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Incidence of fentanyl induced cough and fentanyl induced cough as a risk factor for post operative nausea and vomiting

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ABSTRACT

Background: Fentanyl-induced cough (FIC) is an undesirable side effect associated with intravenous injection of the opioid fentanyl, which can lead to an increase in intraocular, intrathoracic, and intraabdominal pressures. The incidence of FIC is reported to be 18–65%, more common in young females, who are also at high risk population for post-operative nausea and vomiting (PONV). FIC and PONV are both common anesthesia-related events that seem to have common risk factors. **Aims and Objectives:** The objectives of the study were to find out the incidence of FIC in female patients undergoing elective surgery under general anesthesia and if FIC was a risk factor for developing PONV. **Materials and Methods:** A randomized, prospective study was done to compare the incidence of FIC and its correlation with PONV. 263 adult female patients belonging to American Society of Anesthesiologists status I and II, aged 18–59 years, posted for elective surgery under general anesthesia were studied over a period of 2 years. Pre-operatively, fentanyl (2 mg/kg body weight) was injected intravenously over 10 s as premedication, and the occurrence of any episode of cough within 60 s of fentanyl administration was taken as FIC. The incidence and severity of PONV were assessed in the same study population for a 24-h period. The incidence of FIC during general anesthesia in the study population was noted, and its correlation with PONV was analyzed. **Results:** The incidence of FIC in the study population was found to be 27%. The incidence of PONV in the FIC group was found to be 38%, as compared to 29.7% in the non-FIC group. FIC group had a higher incidence of PONV than the non-FIC group, but it was statistically insignificant (P = 0.254). **Conclusion:** The incidence of PONV was slightly higher in the FIC group than in the non-FIC group, but it was not statistically significant.

Key words: Cough; Fentanyl; General anesthesia; Post-operative nausea and vomiting

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INTRODUCTION

Fentanyl is used routinely before induction of anesthesia owing to its favorable characteristics like fast onset, short duration of action, significant dose-dependent analgesia, and cardiovascular stability, mainly during laryngoscopy and endotracheal intubation. Though opioids are known to possess antitussive activity by acting centrally to suppress cough, intravenous (IV) application of fentanyl can trigger an irritating cough. Any episode of cough occurring within 60 s of fentanyl administration is classified as fentanyl-induced cough (FIC).[1]

FIC was first reported more than two decades ago. It has an incidence in the range of 18–65%. This wide range in incidence is due to differences in the dose and speed of fentanyl injection, as well as the presence or absence of effective pretreatment. FIC is an undesirable side effect associated with an increase in intraocular, intrathoracic and intra-abdominal pressures. FIC is usually transient, benign, and self-limiting for most patients, but at times it can be

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spasmodic or explosive and even life-threatening requiring immediate intervention.[2]

FIC is thought to be caused by inhibition of the central sympathetic system, which leads to vagal predominance, reflex bronchoconstriction due to stimulation of tracheobronchial tree receptors, or histamine release.[1] There are many hypotheses regarding FIC,[3] though the exact mechanism is not clear.

The incidence of FIC is higher in younger age groups (infants and children secondary to more number of cough receptors), patients of Asian ethnicity, and non-smokers with a higher dose of fentanyl, a faster speed of injection,[4] and administration through the central veins.[5]

One of the most significant and distressing symptoms following surgery and anesthesia is post-operative nausea and vomiting (PONV). With an incidence of 30–80%, PONV remains as one of the most common causes of patient discomfort following anesthesia. It is consistently listed as one of the anesthetic outcomes that patients would prefer to avoid in pre-operative surveys.[6]

Women, general anesthesia, laparoscopic and gynecological surgeries, opioids, prior history of motion sickness or vomiting after previous surgery, and age <50 years are associated with a higher incidence of PONV.

Probably, FIC and PONV may share some common mechanisms. Histamine release may be attributed to being the common factor correlating FIC with PONV. FIC is more common in young females, who are also at high risk for PONV. Hence, we designed this prospective study to assess whether patients who have FIC during the induction of anesthesia have an increased incidence of PONV. The objectives of the study were to find out the incidence of FIC in female patients undergoing elective surgery under general anesthesia and if FIC was a risk factor for developing PONV.

Aims and objectives

The objectives of the study were to find out the incidence of FIC in female patients undergoing elective surgery under general anaesthesia and if FIC was a risk factor for developing PONV.

MATERIALS AND METHODS

This prospective randomized controlled observational clinical study was conducted after approval from the Institutional Ethical Committee (no. 305/2019). The study was registered at the ISRCTN registry with trial registration number ISRCTN83969715.

After obtaining written informed consent, 263 female patients aged 18–59 years belonging to the American Society of Anesthesiologists (ASA) I/II patients who underwent elective surgery under general anesthesia were included. Patients with known hypersensitivity to fentanyl, history of bronchial asthma or chronic obstructive pulmonary disease, positive smoking status, recent respiratory or gastrointestinal infection (2 weeks), pre-operative use of an angiotensin-converting enzyme inhibitor, prior history of PONV or motion sickness, laparoscopic surgeries, and pregnant females were excluded.

All patients were kept nil per oral for 6 h for solids and 2 h for clear liquids. On arrival in the operating room, the electrocardiogram, non-invasive arterial pressure, pulse oximetry, and capnography monitors were connected. IV access was secured using a 20G IV cannula. All patients were pre-oxygenated with 100% oxygen for 3 min and premedicated with IV glycopyrrolate 0.2 mg, IV ondansetron 4 mg, and IV midazolam 1 mg.

Inj. fentanyl was diluted with sterile water in a 10 mL syringe up to 20 mcg/mL, and 2 mcg/kg was injected through an IV cannula over 10 s after one minute of premedication.

An anesthesiologist recorded the occurrence of any episode of cough within 60 s of fentanyl administration as FIC.

General anesthesia was induced with IV propofol 1.5–2 mg/kg after cough cessation or 1 min after fentanyl injection. IV atracurium 0.5 mg/kg was used to facilitate tracheal intubation. Maintenance of anesthesia was done with isoflurane in an air-oxygen mixture (50:50) to maintain a minimum alveolar concentration of 0.8–1%. Analgesia was maintained with IV fentanyl (20 mcg/h). Upon completion of the procedure, patients were reversed with IV neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg). The trachea was extubated upon resumption of spontaneous ventilation, and the patient was transferred to the recovery room.

All post-operative assessments were made by observers blinded to the occurrence of FIC. The occurrence of PONV was predicted based on the Apfel score. Apfel score has four variables (female sex, history of motion sickness or PONV, non-smokers, opioids in post-operative treatment are planned). Each variable carries 1 point, and it is graded as 1–20%, 2–40%, 3–60%, or 4–80%.[7] All the patients in our study had an Apfel score of 3.

The incidence and severity of PONV within 24 h of surgery were assessed by nurses in the ward. The severity of nausea and vomiting was recorded on a score of 0, 1,

or 2 (0=no nausea or vomiting, 1=mild nausea or vomiting not requiring treatment, and 2=moderate nausea, mild vomiting and requiring treatment, and 3=severe nausea or vomiting requiring medication.[8] Patients who experienced any degree of nausea or vomiting within the first 24 h after surgery were classified as having PONV.

IV Metoclopramide (10 mg) was administered as the rescue antiemetic when PONV ≥2.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as mean±standard deviation (min-max) and results on categorical measurements are presented as number (%). A chi-square or Fisher exact test has been used to find the significance of study parameters on a categorical scale between two or more groups. Significance is assessed at the 5% level of significance. The statistical software, namely Statistical Package for Social Sciences 22.0, and R environment version 3.2.2 were used for the analysis of the data, and Microsoft Word and Excel were used to generate graphs, tables, etc.

The sample size was calculated based on a study conducted by Li et al., in 2015 to investigate whether patients with FIC during induction of anesthesia have an increased risk of PONV.

The reported prevalence of PONV in female patients who undergo general anesthesia is 45%. Hence, to estimate the prevalence of PONV with an absolute precision of 6% and a 95% confidence interval, the required minimum sample size was 263 female patients who underwent surgery. The sample size was calculated using nMaster 2.0 software.

RESULTS

A total of 263 female patients belonging to ASA 1 and 2 in the age group 18–59 years who underwent general anesthesia were studied. The mean age of the study group was 41.25±11.45 years.

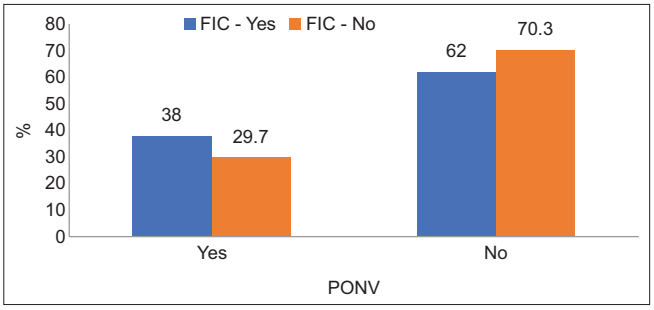

Figure 1: Distribution of fentanyl-induced cough by post-operative nausea and vomiting status

The incidence of FIC among 263 patients was 27%. All the patients were followed up 24 h post-operatively for any incidence of PONV. It was found out that the FIC group had a higher incidence of PONV when compared to the non-FIC group (38% vs. 29.7%), but the difference was not significant (P=0.254) (Figure 1).

The incidence of PONV following general anesthesia in 263 female patients was found to be around 32%.

DISCUSSION

Opioids decrease coughing due to their central antitussive action. But rapid IV bolus administration of synthetic opioids is associated with coughing in many patients.[1] This cough is undesirable as it can increase the risk of aspiration in vulnerable patients. It can also increase intracranial pressure and can be detrimental to patients with open globe injuries or head injuries. Hence, prevention of FIC is a priority.

The incidence of FIC was found to be 27% in our study when fentanyl was administered intravenously over a period of 10 s at 2 mcg/kg body weight in females undergoing elective surgery under general anesthesia. Previous studies have shown that the incidence of FIC ranges from 18% to 65%,[2] depending on various factors like dose, route, speed of injection, and pretreatment with other pharmacological measures. FIC has been reported to occur within 30 s after fentanyl administration. Hence, we decided to observe for a period of 60 s after fentanyl administration. The incidence of FIC observed in our study (27%) is comparable to previous studies. Li et al., did a study in 502 adult non-smoking gynecological surgical patients and found that 134 patients developed FIC, with an incidence of 31%.[1]

A meta-analysis by Kim et al., to assess the efficacy of pharmacological and non-pharmacological interventions to reduce the incidence of FIC found that the incidence of FIC was approximately 31%.[2] Yu et al., showed that dilution of fentanyl along with prolonged injection time could eliminate FIC, and the incidence of FIC was 32%.[9]

The mechanism of FIC is currently unclear; there are several hypotheses. The opioid receptor hypothesis says that stimulation of c-fiber receptors (J receptors) on the proximal bronchial mucosa can lead to bronchoconstriction and cough. Citrate in fentanyl preparations can stimulate type C-fiber, release neuropeptides, and cause cough. Yet another hypothesis is that IV fentanyl causes histamine release from mast cells, causing cough.[10] Muscle stiffness caused by IV fentanyl can cause sudden adduction of the vocal cords or soft tissue obstruction on the glottis, which leads to cough.[11]

Naldan et al., conducted a study to observe the effect of pheniramine maleate on FIC during anesthesia induction and concluded cough incidence to be significantly decreased in both pheniramine and lidocaine treatment groups. IV pheniramine is as effective as lidocaine in preventing FIC.[12] As the administration of an antihistaminic reduced the incidence of FIC, they concluded that histamine release could be a probable mechanism for FIC. Also, research conducted on mice by Kamei et al., postulated that histamine appears to be involved in the production of FIC.[11]

There are many effective methods to prevent FIC, e.g., pretreatment with either propofol.[13] (or $beta_2$ agonists or lidocaine)[14] or $alpha_2$ agonists.[15] Priming with small doses of fentanyl before injecting the full dose, diluting the drug,[9] or slowing the rate of IV injection[16] can also help in the prevention of FIC. Various non-pharmacological measures like huffing maneuvers, spirometry before fentanyl administration, and swallowing after fentanyl injection were also found to reduce the incidence of FIC in other studies.[17]

The incidence of PONV in the FIC group was 38%, compared to 29.7% in the non-FIC group in our study. Although the FIC group had a higher incidence of PONV than the non-FIC group, it was not statistically significant. (P=0.254). The incidence of PONV at 1, 2, 3, 4 h, and 24 h post-operatively were found to be comparable in both FIC and non-FIC groups in our study.

Mauermann et al., studied the association between intraoperative fentanyl dosing and PONV and pain and found that higher intraoperative fentanyl dosing was independently associated with a higher incidence of PONV.[18] Li et al., concluded that the incidence of PONV in the FIC group was significantly higher than non-FIC group (56.5% vs. 38.2%, P<0.0001) and concluded that FIC is a predictive risk factor for the incidence of PONV.[1]

Kimura et al., concluded that histamine is released during surgical and an esthetic stress and could be correlated with episodes of PONV.[19] Therefore, from previous studies, it can be postulated that histamine release may be one of the causative mechanisms between FIC and PONV.[20] Therefore, it can be concluded that a higher incidence of FIC might be associated with a higher incidence of PONV. But future research is required to determine whether antihistamines can decrease the incidence of FIC and subsequently the incidence of PONV in patients who have FIC during the induction of general anesthesia.

Limitations of the study

As all the patients were female, we cannot extrapolate our results to the general population. We included only ASAI and ASAII patients; hence, we cannot predict whether the outcome can change with ASA grading.

CONCLUSION

The incidence of PONV was slightly higher in the FIC group than in the non-FIC group, but it was not statistically significant. Probably, FIC and PONV may share a common causative agent, such as histamine. Hence, further studies are required to find any strong association between FIC and PONV.

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SJ- Literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis; **ANK-** Concept, design, definition of intellectual content, clinical protocol, editing, and manuscript revision; **RR-** Design of study, statistical analysis and interpretation; **URS-** Literature survey and preparation of figures, manuscript preparation and submission of article; **DB-** Review manuscript; **AK-** Coordination and manuscript revision.

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