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Research Article

Effect of Different Doses of Ketamine on Fentanyl-Induced Cough

Azim Honarmand[1], Mohammadreza Safavi[1], Nasim Cheshmaviz[2]*

[1]Department of Anesthesiology and Critical Care, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

[2]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

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ABSTRACT

Background: Reflex cough is a common complication after fentanyl injection during anesthesia. Several studies have tried different medications to control fentanyl-induced cough (FIC).
Aim: Our study evaluated the effect of different ketamine dosage on preventing fentanyl induced cough.
Methods: We randomly assigned 80 participants into four groups. Group 1 was administered 0.15 mg/kg, Group 2 received 0.2 mg/kg, Group 3 was given 0.25 mg/kg of intravenous ketamine one minute prior to fentanyl injections, while Group 4 received an equivalent volume of 0.9% normal saline.
Results: The incidence and severity of cough was evaluated by FIC score. The incident of cough was significantly lower in Groups 3, 2 and 1 in comparison to Group 4 (0, 5, 30 respectively vs 85, $p<0.001$). The cough severity was significantly lower in Groups 3, 2 and 1 in comparison to Group 4 ($p<0.001$).
Conclusion: Intravenous ketamine 0.25 mg/kg, significantly decreased the severity and frequency of cough compared with 0.20 and 0.15 mg/kg IV ketamine.

Introduction

Fentanyl is frequently utilized as a preinduction adjunct in anesthesia due to its rapid onset, potent analgesic effects, short action duration, cardiovascular stability, and minimal histamine release. Nonetheless, the administration of an intravenous (IV) bolus of fentanyl often leads to reflex coughing. Reports indicate that the occurrence of fentanyl-induced cough (FIC) can be as high as 65% [1-2]. Although this cough is usually temporary and resolves on its own in the majority of patients, it can sometimes be persistent and troublesome. It is crucial to prevent FIC in patients with certain preexisting conditions, such as open eye injuries, elevated intracranial pressure, pneumothorax, dissecting aortic aneurysms, or reactive airway disease. FIC may be more intense or occur more frequently in patients with certain coexisting conditions [3-5]. Ketamine suppresses the central nervous system and the transmission of pain signals toward the limbic system by the blockage of glutamate receptors in the thalamus. The complete mechanism of action of Ketamine remains unclear. Research has indicated that ketamine enhances dopaminergic neurotransmission in the brain; however, this effect may not be due to the inhibition of dopamine reuptake but rather through indirect or downstream mechanisms, specifically by antagonizing the N-methyl-D-aspartate (NMDA) receptor. Ketamine can reversibly reduce FIC [6-7]. In the previous study IV ketamine at 0.15 mg/kg decreased the FIC in adult from 21.6 in placebo group to 7.2 in case group [8]. According to our investigation there was no study to evaluate effect of two other higher ketamine dosage, 0.20 and 0.25 mg/kg to prevent FIC. So, the current study was designed to answer this question.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: nasimcheshmaviz6975@gmail.com

Methods

Study design

This randomized clinical trial was done in Al-Zahra hospital, Isfahan, Iran in 2022 and approved by the Ethics committee of Isfahan University of Medical Sciences (Ethics code: IR.MUI.MED.REC.1401.079 and Iranian Registry of Clinical Trials (IRCT) (IRCT20200825048515N55).

Inclusion and exclusion criteria

The inclusion criteria included those classified as class I or II based on the American Society of Anesthesiologists (ASA), aged 18 to 65 years being candidates for general anesthesia, and providing written informed consent. Those with a history of asthma reactive airway disease, or other airway disorders, an upper respiratory tract infection within the two weeks prior to surgery, high intracranial pressure, a history of hypertension, diabetes, cardiovascular complications, tachycardia, kidney or liver failure, or any potential issues with intubation were excluded. The exclusion criteria were any change in the method of anesthetics and if laryngoscopy time was exceeded than 15 seconds.

Study population

Eighty patients participated in the study and were randomly alloctaed to four groups (n=20), using random allocation software [9]. Each patient received a code corresponding to their treatment groups and medications. The medical assessors, patients, data analysts and physicians were blinded to the drugs and treatment groups.

Study protocol

General anesthesia was induced with an injection of sodium thiopental (5 mg/kg), atracurium (0.6 mg/kg), and fentanyl (4 µg/kg). Group 1 was treated with 0.15 mg/kg of IV ketamine 1 minute prior to fentanyl administration; Group 2 was treated with 0.2 mg/kg of IV ketamine ketamine 1 minute prior to fentanyl; Group 3 received 0.25 mg/kg of IV ketamine 1 minute prior to fentanyl; and Group 4 was treated with an equivalent volume of 0.9% normal saline. Patients were monitored and assessed for the occurrence and severity of coughs at 1 minute and 3 minutes following fentanyl injections. The severity of coughs was assessed and categorized according to the frequency of episodes: grade 0 (no cough), mild (1 to 2 episodes), moderate (3 to 4 episodes), and severe (≥5 episodes), as described by Guler and colleagues [1]. Additionally, mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and oxygen saturation levels were recorded for all patients at rest (prior to the administration of the anesthetic) and every 3 minutes for up to 10 minutes following laryngoscopy and tracheal intubation. We also timed the duration of cough using a chronometer, noted the mean extubation time (the interval from stopping the anesthetic to extubation), and recorded the duration of recovery based on the Modified Aldrete Score [10]. All data were analyzed using SPSS 24 at a significance level of <0.05. The quantitative data were assessed using the ANOVA statistical test, while the qualitative data were evaluated with the Chi-square test.

Results

The followed diagram of enrolled patients is shown in (Figure 1). The groups showed no significant difference in age, gender, and weight ($P > 0.05$) (Table 1). The incident of cough was significantly lower in Groups 3, 2 and 1 in comparison to Group 4 (0, 5, 30 respectively vs 85, $P < 0.001$). Same measurements showed that the incident of cough was significantly lower in Group 1 in comparison to Group 3 ($P=0.008$) and Group 2 in comparison to Group 1 ($P=0.037$), but the incident of cough between Group 2 and Group 3 didn't show any significant difference ($P=0.311$) (Table 2). The cough severity was significantly lower in Groups 3, 2 and 1 in comparison to Group 5 ($P<0.001$). The cough severity was significantly lower in Group 1 in comparison to Group 3 ($P < 0.001$) but the difference between Group 1 vs group 2 ($P=0.102$) and Group 2 vs Group 3 ($P=0.311$) wasn't significant (Table 3). That was no significant different between the groups in SBP, DMP, MAP and SPO2 ($P>0.05$) (Table 4). The heart rate changes at 9 and 12 after tracheal intubation was significantly higher in Group 1 and 2 and 3 vs Group 4 ($P<0.05$). The groups showed no significant difference in tachycardia, bradycardia and hypotension ($P>0.05$) (Table 5).

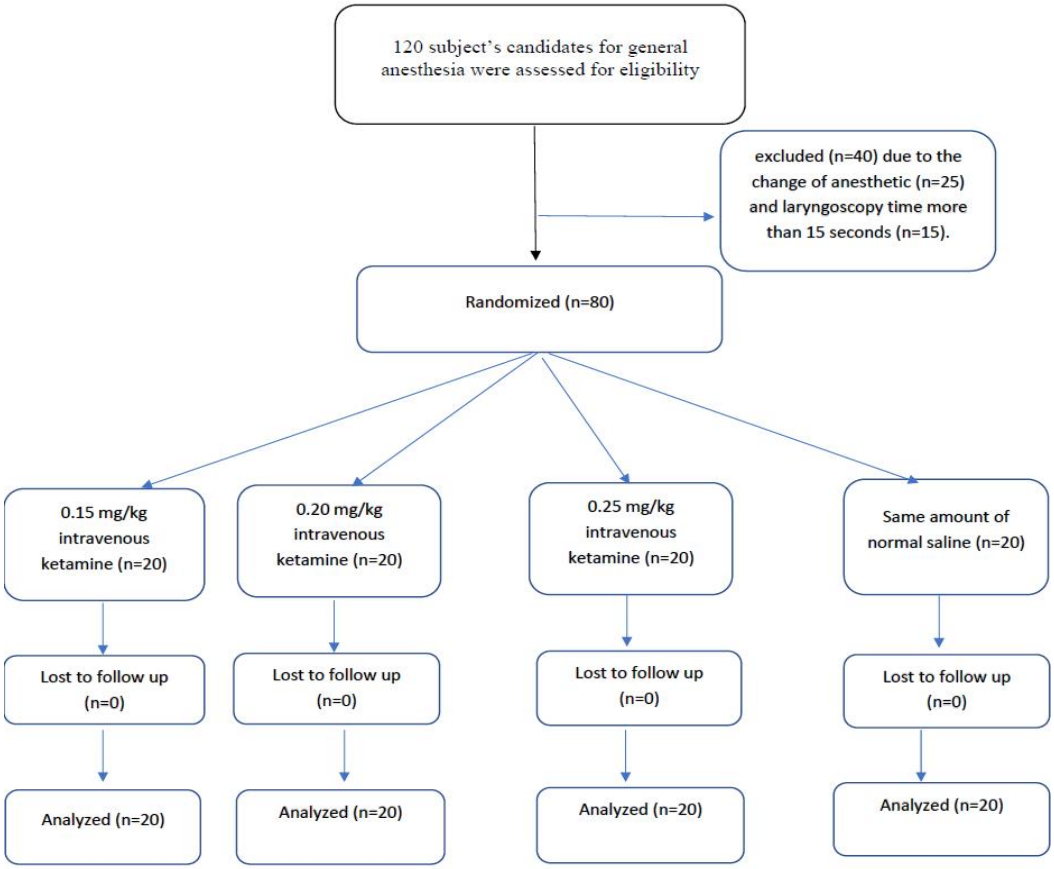

Figure 1- Study protocol

Table 1- Analysis of primary demographic data among patients

Variable	Total n=80	Group 4 n=20	Group 1 n=20	Group 2 n=20	Group 3 n=20	P value
Age						
mean ± SD	44.23±14.77	50.05±12.48	46.90±13.07	41.55±14.66	38.45±16.74	0.058
median	42.5	50.5	45.0	40.0	31.5	
range	18-65	25-65	20-65	18-63	18-64	
Sex						
Female N (%)	42 (52.5%)	12 (60%)	10 (50.0%)	10 (50.0%)	10 (50%)	0.898
Weight						
mean ± SD	69.76±9.63	70.0±9.10	72.80±8.78	69.20±11.41	67.05±8.82	0.262

Table 2- Analysis of cough severity and cough time

Variable	Total n=80	Group 4 n=20	Group 1 n=20	Group 2 n=20	Group 3 n=20	P value
Cough n (%)						
Yes	56 (70.0%)	17 (85.0%)	6 (30.0%)	1 (5.0%)	0	<0.001
no	24 (30.0%)	3 (15.0%)	14 (70.0%)	19 (95.0%)	20 (100%)	
Cough severity n(%)						
None	56 (70.0%)	3 (15.0%)	14 (70.0%)	19 (95.0%)	20 (100%)	<0.001
Mild	16 (20.0%)	11 (55%)	4 (20.0%)	1 (5.0%)	0	
Moderate	6 (7.5%)	4 (20.0%)	2 (10.0%)	0	0	
severe	2 (2.5%)	2 (10.0%)	0	0	0	
Cough time						
mean ± SD	23.33±3.80	23.53±4.24	22.50±2.73	25.00	0	0.766

Table 3- Analysis of cough time, extubation time and recovery time.

Variable	Total n=80	Group 4 n=20	Group 1 n=20	Group 2 n=20	Group 3 n=20	P value
Cough time mean ± SD	23.33±3.80	23.53±4.24	22.50±2.73	25.00	0	0.766
Extubation time mean ± SD	28.25±6.11	29.50±7.93	29.00±5.28	27.50±5.73	27.00±5.23	0.544
Recovery time mean ± SD	61.63±11.98	67.50±14.18	61.50±11.01	59.00±11.53	58.50±9.33	0.068
Hallucination n (%)						0.567
Yes	2 (2.5%)	20 (100%)	1 (5.0%)	0	1 (5.0%)	
No	78 (97.5%)	0	19 (95.0%)	20 (100%)	19 (95.0%)	

Table 4- Analysis of heart rate.

Variable	Total n=80	Group 4 n=20	Group 1 n=20	Group 2 n=20	Group 3 n=20	P value
Heart rate						
0	83.69±14.49	80.45±13.27	83.55±15.81	85.85±13.69	84.90±15.55	0.505
3	85.30±14.03	80.75±13.37	85.45±15.09	86.60±12.30	88.40±15.07	0.290
6	90.78±16.53	84.15±14.56	88.10±19.09	93.35±12.18	97.50±17.41	0.068
9	85.79±15.01	79.35±10.17	82.60±17.21	87.55±11.93	93.65±16.51	0.017
12	83.61±14.73	78.50±10.66	80.40±17.93	82.60±11.52	92.95±14.24	0.003
15	82.01±14.12	78.75±10.62	79.10±16.29	81.45±14.15	88.75±13.52	0.052

Table 5- Analysis of O2 saturation, tachycardia, bradycardia, hypertension and hypotension

Variable	Total n=80	Group 4 n=20	Group 1 n=20	Group 2 n=20	Group 3 n=20	P value
O2 saturation						
0	97.68±1.79	97.15±2.05	97.10±1.88	98.55±1.31	97.70±1.55	0.047
3	98.20±1.72	97.80±2.21	97.80±1.90	98.70±1.17	98.50±1.31	0.534
6	98.99±1.11	98.80±1.39	98.55±1.27	99.40±0.75	99.20±0.76	0.124
9	99.19±0.94	99.15±0.98	98.95±1.05	99.35±0.81	99.30±0.92	0.543
12	99.35±0.99	99.30±0.86	99.15±1.34	99.45±0.94	99.50±0.76	0.806
15	99.25±0.98	99.20±0.95	99.15±1.13	99.30±1.03	99.35±0.87	0.888
Tachycardia	21 (26.25%)	3 (15.0%)	4 (20.0%)	5 (25.0%)	9 (45.0%)	0.152
Bradycardia	7 (8.75%)	1 (5.0%)	4 (20.0%)	1 (5.0%)	1 (5.0%)	0.243
Hypertension	27 (33.75%)	11 (55.0%)	7 (35.0%)	6 (30.0%)	3 (15.0%)	0.065
Hypotension	1 (1.25%)	0	0	0	1 (5.0%)	0.392

Discussion

Fentanyl and its derivatives, including sufentanil, alfentanil, and more recently remifentanil, are the most commonly utilized opioids in clinical anesthesia. These synthetic, highly potent opioids, which are derived from phenylpiperidine, are primarily used for their analgesic properties, particularly before the induction of anesthesia [11]. Like other opioids, fentanyl is associated with several side effects, such as nausea, constipation, dry mouth, drowsiness, weakness, hypoventilation, and apnea. An additional significant side effect is cough induced by fentanyl. Administering a bolus of fentanyl during the induction of anesthesia can trigger coughing to varying extents Coughing has also been reported following the bolus administration of alfentanil, sufentanil, and remifentanil during the induction of anesthesia. For most patients, this side effect is usually transient, benign, and self-limiting; however, it can occasionally be spasmodic, explosive, and potentially life-threatening [12-15]. Several studies have explored ways to decrease the occurrence of cough induced by fentanyl by using commonly available anesthetic adjuncts, such as lidocaine, propofol, atropine, ephedrine, and midazolam, with varying degrees of success. Some research has indicated that excitatory amino acids and NMDA receptor antagonists, such as ketamine, may help modulate the cough reflex [8].

We assessed 80 participants who were categorized into four groups: one receiving 0.15 mg/kg IV ketamine, another receiving 0.2 mg/kg IV ketamine, a third

receiving 0.25 mg/kg IV ketamine, and a control group receiving 0.9% normal saline. Our findings indicated that the incidence of coughs was significantly reduced in all ketamine groups than in Group 4. Additionally, the incidence of coughs in Group 3 was significantly lower in comparison to Group 1. We also found that the severity of coughs was notably less in all groups when compared to Group 4. Several studies have explored the impact of ketamine on cough induced by fentanyl.

Various efforts have been made to decrease the occurrence of cough during the induction of anesthesia, with mixed results. Agarwal et al. assessed 200 patients classified as ASA status I and II, aged 18 - 60 years, and reported a 28% incidence of cough after fentanyl (2 µg/kg IV) administration to the controls. Administering aerosol inhalations of sodium chromoglycate (4%), beclomethasone (0%), or salbutamol (which resulted in a 6% cough incidence), 15 minutes before the operating room enterance was linked to a lower incidence of cough [16]. Additionally, according to Horng et al., pretreating patients with IV clonidine (2 µg/kg, 2 minutes prior to the IV fentanyl bolus injection) effectively prevented the cough reflex caused by fentanyl in ASA I and II 18 – 80-year old patients, although they also noted some hemodynamic changes [17]. In another study in 2010, Guler et al. compared the effect of 0.5 mg/kg ketamine and 0.1 mg/kg lidocaine on FIC and concluded that cough incidence and intensity were significantly lower in the ketamine group in comparison to the lidocaine group [1]. Nazemroaya et al. reported that anesthesia induced by ketamine during general anesthesia increased blood pressure and, heart rate, but due to lower medical complication Such as cough, headache, laryngospasm, myalgia and nausea finally, it is a more appropriate choice than sodium thiopental [18]. The most important limitation of our study can be relatively small sample size which we recommend future studies with larger samples and other drugs investigate the management of FIC.

Conclusion

Our study showed that administration of 0.25 mg/kg ketamine is an effective dosage in the prevention of fentanyl induced cough. We believe that this method is an effective way to prevent fentanyl-induced cough and anesthesiologists should consider this method in daily practice.

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