

# Incidence of Fentanyl-induced Cough and Effect of Dose: Randomized Placebo-controlled Trial

## Fentanilin İndüklediği Öksürük İnsidansı ve Dozun Etkisi: Randomize Plasebo Kontrollü Çalışma

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### Abstract

**Objective:** Fentanyl is one of the opioids commonly used in the induction of general anesthesia and can cause coughing. The cough that occurs can be a problem in patients for whom it is necessary to avoid pressure increase. This study aimed to determine the incidence of fentanyl-induced cough (FIC) and the difference between the doses used.

**Method:** This prospective randomized placebo-controlled trial included 750 ASA I-II patients aged 18-65 years who underwent elective surgery under general anesthesia. The patients were randomly divided into three groups. 1 µg kg<sup>-1</sup> fentanyl was used to induce the patients in group 1, and 2 µg kg<sup>-1</sup> fentanyl was used for the induction of the patients in group 2. In the installation of patients in group K, the control group, fentanyl was not used, and a placebo was administered. All patients were observed for 60 seconds after fentanyl injection. The cough severity (mild: 1-2, moderate: 3-4, severe: >5 times), time of cough and demographic data of the patients were recorded and compared.

**Results:** Demographic data were similar among the groups. Cough was observed in 15 patients (6%) in group 1 and 80 patients (32%) in group 2. Incidences of FIC were 6%, 32%, and 0% in groups 1, 2, and K, respectively. While all of group 1 was mild, 82% of the cough observed in group 2 was mild, and 18% was moderate. The incidence and severity of cough in group 2 were significantly higher than in group 1 (p<0.001).

**Conclusion:** Reducing the dose of fentanyl significantly decreases the severity and incidence of cough. We recommend reducing the induction dose to avoid undesirable pressure increases such as intracranial and intraocular surgeries.

**Keywords:** Cough, fentanyl, general anesthesia

### Öz

**Amaç:** Fentanil, genel anestezi indüksiyonunda yaygın olarak kullanılan ve öksürüğe sebep olabilen opioidlerdendir. Meydana gelen öksürük basınç artışından kaçınmanın gerekli olduğu hastalarda problem oluşturabilmektedir. Bu çalışmanın amacı, fentanilin indüklediği öksürük (FİÖ) insidansını belirlemek ve kullanılan dozlar arasındaki farkı saptamaktır.

**Yöntem:** Prospektif randomize plasebo kontrollü bu çalışmaya genel anestezi altında elektif operasyona alınan 18-65 yaş arası, ASA I-II 750 hasta dahil edildi. Hastalar randomize olarak üç gruba ayrıldı. Grup 1'deki hastaların indüksiyonunda 1 µg kg<sup>-1</sup>, grup 2'deki hastaların indüksiyonunda 2 µg kg<sup>-1</sup> fentanil kullanıldı. Kontrol grubu olan grup K'daki hastaların indüksiyonunda fentanil kullanılmayıp plasebo uygulandı. Fentanil enjeksiyonu sonrası tüm hastalar 60 sn gözlemlendi. Hastaların öksürük şiddeti (hafif: 1-2, orta: 3-4, şiddetli: >5 adet) ve zamanı ile demografik verileri kaydedilerek karşılaştırıldı.

**Bulgular:** Demografik veriler gruplar arasında benzerdi. Grup 1'de 15 hastada (%6) ve grup 2'de 80 hastada (%32) öksürük gözlemlendi. FİÖ insidansı grup 1, 2 ve 3 için sırasıyla %6, %32 ve %0 bulundu. Grup 1'deki öksürüğün tamamı hafif şiddetteyken grup 2'de gözlenen öksürüğün %82'si hafif ve %18'i orta şiddetteydi. Grup 2'deki öksürük insidansı ve şiddeti grup 1'e göre anlamlı olarak yüksek bulundu (p<0,001).

**Sonuç:** Fentanil dozunun azaltılması, öksürük şiddeti ve insidansını anlamlı olarak azaltmaktadır. İntrakraniyal ve intraoküler cerrahiler gibi istenmeyen basınç artışlarından kaçınmak için indüksiyon dozunun azaltılmasını öneriyoruz.

**Anahtar kelimeler:** Fentanil, genel anestezi, öksürük



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## Introduction

Fentanyl is one of the synthetic opioids widely used in the induction of general anesthesia due to its rapid onset of action, strong analgesic effect, and cardiovascular stability. Although opioids generally have antitussive effects, paradoxically, intravenous (iv) administration of fentanyl can cause coughing. This condition is known as fentanyl-induced cough (FIC) (1-3).

It is precisely unknown by which mechanism the cough during anesthesia induction occurs. In the suggested opinions, it has been stated that sudden adduction and supraglottic obstruction due to opioid administration may be the cause (4). Although this situation is temporary and self-limiting in most patients, it can lead to dangerous results in some cases.

Life-threatening airway obstructions and aspiration pneumonia secondary to severe FIC have been reported (5). FIC causes an increase in intracranial, intraocular, and intraabdominal pressures. Open eye injury, pneumothorax, cerebral aneurysm, intracerebral hernia, and dissection may cause problems in patients with aneurysms. Premedication with drugs and various methods have been tried to prevent this situation (1-9). Although there are not enough incidence studies in our country, when the literature is examined, the incidence varies in a wide range between 3% and 80% in studies conducted with different doses (10).

This study aims to determine the incidence of cough caused by fentanyl, which is frequently used in anesthesia induction, and to determine the effect of two different induction doses.

## Materials and Methods

After the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital ethics committee, a prospective placebo-controlled randomized study was started (date: 07.07.2021 number: 223). An informed consent form was obtained from the patients participating in the study. The principles of the Declaration of Helsinki complied with the investigation.

Patients between the ages of 18 and 65 years, who underwent elective surgery under general anesthesia by general surgery, urology, gynecology, and orthopedics and who underwent elective surgery from the ASA I-II Physical status, were included in the study. As exclusion criteria, patients with a history of chronic obstructive pulmonary disease, asthma

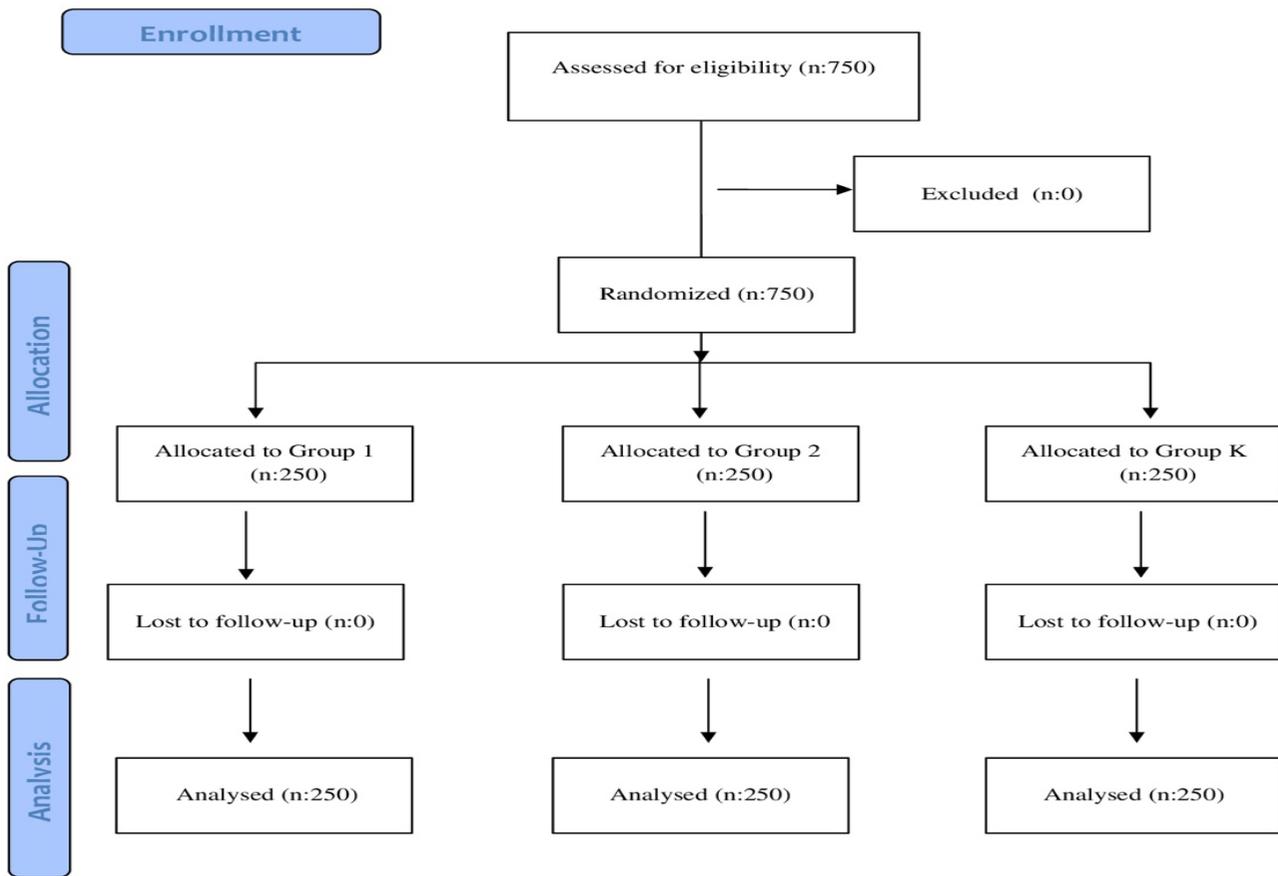
or upper respiratory tract infection, those smoking, those having angiotensin-converting enzyme inhibitors in the previous two weeks and having chronic cough, those who could not be observed for 60 seconds for cough due to hemodynamic or respiratory problems and high intracranial pressure, intraocular or intra-abdominal pressure were excluded from the study. Patients were randomized into three groups by choosing opaque envelopes extended to them. 1  $\mu\text{g kg}^{-1}$  fentanyl was used to induce the patients in group 1, and 2  $\mu\text{g kg}^{-1}$  fentanyl was used for the induction of the patients in group 2. In the installation of patients in group K, the control group, fentanyl was not used, and a placebo was administered (Figure 1). After a routine electrocardiogram, non-invasive blood pressure, pulse oximetry monitoring, and 20 Gauge iv vascular access, the balanced crystalloid infusion was started in the patients taken to the operation room. No premedication was applied to all three groups. Patients in group 1 were injected intravenously with 1  $\mu\text{g kg}^{-1}$  fentanyl in 2 seconds, patients in group 2 were injected with 2  $\mu\text{g kg}^{-1}$  fentanyl in 2 seconds, and patients in group K were injected with placebo saline in 2 seconds. All patients were observed for 60 seconds by the same anesthesia technician who was blinded to the study. The cough, severity, and time of occurrence were recorded in patients with cough. When assessing the severity of cough, it was classified as mild: 1-2, moderate: 3-4, and severe: >5. Based on the duration of the cough, it was classified as first 5 seconds, 6-10 seconds, 11-30 seconds, and 31-60 seconds. Evaluating the frequency and severity of cough, Zhou et al.'s (1) study was taken as a reference.

After all, patients were observed for 60 seconds, and the study was terminated to determine the cough's presence, severity, and duration. For induction, 0.03 mg  $\text{kg}^{-1}$  midazolam and 2-3 mg  $\text{kg}^{-1}$  propofol were used. 1-2  $\mu\text{g kg}^{-1}$  fentanyl was administered to the control group, and surgery was started after endotracheal intubation using 0.6 mg  $\text{kg}^{-1}$  rocuronium as a neuromuscular blocker.

Hung et al. (7) took their work as a reference in calculating the sample size. In their pilot study, the incidence of cough was determined as 20% due to bolus administration of 150  $\mu\text{g IV}$  fentanyl. At least 199 in each group were required to achieve  $\alpha:0.05$  and 80% power ( $\beta:0.2$ ) (7). The sample size was kept more extensive than the reference study, as 750, with 250 patients in each group.

## Statistical Analysis

SPSS Inc., Chicago, USA (SPSS v22.0) program was used for statistical analysis. The conformity of the variables to the



**Figure 1.** Consort flow chart of the study

normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). The chi-square test was used in the evaluation of qualitative data. The Kruskal-Wallis test was used to analyze quantitative data that did not have a normal distribution. The statistical significance limit was accepted as  $p < 0.05$ .

## Results

There was no significant difference between the groups regarding age, body mass index, and gender distribution of the patients. Demographic data of the groups are shown in Table 1. All patients were observed for 60 seconds after iv injection and the study was terminated. None of the patients had hemodynamic instability and oxygen desaturation ( $SpO_2 < 92\%$ ) that required termination of the study. Cough was detected in 95 (12.6%) of the patients. While it was observed in 15 patients in group 1 and 80 patients in group 2, the cough was not observed in group K. In both groups, the cough was mainly mild (1-2 times). The incidence was determined as 6% for group 1, 32% for group 2, and 0% for group K. While all of the coughs in group 1 were mild, it was mild in 66 (82%) patients and moderate in 14 (18%) patients

**Table 1. Demographic data of the groups**

	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
<b>Gender (F/M) (n)</b>	130/120	104/146	120/130	0.06
<b>Age (years)</b>	44.8±14.2	43.8±15.4	45.8±12.5	0.61
<b>Body mass index (kg/m<sup>2</sup>)</b>	26.2±3.0	25.9±3.3	26.2±2.7	0.21

Values are the number of patients (n), mean ± standard deviation

in group 2. Severe cough was not observed in either group. Coughing in group 1 was significantly higher than in the control group ( $p < 0.001$ ).

Cough severity and incidence (32%) in group 2 were significantly higher than in group 1 (6%) ( $p < 0.001$ ). In Table 2, cough severity according to the groups is shown. Cough occurred in the first 5 seconds after fentanyl injection in 83% of patients for groups 1 and 2. Cough was observed in the first 10 seconds in 94.7% of the patients. No cough was observed after 30 seconds in any of the patients. In the comparison between the groups, the duration of cough was significantly different for both the first 5 seconds and 6-10 seconds ( $p < 0.001$ ). The cough occurrence times of the groups are shown in Table 3 and Figure 2.

## Discussion

Our study determined that cough induced by fentanyl administered at a dose of  $2 \mu\text{g kg}^{-1}$  iv was significantly higher in the group administered at a dose of  $1 \mu\text{g kg}^{-1}$  than in the control group. The incidence of cough was 32% in group 2, and decreased to 6% in group 1.

It has not been determined precisely how FIC occurs. There are various hypotheses put forward in this regard. In studies, the cough has generally been attributed to a reflection of muscle rigidity and consequent sudden adduction of the vocal folds or supraglottic obstruction of soft tissues.

**Table 2. Cough frequency and severity of the groups**

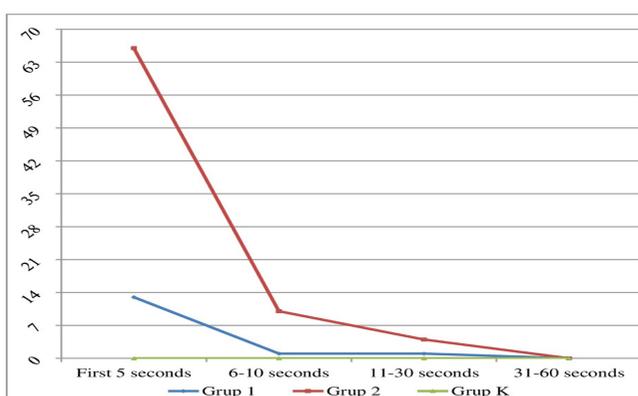
	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
Coughing patient (n)	15	80	0	<0.001
Mild cough (1-2 times) (n)	15	66	0	<0.001
Moderate cough (3-5 times) (n)	0	14	0	<0.001
Severe cough (>5 times) (n)	0	0	0	-

Values are given as the number of patients

**Table 3. Distribution of patients according to the time of cough after fentanyl injection**

	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
First 5 seconds (n)	13	66	0	<0.001
6-10 seconds (n)	1	10	0	<0.001
11-30 seconds (n)	1	4	0	0.99
31-60 seconds (n)	0	0	0	-

Values are given as the number of patients



**Figure 2. Distribution of patients according to the time of cough after fentanyl injection**

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According to other hypotheses, cough is due to the release of histamine by iv administered fentanyl or the secretion of tachykinin by stimulating the pulmonary C-fibers of the citrate. Cough occurs by causing bronchoconstriction in tracheal smooth muscle cells (10). In general, in controlled studies with 9% NaCl, it was reported that cough was higher in the fentanyl group. However, there are also studies reporting that the incidence of cough observed in the placebo group was not different from the fentanyl group. The injection site, administration from angiocath or central venous catheter, genetic factors, and comorbidities may play a role in the emergence of this situation (11). In our study, 9% NaCl was used in the control group, and cough was not detected in any patients.

Cough has also been reported after iv injection of remifentanyl, sufentanyl, and alfentanyl from the same family (12). In studies, the incidence of cough has been reported in a wide range between 3% and 80% (9). Our study found that the average incidence of cough was 12.6%. The literature investigated the effects of the applied dose, administration time, diluting of the fentanyl dose, lowering the concentration, various premedication agents, and methods on the cough (13,14). He et al. (14) investigated the effect of  $1 \mu\text{g kg}^{-1}$  dexmedetomidine in their studies using fentanyl at a dose of  $4 \mu\text{g kg}^{-1}$ . The incidence, 60% in the control group, decreased to 18% in the treated group (14). Hung et al. (7) reported that preemptive administration of a small dose (25  $\mu\text{g}$ ) of fentanyl used in induction in their studies resulted in a significant decrease in the incidence of cough compared to the group given a total dose ( $2 \mu\text{g kg}^{-1}$ ).

Uvelin and Rakic (15) recommended guidelines to prevent the harmful effects of coughing in high-risk patients. Studies have reported that genetic factors may also be influential on fentanyl cough. The incidence, which can reach 80% in the Far East and Asian countries, decreases to 3% in European countries (16,17). The incidence detected in our study is similar to the studies reported in European countries.

Lin et al. (18) reported that age was also influential on fentanyl cough. They attributed the higher incidence in the young than the elderly to the higher irritant receptor activity in the young. Although the mean age of the patients in all three groups was similar in our study, the relationship between age and the presence of cough was not examined. Pandey et al. (13) used  $3 \mu\text{g kg}^{-1}$  fentanyl in their studies and reported the frequency of mild cough as 70% and moderate cough as 30%. In our study, mild cough was detected in 81% and moderate cough in 19%, while severe cough was not

observed. Cough severity was significantly higher in group 2 than in group 1, which is consistent with the literature.

When the literature is examined, there is no consensus on the duration of FIC. Hung et al. (7) proposed the hypothesis that the rate of iv injection created a particular blood concentration in cough formation. Yakıcı et al. (10), in their study examining the effect of iv injection speed of fentanyl, divided the patients into two groups and administered 2 µg kg<sup>-1</sup> fentanyl in 5 and 30 seconds. In both groups, the cough was observed within the first 10 seconds in more than half of the cases (10). In our study, the FIC was observed within the first 5 seconds in 83% of the patients and within the first 10 seconds in 94% of the patients. No cough was observed 30 seconds after IV administration.

### Study Limitations

The limitation of our study is that it was single-centered and it did not analyzed according to age groups. The incidence of FIC can be high in young people.

### Conclusion

In our study, the incidence was determined as 6% for group 1, 32% for group 2, and 0% for group K. The mean incidence in patients was 12.6%. There is a significant relationship between fentanyl dose and the incidence and severity of the cough. We recommend reducing the amount of fentanyl used in induction to avoid cough in cases where local pressure increases may be problematic, such as intracranial or intraocular surgery.

### Ethics

**Ethics Committee Approval:** After the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital ethics committee, a prospective placebo-controlled randomized study was started (date: 07.07.2021 number: 223).

**Informed Consent:** An informed consent form was obtained from the patients participating in the study.

**Peer-review:** Internally and externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., A.S.Ş., Design: K.A., A.S.Ş., Data Collection or Processing: K.A., Analysis or Interpretation: K.A., A.S.Ş., Literature Search: K.A., A.S.Ş., Writing: K.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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