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A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study

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Background. Preinduction i.v. fentanyl bolus is associated with coughing in 28–65% of patients. Fentanyl-induced coughing (FIC) is not always benign and can be remarkably troublesome at the most critical moment of induction of anaesthesia when airway reflex is lost. We postulated that the huffing manoeuvre, a forced expiration against open glottis, just before i.v. fentanyl, may suppress this undesirable spasmodic cough.

Methods. Three hundred patients of ASA I and II, aged 18–60 yr, undergoing elective surgical procedures were randomly allocated into two groups consisting of 150 patients. Both groups received i.v. fentanyl (2.5 $\mu g\ kg^{-1}$). Group I patients breathed normally whereas Group 2 patients were asked to perform huffing manoeuvre just before the fentanyl injection. The incidence of cough was recorded for 1 min before the induction of anaesthesia, and graded as mild (1–2 cough), moderate (3–5 cough), and severe (>5 cough). The incidence of FIC was analysed with Fisher's exact test and severity was analysed with the Mann–Whitney *U*-test. A *P*-value of <0.05 was considered significant.

Results. The incidence of cough was 32% in the control group and 4% in the huffing manoeuvre group ($P<0.00$). In the control group, 12% of FIC cases were moderate to severe in nature whereas no patient suffered severe coughing in the huffing manoeuvre group ($P=0.049$).

Conclusions. A huffing manoeuvre performed just before i.v. fentanyl (2.5 $\mu g\ kg^{-1}$) significantly reduces the incidence and severity of FIC in the majority of the patients.

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Opioid agonists are known to possess anti-tussive activity, although i.v. administration of fentanyl, a synthetic opioid made soluble in a citrate-binding form, paradoxically induces cough.[1–8] Fentanyl-induced cough (FIC) is usually transient, benign, and self-limiting for most patients but at times may be spasmodic or explosive[1] and life threatening[9] 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 $\mu g\ kg^{-1}$) bolus injection.[2] The FIC during induction of general anaesthesia is undesirable as it is known to increase intracranial, intraocular, and intra-abdominal pressures. Various methods have been used to reduce the incidence of FIC.[2–8]

A lower incidence of FIC has been observed in light smokers, and a postulated possible mechanism for FIC might be via C-fibre (also known as rapidly adapting J stretch receptors) activation.[3] In routine practice, we had noticed that some of our patients who incidentally coughed before i.v. administration of fentanyl did not develop FIC. We assumed that this may have happened due to acute conditioning of rapidly adapting stretch receptors in the airway and lungs. A huffing manoeuvre is a gentle voluntary cough or a forced expiration against open glottis which is known to clear the secretions from the upper airway, open closed alveoli, decrease atelactesis, and thereby increasing functional residual volume of the lung.[10–13]

We postulated that the huffing manoeuvre immediately before i.v. administration of fentanyl may suppress undesirable FIC and therefore we have tested this hypothesis in a prospective, randomized, and controlled clinical trial.

Methods

This prospective, randomized, single-blind, and controlled study was conducted after approval from the Institute's Ethics Committee and after obtaining written informed consent from the patients. We considered patients for inclusion if they were aged between 16 and 60 yr, ASA physical status I and II, of either sex, undergoing elective surgical procedures under general anaesthesia.

Patients with body weight exceeding 20% of ideal, history of asthma, chronic cough, upper respiratory tract infection in the previous 2 weeks, smoking, a history of bronchodilator or steroid therapy, or treatment with angiotensin-converting enzyme inhibitors were excluded from the study.

Estimation of sample size was based on a 35% reported incidence of cough after an i.v. bolus of fentanyl, assuming that a huffing manoeuvre would cause a 20% reduction in the incidence of coughing. With α=0.05 and β=0.20, we were required to enrol 137 patients in each group; we recruited 150 patients to account for any dropouts.

Patients were randomized into two groups of 150 each with the help of a computer-generated table of random numbers. Group 1 (control): served as the control; Group 2 (huffing manoeuvre group): patients were asked to huff (only once) after a deep inspiration. The act of huffing lasted <5 s and was standardized to all patients. Fentanyl injection was started immediately after the completion of huffing manoeuvre. All patients received i.v. fentanyl (2.5 μg kg^{-1}) over a period of 5 s.

All patients received premedication with oral lorazepam 0.04 mg kg^{-1} the evening before and in the morning 2 h before surgery. At the time of the pre-anaesthetic visit, all patients were taught how to perform a huffing manoeuvre. Upon arrival in the operating theatre, continuous ECG lead II, non-invasive arterial pressure (AP), and pulse oximetry (Sp_{O_2}) were instituted. Venous access was established using an 18 G cannula on the dorsum of the non-dominant hand.

An independent observer (D.G.) observed the patients for the presence or absence and number of FIC after fentanyl administration. The primary endpoint was FIC (in terms of both incidence and severity). Any episode of cough within 60 s of fentanyl administration was classified as FIC, and the severity was graded based on the number of coughs (mild 1–2, moderate 3–4, and severe 5 or more). Recorded secondary endpoints included any change in heart rate (HR), AP, or chest rigidity requiring intervention. These were recorded after fentanyl injection for patients who did not cough, or immediately after cessation of cough in patients who had FIC. All patients received i.v. propofol for induction of anaesthesia.

The method of statistical analysis was decided prospectively and incorporated the intention-to-treat principle. Patient characteristic data were analysed with a one-way ANOVA for continuous variables and χ^2 test for categorical variables. The incidence of FIC was analysed with Fisher's exact test and severity was analysed with the Mann–Whitney *U*-test; a two-way ANOVA was applied to evaluate the changes in HR and AP before and after injection between the groups. The package SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P<0.05$ was considered significant.

Results

A total of 349 consecutive patients were evaluated from September 2007 to April 2009. Forty-nine patients were excluded from the study due to a history of asthma, upper respiratory tract infection in the previous 2 weeks, smoking, and treatment with angiotensin-converting enzyme inhibitors. Therefore, 150 patients in each group were included and subjected to further statistical analysis (Fig. 1).

The patient characteristics (age, weight, and gender) in the two groups were comparable (Table 1). The incidence of FIC in the control group was higher than that of the huffing manoeuvre group (32% *vs* 4%; P=0.00) (Table 2). Furthermore, 18 patients in the control group had moderate to severe FIC whereas none of the patients in the huffing manoeuvre group had such a severity (P=0.049). Overall severity of FIC measured as median (inter-quartile range) was higher in the control group compared with the huffing manoeuvre group [2 (3) *vs* 1.5 (1); P=0.006]. The FIC occurred within 30 s of fentanyl administration in all patients, irrespective of the groups. There was no difference between the groups in the changes in systolic AP before and after the huffing manoeuvre (data not shown) (groups and measures interaction, $P>0.05$).

Discussion

Our study demonstrates that a huffing manoeuvre performed immediately before i.v. fentanyl (2.5 μg kg^{-1}) decreases the incidence of cough from 32% to 4%. No active complaints were reported by patients and no significant haemodynamic changes were observed during or after the huffing manoeuvre.

Cough is a well-integrated reflex, which has afferent limb consisting of receptors and afferent nerves, the central cough centre in the brainstem, and the efferent limb consisting of motor nerves supplying the muscles of coughing. Stimuli that can initiate the cough process can be central or peripheral in the lungs or outside the lungs. FIC is an involuntary act of coughing triggered by fentanyl

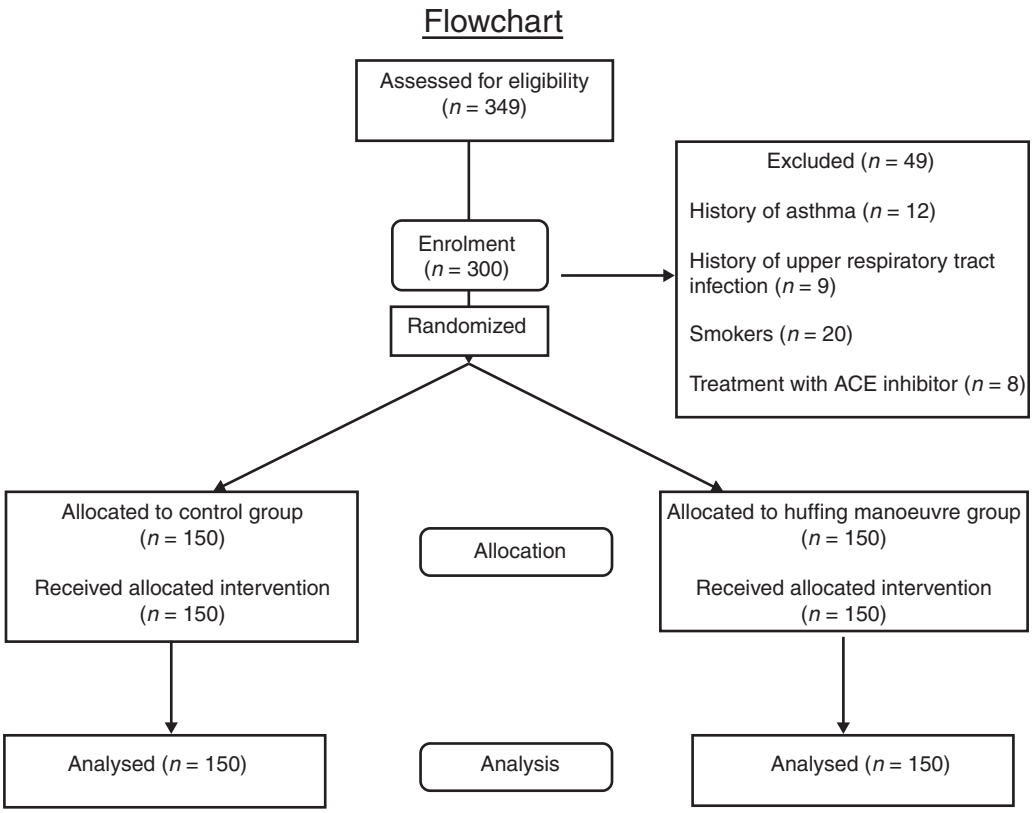

Fig 1 Number of patients included and excluded from the study.

Table 1 Patient characteristic data presented either as mean (range), mean (SD) or as numbers. No significant differences between the groups by one-way ANOVA for continuous variables and χ^2 test for categorical variables ($P>0.05$)

Parameters	Groups		*P*-value
	Control ($n=150$)	Huffing manoeuvre ($n=150$)	
Age (yr)	48.43 (17–58)	46.39 (16–60)	0.56
Sex (M/F)	86/64	91/59	0.56
Weight (kg)	59.83 (10.48)	62.09 (10.52)	0.63
Height (cm)	165.7 (6.1)	166.68 (5.65)	0.15

Table 2 Incidence and severity of cough; data are presented as numbers. Significant difference between the groups has been observed in incidence of cough by the Fisher's exact test and severity of cough by the Mann–Whitney *U*-test. Severity of cough=number of coughs observed at 1 min of fentanyl injection: mild (1–2), moderate (3–5); and severe (>5). *$P<0.05$ *vs* control

Variables	Groups		*P*-value
	Control ($n=150$)	Huffing manoeuvre ($n=150$)	
Incidence of cough	48 (32%)	6.0 (4%)*	0.000
Severity of cough			
Mild	30	6.0	0.049
Moderate	12	0	
Severe	6	0	

which at times may be severely explosive and spasmodic. The incidence of FIC observed in our control group (32%) is comparable with that reported by others.[5 6]

Bohrer and colleagues 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.[3 4 14 15] This suggestion was based on the finding that J-receptors are readily accessible via the pulmonary circulation and are more sensitive to chemical irritants.[16 17] In humans, fentanyl constricts tracheal smooth muscle[18] and hence the 'irritant' receptors nearby may be stimulated secondary to deformation of the tracheobronchial wall.[15] These receptors, when stimulated, can trigger the cough reflex via the vagal afferent pathway.[19] Irritant receptors, also known as rapidly adapting or cough receptors, appear to be the more likely candidate for cough because they are highly concentrated in the walls of proximal tracheobronchial airways and found superficially within the mucosa.[20] The latter explains their ability to respond to weak chemical irritation that leads to coughing.

Coughing may also reduce lung volume to below the closing capacity.[13] If this occurs during the process of induction, a dangerous increase in pulmonary shunt and consequential hypoxia may occur. The huffing manoeuvre consists of forced expiration, from mid to low lung volume, which avoids glottic closure which is followed by a period of relaxed diaphragmatic breathing. During huffing, the peak linear velocity of airflow in large alveoli is less than that developed during coughing. A huffing manoeuvre is sufficient to decrease the cross-sectional

diameter of airways sufficient to increase linear velocities and aid secretion movement.[21] The huffing manoeuvre might cause preconditioning of stretch receptors of trachea and bronchial tree and hence prevent FIC.

Inhalation of β_2-agonist, steroid, and mast cell stabilizer (sodium chromoglycate) aerosol has been shown to reduce the incidence of FIC,[6 7] but their use is not practical as patients need to receive this 15–30 min before fentanyl injection. I.M. morphine (0.2 mg kg^{-1}) injection 1 h before i.v. fentanyl (1.5 μg kg^{-1}) has been found to reduce the incidence of FIC,[8] but is not clinically practical due to the relatively long time interval and delayed induction of anaesthesia. Lui and colleagues[7] used terbutaline nebulization 15 min before fentanyl administration, to suppress FIC, and found significant reduction in the incidence of FIC. Again, the procedure is quite cumbersome and uncomfortable to many patients and is associated with tachycardia. Recently, Horng and colleagues[22] have used pretreatment with clonidine (2 μg kg^{-1} over 2 s) to suppress FIC. Although clonidine was successful in halving the incidence of FIC, it was associated with haemodynamic disturbances.

Several studies have shown that pharmacological methods can prevent FIC, which may provoke some adverse events.[2–8] Lidocaine was reported to effectively inhibit FIC in clinical anaesthesia practice,[2 4 5] but justification of pre-treatment with lidocaine was questioned by Schlimp and Wiedermann[23] because lidocaine may have arrhythmogenic effects, and its vasodilatory effect could even augment the cardiovascular depression of induction agents. I.V. ephedrine (5 mg) 1 min before fentanyl injection seems promising for attenuating FIC,[2] but it is relatively contraindicated in patients with coronary artery disease or moderate to severe hypertension.

The principal outcome measure, cough incidence and severity, was an objective indicator. As the patients were asked to produce a huffing manoeuvre (an objective method), it was difficult to blind the observer for two groups. This would be a limitation of the study, although we believe it is unlikely to affect the validity of our results.

In conclusion, a huffing manoeuvre immediately before the administration of i.v. fentanyl (2.5 μg kg^{-1}) is a feasible and convenient way to reduce the incidence of FIC. The method is instant, simple, inexpensive, and effective and does not require administration of any pharmacological agent.

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