Academic Journal of Medical Sciences
ISSN: 2708-2725
ORIGINAL ARTICLE

Intravenous Low Dose Ketamine versus Lidocaine versus Placebo in Suppressing Fentanyl Induced Cough: A Comparative Study

Rozh M. Abdulrahman[1*], Amir M. K. Boujan[2], Rekout F. Mohammed[3], Wehid I. Seniar[4]

Authors' Information
1.MBChB, Trainee at Kurdistan Board of Medical Specialities -Erbil city-Kurdistan region-Iraq.
2 .MBChB, F.I.C.M.S; Consultant Anesthesiologist, College of Medicine, University of Sulaimani, Iraq.
3. MBChB, F.I.C.M.S; Senior Anesthesiologist, Erbil, Iraq
4. MBChB, CABA & IC; Senior Anesthesiologist, Erbil, Iraq.

****Corresponding author:***
Rozh M. Abdulrahman
rozhmuzafar@gmail.com

Funding information
Self-funded

Conflict of interest
None declared by authors

***Received** : August, 2022*
***Published**: October, 2022*
***DOI:**10.5281/zenodo.7683113*

Abstract

***Background**: Fentanyl is a preferred narcotic in anesthesia, especially with respect to a pre-induction adjunct agent. It elicit a brief cough in up to 50% of patients when the drug is injected by intravenous bolus which in turn could increase intracranial pressure and intraocular pressure and also could increase heart rate and blood pressure in susceptible patient.*
***Aim**: We designed this study to compare effectiveness of low dose ketamine and lidocaine in the prevention of fentanyl-induced cough.*
***Material and Methods**: This prospective double blinded, randomized placebo, control study, was conducted in Erbil public and private general Hospitals. We selected 150 patients, age 18-60 years, who underwent elective operation under general anesthesia; 50 cases of them received ketamine, 50 cases received lidocaine 50 cases received normal saline. Any episodes of cough were classified as coughing and was observed for one minute after fentanyl administration by a blinded observer. Blood pressure, heart rate, and pulse oximetry oxygen saturation (Spo2) were recorded before giving ketamine or lidocaine or 0.9% saline and 1 minute after fentanyl injections.*
***Results**: in this study, 25.3% of the whole sample developed cough after fentanyl injection. However, 42% in the control group developed cough, compared with 26% of patients in the Lidocaine group, and 8% in the Ketamine group ($p < 0.001$).*
***Conclusion**: Low dose ketamine can effectively suppress fentanyl induced cough and it is a better drug compared to lidocaine.*

Keywords**: **Fentanyl induced cough, Ketamine, Lidocaine, cough suppression.

1. INTRODUCTION

Fentanyl as a selective μ-opioid receptor agonist is the preferred narcotic in anesthesia, especially with respect to a pre-induction adjunct agent. Major preferences of this drug include; rapid onset, the brief duration of action, cardiovascular stability, and low histamine release. The antitussive actions of opioids are well known and central in origin. Opioids blunt or eliminate somatic and autonomic responses to tracheal intubation. They allow patients to tolerate endotracheal tube placement without coughing or "bucking." (1) Conversely, fentanyl, sufentanil, and alfentanil curiously elicit a brief cough in up to 50% of patients when the drug is injected by intravenous bolus. Fentanyl, administered through a peripheral intravenous cannula, provoked cough when it was injected rapidly (2).

Jong-In Han et al. demonstrated that fentanyl-induced cough has a higher frequency in infants and children (3). Oshima and colleagues suggested that young age is one of the important contributing factors for the occurrence of fentanyl-induced cough(4).

Fentanyl-induced cough is usually a benign and self-limiting phenomenon, but rarely, it can be accompanied with some adverse effects such as; rising intraocular, intracranial, and intra-abdominal pressures, which may require prompt treatment (5). Li and associates reported that nonsmoking women undergoing gynecological surgery who develop fentanyl-induced cough during induction of anesthesia have a higher incidence of postoperative nausea and vomiting (PONV)(6).

The incidence of cough decreased significantly as the injection time was increased (7), as well as by the administration of 1.5 mg/ kg lidocaine 1 minute before fentanyl administration (8). A meta-analysis showed that the lowest effective dose of lidocaine on the risk of opioid-induced cough was 0.5 mg/kg (9).8 It was also reported that preemptive use of fentanyl 25 μg, administered 1 minute before bolus injection of fentanyl (125 or 150 μg), can effectively suppress fentanyl-induced cough (10).9 Propofol, α2 agonists (clonidine, dexmedetomidine), inhalation of β2 agonists (terbutaline, salbutamol), were also effective for suppression of fentanyl-induced cough (11). A prospective randomized controlled study demonstrated that a huffing maneuver, consisting of a forced expiration against open glottis, just before

intravenous fentanyl administration significantly reduced the incidence and severity of fentanyl-induced coughing in the majority of the patients (12).

Since ketamine as a pretreatment for prevention of fentanyl induced cough is less compared to control and lidocaine (which used routinely by anesthetist to decrease pain of injection of propofol) we designed this study to compare effectiveness of low dose ketamine with lidocaine for prevention of fentanyl-induced cough to control.

2. METHODOLOGY

This prospective double blinded, randomized placebo, control study was conducted in Erbil Teaching public and Serdam private general Hospitals from 15th of July to the 15th of September 2022. We selected the sample of study of all patients who had been referred to the hospital for elective operation under general anesthesia. Sample size for this study was 150 patients divided into three equal groups with 50 cases in each, namely, ketamine , lidocaine and placebo groups.

Inclusion criteria:

1. Adult patients aged 18-60 years of both genders
2. Comparable with American Society of Anesthesiologists physical status (ASA) I or II.
3. Candidates for elective surgery under general anesthesia.

Exclusion criteria:

Patients patients with history of COPD, asthma and recent upper respiratory tract infection, emergency operations and obstetric case and any medical history of allergy to local anesthetics.

Interventions and measurements:

patients randomly assigned to receive either intravenous 0.15 mg/kg of ketamine or 1.0 mg/kg of lidocaine over 5 seconds, one minute before administration of 3µg/kg fentanyl injected over 5 seconds. After fentanyl injection we observed the patient for any episodes of cough for one minute and then anesthesia induction started with intravenous anesthetics and muscle relaxant. The control group, who received Normal Saline, were compared with two invention arms to determine the study outcomes. A trained nurse who was blinded to

patients' allocation prepared the syringes containing lidocaine, fentanyl, and normal saline just before induction of general anesthesia.

Any episodes of cough were classified as coughing and was observed for one minute after fentanyl administration by a blinded observer. Blood pressure, heart rate, and pulse oximetry oxygen saturation (Spo2) were recorded before giving ketamine or lidocaine or 0.9% saline and 1 minute after fentanyl injections.

The primary outcome was defined as the cough incidence in each group. Hemodynamic change (blood pressure and heart rate) in patients who developed cough were secondary outcomes in our study.

Demographic and clinical data of the patients were expressed as means ± SD and/ or frequencies and percentage. Scale variables were tested for statistical normal distribution by Shapiro-Wilk test. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions of two or more groups. Mann-Whitney test was used to compare the mean ranks of two groups. Kruskal-Wallis test was used to compare the mean ranks of three groups. A p value of ≤ 0.05 was considered as statistically significant.

3. RESULTS

The total number of the studied sample was 150 patients. One third of them (50) didn't take anything, 50 patients took Lidocaine, and 50 took Ketamine. Around half (40%) of the sample were aged less than 30 years, and 28% were aged 30-39 years. No significant difference in the age distribution of the three groups ($p = 0.202$), 57.3% of the patients were females, but the difference was not significant between the groups ($p = 0.647$) (Table 1).

Cough was developed 25.3% of the total patients. Only 8% of the patients in the Ketamine group developed cough, compared with 26% of patients in the Lidocaine group, and 42% of the control ($p < 0.001$), (Table 2). The post-operative readings of HR, SBP, and DBP were subtracted from the pre-operative readings. The mean difference between the mentioned readings was compared across the three groups and no significant differences was found between the three groups regarding the difference in HR ($p = 0.073$), SBP ($p = 0.419$), and DBP ($p = 0.076$). (Table 3).

In the control group, in general, there was an increase in the HR after the operation among patients who developed cough (mean of difference was -4.19) compared with 8.17 among patients with no cough ($p < 0.001$). The decrease in SBP and DBP after the operation was significantly higher among patients with no cough than among patients with cough ($p = 0.001$ and $p < 0.001$ respectively). In the Lidocaine group, the decrease in HR, SBP and DBP were significantly higher among patients with no cough than among patients with cough. The same pattern can be observed in the Ketamine group, but the differences were not significant (Table 4).

Table 1. Age and gender distribution of the study groups.

	Control No. (%)	Lidocaine No. (%)	Ketamine No. (%)	Total No. (%)	P*
Age					
< 30	21 (42.0)	15 (30.0)	24 (48.0)	60 (40.0)	
30-39	13 (26.0)	20 (40.0)	9 (18.0)	42 (28.0)	0.202
40-49	6 (12.0)	6 (12.0)	10 (20.0)	22 (14.7)	
≥ 50	10 (20.0)	9 (18.0)	7 (14.0)	26 (17.30	
Gender					
Male	24 (48.0)	20 (40.0)	20 (40.0)	64 (42.7)	0.647
Female	26 (52.0)	30 (60.0)	30 (60.0)	86 (57.3)	
Total	50 (100.0)	50 (100.0)	50 (100.0)	150 (100.0)	

* Comparison by by Chi square test.

Table 2. Incidence of cough by group.

	Cough No. (%)	No cough No. (%)	Total No. (%)	P*
Control	21 (42.0)	29 (58.0)	50 (100.0)	
Lidocaine	13 (26.0)	37 (74.0)	50 (100.0)	< 0.001
Ketamine	4 (8.0)	46 (92.0)	50 (100.0)	
Total	38 (25.3)	112 (74.7)	150 (100.0)	

*Comparison by Chi square test.

Table 3. Comparing of the means of difference between the pre and post-operative parameters between the study groups.

	Group	Mean	SD	Mean rank	P*
Difference HR Before-After	Control	2.98	13.31	78.7	0.073
	Lidocaine	4.22	4.89	83.4	
	Ketamine	1.80	4.48	64.3	
	Total	3.00	8.59		
Difference SBP Before-After	Control	9.84	16.49	69.9	0.419
	Lidocaine	14.16	15.77	81.4	
	Ketamine	10.40	10.90	75.1	
	Total	11.47	14.63		
Difference DBP Before-After	Control	5.94	10.39	67.2	0.076
	Lidocaine	8.42	7.18	86.4	
	Ketamine	5.90	5.44	72.8	
	Total	6.75	7.98		

SD: standard deviation, * Kruskal-Wallis test used in comparisons.

Table 4. Comparing the means of difference between the pre and post-operative parameters between those with cough and no cough in each of the study groups.

	Cough			No cough			P*
Difference (pre-post)	Mean	SD	Mean rank	Mean	SD	Mean rank	
Control							
HR	-4.19	14.02	16.7	8.17	10.17	31.8	< 0.001
SBP	1.05	11.63	17.5	16.21	16.7	31.2	0.001
DBP	0.57	8.12	16.9	9.83	10.23	31.6	< 0.001
Lidocaine							
HR	1	5.39	16	5.35	4.22	28.8	0.006
SBP	5.31	13.47	14.5	17.27	15.48	29.3	0.002
DBP	3.62	6.19	15	10.11	6.8	29.1	0.003
Ketamine							
HR	-0.75	2.5	15.8	2.02	4.56	26.3	0.175
SBP	3.75	4.57	14.7	10.98	11.12	26.4	0.132
DBP	2.25	4.19	15.3	6.22	5.46	26.3	0.153

SD: standard deviation * Mann Whitney test used in comparison

4. DISCUSSION

Fentanyl and its derivatives are used as a part of opioid analgesics in the induction and maintenance of general anaesthesia. Intravenous bolus injection of fentanyl and its derivatives often cause cough. Our aim for this study was to assess effectiveness of pretreatment with either lidocaine or low dose ketamine to decrease the rate of fentanyl induced cough.

At first our study showed that 3µg/kg of fentanyl induced cough in 42% of patients in placebo group which was lower than previous reports by Lin JA et al.(2) where incidence was 50% and Lin CS et al. (13) where it was 65% and Dehghanpisheh et al. (14) which was 75% which could be due to wider range of age and heterogenicity and exclusion criteria in this study.

Based on our data in this study, incidence of cough in patients who received 1mg/kg lidocaine as pretreatment was 26% which was almost the same compared to studies by Gecaj-Gashi et al (15). who reported a prevalence of 22% and Chandra et al (16) who reported a prevalence of 20% with 1mg/kg of lidocaine. Other studies who use higher dose of lidocaine(2mg/kg) reported higher prevalence of cough like Schlimp CJ et al. (17) and Dehghanpisheh et al. (14) who reported prevalence of more than 40%. Patients who received low dose ketamine as pretreatment, prevalence of cough was 8% which is almost the same of study by Yeh CC (18) who reports 7% prevalence of cough with 0.15mg/kg of ketamine. Regarding the secondary outcome in our study which was hemodynamic change in patients who developed cough, according to our data we can see that patient who developed cough after fentanyl injection has higher heart rate and blood pressure compared to patient who had no cough which indicate that in patient who have cardiovascular compromise this cough could cause adverse effects. However, we couldn't find studies who compare hemodynamic change in fentanyl induced cough and further study in this regard justified. Although various mechanisms responsible for opioid-induced cough have been postulated, the exact mechanism is still unclear. Opioid could inhibit central sympathetic outflow, therefore activating the vagus nerve. This enhancement of vagal activity was reported as a possible cause of cough and reflex bronchoconstriction. Other possible mechanisms postulated as the cause of opioid-induced cough include pulmonary chemo-

reflex, which is mediated by either rapidly adapting irritant receptors or vagal C-fiber receptors located in proximity to pulmonary vessels, and the trigger stimulus and bronchial hyperirritability theory. The precise mechanisms by which intravenous lidocaine prevent fentanyl-induced cough are not clear. It has been proposed that depression of brain stem functions by lidocaine may be responsible for cough suppression or lidocaine may act by anesthetizing peripheral cough receptors in the trachea and hypopharynx. Although the bronchodilating effect of lidocaine has not been confirmed, the intravenous administration of lidocaine suppress mechanically and chemically induced airway reflexes, including the cough reflex. Ketamine is a non-competitive NMDA(N-Methyl-D-Aspartic acid) receptor antagonist and NMDA receptor was suggested to be involved in regulation of cough reflex (19). Ketamine may attenuate reflex bronchoconstriction or cough through the blockade of NMDA receptor activation, which result in the direct or indirect bronchodilating effects on airway smooth muscle(20).

5. CONCLUSIONS

Based on our result in this study we can conclude that low dose ketamine can effectively suppress fentanyl induced cough and it is a better drug compared to lidocaine in this regard

6. BIBLIOGRAPHY

1. Miller's Anesthesia by Ronald D. Miller, MD , ninth edition.2020

2. Lin JA, Yeh CC, Lee MS, et al. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. Anesth Analg. 2005;101:670–674.

3. Han JI, Lee H, Kim CH, Lee GY. The frequency of fentanyl-induced cough in children and its effects on tracheal intubation. J Clin Anesth. 2010;22:3–6.

4. Oshima T, Kasuya Y, Okumura Y, Murakami T, Dohi S. Identification of independent risk factors for fentanyl-induced cough. Can J Anesth. 2006;53(8):753–8.

5. Tweed WA, Dakin D. Explosive coughing after fentanyl injection. Anesth Analg. 2001;92:1442–5.

6. Li CC, Chen SS, Huang CH, et al. Fentanyl-induced cough is a risk factor for postoperative nausea and vomiting. Br J Anaesth. 2015;115:444–448.

7. Lin JA, Yeh CC, Lee MS, et al. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. Anesth Analg. 2005;101:670–674.

8. Pandey CK, Raza M, Ranjan R, et al. Intravenous lidocaine sup- presses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. Anesth Analg. 2004;99:1696–1698.

9. Sun L, Guo R, Sun L. The impact of prophylactic intravenous lidocaine on opioid-induced cough: a meta-analysis of randomized con-trolled trials. J Anesth. 2014;28:325–333

10. Hung KC, Chen CW, Lin VC, et al. The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. Anaesthesia. 2010;65:4–7.

11. Kim JE, Min SK, Chae YJ, et al. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis. J Anesth. 2014;28:257–266.

12. Ambesh SP, Singh N, Gupta D, et al. A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study. Br J Anaesth. 2010;104:40–43.

13. Lin CS, Sun WZ, Chan WH, Lin CJ, Yeh HM, Mok MS. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Can J Anaesth. 2004 Aug-Sep;51(7):654-9.

14. Dehghanpisheh L, Eghbal M, Bagheri Baravati F, Vatankhah P. Comparison of lidocaine, huffing maneuver and combination of both in prevention fentanyl induced cough before induction of anesthesia: a double-blind, prospective, randomized placebo-controlled study. BMC Anesthesiol. 2021;21(1):1-5.

15. Gecaj-Gashi A, Nikolova-Todorova Z, Ismaili-Jaha V, Gashi M. Intravenous lidocaine suppresses fentanyl-induced cough in children. Cough. 2013;9(1):20-24.

16. Pandey CK, Raza M, Ranjan R, Lakra A, Agarwal A, Singh U, Singh RB, Singh PK. Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. Anesth Analg. 2004;99(6):1696–1698.

17. Schlimp CJ, Wiedermann FJ. Does fentanyl-induced cough justify pre-treatment with IV lidocaine 2 mg/kg-1. Can J Anaesth. 2005;52(2):207-8

18. Yeh CC, Wu CT, Huh BK, Lee MS, Lin SL, J Sheen M, Wong CS. Premedication with intravenous low-dose ketamine suppresses fentanyl-induced cough. J Clin Anesth. 2007 Feb;19(1):53-6.

19. Kamei J, Tanihara H, Igarashi H, Kasuya Y. Effects of N-meth- yl-D-aspartate antagonists on the cough reflex. Eur J Pharmaco 1989; 168: 153-8.

20. Haxhiu MA, Deal EC Jr, Norcia MP, van Lunteren E, Cherniack NS. Effect of N-methyl-D-aspartate applied to the ventral surface of the medulla on the trachea. J Appl Physiol 1987; 63: 1268-74.

Ethical Clearance:

All ethical issues approved by the authors. Patients enrollment and data collection were in accordance with the World Medical Association (WMA), declaration of Helsinki, The Ethical Principles for Medical Research Involving Human Subjects, 2013. Informed signed consent Obtained from all patitents who were partcipated in this study

Citation:

Abdulrahman R.M, Boujan A.M.K, Mohammed R.F, Seniar W. Intravenous Low Dose Ketamine versus Lidocaine versus Placebo in Suppressing Fentanyl Induced Cough: A Comparative Study. AJMS 2022; 8 (4): 21-30.

DOI: *10.5281/zenodo.7683113*