Effect of Tramadol Pretreatment on Sufentanil-Induced Cough

Yi Zou, MD, Yingzi Ling, MD, Gaoyin Kong, MD, Yixun Tang, MD, PhD, Qian Huang, MD, Le Zhang, MD, Lai Wei, MD, PhD

Purpose: *To investigate the effect of tramadol pretreatment on the incidence and severity of sufentanil-induced cough.*
Design: *Randomized controlled trial.*
Methods: *Adults of both genders (N = 304; 18 to 65 years old, American Society of Anesthesiologists physical status I to II), scheduled for elective surgery, were randomized into two groups (n = 152): intravenous administration of tramadol 1 mg/kg (group T) or normal saline (group C). Then sufentanil bolus 0.3 mcg/kg was administered intravenously in 5 seconds. The incidence and severity of cough were observed for 1 minute. Mean arterial pressure, heart rate, nausea, vomiting, and truncal rigidity during induction were also recorded.*
Findings: *Patient characteristics were similar between the two groups. The incidence of cough was significantly lower in group T when compared with group C (7.9% vs 18.4%,* P < *.05); there were nine patients coughing severely in group C, whereas no severe cough occurred in group T (*P < *.05). The mean arterial pressure, heart rate, and incidences of other side effects were comparable between the two groups.*
Conclusions: *Pretreatment of intravenous tramadol 1 mg/kg could be a clinically effective intervention for attenuating sufentanil-induced cough.*

Keywords: *anesthetic induction, cough, tramadol, sufentanil.*

Yi Zou, MD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; Yingzi Ling, MD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; Gaoyin Kong, MD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; Yixun Tang, MD, PhD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; Qian Huang, MD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; Le Zhang, MD, Department of Cardiovascular Disease, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China; and Lai Wei, MD, PhD, Department of Anesthesiology, Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, PR China.

Funding: This research is funded by "Clinical Research Center for Anesthesiology of ERAS in Hunan Province" (2018SK7001).

Yi Zou and Yingzi Ling have contributed equally to this work.

Conflicts of interest: None to report.

Address correspondence to Lai Wei, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, No. 61, Jiefang West Road, Changsha City, Hunan Province, PR China; e-mail address: csweilai1982@126.com.

1089-9472/$36.00
https://doi.org/10.1016/j.jopan.2019.01.013

OPIOID-INDUCED COUGH (OIC) is a common phenomenon during induction of general anesthesia. A bolus of fentanyl, sufentanil, and remifentanil frequently elicits a cough, with an incidence up to 54.3%.[1] Although this complication is usually transient and self-limiting, patients are uncomfortable and OIC potentially increases heart rate (HR) and blood pressure.[2] Furthermore, severe OIC may cause periorbital petechiae and even lead to life-threatening airway obstruction, which requires immediate intervention.[3,4] Therefore, preventing OIC is clinically important.

Various mechanisms responsible for OIC have been proposed. First, the rapidly adapting receptors present on the mucosa of the proximal tracheobronchial airway can be stimulated by fentanyl causing bronchoconstriction.[5] Second, fentanyl and sufentanil are available as citrate salts. Tanaka and Maruyama[6] found that citrate could stimulate C fibers (also known as J-receptors) present on the smooth muscles of trachea and bronchi releasing neuropeptides, which are responsible for coughing. Third, opioids such as sufentanil enhance vagal activity leading to bronchoconstriction, inducing muscle rigidity, which causes sudden adduction of vocal cords, these reflexes may also cause coughs.[7,8]

A meta-analysis demonstrated that beta-2 agonists (terbutaline, salbutamol), lidocaine, alpha-2 agonists (dexmedetomidine), propofol, *N*-methyl-D-aspartate (NMDA) receptor antagonists (ketamine), and a fentanyl priming dose were all effective in preventing fentanyl-induced cough.[9] However, some of these agents have their limits, beta-2 agonists are rarely used in general anesthesia and may be associated with adverse cardiovascular effects.[10] Lidocaine and dexmedetomidine may induce severe bradycardia during laryngoscopy because of vagus nerve stimulation.[11-14] On the other hand, a priming dose of propofol could make patients unconscious, if coughs were elicited, muscle rigidity and vocal cord adduction may cause difficult ventilation.[7,8] Therefore, preventing OIC with NMDA receptor antagonists (ketamine) or fentanyl priming dose (mu-receptor agonism) may be preferred.

Tramadol, a centrally acting analgesic, is commonly used for postoperative analgesia and prevention of perioperative shivering.[15] Tramadol performs as a mu-opioid receptor agonist, serotonin-norepinephrine reuptake inhibitor, NMDA receptor antagonist, nicotinic acetylcholine receptor antagonist, and M1 and M3 muscarinic acetylcholine receptor antagonist.[16] Studies have shown that tramadol is effective in treating neurogenic cough or fentanyl-induced cough; the mechanisms may be NMDA receptor antagonism and mu-receptor agonism.[17,18] Kamei et al[19] found that NMDA receptor antagonists had a marked cough-depressing effect, they also demonstrated that serotonergic and opioid receptors are involved in the antitussive mechanism.[20] Louly et al[21] previously used tramadol to treat a patient with refractory chronic cough and found that cough intensity was significantly lower after tramadol treatment compared with placebo. Furthermore, tramadol inhibits M1 and M3 muscarinic receptors, thus may attenuate vagal stimulation on trachea and bronchi.[22] Therefore, tramadol may be promising to prevent OIC.

Sufentanil, a thienyl analogue of fentanyl, is widely used for anesthetic induction with less impact on hemodynamics and strong analgesic effect. However, a bolus of sufentanil even in a small dose may evoke cough with an incidence from 15.8% to 31.9%.[2,23] The studies of tramadol effect on sufentanil-induced cough are still limited; therefore, this clinical trial was designed to investigate the antitussive effect of tramadol pretreatment on sufentanil-induced cough during anesthetic induction.

Materials and Methods

The randomized controlled study was approved by the Ethics Committee of Hunan Provincial People's Hospital. After consents were obtained, 304 participants aged 18 to 65 years of both genders undergoing laparoscopic cholecystectomy or gynecologic laparoscopic surgery with American Society of Anesthesiologists (ASA) physical status classification I to II were included. Exclusion criteria included a history of smoking, chronic cough, upper respiratory tract infection, asthma, treatment with bronchodilators or steroids, or angiotensin-converting enzyme inhibitors. After entering the operating room, the patients were monitored by electrocardiogram, noninvasive blood pressure, and pulse oximetry; an intravenous cannula was inserted peripherally and Ringer's solution was infused with a rate of 4 to 6 mL/min.

Table 1. Patient Characteristics

Characteristics	Group C (n = 152)	Group T (n = 152)	*P* Value
Gender (M/F)	48/104	40/112	.3
Age (y)	44 ± 11	45 ± 10	.4
Weight (kg)	60 ± 9	60 ± 8	.8
ASA status (I/II)	107/45	105/47	.8

ASA, American Society of Anesthesiologists.

The patients were randomized into two groups with the help of a computer-generated table of random numbers (n = 152). Tramadol group (group T): tramadol hydrochloride injection (UCB Pharma (Zhuhai) Co, Ltd, Zhuhai, China) 1 mg/kg was infused intravenously for 5 minutes before anesthetic induction. Control group (group C): an equal volume of normal saline was infused intravenously for 5 minutes before anesthetic induction.

The patients received 6 to 8 L/min oxygen through a face mask and anesthetic induction was started by a bolus of sufentanil citrate injection (Yichang Humanwell Pharmaceutical Co, Ltd, Hubei, China) 0.3 mcg/kg (5 mcg/mL) over 5 seconds via the peripheral venous access. An experienced observer blinded to the premedication given to the patients evaluated and recorded the occurrence of cough for 1 minute after sufentanil injection. The incidence of cough was recorded as cough manifested or not, cough severity was graded based on the number of cough episodes as mild (1 to 2 times), moderate (3 to 5 times), and severe (>5 times).[1] Other side effects such as nausea and vomiting after tramadol or normal saline infusion, and truncal rigidity after sufentanil injection were also recorded. Then induction was finished by injection of midazolam 0.05 mg/kg, cisatracurium 0.2 mg/kg, and propofol 1 mg/kg. Mean arterial pressure (MAP) and HR were recorded at three time points: before the administration of tramadol or normal saline (T0), 1 minute after sufentanil injection (T1), and 1 minute after endotracheal intubation (T2).

Statistical Analysis

Data are expressed as the mean ± standard deviation, number, proportion, or percentage. Comparison of age and weight was analyzed by unpaired Student's *t* test. The gender, ASA physical status, incidence of nausea, vomiting, truncal rigidity, cough, and cough severity were compared using χ^2 test or Fisher's exact test. Comparison of MAP and HR was analyzed by repeated measures two-way analysis of variance. SPSS 18.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. A *P* value of $< .05$ was considered statistically significant.

Results

Patients (N = 320) were screened for this study; seven patients were withdrawn because of a habit of smoking and nine patients declined to participate. Therefore, a total of 304 patients were enrolled in the study, 152 patients in each group. Patient characteristics including gender, age, body weight, ASA physical status were similar between the two groups (Table 1). The incidence of cough was significantly lower in group T when compared with group C (7.9% vs 18.4%, $P < .05$). Nine patients coughed severely in group C, whereas no severe cough occurred in group T (Table 2). The

Table 2. Incidences and Severity of Cough

Incidences and Severity of Cough	Group C (n = 152)	Group T (n = 152)	*P* Value
Cough incidence, No. (%)	28 (18.4)	12 (7.9)*	.007
Severity of cough, No. (%)			
Mild	14 (9.2)	6 (3.9)	.06
Moderate	7 (4.6)	6 (3.9)	.78
Severe	9 (5.9)	0*	.002

Severity of cough: mild (1 to 2 times), moderate (3 to 5 times), severe (>5 times).
*Significantly different, compared with group C ($P < .05$).

Table 3. Incidences of Nausea, Vomiting, and Truncal Rigidity

Side-effects	Group C (n = 152)	Group T (n = 152)	*P* Value
Nausea, No. (%)	0 (0)	2 (1.3%)	.48
Vomiting, No. (%)	0 (0)	2 (1.3%)	.48
Truncal rigidity, No. (%)	1 (0.7%)	0 (0)	.9

incidences of nausea, vomiting, and truncal rigidity were comparable between the two groups, whereas in group T, four patients with a history of motion sickness experienced nausea or vomiting during or after tramadol infusion, one patient in group C experienced transient truncal rigidity without harmful consequences (Table 3). The MAP and HR decreased significantly after sufentanil injection at T1 and increased significantly after endotracheal intubation at T2 ($P < .05$). At the three time points, the MAP and HR were comparable between the two groups; however, after 1 minute of sufentanil injection, the MAP in group T was significantly lower than group C (Table 4).

Discussion

The results found that premedication of intravenous tramadol 1 mg/kg infusion could reduce the incidence of sufentanil-induced cough, tramadol also attenuated cough severity. The mechanism may include mu-opioid receptor agonism, NMDA receptor antagonism, serotonin reuptake inhibition, and muscarinic receptor antagonism.[16,19,20,22]

Administration of opioids in a bolus during general anesthetic induction often induces coughing.[1] Previous studies showed that slowing down injection speed, change injection order of fentanyl or sufentanil, and pretreatment with different medicines during anesthetic induction could attenuate OIC.[24-26] Hence, to avoid these factors differing between the two groups, sufentanil was injected before the other induction agents in all the patients, and the injection time was 5 seconds as the previous study.[23] The results showed that the incidence of cough after sufentanil injection in group C was 18.4%, which was similar to the previous studies (15.8% and 31.9%).[2,23]

Elmawgoud[18] conducted a double-blind, randomized controlled trial of tramadol against placebo, treating patients receiving fentanyl bolus during anesthetic induction. The author found that the incidence of fentanyl-induced cough was significantly reduced by premedication of intravenous infusion of tramadol 1 mg/kg in 15 minutes, however, the sample size in the research was limited and the infusion rate of tramadol was 15 minutes, which was time-consuming in clinical situation. Previous studies showed that tramadol was effective in treating patients suffering perioperative shivering,[15,27] the authors found that after intravenous infusion of tramadol, all the shivering ceased within 2.1 ± 1.0 minutes.[15]

Table 4. Vital Signs in Different Time Points

Vital Signs	Group (n = 152)	T0	T1	T2
MAP (mm Hg)	Group C	90.4 ± 9.9	83.7 ± 8.0*	101.8 ± 14.2*,†
	Group T	89.1 ± 7.1	80.5 ± 8.3*,‡	99.5 ± 13.6*,†
HR (bpm)	Group C	75.7 ± 10.2	68.2 ± 9.7*	85.7 ± 11.2*,†
	Group T	76.2 ± 9.7	65.98 ± 10.8*	84.39 ± 11.6*,†

HR, heart rate; MAP, mean arterial pressure; T0, before the administration of tramadol or normal saline; T1, 1 minute after sufentanil injection; T2, 1 minute after endotracheal intubation.

*Significantly different, compared with T0 in the same group ($P < .05$).

†Significantly different, compared with T1 in the same group ($P < .05$).

‡Significantly different, compared with group C at the same time ($P < .05$).

On the basis of the rapid onset property of tramadol, the infusion rate of tramadol in the present study was 5 minutes. The results showed that after intravenous infusion for 5 minutes, tramadol significantly reduced the incidence of sufentanil-induced cough during anesthetic induction. Moreover, there were nine patients who coughed severely in group C, whereas no severe cough occurred in group T. Thus, the present study indicated that premedication of 1 mg/kg of tramadol could suppress sufentanil-induced cough in a short time after infusion.

Nausea and vomiting are the most frequent complications of tramadol, the incidence of nausea and vomiting after intravenous tramadol administration could be 5% to 16.7%.[15,27] Considering the relatively high incidence of nausea and vomiting of tramadol, an intravenous push of tramadol bolus was avoided in the present study. The results showed that there were only four patients who had a history of motion sickness experienced nausea or vomiting during or after tramadol infusion in group T, the incidence (2.6%) was not significantly different from group C. This indicated that a low dose and slow infusion rate of tramadol (1 mg/kg in 5 minutes) could be used safely in patients without a history of motion sickness.

Shen et al[1] reported that all coughing occurred within 1 minute (24 ± 4.3 seconds) after sufentanil administration; therefore, cough was evaluated and observed for 1 minute. In the present study, after a sufentanil bolus, all the coughs occurred and ceased within 1 minute regardless of severity, this is consistent with the result from Shen et al.[1] Furthermore, Yuan et al[7] reported that sufentanil injection might induce muscle rigidity, which was also a complication of fentanyl and might cause respiratory compromise.[28] In the present study, a 32-year-old male in group C experienced truncal rigidity after sufentanil bolus, and manual ventilation became difficult, his SpO_2 dropped to 91% and then increased to 100% after continuous manual ventilation and the onset of muscular relaxant. The incidence of truncal rigidity in the present study was low (0.7%), and the complication does not appear to be a contraindication to use of sufentanil. However, respiratory compromise should be readily recognized and treated after sufentanil administration.

In the present study, the MAP and HR increased obviously during patients coughing and decreased even lower than the baseline (T0) after coughs disappeared. This may be because of sedation and sympathetic nerve inhibition by sufentanil.[29] However, although cough incidence in group T was lower than group C, decreasing of HR in group T was not significantly different compared with group C at T1. It was speculated that after cough disappeared, the HR decreased rapidly in both the groups. Meanwhile, the results showed that premedication of tramadol 1 mg/kg could be used safely during anesthetic induction without any cardiovascular events.

Limitation

The present study has its own limitations. First, all patients enrolled were undergoing laparoscopic cholecystectomy or gynecologic laparoscopic surgery, so there were more females than males recruited; however, to our knowledge, gender does not relate to OIC.[29] Therefore, this limitation may not affect the conclusion of the study. Second, this is a single-blind research, if the premedication giver in the study was blinded to the agent, the results may be more persuasive. Third, we did not investigate the effect of different doses of tramadol on the occurrence and reflex degree of sufentanil-induced cough. Finally, considering the side effects of nausea and vomiting, intravenous tramadol should be administered slowly and not be used to prevent OIC in patients with a high risk of nausea and vomiting.

Conclusions

The present study suggested that pretreatment with 1 mg/kg of tramadol could suppress the incidence and severity of cough induced by sufentanil during anesthetic induction. Therefore, premedication of tramadol could be a clinically effective intervention for attenuating sufentanil-induced cough.

References

1. Shen JC, Xu JG, Zhou ZQ, Liu HJ, Yang JJ. Effect of equivalent doses of fentanyl, sufentanil, and remifentanil on the incidence and severity of cough in patients undergoing abdominal surgery: A prospective, randomized, double-blind study. *Curr Ther Res Clin Exp*. 2008;69:480-487.
2. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: A randomized controlled trial. *Pharmacol Rep*. 2015;67:52-55.
3. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg*. 2001;92:1442-1443.
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. Lui PW, Hsing CH, Chu YC. Terbutaline inhalation suppresses fentanyl-induced coughing. *Can J Anaesth*. 1996;43:1216-1219.
6. Tanaka M, Maruyama K. Mechanisms of capsaicin- and citric-acid-induced cough reflexes in guinea pigs. *J Pharmacol Sci*. 2005;99:77-82.
7. Yuan YH, Xu PF, Ge HQ, Lu ZH, Xu M. Sufentanil induced muscle rigidity identified by ventilator graphics in medical intensive care unit. *Chin Med J (Engl)*. 2013;126:3396.
8. Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. *Anesthesiology*. 1997;87:1070-1074.
9. Kim JE, Min SK, Chae YJ, Lee YJ, Moon BK, Kim JY. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: A meta-analysis. *J Anesth*. 2014;28:257-266.
10. Arcaro I, Fischer BL, Lascola KM, Clark-Price SC. Effects of intravenous terbutaline on heart rate, arterial pressure and blood gases in anesthetized horses breathing air. *Vet Anaesth Analg*. 2017;44:70-76.
11. Demczuk RJ. Significant sinus bradycardia following intravenous lidocaine injection. *Anesthesiology*. 1984;60:69-70.
12. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet*. 2017;56:893-913.
13. Latuska RF, Kuhl NO, Garrett CG, Berry JM, Gelbard A. Severe bradycardia associated with suspension laryngoscopy. *Laryngoscope*. 2016;126:949-950.
14. Suzuki M, Kirchner JA. Laryngeal reflex pathways related to rate and rhythm of the heart. *Ann Otol Rhinol Laryngol*. 1967;76:774-780.
15. Bansal P, Jain G. Control of shivering with clonidine, butorphanol, and tramadol under spinal anesthesia: A comparative study. *Local Reg Anesth*. 2011;4:29-34.
16. Scott LJ, Perry CM. Tramadol: A review of its use in perioperative pain. *Drugs*. 2000;60:139-176.
17. Dion GR, Teng SE, Achlatis E, Fang Y, Amin MR. Treatment of neurogenic cough with tramadol: A pilot study. *Otolaryngol Head Neck Surg*. 2017;157:77-79.
18. Elmawgoud AA. Effect of tramadol on fentanyl induced cough: A double-blind, randomized, controlled study. *Egypt J Anaesth*. 2013;29:301-304.
19. Kamei J, Tanihara H, Igarashi H, Kasuya Y. Effects of N-methyl-D-aspartate antagonists on the cough reflex. *Eur J Pharmacol*. 1989;168:153-158.
20. Kamei J. Role of opioidergic and serotonergic mechanisms in cough and antitussives. *Pulm Pharmacol*. 1996;9:349-356.
21. Louly PG, Medeiros-Souza P, Santos-Neto L. N-of-1 double-blind, randomized controlled trial of tramadol to treat chronic cough. *Clin Ther*. 2009;31:1007-1013.
22. Nakamura M, Minami K, Uezono Y, et al. The effects of the tramadol metabolite O-desmethyl tramadol on muscarinic receptor-induced responses in Xenopus oocytes expressing cloned M1 or M3 receptors. *Anesth Analg*. 2005;101:180-186.
23. Agarwal A, Gautam S, Nath SS, Gupta D, Singh U. Comparison of the incidence and severity of cough induced by sufentanil and fentanyl: A prospective, randomised, double-blind study. *Anaesthesia*. 2007;62:1230-1232.
24. Yu H, Yang XY, Zhang X, et al. The effect of dilution and prolonged injection time on fentanyl-induced coughing. *Anaesthesia*. 2007;62:919-922.
25. Wang L, Yao JH, Zhu JJ, Liu B, Zhu JG, Zhou DC. Effect of optimizing anesthetic injecting sequence during induction on fentanyl-induced coughing. *Zhonghua Yi Xue Za Zhi*. 2010;90:921-923.
26. Shuying L, Ping L, Juan N, Dong L. Different interventions in preventing opioid-induced cough: A meta-analysis. *J Clin Anesth*. 2016;34:440-447.
27. T M, Kaparti L. A randomised trial comparing efficacy, onset and duration of action of pethidine and tramadol in abolition of shivering in the intra operative period. *J Clin Diagn Res*. 2014;8:GC07-GC09.
28. Çoruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. *Chest*. 2013;143:1145-1146.
29. El Baissari MC, Taha SK, Siddik-Sayyid SM. Fentanyl-induced cough—pathophysiology and prevention. *Middle East J Anaesthesiol*. 2014;22:449-456.