 ± 6.285	91.431 ± 6.306	91.434 ± 6.285	1.000
HR_Pre (Beats/min)	87.697 ± 9.655	87.775 ± 9.640	87.697 ± 9.655	0.997
HR_Post (Beats/min)	86.224 ± 8.428	86.285 ± 8.422	86.224 ± 8.428	0.997

Table 1: Comparison of age, sex, height, weight and hemodynamic parameters

Incidence and severity of cough were compared between two groups and revealed significant reduction of FIC with increase in injection time. (Table2)

Groups	Incidence		Severity				
	No of FIC (Mean ± Standard deviation)	P Value	Nil	Mild	Moderate	Severe	p value
F2	2.6118 ± 2.8635	< 0.001	61	30	29	32	<0.001
F6	0.8079 ± 1.427		106	28	15	2	
F10	0.1908 ± 0.5838		136	15	1	0	

Table 2: Incidence and Severity of Cough after Fentanyl Injection

Frequency of cough between two individual groups compared by Tukey's multiple comparison test. (Table3)

Primary group	Secondary group	Mean differences	Standard error	Significance	95% confidence interval	
					Lower bound	Upper bound
F2	F6	1.804	0.216	0.000	1.3	2.31
	F10	2.421	0.215	0.000	1.91	2.93
F6	F2	-1.804	0.216	0.000	-2.31	-1.3
	F10	0.617	0.216	0.012	0.11	1.12
F10	F2	-2.421	0.215	0.000	-2.93	-1.91
	F6	-O.617	0.216	0.12	-1.12	-0.11

Table 3: Result of post-hoc multiple comparison test to frequency of cough between two individual groups (Tukey's test)

In our study incidence of FIC in the 2 sec group was 59.868%, 6 sec group was 29.801% and in 10 sec group was 10.526%. The incidences in 2 second group and 6 second group corroborated with the incidences found in different studies but in 10 second group the incidence is much less. Our study demonstrates that fentanyl induced cough can definitely be reduced by decreasing the rate of injection of the drug. No active complaints were reported by patients and no significant haemodynamic changes noted.

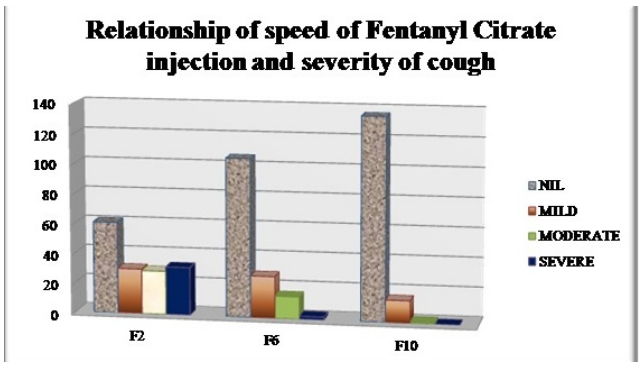

Figure 1: Comparison of severity of cough

Cough is a protective airway reflex that begins with a deep inspiration followed by forced expiration against a closed glottis. The afferent limb consists of sensory nerve endings that are thought to be primarily rapidly adapting receptors and C-fibers at pharynx, larynx, and airways to the level of terminal bronchioles and into the lung parenchyma. Signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius, vaguely identified as the "cough centre. The efferent limb consists of the nerve supplying adductor muscles of vocal cord and expiratory muscles. Exactly how fentanyl mediates cough is not well understood. Central and peripheral mechanisms may operate at different level to mediate FIC. Effective suppression of the cough from 43% to 3% after inhalation of β_2 agonist supports the concept of bronchoconstriction to be a major determinant of FIC [7,8,20]Suppression of cough with beclomethasone [7] inhalation and dexamethasone [19] pretreatment supports the trigger stimulus and bronchial hyperirritability theory [7]. Fentanyl reduces central sympathetic outflow and resultant vagal predominance cause bronchoconstriction. But this is not the primary mechanism as atropine pretreatment does not abolish FIC.

Although rapidly adapting receptors are considered as the primary receptors for cough [4,5,20,21] however, in an in vitro study, Fox [22] found that rapidly adapting receptors are insensitive to tussigenic stimuli. Pulmonary C-fibres are readily activated by chemical stimuli [23-25] and may release tachykinins, which cause secondary mucosal responses and excite the rapidly adapting receptors. Bohrer and colleagues [21] speculated that pulmonary C-fibre receptors, also known as J-receptors present in the lower respiratory tract, with its non-myelinated afferent fibres are most likely involved in the mediation of the pulmonary chemoreflex that leads to cough evoked by fentanyl. The observation of inhibition of cough response from 21.6% to 7.2% after ketamine pretreatment [16] suggested that NMDA receptors which are bronchoconstrictor may also be implicated. α_2 adrenoreceptor agonist reverse fentanyl induced muscular rigidity and reduce the incidence of fentanyl induced cough [17,26].

Several methods have been applied to reduce incidence of FIC with variable success. Ambesh SP et al. [12] has described a huffing manoeuvre (a forced expiration against open glottis), immediately before induction of anaesthesia, prevents fentanyl-induced coughing. Possible mechanism is by preconditioning of stretch receptors of trachea and bronchial tree. But some patients who receive midazolam or propofol during induction of general anaesthesia cannot use this maneuver [12]. Use of one or multiple drugs to control FIC has its own side effects and contraindications. Steroid, β_2 agonist inhalation and mast cell stabilizer reduce the incidence of FIC but necessitate administration 15-30 min prior to fentanyl administration and also precipitates tachycardia [7,8,15,19]. Use of pretreatment with morphine 0.2 mg/kg I.M. 1 hour prior to surgery is also impractical and also has a possibility of postoperative respiratory depression [12]. Recently, Horng and colleagues have used pre-treatment with clonidine (2 mg/kg over 2s) to suppress FIC, but it was associated with severe haemodynamic instability, residual sedation and respiratory depression [17]. Use of Lidocaine is also controversial because of its arrhythmogenic and vasodilatory effect. Its vasodilatory effect could even augment the cardiovascular depression of induction agents [28] .Tang Q et al. [18] studied effect of propofol pre-treatment and opined a priming dose of more than 1 mg/kg of propofol given 1 minute before fentanyl is effective to suppress fentanyl-induced cough in a dose-dependent manner. They suggested using a priming dose of propofol 1.5 mg/kg to suppress cough during the anaesthesia

induction with propofol and fentanyl in clinical practice. But this was associated with hemodynamic instability. At the same time it is also cumbersome to administer propofol in divided doses before and after fentanyl injection.

Shrestha SK et al. [14] studied the effect of preemptive small dose Fentanyl on FIC. They used an arbitrary dose of 25µg 1min prior to fentanyl administration. The pharmacokinetic basis behind the study was observation by Lin et al. [4] that the threshold for fentanyl induced cough may be reached more easily at larger peak plasma concentration. But their study could not explain the basis behind pre-emptive dose of fentanyl and optimum dose for this technique. Another study by Jung et al showed that priming dose of fentanyl didn't reduce the incidence and severity of fentanyl induced cough. [11]

All the methods above have their own limitations. Use of additional drugs not only increase the cost but also exposes the patients to unwanted and sometimes dangerous side effect. Use of some drugs in recommended ways in regular clinical practice is also impractical. Some methods, e.g. inhalation of lignocaine, terbutline etc) may be uncomfortable to the patient and requires patient cooperation. Therefore an ideal method in this respect should include no additional drugs and use of some technique that is easy, practical, cause minimum discomfort to the patient, and does not require patient cooperation.

Jui-An –Lin (2005) [4] studied that injecting fentanyl over 30 seconds and 15 seconds significantly reduced FIC compared to 2 seconds group . Our study not only supports the finding of Jui-An –Lin et al. but further evaluates whether in situations of emergency we can further reduce the time of fentanyl injection to an optimum duration.

Conclusions

In conclusion slow fentanyl citrate injection definitely reduces both the incidence and severity of fentanyl induced cough which is rather a simple, inexpensive, effective, very cost effective way of solving this issue. This method does not require patient cooperation neither does it require administration of any pharmacological agent. We recommend injection time of 10 seconds to get best results.

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