

# Association of Fentanyl Correlated Cough with Post-Operative Nausea and Vomiting

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## Abstract

**Background:** The occurrence of cough related to fentanyl ranges from 18% to 65%. In the case of general anesthesia without antiemetic medication the occurrence of nausea and vomiting is around 10% post operatively and this increases 3 folds within the first day and 7 to 8 folds in high-risk individuals.

**Aim:** To determine if subjects with fentanyl correlated cough at induction of anesthesia might experience higher frequency of nausea and vomiting after surgery.

**Methods:** Our prospective and double blind investigation included 215 non-smoker females subjects, classed I by the American Society of Anesthesiologists, aged 25-46 yrs. and assigned for different plastic elective operative procedures at the Jordanian Royal Rehabilitation Center, KHMC, Amman, Jordan, during the period February 2022-Feb 2023. Fentanyl bolus (2 mcg/kg) was administered over 10 seconds. An anesthesiologist registered frequency of cough during 60 seconds following the bolus. The intensity of nausea and vomiting was scored as 0, 1 or 2 (0=No nausea or vomiting, 1=Tolerable nausea or vomiting and 2=Intractable nausea or vomiting). Subjects with any degree of nausea or vomiting during the first day following surgery were labelled as having PONV. Risk estimation for PONV by Apfel score: Risk points (risk estimation): 1,2,3 and 4. Risk factors (each one risk point): 1 point for female sex; 1 point for no smoking; 1 point for opioids use after surgery and 1 point for past nausea and vomiting after surgery or motion sickness. Multivariate logistic regression was used to evaluate the relation between fentanyl correlated cough and nausea and vomiting after surgery.

**IRB name:** Pharmaceutical, Clinical Research and Professional Ethical Committee of the Royal Medical Services. IRB number: 10-5/2023.

**Results:** 70/215 (32.6%) subjects Group II (GII) experienced fentanyl correlated cough while 145/215 (67.4%) subjects Group I (GI) had no fentanyl correlated cough. The

frequency of nausea and vomiting after surgery in the fentanyl correlated cough group (40/70; 57.1%) was more than in the non-fentanyl correlated cough group (55/145; 37.9%).  $P<0.005$  fentanyl correlated cough was an anticipative risk factor for nausea and vomiting after surgery (OR=1.66, 0.99-2.65). Group I (GI): Subjects who had no fentanyl correlated cough; Group II (GII): Subjects who experienced fentanyl correlated cough.

**Conclusions:** Non-smoking subjects scheduled for various plastic operative procedures with fentanyl correlated cough at induction of anesthesia experienced an increased frequency of nausea and vomiting after surgery.

**Keywords:** Plastic and reconstructive surgery; Non-smokers females; Vomiting; Nausea; After surgery; Cough; Fentanyl; Induction

## Introduction

Nausea and vomiting following surgery can be defined as nausea, vomiting or both occurring during first day following surgery [1].

The frequency of nausea and vomiting following general anesthesia with no antiemetic is 10% in the recovery room and 30% within the first day; increasing up to 70%-80% in high-risk subjects [2]. Nausea and vomiting following surgery are considered the most frequent complaint after surgery [3].

The risk for nausea and vomiting following surgery was easily assessed using Apfel scoring system [4]. If none, one, two, three, or four risk factors were present, the frequency of nausea and vomiting after surgery was 10, 21, 39, 61 and 79%, respectively [1].

Fentanyl-correlated cough can be caused by histamine release, a path common with nausea and vomiting after surgery. Antihistamines could reduce the risk of nausea and vomiting after surgery in subjects with fentanyl-correlated cough.

Fentanyl-correlated cough has a frequency of 18%-65% [5], caused by discrepancy in the dose or speed of fentanyl administration. Fentanyl-correlated cough is mainly temporary and self-limiting [6].

Fentanyl-correlated cough and nausea and vomiting after surgery are more frequent in young non-smoker females, indicating a common mechanism for both.

The goal of our investigation was to determine if subjects with fentanyl correlated cough at induction of anesthesia might experience higher frequency of nausea and vomiting after surgery.

## Materials and Methods

This prospective and double blind investigation included 215 females' subjects, classed-I by the American Society of Anesthesiologists, aged 25-46 years and assigned for different plastic elective operative procedures at the Jordanian Royal Rehabilitation Center, KHMC, Amman, Jordan, during the period February 2022-February 2023, after obtaining written informed consent from all participants and approval from our local Ethical and Research Board Review Committee of the Jordanian Royal medical services.

Subjects with history of smoking, administration of an angiotensin-converting enzyme inhibitor or an antiemetic before

surgery and motion sickness were ruled out.

A fentanyl bolus (2 mcg/kg) was administered over 10 seconds. An anesthesiologist registered frequency of cough for 60 seconds following the bolus. General anesthesia was induced using propofol 2 mg/kg following cough stop or 60 seconds following fentanyl administration. Rocuronium 0.5 mg/kg was used. All subjects received paracetamol 500 mg by intravenous infusion every six hours on regular basis on the first postoperative day.

Frequency and intensity of fentanyl correlated cough before induction and nausea and vomiting one day postoperatively were registered. No preventive antiemetic's were given. The intensity of nausea and vomiting was scored as 0, 1 or 2 (0=No nausea or vomiting, 1=Tolerable nausea or vomiting and 2=Intractable nausea or vomiting).

Subjects with any degree of nausea or vomiting during the first day following surgery were labelled as having PONV. Risk estimation for PONV by Apfel score: Risk points (Risk estimation %): 1 (20%), 2 (40%), 3 (60%) and 4 (80%). Risk factors (each one risk point): 1 point for female sex; 1 point for no smoking; 1 point for opioids use after surgery and 1 point for past nausea and vomiting after surgery or motion sickness [4]. This is explained in **Tables 1 and 2** respectively.

**Table 1:** The intensity of nausea and vomiting.

Score	Nausea/Vomiting intensity	PONV risk estimation (%)
0	No nausea or vomiting	-
1	Tolerable nausea/vomiting	20%
2	Intractable nausea/vomiting	40%

**Table 2:** Risk estimation for PONV by Apfel score.

Risk Points	Risk Estimation (%)
1	20%
2	40%
3	60%
4	80%

**Note:** Risk factors (each one adds one risk point): 1. Female sex; 2. No smoking; 3. Opioids use after surgery; 4. Past nausea and vomiting after surgery or motion sickness [4].

## Results

Out of 215 participants in Group II (GII), 70 individuals (32.6%) reported experiencing cough related to fentanyl. Notably, there

were no significant differences in demographics between those with and without fentanyl-associated cough, as shown in **Table 3**.

**Table 3:** Subject's demographics.

	Group I	Group II
No.	145	70
Fentanyl correlated cough	No	Yes
Age (years) average (range)	34 (25-40)	38 (35-46)
Weight (kg) average (range)	73 (70-80)	69 (65-75)
ASA (I)	145	70
<b>Note:</b> Group I (GI): Subjects who had no fentanyl correlated cough; Group II (GII): Subjects who experienced fentanyl correlated cough.		

Post-surgery, 95 out of 215 participants (44.2%) experienced nausea and vomiting. The occurrence of postsurgical nausea and vomiting was notably higher in the fentanyl-associated cough group (GII; 57.1% (40 out of 70)) compared to the non-fentanyl-associated cough group (GI; 37.9% (55 out of 145)), with a statistically significant difference ( $P < 0.005$ ).

It was observed that fentanyl-associated cough was a predictive risk factor for the frequency of nausea and vomiting after surgery (odds ratio 1.66, 95% confidence interval 0.99-2.65), as presented in **Table 4**. Importantly, all participants had risk factors for post-surgical nausea and vomiting, as detailed in **Table 5**.

**Table 4:** Study outcome.

	GI	GII	P
Fentanyl correlated cough (no, %)	145 (67.4%)	70 (32.6%)	<0.05
Nausea and vomiting after surgery (no, %)	55 (37.9%)	40 (57.1%)	<0.005
Period of anesthesia (hours) average (range)	2.2 (2.0-2.4)	1.9 (1.8-2.2)	>0.05
Overall fentanyl dose (mcg) average (range)	204 (196-224)	200 (188-217)	>0.05
<b>Note:</b> $P < 0.05$ were considered statistically significant.			

**Table 5:** Factors correlated with nausea and vomiting after surgery.

Factor	OR	P
Age (years)	0.53 (0.5-1.67)	>0.05
Weight (kg)	0.57 (0.53-1.34)	>0.05
Period of anesthesia (hours)	0.58 (0.43-1.22)	>0.05
ASA (I)	0.93 (0.88-1.45)	>0.05
Fentanyl correlated cough	1.66 (0.99-2.65)	<0.005
<b>Note:</b> $P < 0.05$ were considered statistically significant.		

For clarity: Group I (GI) refers to participants without fentanyl-associated cough; Group II (GII) refers to participants who experienced fentanyl-associated cough.

## Discussion

This investigation showed that non-smoker females with fentanyl correlated cough experienced more frequency of nausea and vomiting after surgery. Fentanyl-correlated cough was recorded during 0.5 min. following fentanyl administration. The frequency of fentanyl correlated cough in this investigation (32.6%) was similar to others [7].

Although opioids reduce cough, fast intravenous injection of fentanyl may cause intense cough, a risk for aspiration in open globe insult or high intracranial pressure [7,8]. To avoid fentanyl correlated cough, pretreatment with propofol or lignocaine, a small fentanyl dose 1-3 minutes before a larger fentanyl dose or by slowing the rate of fentanyl administration can be used [6]. Smoking and old age reduce the frequency of fentanyl correlated cough [9].

Experimentally, histamine has a role in the fentanyl correlated cough. Fentanyl increases citric acid associated coughs. Fentanyl correlated cough was decreased remarkably by pre-treatment using histamine H1 receptor antagonist. Fentanyl increased histamine production in Bronchoalveolar Lavage (BAL) fluid but not in plasma. Fentanyl increased histamine production in BAL tissue, histamine improved the excitability of the rapidly adapting receptors through H1 receptors and the rapidly adapting receptors increased the cough reflex [10].

Intraoperatively, histamine is secreted in plasma during physical stress as intubation, extubation and operative techniques [11]. Histamine secretion might be correlated with vomiting following surgery. Histamine H1 receptor antagonists are efficient in avoiding nausea and vomiting after surgery [12]. H1 receptor antagonists were efficient or less than serotonin 5HT-3 receptor antagonists in avoiding nausea and vomiting after surgery [13]. Histamine was the mediator sharing fentanyl correlated cough [14] and nausea and vomiting after surgery. One meta-analysis found that dezocine remarkably decreased the frequency and intensity of sufentanyl correlated cough during the induction of general anesthesia [15]. Diphenhydramine 30 mg intravenous bolus administration 2 min prior to fentanyl administration may abort fentanyl correlated cough and PONV in the post anesthesia care unit [16].

In this investigation, only nonsmoker females were followed up. The same opioid protocol after surgery was not applied in all subjects. This investigation monitored subjects for only the first day after surgery. There was a statistically remarkable discrepancy in the frequency of nausea and vomiting following surgery between subjects with and with no fentanyl correlated cough.

There are some limitations that should be considered which are mainly the sample size and the length of follow up. Further studies with a larger sample size and longer follow-up periods are necessary to gain a comprehensive understanding of this association and explore additional preventive measures.

## Conclusion

Our investigation revealed that non-smoker female subjects experiencing fentanyl-correlated cough during the induction of anesthesia were more likely to experience a higher frequency of nausea and vomiting after surgery. Fentanyl-correlated cough, although temporary and self-limiting, appears to be an anticipative risk factor for Postoperative Nausea and Vomiting (PONV). This association may be attributed to the role of histamine, which is involved in both fentanyl-correlated cough and PONV. To mitigate the risk of fentanyl-correlated cough and its subsequent effects on PONV, appropriate measures such as pre-treatment with histamine H1 receptor antagonists or dezocine can be considered.

## Disclosures

### Human subjects

Consent was obtained or waived by all participants in this study. Pharmaceutical, Clinical Research and Professional Ethical Committee of the Royal Medical Services issued approval 10-5/2023. The IRB of the Royal Medical services has approved this clinical research.

### Animal subjects

All authors have confirmed that this study did not involve animal subjects or tissue.

### Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

### Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

### Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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