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CLINICAL TRIAL

Low-dose lidocaine attenuates fentanyl-induced cough: A double-blind randomized controlled trial

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Abstract

Purpose The study aimed to determine the efficacy of lidocaine at different low doses to reduce fentanyl-induced cough (FIC).

Methods Three hundred twenty patients aged from 18 to 60 years with ASA I and II scheduled for general anesthesia were randomly assigned to 4 groups to obtain peripheral intravenous 0.9%NaCl (Group I), lidocaine 0.25 mg/kg (Group II), 0.5 mg/kg (Group III) or 1.0 mg/kg (Group IV) 2 min before 3 μg/kg of fentanyl intravenously in a prospective randomized controlled fashion. The primary result was incidence of cough among comparison groups. The secondary results included severity of cough, hemodynamic response and risk factors of FIC.

Results Thirty-two, 15, 13 and 11 patients (40, 18.8, 16.3 and 13.8%) presented incidence of cough in Groups I, II, III and IV, respectively ($P < 0.05$ Group I vs. II, III and IV). No significant difference was observed in the incidence and severity of cough among the lidocaine groups ($P > 0.05$). Multivariate analysis showed that age ≤ 40 years, nonsmoking and patients not receiving the prior lidocaine injection were risk factors of FIC ($P = 0.007$, 0.013 and 0.001, respectively).

Conclusion The study implied intravenous lidocaine 0.25 mg/kg for 2 min before fentanyl injection was the most effective dose to suppress FIC and could be applied in daily practice. Patients aged less than 40 years and nonsmoking were risk factors of FIC, regardless of sex and underlying disease.

Keywords Cough · Fenanyl · Lidocaine · Low dose

Introduction

Fentanyl is one of the common opioids used during the pre-induction period because of the rapid onset, short duration and reduced cardiovascular effects. However, cough is a frequently adverse effect after fentanyl injection [1]. Even though fentanyl-induced cough (FIC) occurs in a short period, immediate management should be provided [2–7] because FIC is related to the magnification of intraocular, intracranial and intra-abdominal pressure [2, 7] and also periorbital or conjunctival petechiae [2].

However, FIC mechanisms are not well elucidated, but several mechanisms have been described. For example, fentanyl stimulates μ receptors and elicits neuronal transmission to activate receptors on the brainstem or transmits through the C-fiber of the vagus nerve to stimulate mucosal receptors on the proximal bronchus causing bronchoconstriction and cough [8].

Nevertheless, prior studies showed various methods to attenuate or treat FIC including nonpharmacologic approaches to suppress the incidence of FIC such as preoperative incentive spirometry [9], the huffing maneuver [10] and swallowing instantly before receiving intravenous fentanyl [11]. Other methods included pharmacologic administration of preemptive low-dose fentanyl [12–14], pre-injection with clonidine (α2-adrenoceptor agonist) [15] or ketamine [16], durieux [17], propofol [18, 19], pheniramine maleate [20], dexamethasone [21], vecuronium [22], MaSo4 [23, 24], pre-inhalation of salbutamol or terbutaline [7, 25], beclomethasone or sodium chromoglycate [8], terbutaline inhalation [9] and lidocaine [26–30].

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Interestingly, lidocaine is a local anesthetic medication which has rapidly expanded in common practice, is easy to use and can be applied in multiple routes such as topical, inhalation, perioperative intubation and extubation [26, 27] Moreover, regional anesthesia is a requisite high volume of local anesthetic [31–34] as a consequence of side effects or toxicity, especially involving many routes of administration in the same patient [35].

Unfortunately, the outcomes of using a very low dose (0.25 mg/kg of lidocaine) have not been investigated. Consequently, this constitutes the first prospective controlled study aimed to demonstrate the effectiveness of lidocaine 0.25 mg/kg to suppress FIC compared with lidocaine 0.5 to 1 mg/kg to minimize adverse effects of lidocaine from multiple sites of injection or high-volume injection in the same patient.

Methods

Study design

The study employed a prospective, single center, block-randomized, patient/assessor-blinded design and active-controlled trial. After the Institutional Review Board of the Royal Thai Army Medical Ethics Committee approved and registered the study in the Thai Clinical Trials Registry (TCTR20191207001), 343 patients provided informed consent and attended the operating theater, Phramongkutklao Hospital, from November 2019 to December 2020. The inclusion criteria included patients aged 18 to 60 years with scheduled general anesthesia and American Society of Anesthesiologists (ASA) physical status classification I or II. The exclusion criteria comprised patients indisposed to participate, patients reporting a record of substance use disorders, chronic opioid use, opioid tolerance or opioid-induced hyperalgesia, presenting a history of allergy to lidocaine or fentanyl, history of chronic obstructive pulmonary disease, bronchial asthma, recent respiratory tract infection less than two weeks. Additional criteria included impaired kidney or liver function, or having been treated with angiotensin converting enzyme inhibitors or beta blockers, symptomatic bradycardia, tachyarrhythmia, left bundle branch block and second- or third-degree atrioventricular block, pregnancy and language barrier.

Randomization and allocation

All patients completed preoperative evaluation using only one anesthesiologist, and any anesthetic premedication was prohibited. Solid food was allowed until 8 h before the scheduled operative time, and clear liquids were permitted until 3 h before this time. The patients were randomly assigned in four groups equivalently using a computer-generated table and sealed envelopes. The random records were preserved and released by an anesthesia resident uninvolved in this study.

In all, 0.9% NaCl, 0.25, 0.5 and 1 mg/kg of lidocaine were established in Groups I, II, III and IV, respectively. All participants and one anesthesiologist who injected the solution and assessed the outcomes were blinded to the allocation groups.

Procedures

The procedures were performed in the inpatient department under general anesthesia. A nurse anesthetist started an intravenous infusion of isotonic balance solution since the patients had been admitted. No pre-medication was given. All patients were monitored for noninvasive blood pressure, electrocardiography and pulse oximetry on arrival at the operating theater. Lidocaine or 0.9% NaCl was injected within 3 to 4 s before two min of 3 μg/kg intravenous fentanyl from 3 to 4 s. A stopwatch was monitored during the injection periods. Subsequently, anesthetic induction was performed after fentanyl injection for 3 min.

Outcome measurement

The primary result was incidence of cough among group comparisons. The secondary results involving severity and risk factor of cough and hemodynamic response (systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were documented at two time points: 3 min before fentanyl injection (baseline) and at 3 min after starting fentanyl injections. Severity of coughing was established as episodic number of coughs (mild 1 to 2, moderate 3 to 4 and severe 5 or more) [30]. All outcomes were assessed within 3 min after fentanyl injection and completely supervised by one blinded anesthesiologist.

Statistical analysis

The sample size was calculated from a related study showing a 20% reduction of FIC after intravenous lidocaine administration and assuming incidence of FIC was 30% [14]. The result showed 79 patients per group were obliged to attain a significance level of 0.05 with 80% power of test. Categorical data were presented as percentage, and continuous data were presented as mean and standard deviation (SD). One-way ANOVA with multiple comparison tests and Bonferroni correction and Chi-squared test were executed to compare the differences between groups in categorical and continuous variables. Univariable analysis was implemented with two-sample t-test for numerical and Chi-squared test or Fisher's exact test (count less than 5) for hypothesized factors to correlate with cough. Multivariable analysis was performed using backward binary stepwise logistic regression and the

last model used an enter method to define risk factors of FIC. All data were analyzed using SPSS, version 26.0 (IBM Corp. Released 2011, IBM SPSS for Windows, Armonk, NY, USA). Results were expressed as odds ratio (OR) with 95% confidence interval (CI). A *P*-value of less than 0.05 was considered statistically significant.

Results

Three hundred forty-two patients were screened for inclusion. Of these, 22 were excluded because the operation was canceled for 6 patients, and pre-medication was administrated for 16 patients leaving 320 eligible patients for randomization and allocated in equal groups of 80. After randomization, none of the patients dropped out of the study or discontinued the allocated intervention as shown in Fig. 1. No clinically significant difference was observed among groups ($P > 0.05$) regarding demographic data including age, sex, weight, height, body mass index, underlying disease, smoking, alcohol consumption, ASA classification and operation type as presented in Table 1

Thirty-two patients (40%) of the control group (Group I) presented cough. The incidence of cough was noted among 15, 13 and 11 patients (18.8, 16.3 and 13.8%) in Groups II, III and IV, respectively. Significant differences were observed between Groups I and II ($P = 0.003$), Groups I and III ($P = 0.001$) and Groups I and IV ($P < 0.001$). However, no significant difference was observed in the incidence of cough between lidocaine groups. [Groups II and III ($P = 0.677$), Groups II and IV ($P = 0.391$) and Groups III and IV ($P = 0.658$)] as presented in Table 2 and Fig. 2. Severity of cough in Group II exhibited a weighty trend toward possible mild cough compared with Groups III and IV [Group II vs. III vs. IV: 11 (13.8%) vs. 8 (10%) vs. 8 (10%), respectively; $P = 0.684$], and none of the patients in Group IV presented severe cough. Unfortunately, no significant difference was found in severity of cough between lidocaine groups (Groups II vs. III vs. IV) ($P > 0.05$) as shown in Table 2.

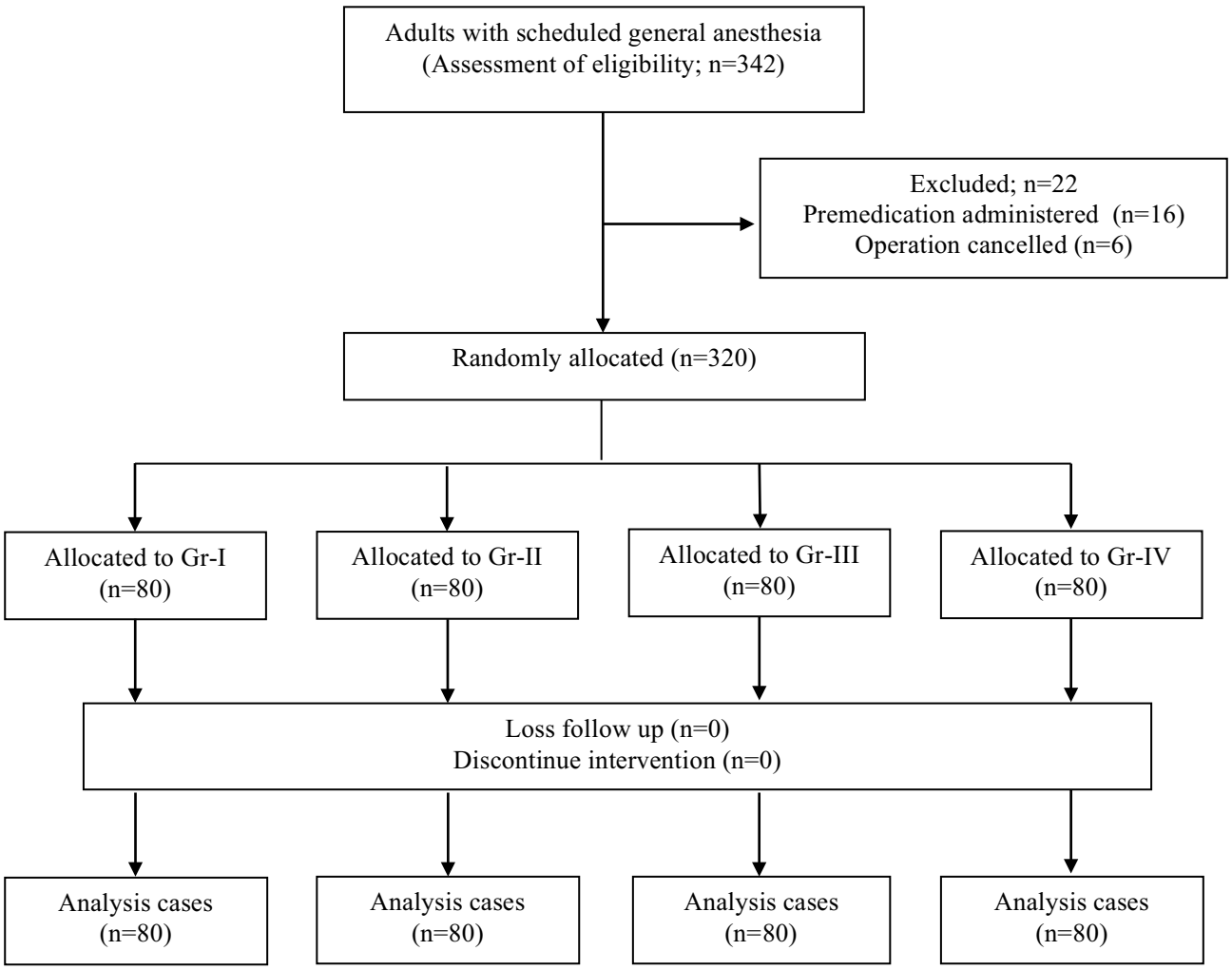

Fig. 1 CONSORT diagram of the study

Table 1 Demographic data and baseline characteristics

Variables	Group I 0.9%NaCl ($n=80$)	Group II lidocaine 0.25 mg/kg ($n=80$)	GroupIII lidocaine 0.5 mg/kg ($n=80$)	Group IV lidocaine 1 mg/kg ($n=80$)	*p*-value
Gender					
Female	40 (50%)	46 (57.5%)	43 (53.8%)	48 (60%)	0.602
Male	40 (50%)	34 (42.5%)	37 (46.3%)	32 (40%)	
Age	46.41 ± 12.67	50.56 ± 13.28	50.41 ± 13.75	51.46 ± 13.76	0.081
BW	65.59 ± 10.72	64.92 ± 11.06	65.89 ± 9.92	65.38 ± 10.69	0.951
Height	164.45 ± 9.49	164.25 ± 7.48	164.86 ± 7.15	164.7 ± 8.66	0.968
BMI	24.22 ± 3.27	24.03 ± 3.58	24.25 ± 3.46	24.06 ± 3.17	0.969
Underlying diseases					
HT	26 (32.5%)	27 (33.8%)	32 (40%)	18 (22.5%)	0.123
DM	11 (13.8%)	11 (13.8%)	12 (15%)	9 (11.3%)	0.917
DLD	16 (20%)	13 (16.3%)	16 (20%)	13 (16.3%)	0.859
Others	8 (10%)	8 (10%)	5 (6.3%)	8 (10%)	0.795
Smoking	9 (11.3%)	10 (12.5%)	17 (21.3%)	12 (15%)	0.293
Drinking	13 (16.3%)	18 (22.5%)	10 (12.5%)	12 (15%)	0.370
ASA class					
1	48 (60%)	51 (63.7%)	38 (47.5%)	45 (56.3%)	0.192
2	32 (40%)	29 (36.3%)	42 (52.5%)	35 (43.8%)	
Operations					
Breast	5 (6.3%)	7 (8.8%)	8 (10%)	13 (16.3%)	0.801
ENT	12 (15%)	8 (10%)	8 (10%)	9 (11.3%)	
Eye	4 (5%)	5 (6.3%)	3 (3.8%)	3 (3.8%)	
Lower abdomen	16 (20%)	21 (26.3%)	20 (25%)	19 (23.8%)	
Neurologic	7 (8.8%)	4 (5%)	6 (7.5%)	2 (2.5%)	
Orthopedic	12 (15%)	15 (18.8%)	14 (17.5%)	12 (15%)	
Plastic	6 (7.5%)	5 (6.3%)	4 (5%)	1 (1.3%)	
Upper abdomen	6 (7.5%)	3 (3.8%)	7 (8.8%)	10 (12.5%)	
Urologic	12 (15%)	12 (15%)	10 (12.5%)	11 (13.8%)	

Value presented as mean ± SD. and n (%). *P*-value corresponds to ANOVA test and Chi-squared test. *BMI* Body mass index, *HT* hypertension, *DM* diabetes mellitus, *DLD* dyslipidemia, *ENT* ear–nose–throat

Overall, average SBP, DBP and HR were significantly reduced from baseline at 3 min after fentanyl injection in all groups ($P<0.05$). However, no significant difference was observed among groups comparisons ($P>0.05$) as shown in Tables 3, 4 and Fig. 3).

Univariate analysis showed significant risk factors were associated with FIC among patients aged younger than 40, body mass index less than 25, no underlying hypertension, diabetes mellitus and dyslipidemia, no history of smoking, ASA classification I and no pre-lidocaine administration ($P<0.05$) as shown in Table 5.

Multivariate analysis using backward binary stepwise logistic regression and the last model using an enter method to define risk factors of FIC revealed that

Table 2 Incidence and severity of fentanyl-induced cough among the groups

	Group I 0.9%NaCl ($n=80$)	Group II lidocaine 0.25 mg/kg ($n=80$)	Group III lidocaine 0.5 mg/kg ($n=80$)	Group IV lidocaine 1 mg/kg ($n=80$)	*p*-value
Cough	32 (40%) [a,b,c]	15 (18.8%) [a]	13 (16.3%) [b]	11 (13.8%) [c]	<0.001*
Severity					
Mild	20 (25%)	11 (13.8%)	8 (10%)	8 (10%)	0.684
Moderate	9 (11.3%)	2 (2.5%)	4 (5%)	3 (3.8%)	0.743
Severe	3 (3.7%)	2 (2.5%)	1 (1.3%)	0 (0%)	0.352

Value presented as n (%). *P*-value corresponds to Chi-squared test

[a]Group I vs II, [b]Group I vs III, [c]Group I vs IV

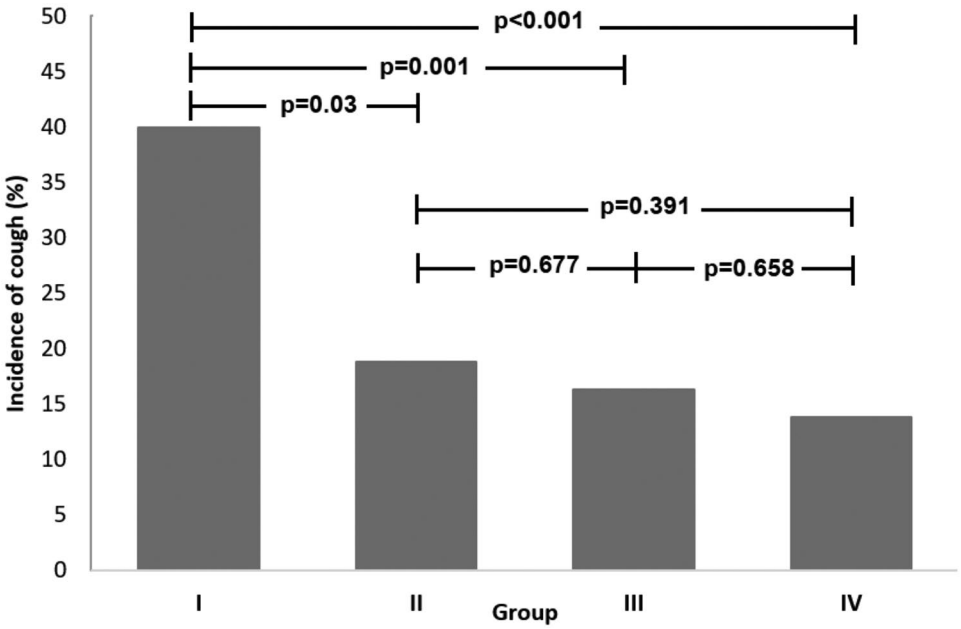

Fig. 2 Comparison of incidence of cough between groups

patients younger than 40 had 2.96 times the risk of cough [$P = 0.007$; adjusted odds ratio (adjusted OR) 2.96, 95% CI 1.35 to 6.5], as well as patients reporting no smoking had 6.5 times the risk of cough [($P = 0.013$; adjusted OR 6.5, 95%CI 1.49 to 28.41). In addition, no pre-lidocaine injection produced 4.52 times the incidence of cough [$P = 0.001$; adjusted OR 4.52, 95% CI 1.93 to 10.56].

Additionally, no serious adverse effects of lidocaine either neurotoxicity or cardiotoxity was found during the study.

Discussion

FIC occurs commonly, especially in pre-anesthetic induction. Related studies have revealed that the incidence of FIC varies between 18 and 65% [7, 8, 28, 29, 35–38]. The study showed the incidence of FIC occurred in up to 40% of patients, which was higher than that reported in related studies showing 34.22 to 35% after 3 μg/kg of fentanyl was administered using a peripheral intravenous route [28, 29]. The higher incidence of FIC was probably due to a rapid

Table 3 Hemodynamic responses at pre- and post-fentanyl administration

	Group I 0.9%NaCl ($n = 80$)	Group II lidocaine 0.25 mg/kg ($n = 80$)	Group III lidocaine 0.5 mg/kg ($n = 80$)	Group IV lidocaine 1 mg/kg ($n = 80$)	*p*-value
SBP					
Baseline	134 ± 13.9	134.48 ± 13.07	137.05 ± 14.86	135.28 ± 13.79	0.527
After	123.28 ± 13.96	125.08 ± 12.43	124.83 ± 14.74	126.2 ± 13.59	0.604
Change	-10.72 ± 11.48	-9.4 ± 8.23	-12.22 ± 14.74	-9.07 ± 9.84	0.280
p-value (within group)	< 0.001*	< 0.001*	< 0.001*	< 0.001*	
DBP					
Baseline	78.28 ± 10.92	80.59 ± 7.71	80.18 ± 9.9	77 ± 9.93	0.068
After	74.29 ± 9.57	74.45 ± 8.25	73.76 ± 11.27	73.27 ± 9.61	0.868
Change	-3.99 ± 11.05	-6.14 ± 6.52	-6.41 ± 8.83	-3.73 ± 6.92	0.091
p-value (within group)	0.002	< 0.001*	< 0.001*	< 0.001*	
HR					
Baseline	77.23 ± 11.59	77.75 ± 9.99	78.86 ± 11.56	76.25 ± 12.06	0.529
After	72.13 ± 11.7	73.81 ± 10.64	74.29 ± 10.72	72.05 ± 11.92	0.476
Change	-5.1 ± 9.07	-3.94 ± 6.48	-4.58 ± 6.93	-4.2 ± 6.78	0.772
p-value (within group)	< 0.001*	< 0.001*	< 0.001*	< 0.001*	

Value presented as mean ± SD. *P*-value corresponds to Paired t test (within group) and ANOVA test (between groups)

fentanyl injection from 3 to 4 s. Lui et al. observed 43% after 5 µg/kg of fentanyl was administered using a peripheral intravenous route over 5 s [25]. Lin et al. showed 65% following 2.5 µg/kg of fentanyl using a peripheral intravenous route within 2 s [36]. These results were coupled with findings of 28% cough incidence after peripheral intravascular fentanyl 1.5 µg/kg injection by Phua et al. [38]: The same incidence from 2 µg/kg of fentanyl injected by peripheral intravenous route more than 5 s was reported by Agarwal et al. [7]. Moreover, Lin JA et al. established a long duration of fentanyl injection diminished the incidence of FIC [37].

As mentioned above, the incidence of FIC depended on dose and velocity of fentanyl injection, which increased significantly with rapid injection time [37]. Yu H et al. revealed that diluted fentanyl 50 to 10 mcg/ml attenuated FIC [39]. Therefore, the study recommended a medium dose of fentanyl (3 µg/kg) and adopted the injection time of fentanyl from 3 to 4 s, for which dose and injection time is commonly used in daily practice.

Even though the mechanisms of FIC were not well demonstrated, numerous theories have been proposed to reduce central sympathetic system symptoms producing vagal dominance and provoking cough and reflex bronchoconstriction [7, 25, 40]. In addition, lidocaine has been proposed to block the peripheral cough receptors in the trachea [26, 27, 41] and provide suppression both through chemical and mechanical airway reflexes [42, 43]: thus, reducing bronchoconstriction.

With reference to multimodal analgesia, local anesthetic injection was increased following many procedures [31, 32]. Consequently, the accumulated dose of lidocaine in either different routes of injection or high volume of injection [33, 34] may lead to adverse side effects [44]. For this purpose, the study indicated very low dose of lidocaine (0.25 mg /kg) two min before fentanyl administration to alleviate the adverse outcomes from accumulated doses of lidocaine and revealed 0.25 mg/kg was effective as 0.5 to 1 mg/kg of lidocaine to suppress FIC compared with placebo. However, no difference in the incidence of cough was found within lidocaine groups according to Pandey et al. showing that 0.5 to 1.5 mg/kg of lidocaine significantly suppressed FIC [28] and Golmohammadi M et al. revealed that 1 mg/kg of lidocaine pre-injection significantly alleviated the incidence of FIC [13]. Furthermore,

Table 4 Univariate logistic regression for fentanyl-induced cough

Factors	Cough ($n=71$)	None ($n=249$)	OR (95%CI)	p-value
Gender				
Female	36 (50.7%)	141 (56.6%)	Reference	1
Male	35 (49.3%)	108 (43.4%)	1.27 (0.75, 2.15)	0.376
Age				
< 40	30 (42.3%)	45 (18.1%)	4.8 (2.49, 9.26)	< 0.001*
40–50	21 (29.6%)	60 (24.1%)	2.52 (1.27, 4.99)	0.008*
> 50	20 (28.2%)	144 (57.8%)	Reference	1
BMI				
< 25	56 (78.9%)	163 (65.5%)	1.97 (1.05, 3.69)	0.034*
> = 25	15 (21.1%)	86 (34.5%)	Reference	1
Underlying				
No HT	63 (88.7%)	154 (61.8%)	4.86 (2.23, 10.58)	< 0.001*
No DM	70 (98.6%)	207 (83.1%)	14.2 (1.92, 105.11)	0.009*
No DLD	67 (94.4%)	195 (78.3%)	4.64 (1.62, 13.29)	0.004*
No Others	66 (93%)	225 (90.4%)	1.41 (0.52, 3.83)	0.503
No Smoking	68 (95.8%)	204 (81.9%)	5 (1.51, 16.61)	0.009*
No Drinking	61 (85.9%)	206 (82.7%)	1.27 (0.6, 2.68)	0.525
ASA class				
1	57 (80.3%)	125 (50.2%)	4.04 (2.14, 7.62)	< 0.001*
2	14 (19.7%)	124 (49.8%)	Reference	1
SBP change	-10.7 ± 12.92	-10.26 ± 10.88	1 (0.97, 1.02)	0.769
DBP change	-5.46 ± 10.32	-4.95 ± 8.02	0.99 (0.96, 1.02)	0.656
HR change	-3.77 ± 7.66	-4.65 ± 7.28	1.02 (0.98, 1.05)	0.379
Group				
Placebo	32 (45.1%)	48 (19.3%)	4.18 (1.92, 9.1)	< 0.001*
lidocaine 0.25 mg/kg	15 (21.1%)	65 (26.1%)	1.45 (0.62, 3.38)	0.393
lidocaine 0.5 mg/kg	13 (18.3%)	67 (26.9%)	1.22 (0.51, 2.91)	0.658
lidocaine 1 mg/kg	11 (15.5%)	69 (27.7%)	Reference	1

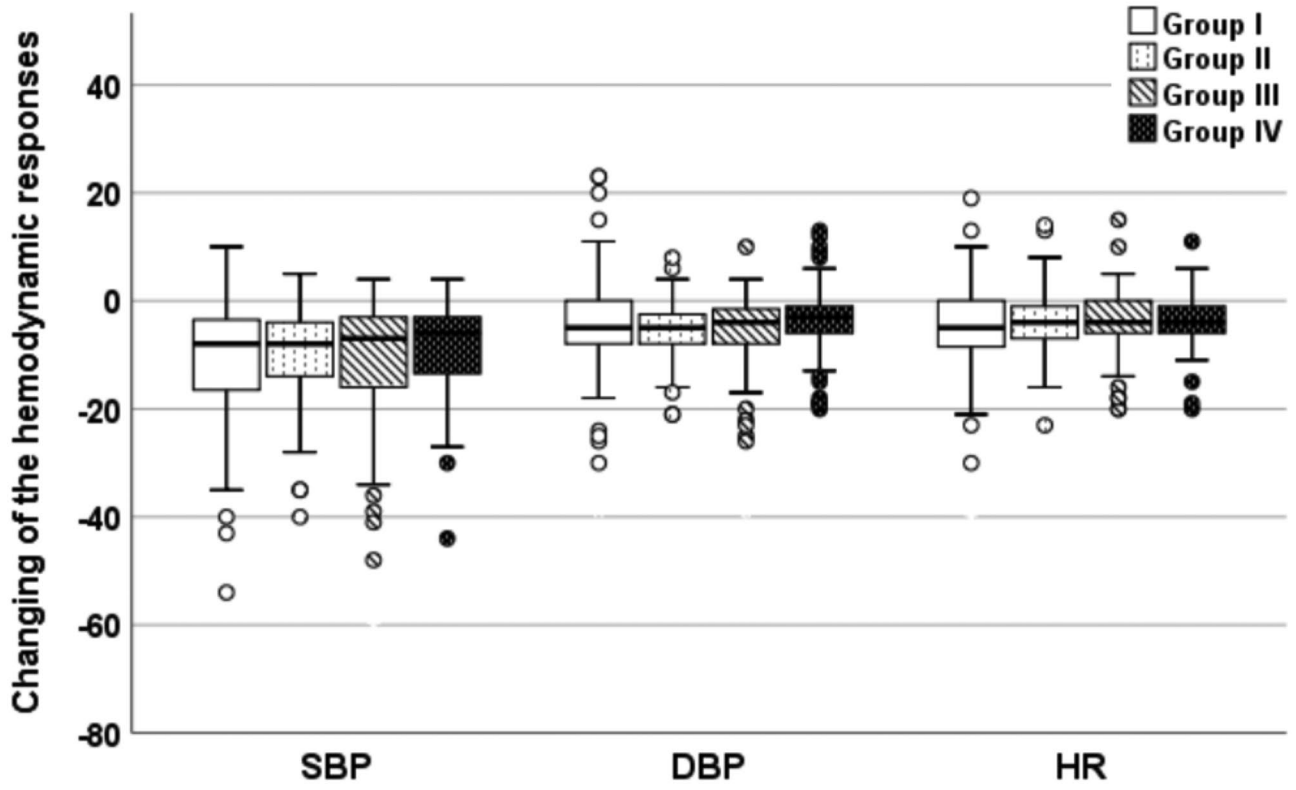

Fig. 3 Comparison of changes in hemodynamic response

Table 5 Multivariate logistic regression and the last model using a enter method to define risk factors of fentanyl-induced cough

Factors	Adjusted OR (95%CI)	*p*-value
Age		
< 40	2.96 (1.35, 6.5)	0.007*
40–50	1.34 (0.62, 2.91)	0.460
> 50	Reference	1
BMI		
< 25	1.56 (0.74, 3.29)	0.245
> = 25	Reference	1
Underlying		
No HT	2.44 (0.82, 7.28)	0.109
No DM	5.69 (0.67, 48.38)	0.111
No DLD	1.27 (0.31, 5.15)	0.737
No Smoking	6.5 (1.49, 28.41)	0.013*
ASA class		
1	0.83 (0.3, 2.29)	0.718
2	Reference	1
Group		
Placebo	4.52 (1.93, 10.56)	0.001*
lidocaine 0.25 mg/kg	1.54 (0.63, 3.81)	0.346
lidocaine 0.5 mg/kg	1.36 (0.53, 3.43)	0.522
lidocaine 1 mg/kg	Reference	1

in a recent study, a meta-analysis showed no significant difference between low doses (0.5 to 1 mg/kg) and high doses (1.5 to 2 mg/kg) of lidocaine at reducing the incidence of FIC[45].

Interestingly, the study found lidocaine injection for 2 min before fentanyl injection could reduce the incidence of cough in which the duration was longer than related studies using fentanyl injection following lidocaine injection within 1 min [28, 29, 35, 38, 46]. More precisely, the onset of intravenous lidocaine showed in 45 to 30 s with maximum effect at 1 to 2 min [47] and Mikawa et al. found that intravenous lidocaine two min before extubation of an endotracheal tube reduced the cough reflex [48]. Consequently, the study reported 2 min prior fentanyl injection could provide the maximum peak effect of lidocaine.

In spite of significantly reduced FIC doses of lidocaine, the trend toward dose-dependent character and plasma level according to related studies indicated increased doses of lidocaine showed additional effects of reducing cough from endotracheal intubation [42]. However, no significant difference was found among lidocaine groups.

Nevertheless, the study showed statistical difference from baseline regarding the hemodynamic response (SBP, DBP and HR) in all groups, but no statistical difference was found between lidocaine and placebo groups after fentanyl injection. Similarly, related studies showed fentanyl and lidocaine

injection alleviated hemodynamic response during tracheal intubation [49].

In addition, the study found risk factor of FIC increased in age below 40 and nonsmoking subjects the same as reported by related studies [36, 50, 51]. However, sex or underlying disease including diabetes mellitus, hypertension and dyslipidemia were unrelated to the risk factors of FIC, according to a recent study [52] in which incremental titration of fentanyl could be applied for patients with underlying who experienced acute and chronic intractable pain.

The present study encountered a number of limitations. Firstly, the study demonstrated lidocaine was administrated within 2 min before fentanyl injection, in which related studies disclosed the duration of cough reduction from lidocaine was 5 to 8 min [42, 53, 54]. However, the same studies found the peak effect of lidocaine at 1 to 2 min [47]. Secondly, a dose solely established by body weight might have produced different effects. Thirdly, the incidence and severity of cough were not assessed over 3 min after fentanyl administration for which FIC probably rose over 3 min after fentanyl injection. However, many related studies have summarized that FIC occurred within 15 s after injection and none of the patients presented cough after 15 s [20].

Conclusion

The study implied intravenous lidocaine 0.25 mg/kg for 2 min before fentanyl injection was the most effective dose to suppress FIC and could be applied in daily practice. Findings indicated patients aged less than 40 years and nonsmoking were risk factors of FIC, regardless of sex and underlying disease.

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Declarations

Conflict of interest None.

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References

1. Iida K, Handa M, Fukuda K, Saita N, Kasahara M, Koukita Y et al (2009) Incidence and onset time of fentanyl-induced cough depends on the dose of IV fentanyl. Masui 58(8):962–965
2. Tweed WA, Dakin D (2001) Explosive coughing after bolus fentanyl injection. Anesth Analg 92(6):1442–1443
3. Sharpey-Schafer EP (1953) Effects of coughing on intrathoracic pressure, arterial pressure and peripheral blood flow. J Physiol 122:351–357
4. Reisin L, Blaer Y, Jafari J, Manoach M (1994) Cough-induced nonsustained ventricular tachycardia. Chest 105:1583–1584
5. Irani F, Sanchis J (1971) Inspiration- and cough-induced atrioventricular block. Can Med Assoc J 105:735–736
6. Benedict EB (1961) Rupture of the bronchus from bronchoscopy during a paroxysm of coughing. JAMA 178:509–510
7. Agarwal A, Azim A, Ambesh S, Bose N, Dhiraj S, Sahu D et al (2003) Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. Can J Anaesth 50(3):297–300
8. Bohrer H, Fleischer F, Werning P (1990) Tussive effect of a fentanyl bolus administered through a central venous catheter. Anaesthesia 45:18–21
9. Goyal VK, Bhargava SK, Baj B (2017) Effect of preoperative incentive spirometry on fentanyl-induced cough: a prospective, randomized, controlled study. Korean J Anesthesiol 70(5):550–4
10. Ambesh SP, Singh N, Gupta D, Singh PK, Singh U (2010) A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study. Br J Anaesth 104(1):40–43
11. Sako S, Tokunaga S, Tsukamoto M, Yoshino J, Fujimura N, Yokoyama T (2017) Swallowing action immediately before intravenous fentanyl at induction of anesthesia prevents fentanyl-induced coughing: a randomized controlled study. J Anesth 31(2):212–218
12. Du BX, Cao L, Zhao WL, Xu ZH, Song J, Shi XY (2014) Preemptive small dose of fentanyl suppresses fentanyl-induced cough: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 7(4):826–36
13. Golmohammadi M, Shajiee S, Sane S, Valie M (2018) Comparison of the effects of pretreatment intravenous fentanyl or intravenous lidocaine on suppression of fentanyl-induced cough in children: a randomized, double-blind, controlled clinical trial. Electron Physician 10(6):6877–6883
14. Hung KC, Chen CW, Lin VC, Weng HC, Hsieh SW (2010) The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. Anaesthesia 65(1):4–7
15. Horng HC, Wong CS, Hsiao KN, Huh BK, Kuo CP, Cherng CH et al (2007) Pre-medication with intravenous clonidine suppresses fentanyl-induced cough. Acta Anaesthesiol Scand 51(7):862–865
16. Yeh CC, Wu CT, Huh BK, Lee MS, Lin SL, Sheen J, M, et al (2007) Premedication with intravenous low-dose ketamine suppresses fentanyl-induced cough. J Clin Anesth 19(1):53–56
17. Durieux ME (1995) Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesth Analg 81(1):57–62
18. Sedighinejad A, Naderi Nabi B, Haghighi M, Imantalab V, Hadadi S, Erfani Sayar R et al (2013) Propofol is Effective to Depress Fentanyl-Induced Cough during Induction of Anesthesia. Anesth Pain Med 2(4):170–173
19. Firouzian A, Emadi SA, Baradari AG, Mousavi R, Kiasari AZ (2015) Can low dose of propofol effectively suppress fentanyl-induced cough during induction of anaesthesia? A double blind randomized controlled trial. J Anaesthesiol Clin Pharmacol 31(4):522–525
20. Ozmen O, Kara D, Karaman EU, Karakoc F, Karakaya MA, Arslan Z (2016) Pheniramine Maleate is more effective than Lidocaine on Fentanyl Induced Cough. Pak J Med Sci 32(3):715–719
21. Yu MS, Kim JY, Kim HY (2011) Intravenous dexamethasone pretreatment reduces remifentanil induced cough. Korean J Anesthesiol 60(6):403–407
22. Horng HC, Lin BF, Wang TC, Lin SL, Liaw WJ, Wang HJ et al (2012) Priming dose of intravenous rocuronium suppresses fentanyl-induced coughing. Acta Anaesthesiol Taiwan 50(4):147–149
23. An LJ, Gui B, Su Z, Zhang Y, Liu HL (2015) Magnesium sulfate inhibits sufentanil-induced cough during anesthetic induction. Int J Clin Exp Med 8(8):13864–13868

24. Liu HL, An LJ, Su Z, Zhang Y, Gui B (2015) Magnesium sulphate suppresses fentanyl-induced cough during general anesthesia induction: a double-blind, randomized, and placebo-controlled study. Int J Clin Exp Med 8(7):11332–11336
25. Lui PW, Hsing CH, Chu YC (1996) Terbutaline inhalation suppresses fentanyl-induced coughing. Can J Anesth 43:1216–1219
26. Clivio S, Putzu A, Tramèr MR(2019) Intravenous lidocaine for the prevention of cough: Systematic review and meta-analysis of randomized controlled trials. Anesth Analg 1249–55
27. Sun L, Guo R, Sun L (2014) The impact of prophylactic intravenous lidocaine on opioid-induced cough: a meta-analysis of randomized controlled trials. J Anesth 28(3):325–333
28. Pandey CK, Raza M, Ranjan R, Singhal V, Kumar M, Lakra A et al (2005) Intravenous lidocaine 0.5 mg.kg-1 effectively suppresses fentanyl-induced cough. Can J Anaesth 52(2):172–5
29. Pandey CK, Raza M, Ranjan R, Lakra A, Agarwal A, Singh U et al (2004) Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. Anesth Analg 99(6):1696–1698
30. Munjupong S, Malaithong W, Mansumruatkan T , Chantrapannik E , Oofuvong M (2019) Efficacy of Very Low Dose IV Lidocaine in Preventing Cough and Sore Throat After Awakening from General Anesthesia: A Randomized Controlled Trial. J Med Assoc Thai 102(9):1009–15
31. Møiniche S, Jørgensen H, Wetterslev J, Dahl JB (2000) Local anesthetic infiltration for postoperative pain relief after laparoscopy: a qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. Anesth Analg 90(4):899–912
32. Gupta A (2010) Wound infiltration with local anaesthetics in ambulatory surgery. Curr Opin Anaesthesiol 23:708–713
33. Fowler SJ, Christelis N (2013) High volume local infiltration analgesia compared to peripheral nerve block for hip and knee arthroplasty-what is the evidence? Anaesth Intensive Care 41(4):458–462
34. Techasuk W, Bernucci F, Cupido T, González AP, Correa JA, Finlayson RJ et al (2014) Minimum effective volume of combined lidocaine-bupivacaine for analgesic subparaneural popliteal sciatic nerve block. Reg Anesth Pain Med 39(2):108–111
35. Dunn LK, Durieux ME (2017) Perioperative Use of Intravenous Lidocaine. Anesthesiology 126(4):729–737
36. Lin CS, Sun WZ, Chan WH, Lin CJ, Yeh HM, Mok MS (2004) Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Can J Anaesth 51:654–659
37. Lin JA, Yeh CC, Lee MS, Wu CT, Lin SL, Wong CS (2005) Prolonged injection time and light smoking decrease the incidence of fentanyl- induced cough. Anesth Analg 101:670–674
38. Phua WT, Teh BT, Jong W, Lee TL, Tweed WA (1991) Tussive effect of a fentanyl bolus. Can J Anaest 38:330–334
39. Yu H, Yang XY, Zhang X, Li Q, Zhu T, Wang Y et al (2007) The effect of dilution and prolonged injection time on fentanyl-induced coughing. Anesthesia 62:16–19
40. Yasuda I, Hirano T, Yusa T, Satoh M (1978) Tracheal constriction by morphine and by fentanyl in man. Anesthesiology 49:117–119
41. Poulton TJ, James FR (1979) Cough suppression by lidocaine. Anesthesiology 50:470–472
42. Yukioka H, Hayashi M, Terai T, Fujimori M (1993) Intravenous lidocaine as a suppressant of coughing during tracheal intubation in elderly patients. Anesth Analg 77:309–312
43. Nishino T, Hiraga K, Sugimori K (1990) Effects of i.v. lidocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane. Br J Anaesth 64:682–687
44. Schlimp CJ, Wiedermann FJ (2005) Does fentanyl-induced cough justify pre-treatment with iv lidocaine 2 mg.kg-1. Can J Anaesth 52(2):207
45. Tan W, Li S, Liu X, Gao X, Huang W, Guo J, Wang Z (2018) Prophylactic Intravenous Lidocaine at Different Doses for Fentanyl-Induced Cough (FIC): A Meta-Analysis. Sci Rep 8(1):9946
46. Bang SR, Ahn HJ, Kim HJ, Kim GH, Kim JA, Yang M et al (2010) Comparison of the effectiveness of lidocaine and salbutamol on coughing provoked by intravenous remifentanilduring anesthesia induction. Korean J Anesthesiol 59:319–322
47. Savitha KS, D'Souza JS, Kothari AN (2014) Attenuation of hemodynamic response to extubation with I.V.lignocaine:A randomized clinical trial. J Evol Med Dental Sci 3(4):838–46
48. Mikawa K, Nishina K, Takao Y, Shiga M, Maekawa N, Obara H (1997) Attenuation of cardiovascular responses to tracheal extubation: comparison of verapamil, lidocaine, and verapamil-lidocaine combination. Anesth Analg 85(5):1005–1010
49. Thippeswamy RR, Shetty SR (2018) Intravenous low dose fentanyl versus lignocaine in attenuating the hemodynamic responses during endotracheal intubation: A randomized double-blind study. Anesth Essays Res 12:778–785
50. Oshima T, Kasuya Y, Okumura Y, Murakami T, Dohi S (2006) Identification of independent risk factors for fentanyl-induced cough. Can J Anaesth 53:753–758
51. Jung HJ, Kim JB, Im KS, Cho HJ, Kim JW, Lee JM (2011) Effects of a priming dose of fentanyl during anaesthesia on the incidence and severity of fentanyl-induced cough in current, former and non-smokers. J Int Med Res 39(6):2379–2384
52. Zhao X, Wang H, Wang HJ, Wang Y, Xing YA, Li ST et al (2021) Risk Factors for Fentanyl-Induced Cough Following General Anesthesia in Adults: A Retrospective Study from a Single Center in China. Med Sci Monit 27:e930369
53. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M (1985) Intravenous lidocaine as a suppressant of coughing during tracheal intubation. Anesth Analg 64:1189–1192
54. Nishino T, Hiraga K, Sugimori K (1990) Effects of i.v. lignocaineon airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane. Br J Anaesth 64:682–687