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Fentanyl-induced cough is a risk factor for postoperative nausea and vomiting

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Abstract

Background: Postoperative nausea and vomiting (PONV) and fentanyl-induced cough (FIC) are two common anaesthesia-related events, which seem to have common risk factors. In this prospective cohort study, we investigate whether patients who have FIC during induction of anaesthesia have an increased incidence of PONV.

Methods: We studied adult non-smoking gynaecological surgical patients enrolled between July 1, 2011 and July 30, 2012. The presence of FIC during induction and the occurrence of PONV were recorded. Fentanyl-induced cough and other perioperative variables were subjected to multivariate analysis to determine the association between FIC and PONV.

Results: All 502 patients enrolled in this study had at least two risk factors for PONV, and 154 (31%) developed FIC. The incidence of PONV in the FIC group was higher than in the non-FIC group (56.5 *vs* 38.2%; $P<0.0001$). Multivariate logistic regression analysis found FIC to be a predictive risk factor for the development of PONV (adjusted odds ratio 2.08, 95% confidence interval 1.41–3.07).

Conclusions: Non-smoking women undergoing gynaecological surgery who develop FIC during induction of anaesthesia have a higher incidence of PONV.

Key words: analgesics opioid, fentanyl; cough; postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV), defined as nausea, vomiting, or both within 24 h after operation, is a long-standing concern for anaesthetists.[1] The incidence after general anaesthesia with an inhalational agent, opioid, and no antiemetic prophylaxis is ~10% in the recovery room[2] and 30% during the first 24 h;[3 4] this increases up to 70–80% in high-risk populations.[3] Postoperative nausea and vomiting not only limits patient mobility,[5] delays discharge from the postanaesthesia care unit (PACU), and increases care cost,[6 7] but was also ranked as the most common postoperative complaint in a recent report.[8] Several predictive

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Editor's key points

- More accurate prediction of which patients are most likely to experience postoperative nausea and vomiting (PONV) would be helpful.
- Fentanyl-induced cough immediately before induction of anaesthesia occurs in about 30% of patients.
- Fentanyl-induced cough may be attributable to histamine release, a pathway shared by PONV.
- Antihistamines might decrease the risk of PONV in patients with fentanyl-induced cough.

models have been developed to stratify the risk for PONV. However, a simplified scoring system by Apfel and colleagues[9 10] compares favourably against other scoring systems. The Apfel score included four predictive risk factors for PONV (female gender, history of motion sickness or PONV, non-smoking status, and use of postoperative opioids) and if none, one, two, three, or four risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79%, respectively.[3]

Fentanyl is one of the most commonly administered parenteral opioid analgesics for balanced anaesthesia. Fentanyl-induced cough (FIC), first reported more than two decades ago, has an incidence between 18 and 65%.[11 12] The range of incidence is attributable to differences in the dose and speed of fentanyl injection and the presence or absence of effective pretreatment. Fentanyl-induced cough is usually transient and self-limiting in most patients. Several severe complications have been reported.[13 14]

In our experience, FIC is more common in young female non-smokers, which is also the high-risk population for PONV. This suggests that FIC and PONV may share some common mechanisms. Therefore, we designed this prospective cohort study to assess whether FIC is a risk factor for PONV.

Methods

The National Taiwan University Hospital Committee Review Board approved the study protocol. As the study did not require a deviation from standard clinical care, the ethics committee waived the requirement for written consent from the patients. The study was performed in female patients undergoing elective, inpatient, non-malignant uterine or ovarian surgery via laparotomy from July 1, 2011 to July 30, 2012. Inclusion criteria were age between 18 and 60 yr and ASA physical status classification I and II. Patients with pre-existing lung or cardiac disease, impaired kidney or liver function, obesity (body mass index>30 kg m^{-2}), pregnancy, history of bronchial asthma or chronic obstructive pulmonary disease, history of smoking, respiratory, or gastrointestinal tract infection in the previous 2 weeks, preoperative use of an angiotensin-converting enzyme inhibitor, an antiemetic, a bronchodilator, or a steroid, a history of PONV or motion sickness, and postoperative intensive care unit admission were excluded from the study.

Estimation of sample size was based on a 60% incidence of PONV in our patient group, assuming that patients without FIC would have a 30% relative reduction rate in the incidence of PONV. With α=0.05 and β=0.20, a minimum of 131 patients in each group was required. We assumed a 30% incidence of FIC.[12 15]

All patients fasted overnight and received no premedication. Before being taken to the operating room, venous access was established using a 22-gauge cannula on the dorsum of the hand, connected to a T-connector. On arrival in the operating room, continuous ECG lead II, non-invasive arterial pressure and pulse oximetry monitoring were instituted. A fentanyl bolus (2 μg kg^{-1}) was then injected via the T-connector over 5 s. An anaesthetist recorded the occurrence of cough up to 1 min after the bolus. General anaesthesia was induced with propofol 2–2.5 mg kg^{-1} after cough cessation or 1 min after fentanyl injection. Cisatracurium, 0.2 mg kg^{-1}, was used to facilitate tracheal intubation. Maintenance of anaesthesia consisted of desflurane or sevoflurane in an air–oxygen mixture. Intermittent bolus doses of 50 μg fentanyl were administered as needed for intraoperative analgesia. The total dose of intraoperative fentanyl used varied between 150 and 250 μg. Upon completion of the procedure, residual muscle relaxant effect was antagonized with neostigmine 2.5 mg and atropine 1 mg, and the volatile anaesthetic was discontinued. The tracheal tube was removed upon resumption of spontaneous ventilation, and the patient was then transferred to the PACU.

All postoperative assessments were made by observers blinded to whether the patient experienced FIC. The incidence of patient complaints of nausea or vomiting was recorded by a trained nurse in the PACU. The need for postoperative opioid and antiemetics was assessed by the on-duty anaesthetist in the PACU and the consulting anaesthetist on the ward. No prophylactic antiemetics were administered. All patients who received a postoperative antiemetic were given prochlorperazine 5 mg i.m. The National Health Insurance of Taiwan does not pay for postoperative i.v. patient-controlled analgesia; therefore, most patients received ketorolac 30 mg i.v. at the first complaint of postoperative pain and i.v. morphine boluses for subsequent pain complaints. Some patients chose to pay for morphine i.v. patient-controlled analgesia and received this form of postoperative analgesia.

Another group of trained nurse anaesthetists assessed the incidence and severity of PONV 24 h after surgery. The severity of nausea and vomiting was recorded as a score of 0, 1, or 2 (0=no nausea or vomiting, 1=tolerable nausea or vomiting, and 2=intractable nausea or vomiting requiring prochlorperazine 5 mg i.m.). Patients who experienced any degree of nausea or vomiting within the first 24 h after surgery were classified as having PONV.

Statistical analysis

In this analysis, patient-related variables were age, BMI, ASA class, FIC and postoperative use of opioid. The anaesthesia-related variable was the duration of anaesthesia. Patient data were analysed with Student's unpaired *t*-test for continuous variables and the χ^2 test for categorical variables.

The joint contribution of these factors on the incidence of PONV was evaluated by logistic regression. Given that the postoperative use of opioid is the only established modifiable risk factor, we further analysed patients who did and did not receive postoperative morphine separately using the above-mentioned statistics. As all study patients were female non-smokers, those who did and did not receive postoperative morphine corresponded to an Apfel score 3 and 2, respectively. All statistical tests were two sided, and $P<0.05$ were considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA) and Stata version 9.1 (StataCorp LP, College Station, TX, USA).

Results

Of 502 patients enrolled in the study, 154 (31%) had FIC. There were no significant differences between those with and without FIC in terms of patient characteristics or anaesthetic duration

(Table 1). There were 220 patients (44%) who had PONV. The incidence of PONV in the FIC group was significantly higher than in the non-FIC group (56.5 *vs* 38.2%; *P*<0.0001). The result of multivariate logistic regression analysis (Table 2) showed FIC as a predictive risk factor of the incidence of PONV (adjusted odds ratio 2.08, 95% confidence interval 1.41–3.07).

In the subgroup without postoperative morphine use, 104 of 358 patients (29%) suffered from FIC. The incidence of PONV in the FIC group was significantly higher than in the non-FIC group (51.9 *vs* 36.2%; *P*=0.006). Multivariate logistic regression analysis (Table 3) showed FIC as a predictor of the incidence of PONV in this setting (adjusted odds ratio 1.91, 95% confidence interval 1.20–3.05).

In the subgroup with postoperative morphine use, 50 of 144 patients (35%) suffered from FIC. The morphine consumption in the first 24 h after operation ranged from 28 to 46 mg. There was no significant difference between those who did or did not experience PONV (35.1 *vs* 34.1 mg, *P*=0.14). The incidence of PONV in the FIC group is significantly higher than in the non-FIC group (66 *vs* 43.6%; *P* =0.011). Multivariate logistic regression analysis (Table 4) showed FIC as a predictor of the incidence of PONV (adjusted odds ratio 2.70, 95% confidence interval 1.28–5.70).

Table 1 Patient characteristic data presented as mean (SD), mean (range), or numbers. FIC, fentanyl-induced cough; PONV, postoperative nausea and vomiting

Parameters	Groups		P-value
	Without FIC (*n*=348)	With FIC (*n*=154)	
Age (yr)	43.5 (20–60)	43.4 (19–60)	0.89
Height (cm)	158.8 (5.4)	159.3 (5.5)	0.56
Weight (kg)	57.7 (9.7)	58.4 (11.4)	0.50
Duration of anaesthesia (min)	135.5 (56.8)	129.4 (57.3)	0.27
ASA physical status			
ASA I	50 (14.4%)	15 (9.7%)	0.15
ASA II	298 (85.6%)	139 (90.3%)	
Total fentanyl dose (μg)	169.8 (27.7)	166.9 (30.1)	0.30
Postoperative opioid			
No	254 (73%)	104 (67.5%)	0.21
Yes	94 (27%)	50 (32.5%)	
PONV	133 (38.2%)	87 (56.5%)	<0.0001

Table 2 Multivariate logistic regression analysis with factors associated with PONV for all patients (*n*=502). CI, confidence interval; FIC, fentanyl-induced cough; PONV, postoperative nausea and vomiting

Factor	Odds ratio (95% CI)	P-value
Age (yr)	0.99 (0.97–1.01)	0.53
Body mass index (kg m^{-2})	0.99 (0.95–1.04)	0.80
Duration of anaesthesia (min)	1.00 (1.00–1.01)	0.27
ASA physical status (II *vs* I)	1.35 (0.78–2.36)	0.28
Postoperative opioid	1.38 (0.91–2.10)	0.13
FIC	2.08 (1.41–3.07)	<0.0001

Discussion

Our study demonstrates that patients with FIC have a higher incidence of PONV. These results apply only to the patient population we studied, non-smoking women with Apfel scores of 2 or 3. Fentanyl-induced cough has been reported to occur within 30 s after fentanyl injection;[16 17] therefore, our 1 min observation was long enough to detect all FIC. The incidence of FIC observed in our study (31%) is comparable to previous reports.[12 15]

While opiates generally decrease coughing, rapid i.v. bolus administration of fentanyl or fentanyl-derived opioids can induce severe coughing in many patients.[17] This can be undesirable in patients at risk for aspiration,[14] with open globe eye injuries, or with increased intracranial pressure. Effective ways to prevent FIC include pretreatment with propofol, *N*-methyl-D-aspartate receptor antagonists, β_2 agonists, lidocaine, α_2 agonists, giving a small fentanyl dose 1–3 min before a larger fentanyl dose, or by slowing the rate of fentanyl injection.[15] Cigarette smoking and increasing patient age also decrease the incidence of FIC.[16] Benzodiazepines and atropine do not decrease the incidence of FIC.[15]

The mechanism of FIC in humans is unknown. However, histamine appears to be involved in the production of FIC in mice. Fentanyl increases the number of citric acid-induced coughs in mice.[18] This FIC enhancement was abolished by pretreatment with fexofenadine, a histamine H1 receptor antagonist, or moguisteine, a rapidly adapting receptor antagonist. Fentanyl increased histamine concentrations in bronchoalveolar lavage fluid but not in plasma. Thus, in mice, it is likely that fentanyl increased histamine release in bronchoalveolar tissue, histamine enhanced the excitability of the rapidly adapting receptors via H1 receptors, and the rapidly adapting receptors increased the cough reflex.[18] No similar research has been conducted in humans, and the effects of antihistamines on FIC are not known.

Table 3 Multivariate logistic regression analysis with factors associated with PONV for patients who did not receive postoperative morphine (*n*=358). CI, confidence interval; FIC, fentanyl-induced cough; PONV, postoperative nausea and vomiting

Factor	Odds ratio (95% CI)	P-value
Age (yr)	1.00 (0.97–1.02)	0.67
Body mass index (kg m^{-2})	1.04 (0.98–1.10)	0.18
Duration of anaesthesia (min)	1.00 (1.00–1.01)	0.43
ASA physical status (II *vs* I)	1.30 (0.71–2.39)	0.40
FIC	1.91 (1.20–3.05)	0.007

Table 4 Multivariate logistic regression analysis with factors associated with PONV for patients who received postoperative morphine (*n*=144). CI, confidence interval; FIC, fentanyl-induced cough; PONV, postoperative nausea and vomiting

Factor	Odds ratio (95% CI)	P-value
Age (yr)	0.99 (0.94–1.04)	0.71
Body mass index (kg m^{-2})	0.89 (0.82–0.98)	0.018
Duration of anaesthesia (min)	1.001 (0.995–1.007)	0.75
ASA physical status (II *vs* I)	1.18 (0.29–4.76)	0.81
FIC	2.70 (1.28–5.70)	0.009

During surgery, histamine is released into the plasma during times of physical stress, such as intubation, extubation, and surgical manoeuvres, and some patients release much more histamine than others.[19 20] Histamine release can be associated with bouts of postoperative vomiting.[19] Histamine H1 receptor antagonists, including diphenhydramine and cyclizine, are more effective than placebo in preventing PONV.[21–23] In different studies, H1 receptor antagonists were as effective[22] or less effective[24] than serotonin 5HT-3 receptor antagonists in preventing PONV.

Thus, histamine may be the mediator connecting FIC and PONV. Future research will be needed to determine whether antihistamines can decrease the incidence of FIC, or if antihistamines can decrease the incidence of PONV in patients who have FIC during induction of anaesthesia.

Our study has several limitations. First, we studied only nonsmoking women, so we cannot generalize our results to men or to women with higher or lower Apfel scores. Second, funding limitations did not permit us to use the same postoperative opioid regimen in all patients. All patients did receive one of two postoperative morphine regimens. Third, our study followed patients for only 24 h; therefore, we could not investigate the influence of FIC on PONV beyond the first postoperative day. Fourth, we assumed that the incidence of PONV in our patients would be 60%, while the measured incidence was 44%. However, we recruited patients throughout the funding period for the study, enrolled a larger number of patients than the minimum we estimated for each group, and did find a statistically significant difference in the incidence of PONV between patients with and without FIC. Our assumption of the difference in the incidence of PONV between patients with and without FIC was as we expected; we estimated a 30% relative reduction rate in patients without FIC and found a difference of 32%.

In conclusion, female patients with FIC during induction of anaesthesia and an Apfel score of 2 or 3 are more likely to experience PONV after surgery than similar patients without FIC. Future research is needed to determine whether antihistamines can decrease the incidence of PONV in patients with FIC.

Authors' contributions

C.C.L.: study design, data collection and analysis, drafting and revising the article. S.S.C., C.C.H., H.J.Y., and S.Z.F.: data collection and analysis. K.L.C: statistical analysis of the data. B.L.L.: data analysis, drafting and revising the article. L.K.C.: study design, data collection and analysis, statistical analysis of the data, drafting and revising the article.

Declaration of interest

None declared.

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References

1. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; **77**: 162–84
2. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: S24–32
3. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999; **91**: 693–700
4. Franck M, Radtke FM, Apfel CC, *et al*. Documentation of postoperative nausea and vomiting in routine clinical practice. *J Int Med Res* 2010; **38**: 1034–41
5. Apfel CC, Korttila K, Abdalla M, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**: 2441–51
6. Parra-Sanchez I, Abdallah R, You J, *et al*. A time-motion economic analysis of postoperative nausea and vomiting in ambulatory surgery. *Can J Anaesth* 2012; **59**: 366–75
7. Carroll NV, Miederhoff PA, Cox FM, Hirsch JD. Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. *J Clin Anesth* 1994; **6**: 364–9
8. Lehmann M, Monte K, Barach P, Kindler CH. Postoperative patient complaints: a prospective interview study of 12,276 patients. *J Clin Anesth* 2010; **22**: 13–21
9. Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. *Can J Anaesth* 2002; **49**: 237–42
10. Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. *Br J Anaesth* 2002; **88**: 234–40
11. Hung KC, Chen CW, Lin VCH, Weng HC, Hsieh SW. The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. *Anaesthesia* 2010; **65**: 4–7
12. Lin CS, Sun WZ, Chan WH, Lin CJ, Yeh HM, Mok MS. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. *Can J Anaesth* 2004; **51**: 654–9
13. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001; **92**: 1442–3
14. Lim KJ, Lee SK, Lee HM, *et al*. Aspiration pneumonia caused by fentanyl-induced cough -a case report-. *Korean J Anesthesiol* 2013; **65**: 251–3
15. Kim JE, Min SK, Chae YJ, Lee YJ, Moon BK, Kim JY. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis. *J Anesth* 2014; **28**: 257–66
16. Oshima T, Kasuya Y, Okumura Y, Murakami T, Dohi S. Identification of independent risk factors for fentanyl-induced cough. *Can J Anaesth* 2006; **53**: 753–8
17. Lin JA, Yeh CC, Lee MS, Wu CT, Lin SL, Wong CS. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. *Anesth Analg* 2005; **101**: 670–4
18. Kamei J, Nakanishi Y, Asato M, Ikeda H. Fentanyl enhances the excitability of rapidly adapting receptors to cause cough via the enhancement of histamine release in the airways. *Cough* 2013; **9**: 3
19. Kimura K, Rüsch D, Strasser C, *et al*. Influence of histamine release on postoperative vomiting (POV) following gynaecological laparoscopic surgery. *Inflamm Res* 2004; **53**: S148–53
20. Nies C, Krack W, Lorenz W, *et al*. Histamine release in conventional versus minimally invasive surgery: results of a randomised trial in acute cholecystitis. *Inflamm Res* 1997; **46**: S83–4
21. Lin TF, Yeh YC, Yen YH, Wang YP, Lin CJ, Sun WZ. Antiemetic and analgesic-sparing effects of diphenhydramine added to morphine intravenous patient-controlled analgesia. *Br J Anaesth* 2005; **94**: 835–9
22. Cholwill JM, Wright W, Hobbs GJ, Curran J. Comparison of ondansetron and cyclizine for prevention of nausea and vomiting after day-case gynaecological laparoscopy. *Br J Anaesth* 1999; **83**: 611–4

23. Kranke P, Morin AM, Roewer N, Eberhart LH. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. *Acta Anaesthesiol Scand* 2002; **46**: 238–44

24. Piwko C, Lasry A, Alanezi K, Coyte PC, Ungar WJ. Economic evaluation of ondansetron vs dimenhydrinate for prevention of postoperative vomiting in children undergoing strabismus surgery. *Paediatr Anaesth* 2005; **15**: 755–61

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