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REVIEW ARTICLE

Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis

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Abstract Fentanyl-induced cough (FIC) is often observed after intravenous bolus administration of fentanyl during anesthesia induction. This meta-analysis assessed the efficacy of pharmacological and nonpharmacological interventions to reduce the incidence of FIC. We searched for randomized controlled trials comparing pharmacological or nonpharmacological interventions with controls to prevent FIC; we included 28 studies retrieved from PubMed, Embase, and Cochrane Library. Overall incidence of FIC was approximately 31 %. Lidocaine [odds ratio (OR) = 0.29, 95 % confidence interval (CI) 0.21–0.39], *N*-methyl-D-aspartate (NMDA) receptor antagonists (OR 0.09, 95 % CI 0.02–0.42), propofol (OR 0.07, 95 % CI 0.01–0.36), α_2 agonists (OR 0.32, 95 % CI 0.21–0.48), β_2 agonists (OR 0.10, 95 % CI 0.03–0.30), fentanyl priming (OR 0.33, 95 % CI 0.19–0.56), and slow injection of fentanyl (OR 0.25, 95 % CI 0.11–0.58)] were effective in decreasing the incidence of FIC, whereas atropine (OR 1.10, 95 % CI 0.58–2.11) and benzodiazepines (OR 2.04, 95 % CI 1.33–3.13) were not effective. This meta-analysis found that lidocaine, NMDA receptor antagonists, propofol, α_2 agonists, β_2 agonists, and priming dose of fentanyl were effective in preventing FIC, but atropine and benzodiazepines were not. Slow injection of fentanyl was effective in preventing FIC, but results depend on the speed of administration.

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Introduction

Fentanyl-induced cough (FIC) is often observed after intravenous bolus administration of fentanyl during anesthesia induction. The incidence of FIC is from 18 % to 65 % [1, 2] although is usually brief and self-limiting. However, coughing is undesirable during anesthesia induction because it is associated with increased intracranial (ICP), intraocular, and intra-abdominal pressures. Furthermore, severe FIC can cause multiple conjunctival and periorbital petechiae [3] and lead to upper airway obstruction that might require immediate intervention [4]. Therefore, it is clinically important to prevent FIC. Various interventions, including lidocaine, *N*-methyl-D-aspartate (NMDA) receptor antagonists, propofol, α_2 agonists, β_2 agonists, atropine, benzodiazepines, priming, and slow injection of fentanyl, have been used to reduce the incidence of FIC [2, 5–11]. However, the prophylactic efficacy of these measures remains controversial, and to date, no meta-analysis has been performed to evaluate their efficacy in preventing FIC. The purpose of this meta-analysis of randomized trials was to analyze the efficacy of pharmacological and nonpharmacological interventions to reduce the incidence of FIC.

Methods

This study followed the guidelines recommended in the Cochrane Handbook for Systematic Reviews of Interventions [12] and the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) statement [13]. We searched PubMed, Embase, and Cochrane Library databases using the following terms: "fentanyl" AND ("cough" OR "coughing"). For gathering all available evidence, we hand searched the references cited in selected articles for additional studies. The language of publication was not restricted. The last database search date was March 2013. We searched for clinical and randomized controlled trials that compared pharmacological or nonpharmacological interventions with controls, the latter receiving no treatment to prevent FIC. Reviews, abstracts, correspondence, and letters were excluded. The title and abstract of each identified article were read by a single primary investigator (JHK) who completed the screening process. When an article met our selection criteria, its quality was assessed and data extracted by two independent reviewers (JHK, JYK). Any conflicting results were resolved by discussion between the two reviewers. Extracted data included patient characteristics, dose, timing, route prophylactic agent administration, intervention technique, and fentanyl dose and injection speed. The primary outcome was the number of patients coughing during IV fentanyl administration.

Statistical analysis

Review Manager 5.1 software (RevMan 5.1, The Cochrane Collaboration, Oxford, UK) was used for statistical analysis. Results are expressed as odds ratio (OR) [95 % confidence interval (CI)], I^2, and P value for heterogeneity. Analysis of FIC incidence was performed using the OR computed with the Mantel–Haenszel method (fixed or random effect models). Forest plots were used to graphically represent and evaluate treatment effect. OR represents the likelihood of FIC in the treatment group compared with the control group. A 95 % CI for OR <1 was considered to represent statistical significance, and it indicates efficacy in FIC prevention. Statistical heterogeneity was assessed with the I^2 value; $I^2 > 40$ % and a P value <0.1 were considered the threshold for heterogeneity, and a random effects model was applied. If data were homogeneous ($P \geq 0.1$), a fixed effect model was applied. For investigating heterogeneity, subgroup analysis was performed according to the dose of intervention drug, speed of fentanyl administration, or timing modalities, whichever was appropriate. To reduce issues related to the unit of analysis in studies with more than two intervention groups, the number of patients in the control group and the FIC count were divided into more than two control groups within each meta-analysis. Bias related to unpublished studies was assessed using the funnel plot if at least ten studies of each intervention were included. However, we were not able to create a funnel plot due to the small number of studies in our meta-analysis. To evaluate relative efficacy of interventions, statistical testing of indirect comparison was carried out. For indirect comparison of individually significant interventions including three or more studies, mixed effects metaregression was performed using R in with the metafor package [14], and summary statistic values are presented as relative risk (RR) (95 % confidence interval).

Results

A total of 879 articles were found with the search criteria, and 36 were considered as being potential clinical trials that could be included. The selection process is summarized in Fig. 1. The meta-analysis finally assessed 28 articles (5,660 patients in intervention groups and 3,188 patients in control groups). Interventions used to prevent FIC were as follows: administration of lidocaine, NMDA receptor antagonists (ketamine, dextromethorphan), propofol, α_2 agonists (clonidine, dexmedetomidine), β_2 agonists (terbutaline, salbutamol), atropine, benzodiazepines (midazolam, temazepam), fentanyl (for priming), beclomethasone, sodium cromoglycate, morphine, pentazocine, dezocine, ephedrine, rocuronium, slow injection method, dilution, and huffing maneuver (Table 1). Beclomethasone, sodium cromoglycate, morphine, pentazocine, dezocine, ephedrine, rocuronium, dilution, and huffing maneuver were used in single studies and not included in the meta-analysis.

Overall incidence of FIC in the control group was approximately 31.4 %. Efficacy of each intervention is summarized in Table 2. Intravenously administered lidocaine was effective in suppressing FIC (OR = 0.29, 95 % CI 0.21–0.39, $I^2 = 0$ %, $P = 0.51$) (Fig. 2). Subgroup analysis according to lidocaine dosage (0.5–1.0 mg/kg, 1.5–2.0 mg/kg) showed it was effective in preventing FIC irrespective of dosage (OR = 0.37, 95 % CI 0.22–0.63, $I^2 = 0$ %, $P = 0.89$; OR = 0.26, 95 % CI 0.17–0.38, $I^2 = 32$ %, $P = 0.23$, respectively).

Intravenous administration of α_2 agonists decreased the incidence of FIC (OR = 0.32, 95 % CI 0.21–0.48, $I^2 = 45$ %, $P = 0.14$). When subgroup analysis was performed according to the type of α_2 agonists (clonidine, dexmedetomidine), heterogeneity was not corrected. Except in one substudy using a high dose of dexmedetomidine (1.0 μg/kg), heterogeneity was within acceptable ranges (OR = 0.38, 95 % CI 0.27–0.65, $I^2 = 0$ %, $P = 0.81$). Slow injection speed during fentanyl administration decreased the incidence of FIC (OR = 0.25, 95 % CI 0.11–0.58, $I^2 = 69$ %, $P = 0.004$) (Fig. 3). Heterogeneity was assessed by injection speed during administration. Injection of fentanyl over a period of less than 15 s was not effective in preventing FIC (OR = 0.50, 95 % CI

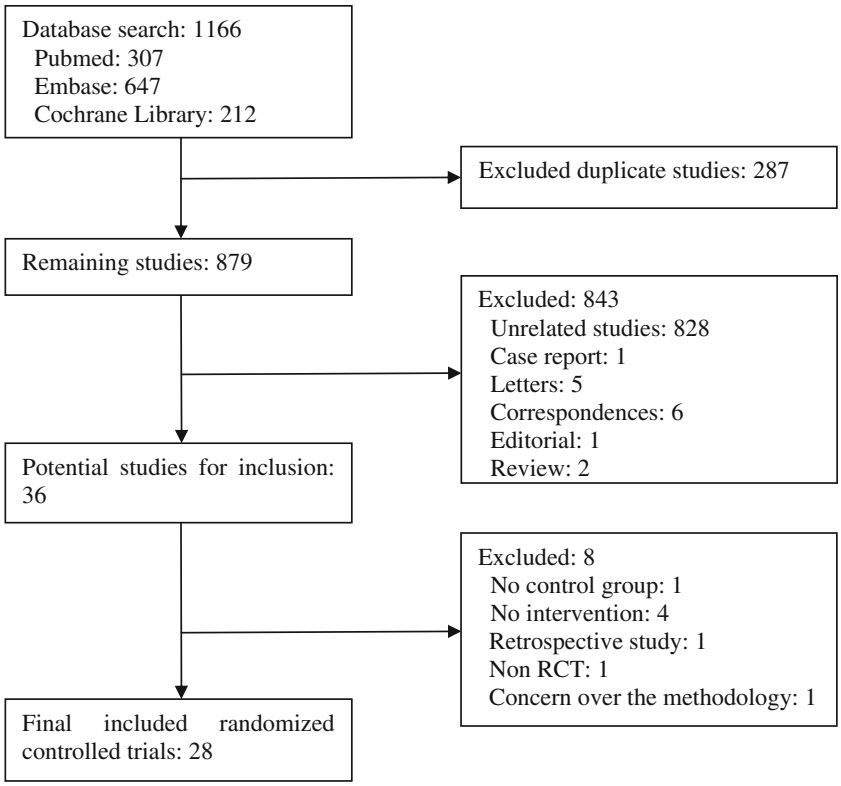

Fig. 1 Study diagram

0.18–1.43, $I^2 = 55$ %, $P = 0.08$); however, injection over a 30-s period was effective in preventing FIC (OR = 0.11, 95 % CI 0.07–0.19, $I^2 = 0$ %, $P = 0.73$).

Propofol was effective in attenuating FIC (OR = 0.07, 95 % CI 0.01–0.36, $I^2 = 72$ %, $P = 0.01$). Subgroup analysis according to propofol dosage ($\leq$1.0 mg/kg, $\geq$1.5 mg/kg) caused a decrease in heterogeneity, in which both doses of propofol were effective in attenuating FIC (OR = 0.26, 95 % CI 0.11–0.64, $I^2 = 0$ %, $P = 0.53$; OR = 0.01, 95 % CI 0.00–0.07), $I^2 = 0$ %, $P = 0.66$, respectively). Inhalation of β_2 agonists (terbutaline, salbutamol) was also effective in suppressing FIC (OR = 0.10, 95 % CI 0.03–0.30, $I^2 = 21$ %, $P = 0.26$). Priming low-dose of fentanyl decreased the incidence of FIC (OR = 0.33, 95 % CI 0.19–0.56, $I^2 = 73$ %, $P = 0.0001$). Although heterogeneity was explored using the priming dose, it was not corrected using the main fentanyl dose and interval of priming time. NMDA receptor antagonists (ketamine, dextromethorphan) effectively suppressed FIC (OR = 0.09, 95 % CI 0.02–0.42, $I^2 = 86$ %, $P < 0.001$). Heterogeneity was not decreased by analyzing the studies according to dose and type of antagonists and fentanyl dose. Atropine and benzodiazepines were ineffective in preventing FIC (OR = 1.10, 95 % CI 0.58–2.11, $I^2 = 0$ %, $P = 1.00$; OR = 2.04, 95 % CI 1.33–3.13, $I^2 = 21$ %, $P = 0.26$, respectively). Indirect comparisons were carried out for five statistically significant interventions: RR (95 % CI) of NMDA receptor antagonists, slow injection, lidocaine, priming dose of fentanyl, and α_2 agonists were OR 0.21, 95 % CI 0.08–0.53, OR 0.33, 95 % CI 0.16–0.66, OR 0.46, 95 % CI 0.36–0.59, OR 0.51, 95 % CI 0.35–0.74, and OR 0.59, 95 % CI 0.46–0.74, respectively. RR of NMDA receptor antagonists was lower than those of fentanyl priming dose and α_2 agonists ($P = 0.019$ and 0.016, respectively). RR of slow injection was lower than that of α_2 agonists ($P = 0.043$).

Discussion

This meta-analysis demonstrated that lidocaine, NMDA receptor antagonists, propofol, α_2 agonists, β_2 agonists, and fentanyl priming dose were all effective in preventing FIC, but atropine and benzodiazepines were not. Slow injection of fentanyl seems to be effective in preventing FIC, but it depends on the speed of administration (>30 s).

Although various mechanisms responsible for FIC have been proposed, the exact mechanism remains unclear. Fentanyl could inhibit central sympathetic outflow, thereby activating the vagus nerve. This enhancement of vagal activity was reported as a possible cause of cough and reflex bronchoconstriction [8, 22]. Other possible mechanisms included a pulmonary chemoreflex mediated by rapidly adapting receptors (irritant receptors) or vagal C-fiber receptors located in proximity to pulmonary vessels

Table 1 Characteristics of randomized controlled studies

Study (author, year)	Sample size (*n*)	Number of coughing patients in the control group (%)	Intervention	Incidence of cough (%)	Fentanyl dose	Fentanyl injection speed	Age (years)
Pandey, 2004 [5]	502	86/251 (34)	Saline	34	3 μg/kg	5 s	18–60
			Lidocaine 1.5 mg/kg	13*			
Pandey, 2005 [15]	320	28/80 (35)	Saline	35	3 μg/kg	5 s	18–60
			Lidocaine 0.5 mg/kg	14*			
			Lidocaine 1 mg/kg	15*			
			Lidocaine 1.5 mg/kg	14*			
Lin, 2004 [1]	118	20/31 (65)	Saline	65	2.5 μg/kg	2 s	18–65
			Lidocaine 2 mg/kg	14*			
			Propofol 0.6 mg/kg	37			
			Ephedrine 5 mg	21*			
Guler, 2010 [16]	300	23/100 (23)	Saline	23	1.5 μg/kg	2 s	18–65
			Lidocaine 1 mg/kg	11*			
			Ketamine 0.5 mg/kg	0*			
Horng, 2007 [6]	300	58/150 (39)	Saline	39	2 μg/kg	2 s	18–80
			Clinidine 2 μg/kg	17*			
He, 2012 [17]	300	61/100 (61)	Saline	61	4 μg/kg	2 s	18–60
			Dexmedetomidine 0.5 μg/kg	40*			
			Dexmedetomidine 1 μg/kg	18*			
Yu, 2012 [18]	440	45/110 (41)	Saline	41	3 μg/kg	2 s	18–65
			Midazolam 0.06 mg/kg	64*			
			Dexmedetomidine 0.6 μg/kg	2*			
			Dexmedetomidine 0.6 μg/kg + midazolam 0.06 mg/kg	0*			
Yeh, 2007 [7]	360	39/180 (22)	Saline	22	1.5 μg/kg	5 s	18–65
			Ketamine 0.15 mg/kg	7*			
Tang, 2010 [11]	120	24/30 (80)	Intralipid	80	2.5 μg/kg	2 s	25–60
			Propofol 1 mg/kg	40*			
			Propofol 1.5 mg/kg	7*			
			Propofol 2 mg/kg	3*			
Phua, 1991 [10]	250	14/50 (28)	None	28	1.5 μg/kg	Not mentioned	Not mentioned
			Atropine 0.01 mg/kg	30			
			Midazolam 7.5 mg (po)	40			
			Morphine 0.2 mg/kg (IM)	6*			

Table 1 continued

Study (author, year)	Sample size (*n*)	Number of coughing patients in the control group (%)	Intervention	Incidence of cough (%)	Fentanyl dose	Fentanyl injection speed	Age (years)
Lui, 1996 [8]	131	13/30 (43)	Saline	43	5 μg/kg	5 s	16–45
			Terbutaline 5 mg (inhalation)	3*			
			Atropine 0.01 mg/kg	46			
Hung, 2010 [9]	600	37/200 (19)	Saline	19	150 μg	Not mentioned	18–75
			Fentanyl 25 μg	4*	125 μg		
			Fentanyl 25 μg	8*	150 μg		
Jung, 2011 [19]	800	34/200 (17)	None	17	2.0 μg/kg	3–5 s	18–75
			Fentanyl 0.5 μg/kg 1 min	10	1.5 μg/kg		
			Fentanyl 0.5 μg/kg 2 min	13	1.5 μg/kg		
			Fentanyl 0.5 μg/kg 3 min	12	1.5 μg/kg		
Gu, 2012 [20]	400	68/100 (68)	Saline	68	2.5 μg/kg	5 s	22–70
			Fentanyl 0.5 μg/kg	5*	2.0		
			Fentanyl 1 μg/kg	40*	1.5		
			Fentanyl 1.5 μg/kg	64	1.0		
Shrestha, 2012 [21]	150	15/50 (30)	Saline	30	150 μg	Not mentioned	18–75
			Fentanyl 25 μg	8*	125 μg		
			Fentanyl 25 μg	14*	150 μg		
Agarwal, 2003 [22]	200	14/50 (28)	None	28	2 μg/kg	5 s	18–60
			Salbutamol(inhalation)	6*			
			Beclomethasone(inhalation)	0*			
			Sodium cromoglycate (inhalation)	4*			
Dimitriou, 2006 [23]	50	6/26 (23)	None	23	2–3 μg/kg	Not mentioned	Not mentioned
			Temazepam 20 mg (po)	21			
Ai, 2010 [24]	277	21/93 (23)	Saline	23	2 μg/kg	2 s	19–63
			Pentazocine 0.5 mg/kg	4*			
Sun, 2011 [25]	120	42/60 (70)	Saline	70	5 μg/kg	2 s	20–60
			Dezocine 0.1 mg/kg	0*			
Horng, 2012 [26]	260	30/130 (23)	Saline	23	1.5 μg/kg	2 s	18–80
			Rocuronium 0.06 mg/kg	9*			
Mukherjee, 2012 [27]	320	91/152 (60)	Antacid (po)	60	2 μg/kg	2 s	18–60
			Dextromethorphan 40 mg (po)	4*			
Elmenesy, 2011 [28]	60	11/30 (36)	Water (po)	37	2 μg/kg	2 s	Not mentioned
			Dextromethorphan 60 mg (po)	13*			
Ambesh, 2009 [29]	300	48/150 (32)	Normal breathing	32	2.5 μg/kg	5 s	18–60
			Huffing maneuver	4*			

Table 1 continued

Study (author, year)	Sample size (*n*)	Number of coughing patients in the control group (%)	Intervention	Incidence of cough (%)	Fentanyl dose	Fentanyl injection speed	Age (years)
Lin, 2005 [2]	450	27/150 (18)	Fentanyl injection over 2 s	18	<70 kg;100 μg, >70 kg; 150 μg	2, 15, 30 s	18–80
			Fentanyl injection over 15 s	8*			
			Fentanyl injection over 30 s	1*			
Schäpermeier, 2008 [30]	464	4/117 (3)	Saline injection over 2 s	2	1.5 μg/kg	2, 5, 10 s	Not mentioned
			Fentanyl injection over 2 s	3			
			Fentanyl injection over 5 s	6			
			Fentanyl injection over 10 s	3			
Yu, 2007 [31]	200	16/50 (32)	Injection over 5 s (50 μg/ml)	32	3 μg/kg	5, 30 s	18–65
			Injection over 5 s (25 μg/ml)	16			
			Injection over 5 s (10 μg/ml)	12*			
			Injection over 30 s (10 μg/ml)	2*			
Chen, 2009 [32]	75	11/25 (44)	Fentanyl injection over 2 s	44	4 μg/kg	2, 15 s	18–70
			Fentanyl injection over 2 s (into the lower leg vein)	52			
			Fentanyl injection over 15 s	8*			
Yakici, 2013 [33]	981	114/493 (23)	Fentanyl injection over 5 s	23	2 μg/kg	5, 30 s	18–65
			Fentanyl injection over 30 s	4*			

All interventions were administered IV except for the above-mentioned interventions (e.g., PO, IM, inhalation)

PO per os, *IM* intramuscular

* $P < 0.05$ vs. control group in each study

Table 2 Summary of interventions

	No. of studies and references	No. of patients	Odds ratio (95 % confidence interval)	HeterogeneityI^2 %, *P* value
Atropine	2 [7, 9]	165	1.10 (0.58–2.11)	0, 1.00
α_2 agonists	3 [5, 16, 17]	820	0.32 (0.21–0.48)	45, 0.14
β_2 agonists	2 [7, 21]	164	0.10 (0.03–0.30)	21, 0.26
Benzodiazepines	3 [9, 17, 22]	370	2.04 (1.33–3.13)	12, 0.32
Fentanyl priming	4 [8, 18–20]	1,950	0.33 (0.19–0.56)	73, 0.0001
Lidocaine	4 [1, 4, 14, 15]	1,082	0.29 (0.21–0.39)	0, 0.51
NMDA receptor antagonists	4 [6, 15, 26, 27]	924	0.09 (0.02–0.42)	86, <0.001
Propofol	2 [1, 11]	181	0.07 (0.01–0.36)	72, 0.01
Speed of injection	5 [10, 29–32]	1,929	0.25 (0.11–0.58)	69, 0.004

NMDA *N*-methyl-D-aspartate

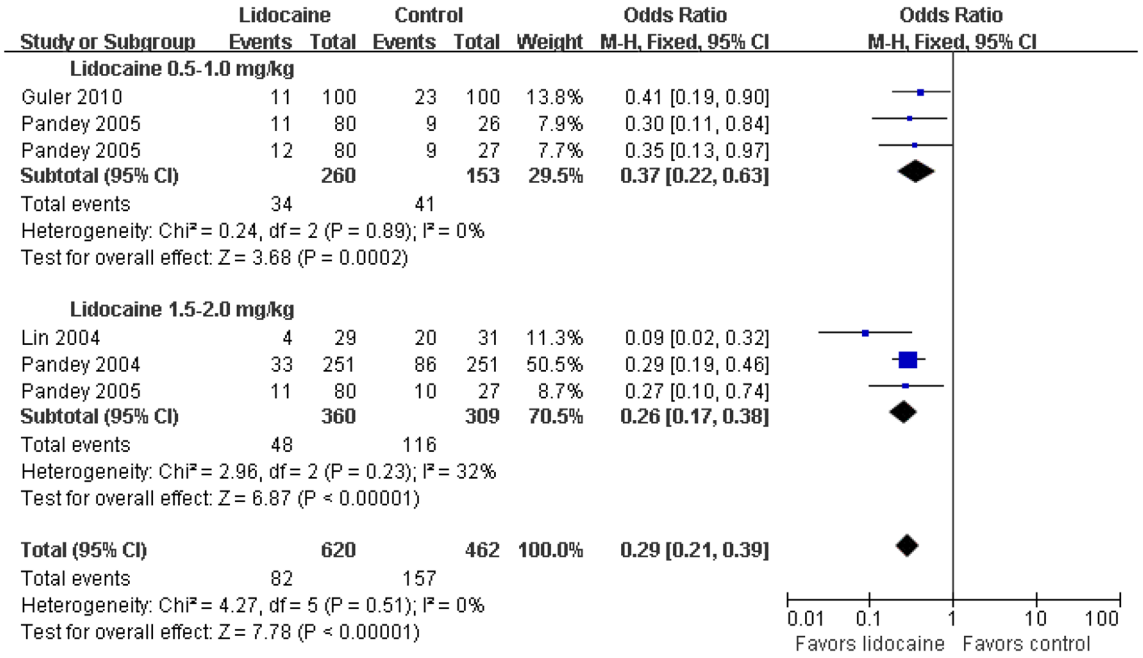

Fig. 2 Effect of lidocaine on fentanyl-induced cough

[34], and stimulation of the irritant receptors in the upper pulmonary mucosa secondary to fentanyl-induced tracheal smooth muscle constriction [35]. A recent study suggested that fentanyl enhances the excitability of rapidly adapting receptors to cause cough [36]. Ketamine, propofol, and β_2 agonists have bronchodilatory effects on airway smooth muscles [37]. The result of our analysis that β_2 agonists, NMDA receptor antagonists, and propofol reduce the incidence of FIC supports the possible role of bronchoconstriction in FIC.

In this analysis, α_2 agonists (clonidine, dexmedetomidine) were effective in preventing FIC. Although actual mechanisms are unknown, the reduction in fentanyl-induced muscle rigidity via the central effect of α_2 agonists may be a possible explanation [38]. Lidocaine was effective in suppressing FIC, irrespective of dosage. However, pretreatment with a high dose of lidocaine could not be justified because lidocaine may have arrhythmogenic effects, and its vasodilatory effect could augment the cardiovascular depression caused by induction agents [39]. The mechanism by which lidocaine suppress cough reflex induced mechanically and chemically remains unknown, but depression of brain-stem function was suggested to be a possibility [40]. Atropine did not suppress FIC, suggesting that vagal efferent pathways, via muscarinic receptors, may not be involved in FIC. Although midazolam has bronchorelaxant effects on airway smooth muscles, benzodiazepine premedication could not reduce the incidence of

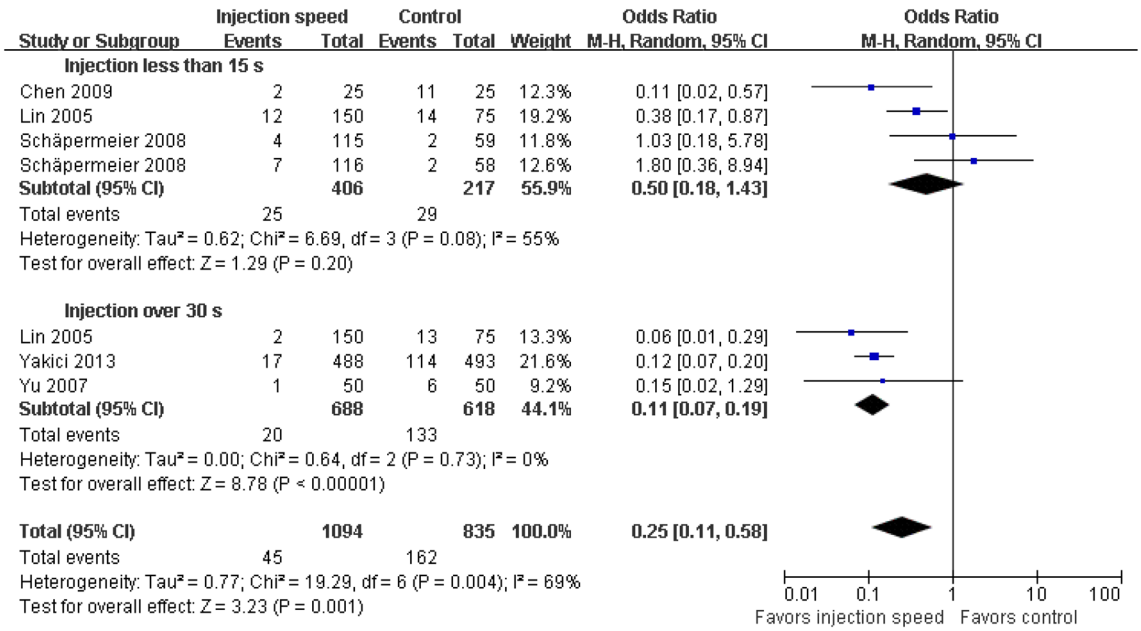

Fig. 3 Effect of injection speed on fentanyl-induced cough

FIC in this analysis. Therefore, FIC may be caused by multiple mechanisms and may be affected by several confounding factors.

Priming with a small dose of fentanyl and slow injection of fentanyl over a period of 30 s could effectively suppress FIC. From a pharmacologic viewpoint, the occurrence of cough is likely to be related to the balance between the time course of the drug's plasma concentration and effect-site concentration. In the remifentanil study, episodes of cough tended to occur when drug plasma concentration was maintained above its effect-site concentration, but no episodes of cough were induced when the difference between plasma concentration and effect-site concentration decreased or during the steady equilibrium state [41]. In this respect, priming with a small bolus dose of fentanyl that is insufficient to trigger an episode of cough while passing through the pulmonary circulation and then enters the systemic circulation may mean that the effect-site concentration could be raised without triggering a cough episode. In addition, fentanyl injection speed is an important factor in preventing FIC, as drug infusion time can affect peak plasma concentration. With prolonged infusion time, peak plasma concentration is reduced. The threshold for FIC is reached more easily at a high plasma concentration peak. If fentanyl is injected over a period of 30 s, the possibility of reaching the threshold of plasma concentration for coughing will be reduced because mean FIC onset time was 15 s. This suggests that the threshold of fentanyl plasma concentration required to induce an episode of cough may be reached within 15 s [7]. Therefore, prolonging the infusion time can decrease the incidence of FIC. In our meta-analysis, when fentanyl was administrated over a period <15 s, injection speed did not reduce the incidence of FIC. Therefore, fentanyl should be administered slowly—at least over a period of >15 s in a routine clinical setting.

There are some limitations to this study. With respect to heterogeneity among the included studies, subgroup analyses were performed to decrease heterogeneity and identify factors that influence the results. However, despite performing subgroup analyses, acceptable statistical heterogeneity was not reached in several interventions (NMDA receptor antagonists, fentanyl priming). Although the value of investigating heterogeneity when there are very few studies is questionable; statistical heterogeneity between studies limits direct comparisons of efficacy. In addition, publication bias cannot be excluded. We did not test for publication bias with funnel plots or other statistical tests, as these are unreliable in analyses of a small number of studies, as was the case in our review [42, 43]. Publication bias toward a small number of trials with positive results does not allow us to draw firm conclusions, and hence, larger observational studies are required. Lastly, besides a list of significant and nonsignificant results from various interventions, comparison in terms of adverse reactions and cost effectiveness are considered to be indispensable in the meta-analysis. However, such data were not mentioned in most original articles, so we could not extract relevant data from selected studies.

In conclusion, this meta-analysis suggests that lidocaine, NMDA receptor antagonists, propofol, α_2 agonists, β_2 agonists, priming with fentanyl, and slow injection of

fentanyl effectively suppress FIC. A future study should elucidate the true efficacy of other interventions that reached statistical significance in a limited number of studies (only one or two studies) and verify the plausible mechanism of FIC.

References

1. 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;51:654–9.
2. Lin JA, Yeh CC, Lee MS, Wu CT, Lin SL, Wong CS. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. Anesth Analg. 2005;101:670–4.
3. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. Anesth Analg. 2001;92:1442–3.
4. Ambesh SP, Singh N, Srivastava K. Fentanyl induced coughing caused life-threatening airway obstruction in a patient with arteriovenous malformation of tongue and hypopharynx. Internet J Anesthesiol. 2009;20:7.
5. 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;99:1696–8.
6. Horng HC, Wong CS, Hsiao KN, Huh BK, Kuo CP, Cherng CH, Wu CT. Pre-medication with intravenous clonidine suppresses fentanyl-induced cough. Acta Anaesthesiol Scand. 2007;51:862–5.
7. 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;19:53–6.
8. Lui PW, Hsing CH, Chu YC. Terbutaline inhalation suppresses fentanyl-induced coughing. Can J Anaesth. 1996;43:1216–9.
9. Hung KC, Chen CW, Lin VC, Weng HC, Hsieh SW. The effect of pre-emptive use of minimal dose fentanyl on fentanyl-induced coughing. Anaesthesia. 2010;65:4–7.
10. Phua WT, Teh BT, Jong W, Lee TL, Tweed WA. Tussive effect of a fentanyl bolus. Can J Anaesth. 1991;38:330–4.
11. Tang Q, Qian Y, Zhang Q, Yang J, Wang Z. Effects of different priming doses of propofol on fentanyl-induced cough during anesthesia induction: a preliminary randomized controlled study. Ups J Med Sci. 2010;115:121–4.
12. Higgins JPT, Green S, editors. Cochrane handbook for the systematic reviews of interventions. Version 5.0.2. Cochrane Collaboration; 2009.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther. 2009;89:873–80.
14. Viechtbauer W. Conducting meta-analyses in R with the metaphor package. J Stat Softw. 2010;36:1–48.
15. Pandey CK, Raza M, Ranjan R, Singhal V, Kumar M, Lakra A, Navkar DV, Agarwal A, Singh RB, Singh U, Singh PK. Intravenous lidocaine 0.5 $mg.kg^{-1}$ effectively suppresses fentanyl-induced cough. Can J Anaesth. 2005;52:172–5.
16. Guler G, Aksu R, Bicer C, Tosun Z, Boyaci A. Comparison of the effects of ketamine or lidocaine on fentanyl- induced cough in patients undergoing surgery: a prospective, double-blind, randomized, placebo-controlled study. Curr Ther Res Clin Exp. 2010;71:289–97.
17. He L, Xu JM, Dai RP. Dexmedetomidine reduces the incidence of fentanyl-induced cough: a double-blind, randomized, and placebo-controlled study. Ups J Med Sci. 2012;117:18–21.
18. Yu J, Lu Y, Dong C, Zhu H, Xu R. Premedication with intravenous dexmedetomidine-midazolam suppresses fentanyl-induced cough. Ir J Med Sci. 2012;181:517–20.
19. Jung HJ, Kim JB, Im KS, Cho HJ, Kim JW, Lee JM. 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. 2011;39:2379–84.
20. Gu C, Zhou M, Wu H, Li F, Tang Q. Effects of different priming doses of fentanyl on fentanyl-induced cough: a double-blind, randomized, controlled study. Pharmacol Rep. 2012;64:321–5.
21. Shrestha SK, Bhattarai B, Shah RS. Preemptive use of small dose fentanyl suppresses fentanyl induced cough. Kathmandu Univ Med J (KUMJ). 2012;10:16–9.
22. Agarwal A, Azim A, Ambesh S, Bose N, Dhiraj S, Sahu D, Singh U. Salbutamol, beclomethasone or sodium cromoglycate suppress coughing induced by iv fentanyl. Can J Anaesth. 2003;50:297–300.
23. Dimitriou V, Spyrou A, Ioakimidou A, Stranomiti J, Koursoumi E, Atsalakis J, Saranteas T. The influence of premedication and smoking. Middle East J Anesthesiol. 2006;18:943–6.
24. Ai Q, Hu Y, Wang Y, Wu S, Qin Z, Wang J, Wang G, Zhang J, An M. Pentazocine pretreatment suppresses fentanyl-induced cough. Pharmacol Rep. 2010;62:747–50.
25. Sun ZT, Yang CY, Cui Z, Zhang J, Han XP. Effect of intravenous dezocine on fentanyl-induced cough during general anesthesia induction: a double-blinded, prospective, randomized, controlled trial. J Anesth. 2011;25:860–3.
26. Horng HC, Lin BF, Wang TC, Lin SL, Liaw WJ, Wang HJ, Wong CS. Priming dose of intravenous rocuronium suppresses fentanyl-induced coughing. Acta Anaesthesiol Taiwan. 2012;50:147–9.
27. Mukherjee A, Kundu AK, Ghosh S, Choudhuri R, Bandopadhyay BK, Dasgupta S. Pre-emptive oral dexmethorphan reduces fentanyl-induced cough as well as immediate postoperative adrenocortico-tropic hormone and growth hormone level. J Anaesthesiol Clin Pharmacol. 2011;27:489–94.
28. Elmenesy TM, Hamden GA, Abo Eldahab HA, El Abd NA. Dextromethorphan reduced fentanyl induced cough and stress hormones release A randomized double blind controlled study. Egypt J Anaesth. 2011;27:25–30.
29. Ambesh SP, Singh N, Gupta D, Singh PK, Singh U. A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study. Br J Anaesth. 2010;104:40–3.
30. Schäpermeier U, Hopf HB. Fentanyl-induced cough does not depend on injection speed: a randomized study. Acta Anaesthesiol Scand. 2008;52:1071–5.
31. Yu H, Yang XY, Zhang X, Li Q, Zhu T, Wang Y, Liu B. The effect of dilution and prolonged injection time on fentanyl-induced coughing. Anaesthesia. 2007;62:919–22.
32. Chen YM, Chen WT, Liang SW, Gu MN. Intravenous injection rate and site of fentanyl affect the incidence and onset time of fentanyl-induced cough. Nan Fang Yi Ke Da Xue Xue Bao. 2009;29:339–40.
33. Yakici Ü, Koltka K, Demircan F, Küçükgöncü S, Orhan Sungur M, Karadeniz M, Özkan Seyhan T. The effect of the intravenous injection rate on the incidence of fentanyl induced cough. Anestzi Dergisi. 2013;1:17–22.
34. Böhrer H, Fleischer F, Werning P. Tussive effect of a fentanyl bolus administered through a central venous catheter. Anaesthesia. 1990;45:18–21.
35. Yasuda I, Hirano T, Yusa T, Satoh M. Tracheal constriction by morphine and by fentanyl in man. Anesthesiology. 1978;49:117–9.
36. Kamei J, Nakanishi Y, Asato M, Ikeda H. Fentanyl enhances the excitability of rapidly adapting receptors to cause cough via the

enhancement of histamine release in the airways. Cough. 2013;9:3.
37. Cheng EY, Mazzeo AJ, Bosnjak ZJ, Coon RL, Kampine JP. Direct relaxant effects of intravenous anesthetics on airway smooth muscle. Anesth Analg. 1996;83:162–8.
38. Hung KC. The possible mechanism of clonidine to suppress fentanyl-induced coughing. Acta Anaesthesiol Scand. 2009; 53:1227–8.
39. Schlimp CJ, Wiedermann FJ. Does fentanyl-induced cough justify pre-treatment with iv lidocaine 2 $mg.kg^{-1}$. Can J Anaesth. 2005;52:207.
40. Poulton TJ, James FM III. Cough suppression by lidocaine. Anesthesiology. 1979;50:470–2.
41. Kim JY, Chae YJ, Kim JS, Park YJ, Min SK. A target-controlled infusion regimen for reducing remifentanil-induced coughs. Korean J Anesthesiol. 2012;63:30–5.
42. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. J Clin Epidemiol. 2005;58:894–901.
43. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol. 2000;53:207–16.