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SCIENTIFIC ARTICLE

The effect of pheniramine on fentanyl-induced cough: a randomized, double blinded, placebo controlled clinical study

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KEYWORDS
Fentanyl;
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Abstract
Background and objectives: There are many studies conducted on reducing the frequency and severity of fentayl-induced cough during anesthesia induction. We propose that pheniramine maleate, an antihistaminic, may suppress this cough. We aim to observe the effect of pheniramine on fentanyl-induced cough during anesthesia induction.
Methods: This is a double-blinded, prospective, three-arm parallel, randomized clinical trial of 120 patients with ASA (American Society of Anesthesiologists) physical status III and IV who aged ≥18 and scheduled for elective open heart surgery during general anesthesia. Patients were randomly assigned to three groups of 40 patients, using computer-generated random numbers: placebo group, pheniramine group, and lidocaine group.
Results: Cough incidence differed significantly between groups. In the placebo group, 37.5% of patients had cough, whereas the frequency was significantly decreased in pheniramine group (5%) and lidocaine group (15%) (Fischer exact test, $p = 0.0007$ and $p = 0.0188$, respectively). There was no significant change in cough incidence between pheniramine group (5%) and lidocaine group (15%) (Fischer exact test, $p = 0.4325$). Cough severity did also change between groups. Post Hoc tests with Bonferroni showed that mean cough severity in placebo differed significantly than that of pheniramine group and lidocaine group ($p < 0.0001$ and $p = 0.009$, respectively). There was no significant change in cough severity between pheniramine group and lidocaine group ($p = 0.856$).
Conclusion: Intravenous pheniramine is as effective as lidocaine in preventing fentayl-induced cough. Our results emphasize that pheniramine is a convenient drug to decrease this cough.

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PALAVRAS-CHAVE
Fentanil;
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Anesthesia

Efeito de feniramina sobre a tosse induzida por fentanil: estudo clínico, randômico, duplo-cego e controlado com placebo

Resumo
Justificativa e objetivos: Há muitos estudos sobre a redução da frequência e gravidade da tosse induzida por fentanil durante a indução da anestesia. Propomos que maleato de feniramina, um anti-histamínico, pode suprimir essa tosse. Nosso objetivo foi observar o efeito de feniramina sobre a tosse induzida por fentanil durante a indução da anestesia.
Métodos: Este é um estudo clínico prospectivo, de três braços paralelos, randômico e duplo-cego, de 120 pacientes com estado físico ASA III e IV (de acordo com a Sociedade Americana de Anestesiologistas), com idades ≥ 18 anos e programados para cirurgia cardíaca aberta eletiva sob anestesia geral. Os pacientes foram divididos aleatoriamente em três grupos de 40 pacientes cada, usando números aleatórios gerados por computador: grupo placebo, grupo feniramina e grupo lidocaína.
Resultados: A incidência de tosse diferiu significativamente entre os grupos. No grupo placebo, 37,5% dos pacientes apresentaram tosse, enquanto que a frequência foi significativamente reduzida no grupo feniramina (5%) e no grupo lidocaína (15%) (teste exato de Fischer, $p = 0{,}0007$ e $p = 0{,}0188$, respectivamente). Não houve alteração significativa na incidência de tosse entre os grupos feniramina (5%) e lidocaína (15%) (teste exato de Fischer, $p = 0{,}4325$). A gravidade da tosse também alterou entre os grupos. Testes *post hoc* com Bonferroni mostraramu que a média da gravidade da tosse no grupo placebo diferiu significativamente das médias dos grupos feniramina e lidocaína ($p < 0{,}0001$ e $p = 0{,}009$, respectivamente). Não houve alteração significativa na gravidade da tosse entre o grupo feniramina e grupo lidocaína ($p = 0{,}856$).
Conclusão: Feniramina por via intravenosa possui a mesma eficácia que lidocaína na prevenção da tosse induzida por fentanil. Os resultados enfatizam que feniramina é um medicamento conveniente para diminuir essa tosse.

Introduction

Intravenous fentanyl which is used mainly for induction of anesthesia frequently causes an irritating cough in the patient.[1] The prevalence of fentanyl-induced cough ranges from 21.6% to 74%.[2–5] It is generally transitory and limited, but it can be harmful in cases with increased intracranial, intraocular or intra-abdominal pressure; cerebral aneurysm, brain trauma and hernia, dissecting aortic aneurysm, pneumothorax or reactive airway disease.[4–7] Although the mechanism of fentanyl-induced cough has not been fully clarified, it is thought that allergic mediators such as histamine may cause it.[8] Various medicaments and methods have been used with varying degrees of success to hinder or relieve this side-effect.[2] One study reported that lidocaine 2 mg/kg iv given one minute before fentanyl decreased the prevalence of cough from 65% (according to the control group) to 14%.[6] Another study reported that iv fentanyl administered in diluted form or more slowly markedly hindered cough.[9]

Many solutions have been proposed for this cough of unidentified origin. We wanted to investigate the effect of pheniramine on fentanyl-induced cough. The purpose of this study was to compare the effect of the antihistaminic *pheniramine maleate* and lidocaine on fentanyl-induced cough.

Method

Design

This is a double-blinded, prospective, three-arm parallel, randomized clinical trial conducted in a research hospital between September 2013 and April 2014. The approval of the Ethics Committee of our hospital and informed consent forms were taken from all patients participating in the study (Decision n° 2013/13). One hundred and twenty ASA (American Society of Anesthesiologists) physical status III and IV patients aged ≥18 and scheduled for elective open heart surgery during general anesthesia, were randomly assigned to one of three groups of 40 patients each, using computer-generated random numbers: placebo group, pheniramine group, and lidocaine group. Dr. ZA was responsible for drug preparation and the allocation sequences (contained in a set of sealed envelopes). The observers and all the patients involved in the study were blinded.

Inclusion criteria

Consecutive patients planned for open heart surgery (coronary artery by-pass, mitral and aortic valve replacement), receiving no premedication, and in the ASA-III and IV class were included.

Table 1 Patient characteristics in three groups.

Feature	Placebo group ($n=40$)	Pheniramine group ($n=40$)	Lidocaine group ($n=40$)	p
Age (yr)	55.98 ± 11.5	61.25 ± 11.84	56.48 ± 12.22	0.094
Male (%)	75	80	60	0.118
Weight (kg)	74.03 ± 12.29	74.02 ± 12.83	74.13 ± 12.27	0.999
Smokers (%)	48.6	33.3	32.4	0.289
Ex-smokers (%)	21.7	14.3	10.7	0.544

Exclusion criteria

Those who had premedication, pharyngitis in the last <3 weeks, chronic obstructive pulmonary disease, chronic cough, drug allergy, history of asthma, treatment with bronchodilators or steroids for the last one month, and who were in the class ASA-V were excluded.

Sample size

Our power analysis showed that using a sample size of 40 patients per group achieves 82% power to detect an effect size (W) of 0.5 using 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Interventions

After the patients entered the operation room, vascular access was established by placing a 22-G cannula in one of the veins in the forearm, and infusion with saline 3 mL/kg was started. As noninvasive monitoring, electrocardiography (ECG), blood pressure (BP), and pulse oxygen saturation (SpO_2) were provided. Measurements were made in every 5 min. If needed ($SpO_2 < 95\%$), oxygen support (4 L/min) was given via an oxygen face mask. One minute before induction and fentanyl administration, pheniramine maleate 45.5 mg iv bolus (Avil, 2 mL ampoule, Sandoz, Turkey) was administered to 40 patients in the pheniramine group, lidocaine (Aritmal 2%, 5 mL, Osel drug, Turkey) 1 mg/kg to 40 patients in the lidocaine group and saline 5 mL to 40 patients in the placebo group, respectively. One minute after the treatment, fentanyl 5 μg/kg iv bolus (Fentanyl 0.05 mg/mL, 10 mL ampoule, Johnson&Johnson, Belgium) was given within 5 s to the patients in each group. The patients were observed for the side-effects of fentanyl, and any side-effect seen was noted down. The severity of cough was recorded as mild (1–2), medium (3–5), and severe (>5). Following, induction was conducted with propofol 2.5 mg/kg and rocuronium 0.6 mg/kg. The patients were manually ventilated for 2.5 min and then orotracheal intubation was completed. The patients were then mechanically ventilated with a 7 mL/kg tidal volume at a rate of 12 breaths per minute. Thereafter, invasive arterial catheterization of left radial artery and central venous catheterization to the right internal jugular vein were provided. The anesthesia was maintained with fusion of 50% O_2/air, 5% desflurane, 2–3 μg/kg remifentanyl and rocuronium (0.1 mg/kg/30 min). After the operation was over, the patients were transferred to the Intensive Care Unit of Cardiovascular Surgery Clinic as intubated, monitored (invasive blood pressure, SpO_2, and ECG), and manually ventilated with oxygen 8 L/min.

Statistics

The frequencies of coughing and the proportions of sex and ASA class were compared using the chi-square test or Fisher's exact test. One-way ANOVA analysis of variance was used to compare the age and weight among the four groups and Post Hoc tests with Bonferroni correction was used to define which groups differ. $p < 0.05$ was considered as statistically significant.

Results

There was no statistically significant difference between the three groups with regard to age, gender, weight, and smoking habits ($p > 0.05$ for all, Table 1).

Cough incidence differed significantly between groups. In the placebo group, 37.5% of patients had cough, whereas the frequency was significantly decreased in pheniramine group (5%) and lidocaine group (15%) (Fischer exact test, $p = 0.0007$ and $p = 0.0188$, respectively; Table 2). There was no significant change in cough incidence between

Table 2 The comparison of cough characteristics in three groups.

Variables	Placebo group ($n=40$)	Pheniramine group ($n=40$)	Lidocaine group ($n=40$)	p
Cough severity (0–3)	0.63 ± 0.93	0.05 ± 0.22	0.2 ± 0.52	<0.0001[a]
Cough incidence, *n* (%)	37.5 (15)	5 (2)	15 (6)	<0.0001
No cough	62.5 (25)	95 (38)	85 (34)	
Mild	17.5 (7)	5 (2)	10 (4)	
Moderate	15 (6)	0	5 (2)	
Severe	5 (2)	0	0	

[a] Oneway ANOVA.

pheniramine group (5%) and lidocaine group (15%) (Fischer exact test, $p = 0.4325$).

Cough severity did also change between groups. Post Hoc tests with Bonferroni showed that mean cough severity in placebo differed significantly than that of pheniramine group and lidocaine group ($p < 0.0001$ and $p = 0.009$, respectively). There was no significant change in cough severity between pheniramine group and lidocaine group ($p = 0.856$).

Discussion

We saw that administration of fentanyl iv bolus caused cough in 37.5% of the patients. We also found that fentanyl-induced cough could be inhibited by pheniramine and lidocaine. The most important finding of this study was that pheniramine maleate, an antihistaminic, reduced fentanyl-induced cough more than lidocaine used for this purpose.

The fentanyl-induced cough reflex occurs frequently following anesthetic induction. Lui et al.[10] administered fentanyl at the dose we used (5 μg/kg) via peripheral venous route and observed cough in 43% of the patients. Yeh et al.[4] observed fentanyl-induced cough due to injection of fentanyl 1.5 μg/kg in 21.6% of their patients. Lin et al.[7] administered fentanyl 2.5 μg/kg within 2 s and found a high cough rate of 65%. A double-blind study reported that with a higher dose of fentanyl (4 μg/kg), cough was seen in 74.4% of the patients.[5] The differences in the prevalence of cough in these studies may depend upon the injection site and route of fentanyl, speed of injection, and dose and concentration of the drug. Also genetic factors and co-morbidities may play a role.

Particularly in open cardiac operations, to maintain stable hemodynamic parameters by inhibiting the stress response of hemodynamics to very painful sternotomy, high-dose narcotic analgesics are used in the induction and maintenance of anesthesia.[11] For this purpose, fentanyl (because it provides rapid onset, short duration, intense analgesia, reduced cardiovascular depression, and low histamine release) is one of the most frequently used opioid analgesics.[12,13] For the same purpose, we also administered fentanyl in doses higher than routinely used. We think that the relatively lower incidence of cough found in our study can be due to two reasons. First, we administered fentanyl within 5 s that is a longer period discussed to other studies. Second, our patients were relatively older than the patients of previous studies.[5,7] As the patients get older, cough reflex is diminished due to lower irritating receptor activity.[7] In a study on children aged 4–10 years, a bolus of fentanyl 3 μg/kg via peripheral venous route caused cough reflex in 43.5% of the children.[14] In Lin et al.'s study,[7] the average age of the controls was 36.8 years.

There are various theories on fentanyl-induced cough. Fentanyl inhibits central sympathetic outflow, causes vagal predominance, and leads to cough and bronchoconstriction, and bronchospasm.[4–6,15] Opioids may induce cough through various mechanisms including through a pulmonary chemoreflex, direct stimulation of the vagal nucleus, the release of neuropeptides after activation of μ-opioid receptors and stimulation of the irritant receptors in upper pulmonary mucosa.[16–19] Yeh et al.[4] reported that fentanyl can cause cough by stimulating the irritant receptors in tracheal smooth muscle. Opioids release histamine from mast cells to a variable degree, with codeine, morphine and meperidine having the greatest histamine-releasing capacity, while tramadol, fentanyl and remifentanyl do not release histamine and are recommended in pulmonary disease requiring opioid administration.[20] On the other hand, Kamei et al.[8] in their study on mice reported that fentanyl causes cough by increasing the quantity of citric acid which induces cough and by significantly increasing the concentration of histamine in bronchoalveolar lavage fluid.

To inhibit the cough reflex, various medicaments are used (ephedrine, beclomethasone, B2-receptor agonist, ketamine, clonidine, propofol). All these medications have bronchorelaxant effect on the airway smooth muscle.[4,5,7,21] Lidocaine, one of the most frequently used medicaments, has been shown to reduce airway reactiveness, possibly via mechanically and chemically induced airway reflexes.[15] Pandey et al.[6] in their double-blind study reported that lidocaine administered one minute before fentanyl could inhibit fentanyl-induced cough.

As known, histamine shows its effects on target tissues such as airway smooth muscle, bronchial epithelium, secretary glands, mast cells and epithelial cells through prominently H1, as well as H2 and H4 receptors. Pheniramine, an H1-receptor antagonist, affects by competing with histamine on H1-receptors. H1-receptor antagonists, in addition to their anti-allergic blockade on the H1-receptors, prevent the release of inflammatory mediators from basophils and mast cells. They also inhibit the migration of eosinophils, basophils and/or neutrophils.[22,23] Therefore we thought that pheniramine may be more effective than lidocaine to alleviate the fentanyl-induced cough.

In our study, we also showed that lidocaine had an important effect on the frequency and severity of fentanyl-induced cough. Additionally, we found that pre-treatment with iv 45.5 mg pheniramine maleate suppressed the fentanyl-induced cough during general anesthesia induction, but more clinical trials are needed to evaluate its effect. In our anesthesia clinic, the use of pheniramine is not routine. Because another indication of pheniramine is its anti-allergic effects due to blood products in patients underwent to open cardiac surgery, we included only these patients in our study.

Conclusion

Intravenous pheniramine is as effective as lidocaine in preventing fentayl-induced cough. Our results emphasize that pheniramine is a convenient drug to decrease this cough.

Conflicts of interest

The authors declare no conflicts of interest.

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