Egyptian Journal of Anaesthesia (2013) **29**, 301–304

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Effect of tramadol on fentanyl induced cough: A double-blind, randomized, controlled study

Ashraf Abd Elmawgoud *

Department of Anesthesia, Faculty of Medicine, Cairo University, Egypt

Received 14 February 2013; revised 6 May 2013; accepted 19 May 2013
Available online 21 June 2013

KEYWORDS

Tramadol;
Fentanyl;
Cough

Abstract *Background:* Tramadol has NMDA antagonist effect and reported to have antitussive effect. The aim of this study to assess the effect of preoperative i.v. tramadol compared to placebo on the incidence and severity of fentanyl induced cough.

Method: In a prospective, randomized, double-blind study, 100 patients ASA I, age 18–50 years old, scheduled for elective laparoscopic surgeries under general anesthesia. Patients were randomly allocated to one of two groups: Tramadol group received i.v. tramadol 1 mg/kg in 100 ml saline and control group received 100 ml saline over 15 min before induction of anesthesia. The incidence and severity of cough was assessed following injection of fentanyl 2 μg/kg. The postoperative analgesic requirements, nausea, and vomiting were also recorded.

Results: The incidence of FIC was significantly less in tramadol treated group being [10 (20%)], compared to control group being [19 (38%)] ($p < 0.05$). Regarding the grade of FIC; 7 out of 10 in tramadol group and 12 out of 19 in control group showed mild form, 3 out of 10 in tramadol group and 4 out of 19 in control group showed moderate form and 3 out of 19 in control group with no patients in tramadol group showed severe form. The postoperative analgesic requirements was significantly less in tramadol group ($p < 0.05$) with no significant difference in postoperative nausea and vomiting between the two groups.

Conclusion: Tramadol 1 mg/kg i.v. infusion 15 min before induction of anesthesia reduced the incidence and severity of cough after fentanyl injection 2 μg/kg with reduction of postoperative analgesic requirements and without changes in postoperative nausea and vomiting compared to placebo.

Introduction

Fentanyl is a commonly used drug during induction of general anesthesia but the associated fentanyl induced cough (FIC) that may range from simple to sudden explosive cough is uncomfortable to the patients and may be harmful in neurosurgery and ophthalmic surgery as it increases the intracranial

* Address: Dar Alshifa Hospital, Kuwait. Tel.: +965 66074003
E-mail address: ahrafaly@hotmail.com

Peer review under responsibility of Egyptian Society of Anesthesiologists.

ELSEVIER Production and hosting by Elsevier

1110-1849 © 2013 Production and hosting by Elsevier B.V. on behalf of Egyptian Society of Anesthesiologists.
Open access under CC BY-NC-ND license. http://dx.doi.org/10.1016/j.egja.2013.05.001

and intraocular pressures [1]. The incidence of FIC ranges from 18% to 65% and its mechanism is unclear [2].

Many techniques have been used to reduce the incidence and severity of FIC including huffing maneuver [3], dilution or slow injection of fentanyl [2]. Several drugs also have been used including selective B_2 agonist, beclomethasone or sodium chromoglycate [4], lidocaine and ephedrine [1], clonidine [5], dexamethasone [6], *N*-methyl-d-aspartate (NMDA) antagonists (ketamine and dexmethorphane) [7,8].

Tramadol hydrochloride is a centrally acting codeine analogue, it has opioid action as a μ opioid receptors agonist, and nonopioid action through inhibition of reuptake of monoamines (serotonin and norepinephrine) and a NMDA receptor antagonist [9].

It was postulated that tramadol as a NMDA receptor antagonist and it has antitussive effect as reported by Lin and his colleagues [10] may be useful in reducing the incidence and severity of FIC. Therefore, this study was conducted in a randomized, double-blinded, controlled manner to assess the effect of preoperative i.v. tramadol compared to placebo on the incidence and severity of FIC and postoperative analgesic requirements.

Methods

After approval of the local ethical committee, an informed written consent was obtained from 100 patients American Society of Anesthesiology (ASA) physical status I, age 18–50 years old, planned for elective laparoscopic surgeries (cholecystectomy, ovarian cystectomy, and varicocelectomy) under general anesthesia in Dar Alshifa hospital (State of Kuwait) from April 2012 to January 2013.

Patients were excluded from the study if they were smokers or having history of bronchial asthma, chronic obstructive pulmonary disease, recent respiratory tract infection, or treated with bronchodilator, steroid, angiotensin converting enzyme inhibitors or if they were allergic to tramadol.

Sedative premedication drugs were not given to the patients, only 40 mg omeprazole i.v. and 10 mg metoclopramide i.v. were given as a premedication. When the patients arrived to the operation theater, patients were randomly allocated into two equally divided groups (50 patients each) by using the closed envelop technique. The patients were shifted to the preparation room where a peripheral cannula was inserted, and they were monitored by electrocardiogram, pulse oximetry, and noninvasive blood pressure. In order to maintain the blind nature of the study, the studied drugs were given by the anesthesia nurse (unaware of the study) according to the instructions written in a sealed envelope.

- Tramadol group: in which tramadol hydrochloride (Tramal, Grünenthal GmbH) 1 mg/kg in 100 ml saline i.v. infusion was given over 15 min before induction of anesthesia using the same dose used by Lin et al. [10].
- Saline group (control group): in which 100 ml of saline i.v. infusion was given over 15 min before induction of anesthesia.

Then, the patients were shifted to the operation room where electrocardiogram, pulse oximetry, and noninvasive blood pressure were attached and induction of general anesthesia was started with fentanyl 2 μg/kg as a first drug over a period of 2 s, and the patients were observed for 1 min for the incidence and the severity of cough. The induction was continued by propofol 2 mg/kg and cisatracurium 0.15 mg/kg to facilitate orotracheal intubation. Anesthesia was maintained with sevoflurane 1–2% in O_2/air (50%/50%). At the end of surgery, sevoflurane was discontinued, the residual muscle relaxant was reversed and the patients were shifted to the recovery room where postoperative pain was treated with pethidine 25 mg i.v. increments and the patients were instructed to start using intravenous patient controlled analgesia (PCA) pethidine (IVAC® PCAM® syringe pump, Cardinal Health) where the PCA pump was adjusted to deliver pethidine bolus dose 10 mg with lockout interval 10 min and maximum 4 hourly dose 200 mg with readjustment of the PCA regimen if analgesia was inadequate.

The following data were recorded by an anesthesia nurse who was blinded for the patient group:

1. The incidence of cough (The number of patients developed cough).
2. The severity of cough using the scale used in the study of He et al. [11] depend on the number of coughs (mild = 1–2; moderate = 3–4; and severe = $\geqslant$5).
3. Peripheral O_2 saturation (SpO_2), heart rate (HR), and mean arterial pressure (MAP) were recorded before fentanyl injection and 1 min after injection, (O_2 desaturation if happened was treated by O_2 and assisted or controlled ventilation, bradycardia if happened was treated by atropine 0.4 mg, and hypotension if happened was treated by rapid i.v. crystalloid).
4. Development of chest wall rigidity after fentanyl injection.
5. Time to first request of postoperative pethidine.
6. The amount of postoperative PCA pethidine consumed (0–6)h, (6–12)h, (12–24)h and (0–24)h.
7. Postoperative nausea and vomiting within 24 h (persistent nausea >30 min and vomiting >2 times) was treated with ondansetron 4 mg i.v.

Statistical analysis

The sample size of 50 patients in each group was calculated using the program of Biostatics version 3.01 based on the result of the previous studies that found that the incidence of FIC was 40% and assuming that tramadol will decrease the incidence of FIC by 50% with the α-error level was fixed at 0.05 and the power was set at 80%.

Data were presented as means (SD) or number (percentage). Numerical data were analyzed by using Student's

Table 1 Patient characteristics and operation time.

Variables	Group (S) (n = 50)	Group (T) (n = 50)
Age (years)	39(13)	41(12)
Sex (male/female)	28/22	31/19
Weight (kg)	79(9)	80(8)
Operation time (min)	52(8)	50(7)

Group S: saline group, group T: tramadol group. Data presented as mean (SD) or number.
No significant differences between the studied groups.

Table 2 Incidence and severity of fentanyl induced cough and chest rigidity.

Variables	Group (S) ($n = 50$)	Group (T) ($n = 50$)
Patients developed cough (%)	19(38)	10(20)*
Grades of cough		
Mild	12(24)	7(14)*
Moderate	4(8)	3(6)
Sever	3(6)	0(0)*
Chest rigidity (%)	0(0)	0(0)

Group S: saline group, group T: tramadol group. Data presented as number (percentage).
* Significant difference ($p < 0.05$) Compared to group S.

Table 4 Time to first request of analgesia and postoperative analgesic requirements.

Variables	Group (S) ($n = 50$)	Group (T) ($n = 50$)
Time to first request of pethidine	5.1(0.6)	9.1(0.9)*
The amount of postoperative pethidine		
0–6 h	125(9.3)	90.8(7.7)*
6–12 h	120(9.8)	84.4(9.1)*
12–24 h	179.2(11.9)	131.4(10.1)*
0–24 h	381(15.9)	279.6(11.5)*

Group S: saline group, group T: tramadol group. Data presented as mean (SD).
* Significant difference ($p < 0.05$) Compared to group S.

unpaired *t*-test. Nonparametric data were analyzed by using the Mann–Whitney *U*-test. A value of $P < 0.05$ was considered significant. All statistical analysis was performed using Microsoft office Excel.

Results

Hundred patients were enrolled into the study (50 in each group) including 59 males and 41 females. There were no significant differences between the two groups regarding age, sex, weight, and operation time (Table 1).

Incidence of FIC was significantly less in tramadol treated group being [10 (20%)], compared to saline group being [19 (38%)] ($p < 0.05$). Regarding the grade of FIC; 7 out of 10 in tramadol group and 12 out of 19 in saline group showed mild form, 3 out of 10 in tramadol group, and 4 out of 19 in saline group showed moderate form and 3 out of 19 in saline group with no patients in tramadol group showed severe form. (Table 2).

There were no patients in both groups developed chest rigidity. (Table 2).

There were no significant differences in hemodynamic changes (HR and MAP) and peripheral O_2 saturation between the two groups at the times of recording. (Table 3).

In tramadol group, the time to first request of pethidine was significantly longer and the amount of postoperative pethidine within 24 h were significantly less compared to saline group ($p < 0.05$) (Table 4).

There were no significant differences in postoperative nausea and vomiting within 24 h between the two groups. (Table 5).

Table 5 Postoperative nausea and vomiting.

	Group (S) ($n = 50$)	Group (T) ($n = 50$)
Nausea	13(26)	11(22)
Vomiting	2(4)	3(6)

Group S: saline group, group T: tramadol group. Data presented as number (percentage).
No significant differences between the studied groups.

Discussion

This study demonstrated that premedication with i.v. tramadol 1 mg/kg reduced the incidence of FIC from 38% in the saline group to 20% when fentanyl was given in a dose of 2 μg/kg as a first drug during induction of anesthesia.

Although opioid drugs have cough depressant effect, i.v. fentanyl paradoxically induces cough [12].

Many theories have been attributed to explain FIC; the first possible theory may be that fentanyl stimulates C-fiber receptors present in the smooth muscles of the trachea, bronchi, and alveolar wall causing constriction with deformation of bronchial mucosa and stimulation of irritant receptors triggering the cough reflex as selective B_2 agonist (Salbutamol) or NMDA antagonists (ketamine) were found to be effective in reducing the incidence of FIC [4,7]. The second possible theory may be that fentanyl induced muscle rigidity as α_2 agonist (clonidine) reduced the incidence of FIC through reversal of muscle rigidity [5].

To my knowledge, there were no reports about the effect of tramadol on FIC, also the effective dose of tramadol that reduce FIC, so I used the dose of 1 mg/kg as that used in the study of Lin et al. [10].

Several reports showed that many physical methods and drugs have been used to decrease the incidence of FIC but showing controversial results.

Coinciding with the results in this study, ketamine 0.15 mg/kg was given 1 min before fentanyl injection. The incidence of

Table 3 Hemodynamic changes and peripheral O_2 saturation.

Time	Group (S) ($n = 50$)			Group (T) ($n = 50$)		
	HR	MAP	SpO_2	HR	MAP	SpO_2
Immediately before fentanyl injection	77(6)	95(3)	97(1)	79(5)	94(2)	96(2)
1 min after fentanyl injection	69(6)	88(2)	98(1)	73(2)	88(2)	98(1)

Group S: saline group, group T: tramadol group. Data presented as mean (SD).
No significant differences between the studied groups.

FIC decreased from 21.6% to 7.2% [7]; premedication with oral dextromethorphane 40 mg 1 h before induction reduced the incidence of FIC from 59.8% to 3.9% [8]; huffing maneuver (forced expiration against open glottis) before induction reduced the incidence of cough response to fentanyl but this maneuver cannot be used in premedicated patients with midazolam; dilution of fentanyl 10 μg/ml with a prolonged injection time reduced FIC [2]; premedication with intravenous clonidine 2 μg/kg decreased FIC from 38.7% to 17.3% with mild reduction in heart rate and blood pressure [5]; intravenous dexmeditomedine 0.5 μg/kg or 1 μg/kg effectively reduced the incidence of FIC [12], also intravenous ephedrine 5 mg and lidocaine 2 mg/kg before fentanyl decreased the incidence of cough response to fentanyl but ephedrine increases heart rate and blood pressure and lidocaine potentiates cardiovascular depressant effect of the induction agents [1].

On the contrary, propofol 0.6 mg/kg before fentanyl failed to decrease the incidence of FIC [1].

From the previously mentioned possible mechanisms of FIC and the drugs tried to reduce it, the results of this study can be explained by the antitussive effect of tramadol as reported by Lin et al. [10] as tramadol has μ opioid receptors agonist effect which is involved in the opioid antitussive effect [13] and NMDA receptor antagonist effect of tramadol.

This study showed no hemodynamic changes or respiratory depression with i.v. tramadol premedication. This is coinciding with the result of the studies of Grossi et al. [14] and Vickers et al. [15].

Patients in tramadol group experienced better postoperative analgesia compared to the control group as evidenced by less pethidine consumption over the first 24 h postoperative and a longer interval of the first request to pethidine. This was in hand with the result of the study of Wang et al. [16] and it can be explained by the preemptive effect of tramadol that blocks the nociceptive input, increases the threshold for pain perception, and decreases activation of pain receptors before the surgical incision [17].

The incidence of postoperative nausea and vomiting in tramadol treated patients were not increased as expected compared to control group, this may be because tramadol loading dose administration over a relative long period of time reduced the incidence of nausea and vomiting [18] or metoclopramide premedication reduced postoperative nausea and vomiting [19].

This study concludes that tramadol 1 mg/kg i.v. infusion 15 min before induction of anesthesia reduced the incidence and severity of cough after fentanyl injection 2 μg/kg with reduction of postoperative analgesic requirements and without increase in postoperative nausea and vomiting compared to placebo. Further studies are still needed to evaluate the effect of tramadol in different doses on the incidence and severity 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] 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. Anesthesia 2007;62:919–22.

[3] 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(1):40–3.

[4] Agarwal A, Aaim A, Ambesh S, Bose N, Dhiraj S, Sahu D, Singh U. Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. Can J Anaesth 2003;50(3):297–300.

[5] 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(7):862–5.

[6] Lin JA, Chen FC, Lee MS, Horng HC, Cherng CH, Yeh CC, Wong CS. Intravenous dexamethasone pretreatment reduces fentanyl-induced cough. J Formos Med Assoc 2007;106(8):649–55.

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

[8] 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(4):489–94.

[9] Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol 2008;27:201–5.

[10] Lin BF, Ju DT, Cherng CH, Hung NK, Yeh CC, Chan SM, Wu CT. Comparison between intraoperative fentanyl and tramadol to improve quality of emergence. J Neurosurg Anesthesiol 2012;24(2):127–32.

[11] 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(1):18–21.

[12] Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. Anesth Analg 2001;92:1442–3.

[13] Takahama K, Shirasaki T. Central and peripheral mechanisms of narcotic antitussives: codeine-sensitive and -resistant coughs. Cough 2007;3:8.

[14] Grossi L, Cappello G, Marzio L. Premedication with tramadol in patients undergoing colonoscopy: a double-blind randomized placebo-controlled study. Digest Dis Sci 2004;49(10):1641–5.

[15] Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia 1992;47:291–6.

[16] Wang F, Shen X, Xu S, Liu Y. Preoperative tramadol combined with postoperative small-dose tramadol infusion after total abdominal hysterectomy: a double-blind, randomized, controlled trial. Pharmacol Rep 2009;61(6):1198–205.

[17] Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001;48:1000–10.

[18] Pang WW, Mok MS, Huang S, Hung CP, Huang MH. Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. Can J Anaesth 2000;47(10):968–73.

[19] Lehmann KA. Tramadol in acute pain. Drugs 1997;53(Suppl. 2):25–33.