RESEARCH ARTICLE

Assessment of the Effect of Intravenous Lidocaine, Dexamethasone and Different Speeds of Injection on Fentanyl-Induced Cough During Cataract Surgery

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Background: Fentanyl which is frequently used during cataract surgery has been found to induce cough. The aim of this study was to evaluate the effect of IV lidocaine and dexamethasone and different speeds of injection of fentanyl on cough induced by this drug.

Methods: In this randomized double blind clinical trial study, patients were allocated randomly to four groups to receive 1 mg.kg^{-1} lidocaine (group i), 0.1 mg.kg^{-1} dexamethasone (group II) and 5 cc normal saline as placebo (group III & IV) intravenously. Four minutes later, all patients were given 1.5 µg.kg^{-1} fentanyl intravenously. Fentanyl was administered within 15 seconds in group I-III and within 2 seconds in group IV. Incidence, number and intensity of cough were recorded. Heart rate and blood pressure were also recorded before administration of drug, 1 minute after administration of drug and 2 minutes after administration of fentanyl.

Results: 139 patients were evaluated. There was no significant difference in demographic features of groups including age, weight, gender and also heart rates and blood pressures. Incidence and intensity of cough was significantly higher in group IV while there was no statistically considerable difference between other groups.

Conclusion: This study demonstrated that slowing injection of fentanyl can effectively reduce the incidence of cough induced by drug; hereby administration of lidocaine or dexamethasone becomes unnecessary in this speed of injection. Additionally cough incidence after fentanyl injection is affected by patients' ethnicity.

Keywords: cataract; fentanyl; cough; lidocaine; dexamethasone

Cataract is a common disease in the elderly and one of the main causes of blindness around the world. Surgery is definite treatment of this sickness which is often done by local anesthesia [1]. Fentanyl as a synthetic opioid with analgesic potency 50 to 100 times greater than morphine, is widely used in medical procedures and interventions [2]. Its onset of action is immediately after intravenous and about 7 to 15 minutes after intramuscular injection. This drug can easily pass through blood brain barrier because of its high fat solubility. Fentanyl also has short effect duration and makes profound sedation [3]. Like other opioid agents, it may cause side effects including nausea and vomiting, xerostomia, constipation, bradycardia and respiratory depression. Muscular rigidity, laryngeal spasm, apnea, bronchoconstriction and seizure have also been reported [4-5].

According to different previous studies, this drug can induce coughing in different degrees [6] which can lead to increased intracranial and intraabdominal pressure [7-9] so it can be potentially dangerous despite of its benign and self limiting property. The exact pathophysiology of cough after fentanyl injection is not still clearly understood. Several studies have proposed different mechanisms for this pharmaceutical side effect including histamine release [10], increased vagal tone, suppression of sympathetic system [11] and stimulation of rapidly adapting pulmonary stretch receptors which lie on the mucosa of proximal airways of tracheobronchial tree [6]. Incidence of this adverse effect is reported 18 to 65% in the former studies [12]. This discrepancy of cough incidence after injection of fentanyl can be attributed to different factors like patients' race and age, speed of injection, sites and doses of drug administration or priming dose of fentanyl [6,13].

Cough during open eye surgeries like cataract operation or corneal graft can be harmful and lead to elevated intraocular pressure for 30 to 40 mm-Hg and evacuation of eye ingredients [14]. For the patients, cough is an unpleasant experience and can reduce his or her cooperation with surgeon and interfere with surgery process.

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Several measures have been done to reduce cough subsequent to the fentanyl including administration of lidocaine [15], dexamethasone [16], Beta2 agonists [6], Alfa2 agonists [17], ketamine [18], propofol [19], dilution [20] and priming doses of Fentanyl [13]. This study was designed to find a safe way to decrease fentanyl-induced cough incidence so the impact of IV lidocaine, dexamethasone and different speed of injection on this important side effect were evaluated.

Methods

The study was performed at Farabi hospital, Tehran University of Medical Sciences in the year 2015. After getting approval from ethics committee of the university this randomized double blind clinical trial study was started. 139 patients of either gender, aged 50 to 90, classified as ASA (American society of anesthesiologists) I & II who were candidate for cataract surgery under local anesthesia was imported to the study. Exclusion criteria consisted of; hepatic or renal failure, uncontrolled hypertension (systolic blood pressure more than 180 mm-Hg and diastolic blood pressure more than 110 mm-Hg), body weight 20% more than ideal (according to body mass index), past history of asthma, chronic obstructive pulmonary disease, chronic cough and sore throat, upper respiratory tract infection, taking angiotensin converting enzyme inhibitors, steroids or bronchodilators during recent 4 weeks, history of allergic reaction to lidocaine or dexamethasone, cigarette smoking, mental disease and cognitive disorder.

In the operation room venous access was inserted by a 20 gauge cannula into the hand's dorsum and connected to a 3 way connector for administration of drugs. All patients were monitored by continuous electrocardiography, pulse oximetry and non invasive blood pressure measurement. Systolic and diastolic blood pressure and heart rate was recorded in three times; before administration of drug (Lidocaine, Dexamethasone or placebo), 1 minute after administration of drug and 2 minutes subsequent to injection of fentanyl. Patients' hydration before and during surgery were in the same manner between groups.

Patients were randomly divided into four groups; group I received 1 $mg.kg^{-1}$ Lidocaine intravenously. Group II received 0.1 $mg.kg^{-1}$ Dexamethasone intravenously. Groups III & IV received 5 cc normal saline intravenously as placebo. Four minutes after administration of drug, fentanyl 1.5 $\mu g.kg^{-1}$ was injected via the peripheral IV line and speed of injection was 15 seconds in groups I, II & III and 2 seconds in group IV. Incidence of cough within two minutes after fentanyl injection was recorded by a general practitioner who was blinded to the patients' group. Cough intensity was also recorded as the following; none, mild (1-2 cough), moderate (3-5 coughs) and severe (more than 5 coughs). This grading was adapted from previous similar studies [21,7,18]. Any possible drug side effects were also recorded.

Data collecting tools consisted of questionnaire, observation and vital signs' monitoring. After collecting patients' data, they were decoded and entered to SPSS (Statistical Product for Social Sciences) software version 20. Quantitative variables are described as mean ± standard deviation, pure number and percentage. Type α and β error was considered respectively 5% and 20% and P-value less than or equal to 0.05 was assumed statistically significant. According to previous studies expected fentanyl-induced cough was 20% and calculated patients' number in each group of our study was 30. To avoid loss and withdrawal, 139 patients' data were gathered finally. One-way ANOVA (analysis of variances) was used to compare age, weight, heart rate, blood pressure and number of patients who experienced cough between groups. To evaluate gender and cough severity among the four groups chi-square test was used.

Results

139 patients were allocated to four groups; 36 persons in group I (Lidocaine group), 34 persons in group II (Dexamethasone group), 35 persons in group III (placebo group over 15 seconds) and 34 persons in group IV (placebo group over 2 seconds). There were no significant differences between groups in demographic features including age, weight and gender (Table 1) and those who coughed and those who didn't cough gender (Table 2).

Totally 24 patients (17.26%) experienced cough in the study. Cough incidence was 8.33% in Lidocaine group (3 cases), 5.88% in Dexamethasone group (2 cases), 22.85% in Placebo group within 15 seconds (8 cases) and 32.35% in Placebo group over 2 seconds (11 cases). Cough intensity was also be recorded and compared between groups (Table 3).

Table 1- Demographic features of groups*

	Lido group (n=36)	Dexa group (n=34)	Saline group Within 15'' (n=35)	Saline group Within 2'' (n=34)	P-value
Age	63.69±12.16	62.73±16.94	65.85±11.21	68.50±10.34	0.192
Weight	73.86±12.05	72.61±11.93	69.94±10.86	73.85±6.51	0.377
Sex(F:M)	22:14	16:18	17:18	14:20	0.395

*Data are described as mean ± standard deviation. Dexa= Dexamethasone; Lido= Lidocaine; F:M= Female to Male ratio)

Table 2- Demographic features among those who coughed and those who didn't cough

		Lido group (n=36)	Dexa group (n=34)	Saline group within 15'' (n=35)	Saline group within 2'' (n=34)	Total	P-value
Age(year)	cough	56.00±1.73	82.50±6.36	67.75±1.08	66.35±3.06	66.86±1.37	0.003
	No cough	64.39±1.24	61.45±1.66	65.29±1.14	69.54±2.12	69.54±2.12	0.13

Table 2- Demographic features among those who coughed and those who didn't cough (Continued)

		Lido group (n=36)	Dexa group (n=34)	Saline group within 15'' (n=35)	Saline group within 2'' (n=34)	Total	P-value
Sex (F:M ratio)	cough	1:2	2:0	3:5	4:7	10:14	0.381
	No cough	21:12	14:18	14:13	10:13	59:56	0.347
Weight (kg)	cough	85.33±23.4	80.00±14.1	68.50±15.8	74.20±5.45	74.17±13.5	0.271
	No cough	72.81±10.5	72.15±11.8	70.38±9.2	73.70±7.0	72.26±9.9	0.681

Table 3- Cough incidence and severity in the groups over 2 minutes after the Fentanyl injection

	Lido group (n=36)	Dexa group (n=34)	Saline group within15'' (n=35)	Saline group within 2'' (n=34)	P-value
Cough incidence	8.33%	5.88%	22.85%	32.35%	0.010
No cough	33	32	27	24	0.022
Mild (1-2)	3	2	5	3	0.702
Moderate (3-5)	0	0	2	7	0.001
Severe (>5)	0	0	1	0	0.393

Cough incidence was significantly higher in group IV (saline group within 2 seconds), while its difference wasn't statistically considerable among other groups (chi-square value=0.067).

There was significant difference between groups in cough intensity (P value=0.013). Incidence of moderate cough had significant statistical difference between groups.

Some drug side effects like allergic reaction, prolonged pain in the site of injection, nausea, vomiting, loss of consciousness, seizure, respiratory depression and cardiovascular events weren't observed in this study.

Discussion

Considering the injection of fentanyl over 15 seconds, our study clarify the preventive effect of lidocaine and dexamethasone on Fentanyl-induced cough. We hypothesized that lengthening time of injection of fentanyl was so effective that it could eliminate any possible difference between groups I-III who received fentanyl over 15 seconds. This idea is compatible with finding of Taregh's study [22]. He assessed the impact of IV lidocaine and prolonged injection time of fentanyl on cough incidence. Group I received placebo prior to injection of 2 $\mu g.kg^{-1}$ fentanyl over 30 seconds, group II was administered 1.5 $mg.kg^{-1}$ lidocaine 1 minute before injection of 2 $\mu g.kg^{-1}$ fentanyl over 5 seconds and group III received placebo prior to injection of 2 $\mu g.kg^{-1}$ fentanyl over 5 seconds. Cough incidence was 2.5% in group I, 9.2% in group II and 22.5% in group III. This study demonstrates that slowing injection rate of fentanyl is a rational way to prevent induction of cough.

Additionally, patients' ethnicity is another factor that determines their susceptibility to represent cough after receiving fentanyl as mentioned in the research of Schäpermeier [23]. In his study, the incidence of cough was 3, 3 and 6% in the German patients who received 1.5 $\mu g.kg^{-1}$ fentanyl over 2, 5 and 10 seconds respectively. He attributed the low incidence of cough in his investigation to the patients' race because in the study of Lin et al. on Chinese patients who were administered about 1.5-2.5 $\mu g.kg^{-1}$ fentanyl over 2 seconds, incidence of cough was 18% [24]. In the study of Tang et al. which was operated in China, prevalence of cough subsequent to administration of a bolus dose of fentanyl 2.5 $\mu g.kg^{-1}$ in control group who just received placebo was 80% [25]. Shen et al. and his collaborators recorded a 33.3% incidence of cough in their Chinese patients who received 2 $\mu g.kg^{-1}$ IV fentanyl over 5 seconds [26]. Schäpermeier believes that difference between Chinese and European people is the reason of this discrepancy. In the study of Nouruzi [27], which was done on Iranian patients, incidence of cough was just 10% in control group who received alfentanil. This number is considerably lower than what is reported in the similar studies implemented in east of the Asia. The same rule was true in our study which recorded lower cough event compared with similar studies in East Asia.

Reduction the speed of fentanyl injection has been also mentioned in the previous researches as a way to prevent fentanyl-induced cough. Choudhuri et al administered fentanyl 2 $\mu g.kg^{-1}$ in 2, 6 and 10 seconds and compared incidence and severity of cough among three groups. Finally he found that slowing administration of fentanyl can efficiently reduce intensity and incidence of fentanyl-induced cough and recommended injection over 10 seconds [28]. Yu et al. and his collaborators suggested that prolonged injection time in addition to diluting fentanyl can efficiently reduce this adverse effect [20]. In Kim et al. and his colleagues' study, the impact of remifentanil's injection speed on its induced cough was evaluated in children. Patients were administered 1.5 $\mu g.kg^{-1}$ intravenous remifentanil over 30, 45 and 60 seconds. Study revealed that by increasing time of injection from 30 to 60 seconds, incidence of cough can effectively be decreased [29].

Different studies have found that administration of lidocaine or dexamethasone is useful to prevent fentanyl-induced cough in contrast with some other investigations that figured it ineffective and unnecessary. Gecaj et al. found that 0.5 $mg.kg^{-1}$ lidocaine 1 minute before 3 $\mu g.kg^{-1}$ fentanyl injected over 5 seconds is useful to prevent coughing [30].

Guler et al. found in his study that incidence and severity of cough is significantly lower in the patients who received 1 $mg.kg^{-1}$ lidocaine 1 minute before injection of 1.5 $\mu g.kg^{-1}$ fentanyl over 2 seconds [18]. In the other hand, Bang et al. suggested that 0.5 $mg.kg^{-1}$ lidocaine 1 minute before remifentanil with target concentration of 5 $ng.ml^{-1}$ hasn't preventive effect on fentanyl induced cough [29].

Yu et al. showed that pretreatment with 10 mg dexamethasone 5 minutes before remifentanil with target concentration of 5 $ng.ml^{-1}$ can efficiently reduce remifentanil induced cough [31]. In the other side, in the study of Nouruzi and Mohamadian the preventive effect of intravenous dexamethasone 0.15 $mg.kg^{-1}$, 5 minutes before injection of alfentanil 10$mg.kg^{-1}$ was not demonstrated [27].

Conclusion

At the end of this study, the preventive effect of prolonged injection time on fentanyl-induced cough was proved. This method can be a safe, simple and inexpensive way to get rid of this pharmaceutical side effect. Additionally, incidence of fentanyl-induced cough may can be affected by their race.

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