

Comparison of Two Dosages of Ketamine in Preventing Fentanyl-Induced Coughs in Children

Abstracts

Background: Fentanyl is a short-acting drug used to induce anesthesia. Here, we aimed to compare the two doses of ketamine to prevent fentanyl-induced cough in children under general anesthesia.

Materials and Methods: This is a randomized, clinical trial which was performed in 2019 in Imam Hossein Hospital in Isfahan, Iran. The study population consisted of children between 6 months and 2 years who were candidates for general anesthesia. Patients were randomized into three groups, each containing 31 patients. Groups 1 and 2 received 0.1 mg/kg and 0.2 mg/kg intravenous ketamine, respectively, 1 min before fentanyl injections. Group 3 received the same volumes of normal saline 0.9%. Patients were observed and evaluated for the incidence and intensity of coughs 1 min and 3 min after fentanyl injections. **Results:** We showed that the frequency of coughs 1 min after fentanyl injection was significantly lower in Group 2 compared to other groups ($P < 0.001$). Three min after fentanyl injection, the frequencies of coughs were significantly lower in Groups 1 and 2 compared to Group 3 ($P < 0.001$). We also showed that the intensity of coughs was significantly lower in Group 2 compared to other Groups 1 and 3 min after fentanyl injection ($P < 0.001$).

Conclusion: The administration of 0.2 mg/kg ketamine is more effective than 0.1 mg/kg dosage in the prevention of fentanyl-induced cough. We also showed that this method could bring more stable hemodynamics and oxygenation saturation inpatients. The comparison of the two dosages was a novel issue in the recent literature.

Keywords: Cough, fentanyl, ketamine

Introduction

Fentanyl is a powerful synthetic opioid that is similar to morphine but is 50–100 times more potent. Fentanyl is a short-acting drug used to induce anesthesia.^[1] In its prescription form, fentanyl is known by such names as Actiq®, Duragesic®, and Sublimaze.^[1,2] Due to the rapid onset of action and the short duration of action, this drug has become the most common drug used to induce anesthesia in children. Intravenous fentanyl is often used for anesthesia and to treat pain. To induce anesthesia, it is given with a sedative-hypnotic, like propofol or thiopental, and a muscle relaxant.^[3] To maintain anesthesia, inhaled anesthetics and additional fentanyl may be used. These are often given in 15–30 min intervals throughout the procedures such as endoscopy, surgeries, and in emergency rooms.^[4] Fentanyl's most common side effects, which affect more than 10%

of people, include diarrhea, nausea, constipation, dry mouth, somnolence, confusion, asthenia (weakness), and sweating. Less frequently, in 3%–10% of people, fentanyl can cause abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, hallucinations, anxiety, depression, flu-like symptoms, dyspepsia (indigestion), shortness of breath, hypoventilation, apnea, and urinary retention.^[5-7] Fentanyl use has also been associated with aphasia.^[8]

One of the side effects of fentanyl is cough which starts almost immediately after injection. This side effect causes the complications such as pneumothorax, increased intracranial pressure and increased eye pressure, ruptured abdominal aortic aneurysms, increased postoperative nausea and vomiting, and even increased airway irritability in children.^[9,10]

The prevalence of cough and its related problems have led to the use of different agents to prevent it. Various

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How to cite this article: Shafa A, Shahhosseini S, Rajaei E. Comparison of two dosages of ketamine in preventing fentanyl-induced coughs in children. *Adv Biomed Res* 2021;10:20.

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Received: 09 September 2020
Revised: 20 September 2020
Accepted: 12 October 2020
Published: 29 July 2021

Access this article online

Website: www.advbiores.net

DOI: 10.4103/abr.abr_218_20

Quick Response Code:



studies have been performed to investigate the ways to reduce cough after fentanyl injection, including the use of lidocaine, magnesium sulfate, dexmedetomidine, propofol, phenyramine maleate, and butorphanols.^[10-12] Lidocaine is a local anesthetic amide drug that also has antiarrhythmic effects. The mechanism of action is by inhibiting the onset and conduction of nerve impulses by reducing the permeability of the nerve cell membrane to sodium, and intravenous injection has a rapid onset of action (1–2 min).^[13] Various studies have been performed on the effectiveness of this drug in reducing cough caused by fentanyl.

Ketamine is a drug that weakens the central nervous system and blocks the transmission of pain messages to the limbic system by blocking glutamate receptors in the thalamic region of the brain. Its full mechanism of action is not well-understood. Ketamine has been found to increase dopaminergic neurotransmission in the brain, but instead of being due to dopamine reuptake inhibition, this may be through indirect/downstream mechanisms, namely through antagonism of the N-methyl-D-aspartate receptor. Studies have shown the reversible effects of ketamine on reducing fentanyl-induced cough.^[14,15]

Since no studies have been performed to compare the efficacy of different dosages of ketamine in reducing fentanyl-induced cough in the induction of general anesthesia in children, we decided to compare the two doses of 0.1 mg/kg and 0.2 mg/kg ketamine to prevent fentanyl-induced cough in children under general anesthesia in Imam Hossein Hospital in Isfahan.

Materials and Methods

This is a randomized clinical trial which was performed in 2019 in Imam Hossein hospital in Isfahan, Iran. The current study was approved by the Research committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1398.318 and Iranian Registry of Clinical Trials (IRCT) code: IRCT20191128045536N1).

The inclusion criteria included age between 6 months and 2 years, being a candidate for general anesthesia, having class 1 and 2 based on the American Society of Anesthesiologists classification and having written informed consent from parents. Patients with the following conditions did not enter the study: having upper respiratory tract infection in the past 2 weeks before surgery, having a history of reactive airway disease, having history of asthma or airway disorders, history of seizure, increased intracranial pressure, and possibility of problematic intubation. The exclusion criteria included intubation attempts more than once and duration of intubation procedure longer than 1 min.

Ninety-one patients entered the study and were randomized into three groups, each containing 31 patients using random

allocation. All patients were given a code based on their treatments groups and drugs, patients, physicians, medical assessors, and data analyzer were not aware of the injected drugs and treatment group. 0.1 mg/kg of midazolam was administered for all patients before interventions, and then, patients were transferred to the operation room. Group 1 received 0.1 mg/kg intravenous ketamine 1 min before fentanyl injections. Group 2 received 0.2 mg/kg intravenous ketamine 1 min before fentanyl injections and Group 3 received the same volumes of normal saline 0.9%. General anesthesia was performed by the injection of 2 µg/kg fentanyl, 0.5 mg/kg atracurium, and 2 mg/kg propofol. Patients were observed and evaluated for the incidence and intensity of coughs 1 min and 3 min after fentanyl injections.

Intensity of coughs was measured and classified based on its episodes: mild (1–2 times), moderate (3–4 times), and severe (5 and more times) as indicated by Guler and others.^[16] Furthermore, mean arterial pressure (MAP), heart rate, and oxygenation saturation levels were measured in all patients 1 min before drug injections, 1 min after drug injections, and 1 and 3 min after fentanyl injections. We also measured mean extubation time and recovery stay duration. All the data were gathered and analyzed using the SPSS software (version 24, IBM Corporation, Armonk, NY).

Results

The study population consisted of 93 children which were divided into three groups [Figure 1]. The primary analysis showed that there were no significant differences between all three groups regarding gender, age, and weight ($P > 0.05$). These data are summarized in Table 1.

We also showed that the frequency of coughs 1 min after fentanyl injection was significantly lower in Group 2 compared to Group 1. Same measurements showed that the frequency of coughs 1 min after fentanyl injection was significantly lower in Group 1 compared to Group 3 ($P < 0.001$). 3 min after fentanyl injection, the frequencies of coughs were significantly lower in Groups 1 and 2 compared to Group 3 ($P < 0.001$) [Table 2].

We also showed that the intensity of coughs was significantly lower in Group 2 compared to Group 1 in

Table 1: Analysis of primary demographic data among patients

Variable	Group 1	Group 2	Group 3	P
Age (month), mean±SD	16.5±6.9	16.6±6.5	17.1±7.2	0.92*
Weight (kg), mean±SD	9.7±2.6	10.1±2.6	10.4±2.9	0.62*
Gender, n (%)				
Male	22 (71)	23 (74.2)	20 (64.5)	0.70**
Female	9 (29)	8 (25.8)	11 (35.5)	

*P based on one-way analysis, **P based on Chi-square test. SD: Standard deviation

1 min after fentanyl injection and also Group 1 had lower intensity of coughs compared to Group 3 ($P < 0.001$). The analysis of coughs intensity 3 min after fentanyl injection showed the same results. These data are summarized in Table 3.

Furthermore, we showed that mean heart rate of patients was not significantly different in all Groups 1 min before ketamine injections and 1 min after ketamine injections ($P = 0.43$ and $P = 0.25$ respectively). We also showed a significant lower heart rate in Group 1 compared to Group 2 and 3 in 1 min and 3 min after fentanyl injection ($P < 0.05$). Analysis of MAP also

indicated no significant differences between Groups 1 min before ketamine injections and 1 min after ketamine injections ($P = 0.63$ and $P = 0.79$, respectively). One min after fentanyl injection and 3 min after fentanyl injection, the MAP of Group 3 was significantly higher than Groups 1 and 2 ($P < 0.05$). However, there were no significant differences between Groups 1 and 2 ($P > 0.05$). Measurements of oxygen saturation also indicated no significant differences between all groups 1 min before and after ketamine injections ($P > 0.05$), but 1 min and 3 min after fentanyl injection, oxygen saturation levels were significantly lower in Group 3 compared to

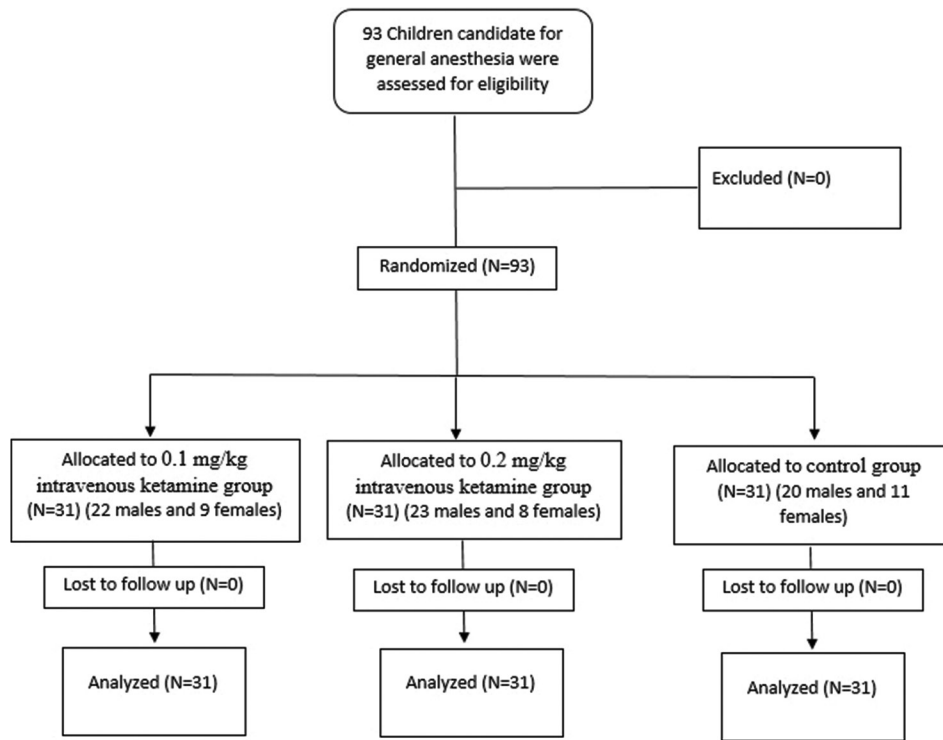


Figure 1: CONSORT flow diagram of the study

Table 2: Comparison of frequencies of coughs in patients

Time	Group 1, n (%)	Group 2, n (%)	Group 3, n (%)	P
1 min after fentanyl injection	17 (54.8)	7 (22.6)	31 (100)	<0.001
3 min after fentanyl injection	3 (9.7)	1 (3.2)	23 (74.2)	<0.001

Table 3: Comparison of coughs intensity among patients

Time	Intensity	Group 1, n (%)	Group 2, n (%)	Group 3, n (%)	P
1 min after fentanyl injection time	No coughs	14 (45.2)	24 (74.4)	0 (0)	<0.001
	Mild	7 (22.6)	7 (22.6)	0 (0)	
	Moderate	10 (32.3)	0 (0)	27 (87.1)	
	Severe	0 (0)	0 (0)	4 (12.9)	
1 min after fentanyl injection	No coughs	28 (90.3)	30 (96.8)	8 (25.8)	<0.001
	Mild	1 (3.2)	1 (3.2)	13 (41.9)	
	Moderate	2 (6.5)	0 (0)	10 (32.3)	
	Severe	0 (0)	0 (0)	0 (0)	

Groups 1 and 2 ($P < 0.05$). These data are summarized in Table 4.

Analysis of mean extubation time and recovery stay duration also showed that the mean extubation time was significantly higher in Group 2 compared to other groups ($P < 0.001$). We also showed that mean recovery stay was significantly lower in Group 1 compared to other groups ($P < 0.001$) [Table 5].

Discussion

Here, in this study, we evaluated 93 children which were divided into three groups of 0.1 mg/kg intravenous ketamine, 0.2 mg/kg intravenous ketamine, and normal saline 0.9%. Our data showed that the frequency of coughs was significantly lower in 0.2 mg/kg intravenous ketamine group compared to others. Furthermore, the frequency of coughs was significantly lower in 0.1 mg/kg intravenous ketamine group compared to Group 3. 3 min after fentanyl injection, the frequencies of coughs were significantly lower in both ketamine groups compared to normal saline group. Our data also showed that the intensity of coughs was significantly lower in 0.2 mg/kg intravenous ketamine group compared to Group 1 in 1 and 3 min after fentanyl injection. We also reported a significant lower heart rate in 0.1 mg/kg intravenous ketamine group compared to other groups in 1 min and 3 min after fentanyl injections. One min and 3 min after fentanyl injection, oxygen saturation levels were significantly lower in the saline group compared to ketamine groups.

There have been some previous studies on the role of ketamine injection for preventing cough after fentanyl

injections. In a study by Yeh *et al.*, in 2007, they showed that 0.15 mg/kg intravenous ketamine could prevent fentanyl-induced cough in adults. They also declared that this agent cause delayed onset time of coughs.^[17] Saleh and other also evaluated 400 adults and showed that 0.15 mg/kg intravenous ketamine is an effective method to reduce fentanyl-induced cough, especially if injected with dexmedetomidine.^[18] Very few studies have evaluated the role of ketamine in preventing the fentanyl-induced coughs in children. Singh and others have indicated that the combination of fentanyl (2 µg/kg) and propofol (3.5 mg/kg) provides better conditions for administering the laryngeal mask airway compared to ketamine injections, but they also declared that fentanyl-induced coughs could cause serious complications in some cases.^[19] In the present study, we showed that both doses of intravenous ketamine (0.2 mg/kg and 0.1 mg/kg) are effective in reducing the frequency and intensity of coughs compared to placebo. We also showed that 0.2 mg/kg dose shows better prevention results.

Ghatak *et al.* evaluated the effects of addition of ketamine, fentanyl, and saline with propofol induction on hemodynamics and laryngeal mask airway insertion conditions and showed that adding 0.5 mg/kg ketamine could stabilize the hemodynamics of children.^[20] These results are also in line with the findings of our study. We showed that the oxygen saturation levels were significantly lower in the saline group compared to ketamine groups. Godambe and other also declared that the injection of ketamine associated with midazolam provides a better sedation in patients requiring brief orthopedic procedures^[21] which emphasizes on the sedative effects of this agent.

Table 4: Comparison of heart rate, mean arterial pressure, and oxygen saturation in patients

Variable	Intensity	Group 1 mean±SD	Group 2 mean±SD	Group 3 mean±SD	P
Heart rate	1 min before ketamine	142.5±18.1	146.9±12.5	146.5±12.6	0.43
	1 min after ketamine	148.8±17.3	154.8±11.8	150.9±12.4	0.25
	1 min after fentanyl	146.4±16.9	152.7±10.5	158.3±11.9	0.003
	3 min after fentanyl	141.3±17.9	148.3±10.3	155.5±11.2	<0.001
MAP	1 min before ketamine	68.2±7.5	67.3±4.7	68.8±5.7	0.63
	1 min after ketamine	70.6±8.4	71.2±4.5	70.1±6.4	0.79
	1 min after fentanyl	69.5±8.1	70.2±5.1	73.1±6.6	0.045
	3 min after fentanyl	66.6±8.4	67.2±5.3	72.1±8.6	0.008
Oxygen saturation	1 min before ketamine	98.4±0.6	98.3±0.4	98.3±0.5	0.64
	1 min after ketamine	98.3±0.7	98.6±0.5	98.4±0.5	0.16
	1 min after fentanyl	98.1±0.7	98.5±0.6	96.7±1.9	<0.001
	3 min after fentanyl	98.9±0.3	98.9±0.3	97.3±1.7	<0.001

MAP: Mean arterial pressure, SD: Standard deviation

Table 5: Comparison of mean extubation time and recovery stay duration inpatients

Variable	Mean±SD			P
	Group 1	Group 2	Group 3	
Mean extubation time (min)	7.9±2.8	14.6±3.9	6.7±3.5	001/0>
Recovery stay duration (min)	46.5±6.4	55±7.6	47.3±7.3	001/0>

SD: Standard deviation

Some other previous studies have indicated that ketamine injections could help to prevent coughing especially in children.^[22,23] Ozturk *et al.* also showed that ketamine is useful agent in inducing sedation and also preventing coughs in children undergoing flexible bronchoscopy,^[24] but so far, no previous data have compared different dosages of ketamine. A key point of the current study was that we measured both frequency and intensity of coughs in children along with hemodynamic characteristics and declared that injection of 0.2 mg/kg ketamine is more effective than 0.1 mg/kg dosages and also than placebo. We believe that anesthesiologists should pay more attention in injection of ketamine with the dosage of 0.2 mg/kg to prevent coughs in children and stabilizing hemodynamics, especially during special conditions such as neurosurgeries or bronchoscopy.

Conclusion

Here, we indicated that administration of 0.2 mg/kg ketamine is more effective than 0.1 mg/kg dosage in the prevention of fentanyl-induced cough. We also showed that this method could bring more stable hemodynamics and oxygenation saturation inpatients. These results were in line with the findings of previous studies, but the comparison of the two dosages was a novel issue in the recent literature. One of the limitations of our study was the lack of proper patient's co-operation and prevention of coughs in children. We suggest that anesthesiologists should pay more attention to the potentials of ketamine in the medical practice.

Financial support and sponsorship

This study was financially granted by the Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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