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Efficacy of Intravenous 0.25 mg/kg Lidocaine Compared with 0.5 mg/kg Lidocaine for Reducing Fentanyl-Induced Cough: a Randomized Controlled Trial

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Abstract

Background: Fentanyl is one of pain medication usually used in anesthetic practice and one common problem after intravenous injection is inducing cough. A 0.5 mg/kg of lidocaine could suppress fentanyl-induced cough, however, the side effect of exceeding doses of lidocaine may cause arrhythmogenic effects and the vasodilatory effects of lidocaine may possibly aggravate cardiovascular depression.

Objectives: The study aimed to compare the efficacy of 0.25 mg/kg and 0.5 mg/kg intravenous lidocaine regarding fentanyl-induced cough in general anesthesia.

Methods: This study was a randomized double-blinded controlled trial. In all 139 participants, who underwent elective surgery between the ages of 18 to 60 years, were allocated in two groups, to receive lidocaine 0.25 mg/kg and 0.5 mg/kg over two minutes before 1 µg/kg of intravenous fentanyl. Coughing was assessed and classified into 3 grades as mild, moderate, or severe. The risk factors of fentanyl-induced cough and side effects were also noted.

Results: Thirteen patients (18.8%) in the 0.25% lidocaine group and eleven patients (15.7%) in the 0.5% lidocaine group experienced fentanyl induced cough. No significant difference was found in the incidence and severity of cough between the two groups (P>0.05).

Conclusion: The present findings indicated that pre-operative IV lidocaine 0.25 mg/kg could be considered an alternative dose to suppress fentanyl-induced cough.

Keywords: cough, fentanyl, general anesthesia, lidocaine

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Background

Fentanyl is one of pain medication usually used in anesthetic practice and one common problem after intravenous injection is inducing cough.[1] The prevalence of fentanyl-induced cough ranges between 21.6 and 74%.[2-5] and can be injurious among patients with increased intracranial, intra-ocular or intra-abdominal pressure[4-8] although the mechanism of fentanyl-induced cough has not been elucidated. Related studies, investigating systemic and local effects have reported that intravenous lidocaine could reduce the hyperactive airway[9], propofol injection pain[10], postoperative pain[11], and either volatile anesthetic requirements or blood pressure among patients undergoing open radical prostatectomy.[12]

Pandey et al. reported 2 mg/kg of injected lidocaine before one minute fentanyl administration decreased the prevalence of cough from 65 to 14%[6] and showed 0.5 mg/kg of lidocaine could suppress fentanyl-induced cough after one minute before injecting fentanyl.[1] However, recent multimodal analgesia protocol, patients nowadays receive multiple routes of lidocaine[13,14], and the side effect of exceeding doses of lidocaine may cause arrhythmogenic effects and the vasodilatory effects of lidocaine may possibly aggravate cardiovascular depression.[9] To extend the knowledge that lidocaine 0.5-1.5 mg/kg were effective to prevent fentanyl-induced cough.[1,6] Thus the aims of this study were to compare doses of lidocaine between 0.25 mg/kg and 0.5 mg/kg to prevent fentanyl induced cough.

Materials and methods

After receiving the Institutional Review Board of Royal Thai Army Medical Ethics Committee approval from Phramongkutklao Hospital in December 2017 to June 2018 (IRBRTA1818/2560), this study was registered with the Thai Clinical Trials Registry (TCTR 20180221002). All participants provided written and informed consent. Eligible patients were adults aged 18-60 years. Patients of ASA physical status I and II, scheduled for elective surgery under general anesthesia, were recruited for the study. However, patients with a history of bronchial asthma, chronic obstructive pulmonary disease, respiratory tract infection, impaired kidney or liver function, on angiotensin converting enzyme inhibitors, having a history of hypersensitivity to local anesthetics and language barrier were excluded.

After confirming the pre-anesthetic evaluation by one of the investigators, all patients were randomized to one of two groups using a computer-generated table and concealed envelope. In the operating room, venous access was established on the dorsum of the nondominant hand and an electrocardiogram, noninvasive blood pressure and pulse oxygen saturation were provided and measured every 5 minutes. The control group (C) received 0.5 mg/kg of intravenous lidocaine over two minutes before 1 µg/kg intravenous fentanyl within 2 seconds and the treatment group (T) received 0.25 mg/kg of intravenous lidocaine over two minutes before intravenous fentanyl 1 µg/kg. Both patients and assessors were blinded. A blinded assessor recorded the number of episodes of coughing in all participants after fentanyl administration. Severity of coughing was graded by the number of episodes of cough (mild 1-2, moderate, 3-5 and severe, 5 or more).[1,6]

Statistical analysis

The sample size was calculated based on a related study by Pandey et al.[1] The probability was 0.1375 among patients assigned to receive intravenous 0.5 mg /kg lidocaine before fentanyl

administration, whereas the probability of the placebo group was 0.35. In addition, from our pilot study revealed incidence of cough for fentanyl 1 mcg/kg rapid injection was 35% and incidence of intravenous 0.5 mg/kg of lidocaine attenuated fentanyl induced cough was 13%. Thus, these results showed that at least 64 patients were needed for each group at the 5% level of significance and 80% confidence to detect a true difference following lidocaine premedication.

Data were expressed as percentages, means and standard deviations for normal distribution data or medians with minimum and maximum for non-normal distribution data. Incidence of cough and other categorical variables were compared using Chi-square test or Fisher's exact test. Comparisons of continuous variables employed the unpaired t-test for variables with normal distributions and Mann-Whitney U test for other variables. Univariable and multivariable analysis was performed using a backward binary stepwise logistic regression to examine and determine risk factors of fentanyl induced cough. All data were analyzed with the Statistical Package for Social Science (SPSS), version 21.0 (SPSS Inc., Chicago, IL, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Three hundred patients assessed for eligibility, 141 patients met the inclusion criteria and were enrolled, two patients dropped out due to emergency surgery as Figure 1.

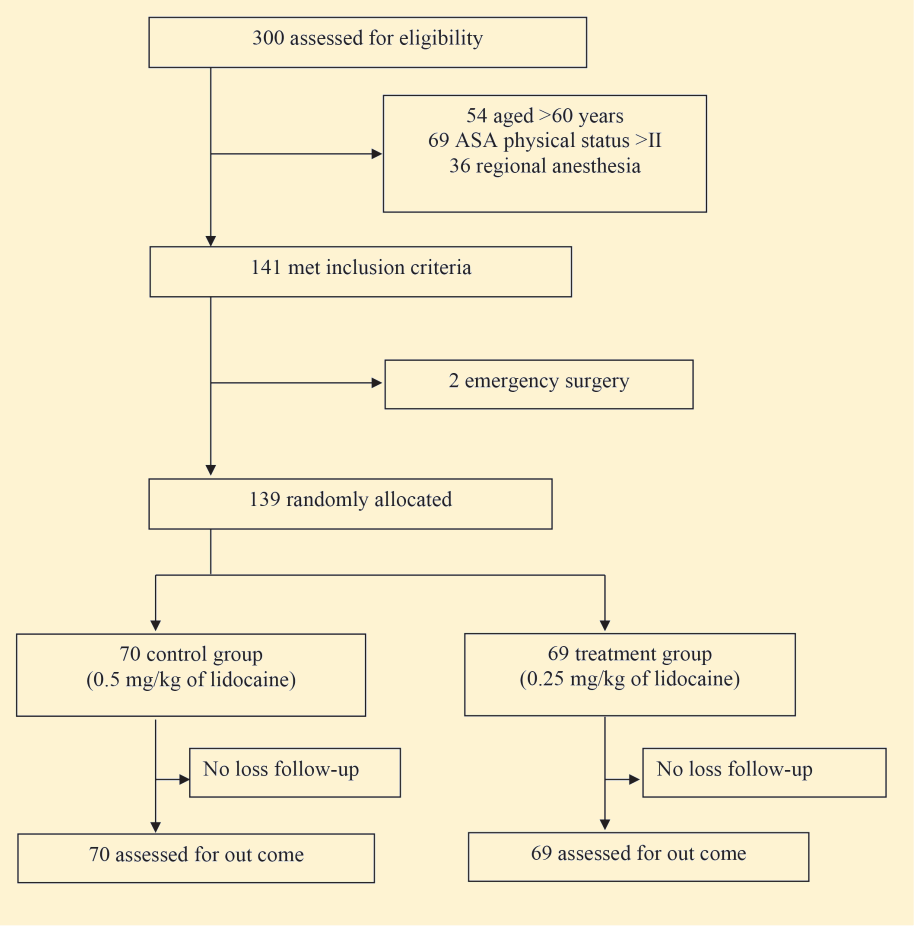


Figure 1 Enrollment randomization

From the 139 enrolled patients, 69 patients were assigned to the treatment group and 70 patients to the control group. The baseline characteristics of the study participants are presented in Table 1 and no significant difference was found between groups regarding sex, age, underlying disease, height, weight, BMI, smoking and ASA classification (*P*>0.05).

Thirteen patients in the treatment group (18.8%) and 11 patients in the control group (15.7%) had fentanyl induced cough. The present study revealed no statistically significant difference between groups referring to overall incidence of cough (P=0.626). Only 2 of 24 cough patients presented severe symptoms. Four patients had moderate and others had mild

Table 1 Baseline characteristics

Baseline characteristics		Group T (n=69) Lidocaine 0.25 mg/kg	Group C (n=70) Lidocaine 0.50 mg/kg	*P*-value
Sex, n (%)	Male	36 (52.2)	34 (48.6)	0.671
	Female	33 (47.8)	36 (51.4)	
Age, mean±SD		42.9±12.9	39.5±12.1	0.104
Underlying disease, n (%)	No	37 (53.6)	38 (54.3)	0.938
	Yes	32 (46.4)	32 (45.7)	
Hypertension, n (%)	No	48 (69.6)	56 (80.0)	0.156
	Yes	21 (30.4)	14 (20.0)	
Diabetes mellitus, n (%)	No	63 (91.3)	62 (88.6)	0.592
	Yes	6 (8.7)	8 (11.4)	
Dyslipidemia, n (%)	No	59 (85.5)	61 (87.1)	0.779
	Yes	10 (14.5)	9 (12.9)	
Height, mean±SD		163.8±8.7	163.6±8.2	0.851
Weight, mean±SD		65.2±11.3	61.6±12.4	0.074
BMI, mean±SD		23.7±4.1	22.5±3.9	0.083
Smoking, n (%)	Smoking	19 (27.5)	21 (30.0)	0.748
	Non-smoking	50 (72.5)	49 (70.0)	
ASA class, n (%)	I	26 (37.7)	27 (38.6)	0.914
	II	43 (62.3)	43 (61.4)	
Type of surgery, n (%)	Abdominal	17 (24.6)	20 (28.6)	0.849*
	ENT	11 (15.9)	10 (14.3)	
	Orthopedic	8 (11.6)	9 (12.9)	
	Plastic	10 (14.5)	12 (17.1)	
	Neurosurgery	6 (8.7)	7 (10.0)	
	Gynecology	12 (17.4)	7 (10.0)	
	Urology	4 (5.8)	2 (2.9)	
	Eye	1 (1.4)	3 (4.3)	

*Fisher's exact test, #Mann-Whitney U test
BMI: body mass index

cough. However, no statistically difference was found in severity of cough between groups (*P*=0.927) as shown in Table 2.

The present study showed no statistically significant risk factor of cough whether it be age, BMI, sex, ASA classification and dosage of lidocaine or underlying disease as shown in Table 3.

Discussion

Opioids are known to have antitussive activity; however, intravenous fentanyl has been reported to induce episodic cough during pre-anesthetic induction[2,8,15] and possibility causes many problems such as increased intracranial, intra-ocular and intra-abdominal pressure.[15,16]

Table 2 Number of patients who had fentanyl induced cough, and severity of the cough

	Group T (n=69) Lidocaine 0.25 mg/kg	Group C (n=70) Lidocaine 0.50 mg/kg	*P*-value
No cough, n (%)	56 (81.2)	59 (84.3)	0.626
Cough, n (%)	13 (18.8)	11 (15.7)	0.927
Severity of cough, n (%)			
Mild	10 (76.9)	8 (72.7)	
Moderate	2 (15.4)	2 (18.2)	
Severe	1 (7.7)	1 (9.6)	

Table 3 Multivariable analysis using multiple logistic regression

		Cough (n=24)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	*P*-value
Age, mean±SD		46.0±11.2	1.04 (1.00-1.08)	1.03 (0.98-1.08)	0.269
BMI, mean±SD		24.5 ±4.2	1.11 (1.00-1.24)	1.14 (0.99-1.31)	0.069
Sex, n (%)	Male	11 (15.7)	1	1	0.314
	Female	13 (18.8)	1.25 (0.52-3.01)	1.68 (0.61-4.60)	
Hypertension, n (%)	No	15 (14.4)	1	1	0.252
	Yes	9 (25.7)	2.05 (0.81-5.23)	2.45 (0.53-11.38)	
Diabetes mellitus, n (%)	No	22 (17.6)	1	1	0.401
	Yes	2 (14.3)	0.78 (0.16-3.74)	0.47 (0.08-2.71)	
Dyslipidemia, n (%)	No	20 (16.7)	1	1	0.581
	Yes	4 (21.1)	1.33 (0.40-4.44)	0.66 (0.15-2.90)	
Smoking, n (%)	Smoking	6 (15.0)	0.79 (0.29-2.17)	0.95 (0.26-3.48)	0.943
	Non-smoking	18 (18.2)	1	1	
ASA class, n (%)	I	9 (17.0)	1	1	0.239
	II	15 (17.4)	1.03 (0.42-2.56)	0.42 (0.10-1.79)	
Dose lidocaine, n (%)	Lidocaine 0.25	13 (18.8)	1.25 (0.52-3.01)	0.93 (0.36-2.38)	0.877
	Lidocaine 0.50	11 (15.7)	1	1	

Even though the mechanism of fentanyl induce cough has not been elucidated, a prior study reported the reasons were histamine release and bronchospasm[17] from sudden adduction in the vocal cord muscles caused by opioid induced muscle rigidity, supraglottic obstruction and histamine release.[18,19] However, several medications have been evaluated for preventing fentanyl induced cough including morphine, turbutaline or salbutamol, cromolyn and recent frequently intravenous lidocaine, shown to decrease the airway reflex through mechanically and chemically induced airway reflexes.[9] In addition, pre-operative and intra-operative intravenous lidocaine improved immediate postoperative pain management and reduced surgery-induced immune alterations.[20] However, lidocaine administration, even within safe dose, was reported to precipitate central nervous system (CNS) toxicity such as numbness of the tongue and lips, ataxia, vertigo, convulsions, respiratory depression and cardiovascular collapse.[21,22]

Hypercarbia is also a risk factor for CNS toxicity of lidocaine as the corresponding increase in cerebral blood flow with hypercarbia delivers lidocaine to the CNS.[23] Therefore, the study required a minimal dose of lidocaine (0.25 mg/kg) to prevent side effects. No significant difference was found in severity of cough between 0.25 mg/kg and 0.5 mg/kg of lidocaine in which one related study revealed 0.5 mg/kg could alleviate fentanyl induced cough.[1] The present study did not find any risk factor associated with fentanyl-induced cough similar to the one related study reporting no effect due to either sex or underlying disease. Conversely, a similar research study by Oshima et al. showed risk factors were decreased with increased age and smoking.[24] Furthermore, the adverse reactions of lidocaine such as arrhythmia and others were not found. The possible reason is the dosage was very low in both groups accordance similar to one related study.[7]

The present study had numbers of limitations. Firstly, the time of the first cough after fentanyl injection and differences between the lidocaine and placebo groups were not recorded in this study. However, many related studies have summarized that lidocaine could significantly alleviate cough more than that in the saline group. In addition, fentanyl induced cough occurred within 15 seconds after injection and none of the patients presented cough after 15 seconds.[25] Secondly, related studies have reported the incidence of fentanyl induced cough depended on the velocity of injection.[2,26] Therefore, rapid fentanyl injection showed a trend to increase the frequency of cough. However, the velocity of fentanyl injection in this study was controlled within 5 seconds and the cause of same incidence of cough even though we use lesser dose of fentanyl might be the speed of injection of fentanyl that we injected within 2 seconds. Thirdly, the incidence of cough on dosage more than 1 µg/kg fentanyl injection was not recorded, but related studies revealed a 20% cough frequency with 2 µg/kg fentanyl[24] and 35% cough frequency with 3 µg/kg fentanyl.[6] Moreover, Lui et al. showed a 43% cough frequency using 5 µg/kg fentanyl.[27] Lastly, our study uses 1 mcg/kg of fentanyl rapid injection instead of 2 mcg/kg of fentanyl because this dose is common use dosage of fentanyl in our institute.

Conclusion

This study indicated that 0.25 mg/kg of lidocaine was equally effective as 0.5 mg/kg of lidocaine and could be considered an alternative method to prevent fentanyl induced cough during anesthesia induction.

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Potential conflict of interests

The authors declare that no conflict of interest exists regarding the publication of this study.

What is already known on this topic?

Related studies, investigating the action of lidocaine to suppress fentanyl induce cough in general anesthesia, indicated the lowest dosage was 0.5 mg/kg. However, a dosage lower than 0.5 mg/kg had not yet been established.

What does this study add?

The study found a minimal dose of lidocaine (0.25 mg/kg) was not significantly different from 0.5 mg/kg of lidocaine on fentanyl-induced cough. No complications, associated with 0.25 mg/kg of lidocaine, were detected.

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