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The effect of two doses of tramadol hydrochloride on fentanyl induced Cough: A double-blinded, randomized, controlled study

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Abstract:

Background: During the induction of general anesthesia, fentanyl is a widely used analgesic. Fentanyl induced cough (FIC) might be a serious complication .Tramadol is a centrally acting codeine analogue, which has an antitussive effect as well as an NMDA antagonist effect. **Our study aims to** evaluate result of the pre-operative administration of 2 different doses of tramadol I.V. on Incidence and severity of fentanyl-induced cough were compared to placebo. **Methodology**: In a prospective, double-blind randomized sample, 150 ASA (I - II) patients between the ages of 20 & 60 who were scheduled for elective surgeries under general anaesthesia were assigned to one of three groups: **End Result**: There was a substantial reduction in the number of cases of FIC in tramadol treated groups, compared to the placebo group being (8(16%)) for group T1 and (7(14%)) for group T 2 compared to the group **S** (18(36%)) with p value (0.019) & (0.022) respectively, When group T1 was compared to group T2, there was no statistically significant difference with p value of (0.736). In terms of the quality of the FIC; 11 from 18 in group **S**, 6 from 8 in group **T1** and 4 from 7 in group **T2** exhibited a mild type, 6 from 18 in group **S**, 2 from 8 in group **T1** and 3 from 7 in group **T2** exhibited mild type, and 1 from 18 in group **S** showed severe form without the presence of patients in **T1** and **T2** groups exhibited severe type. There was no substantial difference between the 3 group in terms of the postoperative nausea and vomiting. **Conclusion:** The Tramadol with different doses; 1mg / kg and 2mg / kg IV 15 minutes. Before anesthesia induction can reduce the incidence & severity of fentanyl-induced cough compared to placebo, but there is no significant distinction between the 2 doses concerning to the incidence & severity of cough.

Keywords: Tramadol; Fentanyl; Cough**.**

1. Introduction:

Fentanyl is a μ-opioid receptor agonist with a clinical potency ratio of 50 to 100 times that of morphine, and is commonly used to induce general anaesthesia (1). Fentanyl induced cough (FIC) can range from simple to sudden explosive cough, which is unpleasant for patients and can be harmful in neurosurgery and ophthalmic surgery because it increases intracranial & intraocular pressures.

The huffing manoeuvre (4), as well as dilution or gradual injection of fentanyl, have both been used to minimise the frequency and seriousness of FIC (3). Selective B2 agonists, sodium chromoglycate or beclomethasone (5), ephedrine and lidocaine (2), clonidine (6), dexamethasone (7), and N-methyl-daspartate (NMDA) antagonists (ketamine & dexmethorphane) have also been attempted (8, 9).

Tramadol hydrochloride is a centrally acting codeine derivative that functions as an opioid receptor agonist as well as a non-opioid action by inhibiting monoamine reuptake (serotonin & norepinephrine) & an NMDA receptor antagonist (10).

Tramadol has an antitussive function as an NMDA receptor blocker, which can be helpful in reducing the frequency and intensity of FIC following fentanyl injection 2 g / kg with a significant decrease in postoperative analgesic requirements & no rise in postoperative nausea & vomiting as compared to placebo (11, 12).

2. Methodology:

Following the ethical committee's approval, an informed consents were got from 150 patients American Society of Anesthesiology (ASA) physical status (I, II), age 20– 60 years of age, arranged for elective surgeries under general anaesthesia in Beni-Suef University Hospital from April 2015 to November 2016. Patients that were not included in the analysis were having chronic obstructive pulmonary disease, history of bronchial asthma, or smokers treated with bronchodilator, or recent respiratory tract infection, steroid, angiotensin-converting enzyme inhibitors, even whether they have a tramadol allergy. All patients were prepared preoperatively by taking full history, examination, routine investigations include CBC, liver and renal function. On arrival to operating theatre, insertion of 20 G intravenous cannula was

done and all patients received ranitidine 50mg I.V. as a premedicated; The patients, on the other hand, had no sedative pre-medicated drugs. All patients had the standard monitoring by ECG with 5 leads, pulse oximetry, & noninvasive blood pressure measurement.

Capnogram and temperature were also reported. The patients were randomly assigned to one of three classes (each with 50 patients) using the closed envelop technique; our drugs were administered 15 minutes prior to anaesthesia induction.

To keep the study's blind nature, our medications were administered by an anaesthesia resident (who was ignorant of the study) who followed directions written in a sealed envelope. Tramadol 1 (T1) group: tramadol hydrochloride 1 mg / kg in 10 ml saline I.V. was administered
15 minutes before anaesthesia induction, using the same dosage as Lin et al. [10] and Abd El-Mawgoud A. et al. [11].

Tramadol 2 group (T2): in which tramadol hydrochloride An I.V. infusion of 2 mg / kg in 10 ml saline was administered over 15 minutes prior induction of anaesthesia.

The Saline group (control group): was received 10 ml of saline I.V. infusion over 15 minutes prior anaesthesia induction.

Fentanyl 2 g / kg was used as a 1st medication to induce general anaesthesia over a 5-second duration, and our patients were monitored for 1 minute for cough occurrence and severity. To allow orotracheal intubation, the induction was proceeded with propofol 2 mg / kg and atracurium 5 mg / kg. Sevoflurane1–2% in O2/air (50 percent /50 percent) was used to sustain anaesthesia. Sevoflurane was discontinued at the close of treatment, the remaining muscle relaxant was reversed, & our patients were transferred to the recovery bed, where postoperative pain was treated with pethidine 25 mg I.V. The following data were recorded by the anesthesia resident:

1. The cough incidence (how many patients, who developed cough).
2. Severity of cough was measured using the scale used in He et al. research [12] Cough severity is determined by the number of coughs (mild equal 1 to 2; moderate equal 3 to 4; and severe more than or equal 5).
3. Heart rate (HR), peripheral oxygen saturation (SpO2), and mean arterial pressure (MAP) were measured prior and after fentanyl injection. If oxygen

desaturation occurred, it was treated with 100 % oxygen and aided or controlled ventilation, if bradycardia occurred, it was treated with atropine 0.4 mg, and if hypotension occurred, it was treated with rapid I.V. crystalloid infusion.

4. Fentanyl injection induced development of chest wall rigidity.
5. I.V. metoclopramide 10 mg was used to treat postoperative nausea and vomiting within 12 hours (persistent nausea more than 30 minutes & vomiting more than 2 times).

3. Results:

A total 150 patients were randomly enrolled into our three study groups (50 per group) containing 73 males & 77 females. There were no significant differences among all groups concerning age, sex, weight, operation time & American Society of Anesthesiologists (ASA) classification **(Table 1).**

Also, there were no statistical significant differences in the hemodynamic changes (HR and MAP) & the peripheral Oxygen saturation within our studied groups at the times of recording. **(Table 2)**

Incidence & severity of cough within our studied groups showed that there was a statistical significant decrease in incidence of FIC in tramadol treated groups, compared to saline group being (8(16%)) for the group T1 and (7(14%)) for the group T 2 compared to the group **S**(18(36%)) with p value (0.019) & (0.022) respectively, while there was no statistical significant difference between group **T1** when compared to group **T2** with p value of (0.736).

As concerning the degree of Fentanylinduced cough (FIC); 11 out of 18 in group **S**, 6 out of 8 in group**T1** and 4 out of 7 in group T2 exhibited mild degree, 6 out of 18 in group **S**, 2 out of 8 in group **T1** & 3 out of 7 in group **T2** showed moderate form, and 1 out of 18 in group **S** showed severe form with no patients in **T1** and **T2**groups showed severe form as shown in **Table (3).**

We didn't record any patients in all groups developed chest wall rigidity after fentanyl injection.

There were no significant differences in postoperative nausea and vomiting within 12 hours among all patients of the studied groups as shown in **Table (4).**

Table (1): Comparison among group S, group T1 and group T2 concerning operation time & demographic data:

	S **(n = 50)**	**T 1** **(n = 50)**	**T 2** **(n = 50)**	**P value**
Sex, no. (%)				P_1=0.998
• Male	23(46)	24(48)	26(52)	P_2=0.689
• Female	27(54)	26(52)	24(48)	P_3=0.841
Age (Year)				P_1=0.633
Mean±SD	34.6±9.8	35.7±11.4	38.2±11.3	P_2=0.104
				P_3=0.258
Weight (Kg) Mean±SD	79.8±13.9	78.5±9.7	81.3±11.4	P_1=0.571 P_2=0.520 P_3=0.227
Operation time **(min)** Mean±SD	125.9±53.9	144.6±96.5	157.5±71.2	P_1=0.406 P_2=0.234 P_3=0.397
ASA, no. (%)				P_1=0.317
• I	47(94)	44(87.8)	40(80)	P_2=0.071
• II	3(6)	6(12.2)	10(20)	P_3=0.413

Group S: group of saline, group T1: group of tramadol (1mg/kg), T2: tramadol group (2mg/kg). Data is provided in the form of Mean ± SD (standard deviation), or the number.

There are no major gaps between our three research groups.

P - Value less than 0.05 [Significant] P - value more than 0.05 [No significant]

Table [2]: Comparison among group S, group T1 and group T2 concerning peripheral O_2 & hemodynamic changes

Saturation:

				T1			T2		
	Heart Rate	Mean Arterial Pressur e	O2 Saturati o n	Heart Rate	Mean Arterial Pressur e	O2 Saturati on	Heart Rate	Mean Arterial Pressur e	O2 Saturati on
Before fentanyl injection (beat/mi n) **Mean±S D**	91.1±13. 6	90.0±19. 8	98.3±1.5	90.6±11. 0	88.7±13. 5	98.0±1. 3	88.6±14. 2	86.5±13. 8	98.6±1. 5
After fentanyl injection (beat/mi n)	84.4±13. 3	80.7±15. 1	95.8±14. 2	88.6±10. 7	84.8±11. 1	98.3±2. 0	85.2±17. 0	79.7±15. 1	98.0±2. 8
Mean ± Standar d deviatio n									

Group S: the group of saline, group T1: the group of tramadol (1mg/kg), T2: tramadol group (2mg/kg).

Data presented asMean±SD (SD), or the number.

Significant difference (p less than 0.05) between T1 & T2 when opposed to group S.

There are no major gaps among T1 and T2 Groups.

Table (3): Comparison among group S, group T1 and group T2 regarding both chest wall rigidity & occurrence & severity of fentanyl induced cough

	S (n =50)	**T1 (n = 50)**	**T2 (n = 50)**	**P value**
Patients developed cough (%)	8(36)	8(16)	7(14)	$_1$ = 0.019* $_2$ = 0.022* $_3$ = 0.736
Grades of cough				
• Mild	11(22)	6(12)	4(8)	$_1$ = 0.041*
• Moderate	6(12)	2(4)	3(6)	$_2$ = 0.020*
• Severe	1(2)	0(0)	0(0)	$_3$ = 0.736
Chest wall rigidity, no. (%)	0(0)	0 (0)	0 (0)	_

Group S: the group of saline, group T1: the group of tramadol (1mg/kg), T2: tramadol group (2mg/kg). Data presented asMean±SD (SD), or the number.

Significant difference (p less than 0.05) between T1 & T2 when opposed to group S.

There are no major gaps among T1 and T2 Groups.

Table (4): Comparison among group S, group T1 and group T2 concerning postoperative nausea and vomiting:

	S (n = 50)	**T1 (n = 50)**	**T2 (n = 50)**	**P value**
Post-operative nausea &vomiting within 2 h., No. (%)	0(0)	1(2)	0(0)	P_1=0.999 P_2=1 P_3=0.999

Group S: group of saline, group T1: group of tramadol (1mg/kg), Tramadol group (2mg/kg)

Numbers are used to represent data (percentage %)

There are no major gaps between our three research groups.

4. Discussion:

Our study demonstrated that premedication with intravenous tramadol 1 mg / kg decrease the incidence of FIC from 36% in placebo (saline) group to 16%, while premedication with intravenous tramadol 2 mg / kg decreased the occurrence of FIC from 36% in placebo group of saline to 14%, when fentanyl was given at 2 µg/kg dose, and there was no statistical significant difference between the 2 different doses of tramadol.

There are few reports discussed the effect of tramadol on (FIC), additionally the effective dose which used was 1 mg/kg in the study of Lin et al.(11) and Abd El-Mawgoud A. (12). Our results were in agreement with Abd El-Mawgoud A.(12) study which showed that premedication with intravenous tramadol 1 mg/kg reduced the incidence of FIC from 38% in the placebo (saline) group to 20% when fentanyl was given at 2 µg / kg dose as the 1st drug during induction of anesthesia.

Coinciding with our study results, ketamine 0.15 mg / kg was given 1 minutes prior the injection of fentanyl. The incidence of FIC reduced from 21.6 % to 7.2 % as shown in Yeh CC et al (8).

Mukherjee A et al (9) concluded that premedication with oral FIC incidence was decreased from 59.8% to 3.9 percent when dextromethorphane 40 mg was given 1 hour before anaesthesia induction.

H. Yu et al (3) study stated that dilution of fentanyl to ten µg.ml-1 with 0.9 % saline combined with aprolonged time of injection eliminates cough caused by fentanyl.

Horng HC et al. reported that pre- medication with intravenous clonidine2 µg / kg reduced FIC from 38.7% to 17.3% with mild decrease in blood pressure & HR (6).

He L et al (13) concluded that intravenous dexmeditomedine 0.5 µg / kg or 1 µg/kg successfully decreased FIC occurrence.

Lin CS et al (2) reported that intravenous lidocaine 2 mg / kg and ephedrine 5 mg prior to fentanyl reduced the frequency of fentanyl-induced cough.

The results of Grossi et al. (14) and Vickerset al. (15) both were in agreement with our study result, as they didn't show any alterations in

hemodynamics or respiratory distress with pre-medication by I.V. tramadol.

Our results were in concordance with Pang WW et al (16), as it was reported that occurrence of nausea and vomiting after surgery in patients treated with tramadol weren't increased compared to control group as expected.

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