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Research Article

The Effect of Hydroxyzine on Fentanyl -Induced Cough in Pediatric Patients: A Prospective, Randomized, Controlled Trial

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Abstract

Study Objective: To observe the effect of hydroxyzine used for premedication on fentanyl -induced cough during induction of anesthesia.

Design: Prospective, randomized, single -blinded, clinical trial.

Setting: Department of Pediatric Surgery and operating room of a Training and Research Hospital.

Patients: 90 ASA physical status I pediatric patients, aged 3 and 12 years, scheduled for elective surgery during general anesthesia.

Interventions: Patients were randomized into one of two groups: a control group (Group C) and a hydroxyzine group (Group H). Group H patients were given 1 mg kg -1 hydroxyzine with 10 ml water to drink 2 h before surgery. No premedication was performed on Group C patients. In both groups 2 µg kg -1 fentanyliv were given for 3 sec to patients before induction of anesthesia.

Measurements: Patients sedation states were evaluated using the Ramsay Sedation Scale (RSS) in the operating room. The presence, onset and severity of cough were recorded.

Main Results: The incidences of cough were 11.1% in Group H and 51.1% in Group C ($p<0.0001$). All coughs in Group H were mild. In Group C, however, 24.4% of coughs were mild, 15.6% were moderate and 11.1% were severe. Significant differences were observed between the two groups in terms of moderate and severe cough ($p=0.026$ and $p=0.028$, respectively). RSS was significantly in favor of Group H ($p<0.0001$). When patients were given hydroxyzine an absolute risk reduction of -0.4 and a relative risk reduction of -0.78 were observed compared to the control group, and the number needed to treat was -2.5.

Conclusion: Hydroxyzine administered orally during the preoperative period is effective in preventing both the incidence and severity of fentanyl -induced cough in child patients. Our results demonstrate that hydroxyzine is a suitable drug for reducing this cough.

Introduction

Fentanyl is frequently used in an additional pre -induction dose in the induction of general anesthesia in child patients. Opioids normally exhibit antitussive effects. However, when administered intravenously, opioids generally cause sudden and temporary cough. Fentanyl -induced cough is seen at high levels among child patients [1]. Oshima et al. [2] reported that young age is a significant risk factor for development of fentanyl -induced cough. Although this cough is temporary and limited in nature, it may sometimes result in loss of venous access and an increase in intraocular, intracranial and intra -abdominal pressures. It can also result in adverse outcomes in conditions such as pneumothorax, reactive airway diseases, brain trauma and aneurysm [3-5]. Indeed, one case of aspiration pneumonia has been reported following cough after fentanyl injection [6]. Although the mechanism involved in fentanyl -induced cough is not completely clear, allergic mediators such as histamine have been implicated. One study reported that fentanyl triggers cough by increasing release of histamine in the airways [7]. Several drugs and methods have been used to prevent this tussive effect of fentanyl, but none has been shown to be completely effective [7-9]. One of the most effective and commonly used drugs for this purpose is lidocaine. In one study the level of cough in child patient was reduced from 43.5% to 16.1% with the administration of lidocaine in a 0.5 mg/kg dose 1. Pheniramine was used as an antihistaminic for this purpose in two other studies, and was shown to be as effective as lidocaine in reducing fentanyl -induced cough [10,11]. Hydroxyzine HCL is an anticholinergic and antihistaminic agent with sedative, anxiolytic and hypnotic properties [12]. Although older, potentially sedating, "first -generation"antihistamines (H1-receptor antagonists)

are commonly used in childhood, their Central Nervous System (CNS) effects have not been well-documented in young subjects [13]. The purpose of this study was to investigate whether hydroxyzine HCL, which exhibits anxiolytic, sedative and antihistaminic effects and which we use for premedication in child patients, has any effect on fentanyl -induced cough during induction of anesthesia.

Materials and Methods

Design

This is single -blind, prospective, multi -arm parallel, randomized clinical trial was conducted in a Turkish research hospital between 1 December, 2015, and 30 April, 2016. Following receipt of approval from our hospital ethical committee (No. BEAH KAEK 2015/14-128), written consent forms were obtained from the parents of all patients to be included in the study. One hundred patients undergoing elective surgery due to undescended testis and inguinal hernia surgery in the pediatric surgery department, ranging from 3 to 12 years old, with no allergy to opioids, local anesthetic or any drug and classified as American Society of Anesthesiologists class I (ASA I) were randomly assigned into one of two groups of 50 patients each, using computer -generated random numbers: a control group (Group C) and a hydroxyzine group (Group H). However, five patients were excluded from each group due to lack of parental approval (2 patients), receipt of insufficient drug dosages (4 patients), and failure to obtain vascular access (4 patients).

Exclusion criteria

Patients with throat infection within the previous 3 weeks, with chronic cough, drug allergy or a history of asthma, with psychological or motor retardation or with mouth -throat deformities, and patients using bronchodilators and/or steroids in the previous months of classified as ASA II or above were excluded.

Sample size

The mean incidence of fentanyl -induced cough in other studies is 50%. We anticipated a decrease in cough of at least 30% with the administration of hydroxyzine. On the basis of an alpha value of 0.05, beta 0.2 and power 80% with anticipated incidences of cough in groups C and H of 50% and 20%, respectively, we calculated that each group would need to contain at least 38 (total 76) individuals. We also anticipated that approximately 30% of patients would fail to meet the inclusion criteria during observation or refuse to take part, and we therefore calculated group sizes of 50 members each.

Interventions

Patients in Group H were given 1mg kg -1 hydroxyzine HCL (Atarax syrup, 2 mg/ml, 200 ml, UCB Pharma, Turkey) to drink with 10 ml water 2 h before surgery. Patients in Group C received no premedication. All patients' sedation states were recorded using the Ramsay Sedation Scale (RSS) by an anesthetist blind to premedication on admission to the operating room. Standard non -invasive monitoring (blood pressure, ECG, SPO2) was then established and values were recorded. Vascular access was next opened on the back of the left hand with a 20 G cannula. Before induction of anesthesia, patients in both groups received fentanyl (Fentanyl 0.05 mg/ml 10 ml vial/Johnson&Johnson) at a dose of 2 µg kg -1 via iv push in 3 sec. Presence of cough, severity (mild: 1-2, moderate 3-5, severe ≥6 times) and time to occurrence were recorded by a blind observer anesthetist for 90 sec after fentanyl injection. The same general anesthesia protocol was then applied to the patients in both groups (induction: thiopental; 5 mg kg -1, atracurium; 0.6 mg kg -1). Patients were manually ventilated with 100% oxygen for 2.5 min, after which mechanical ventilation commenced with the application of a subglottic laryngeal mask (i -gel). Maintenance anesthesia was established with 50% O2/air, 1 -1.5% sevoflurane and rocuronium (0.1 mg kg -1 /30 min). At the end of surgery patients were wakened with the appropriate procedure and taken to the Post Anesthesia Care Unit (PACU). Following 1h observation they were transferred to the ward.

Statistical analysis

The incidences 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 age and weight between the two groups, and post hoc tests with Bonferroni correction were used for identifying differences. $p<0.05$ was considered statistically significant.

Results

No statistical significance was determined in demographic variables such as age, sex, weight and height between the two groups (Table 1). The incidence of cough was 11.1% in Group H (n=5), and 51.1% (n=23) in Group C, the difference being statistically significant ($p<0.0001$). All coughs in Group H were mild, with no cases of moderate or severe cough. In Group C de, 24.4% of coughs were mild, 15.6% were moderate and 11.1% were severe. Statistically significant

Table 1: Patient characteristics in two groups.

Feature	Group H(n=45)	Group C(n=45)	P Value	
Age (Years)	7±2.8	6.8±2.9	0.717	6.9±2.9
Gender (F/M)	14/31	15/30	0.822	29/61
Weight (kg)	24.1±8.8	23.6±8.2	0.578	23.9±8.5
Height (cm)	120.3±15.6	118,7±16,5	0.651	119.5±16.2

Group H: Hydroxyzine group, Group C: Control group, Values are expressed as means±SD except for gender

Table 2: Frequency, severity and onset of cough, and sedation status in groups.

Variables	Group H	Group C	P Value	Total
Cough incidence	11.1 (5)	51.1 (23)	<0.0001	31.1 (28)
Cough severity				
Mild (1-2)	11.1 (5)	24.4 (11)	0.083	17.8 (16)
Moderate (3-5)	0.0 (0)	15.6 (7)	0.026	7.8 (7)
Severe (≥6)	0.0 (0)	11.1 (5)	0.028	5.6 (5)
Onset (sn)	6.6±1.1	5.9±1.9	0.137	6.0 ±1.8
RSS score 1	28.9 (13)	82.2 (37)		55.6 (50)
2	66.7 (30)	17.8 (8)	<0.0001	42.2 (38)
3	4.4 (2)	0.0 (0)		2.2 (2)

Group H: Hydroxyzine group, Group C: Control group, RSS: Ramsay Sedation Scale. Note: RSS 4 and above score were no in patients. Onset (sn): The time interval between fentanyl injection and onset of cough symptom.

Table 3: The comparison of two groups using four-cell crosstab.

	Group H	Group C	Total
Cough present	5	23	28
Cough none	40	22	62
Total subjects	45	45	90
Cough rate (%)	11.1	51.1	31.1

Variable	Abbr.	Result
Absolute risk reduction	ARR	(−)0.4, or (−)40%
Relative risk reduction	RRR	(−)0.78, or (−)78%
Number needed to treat	NNT	(−) 2.5
Relative risk	RR	0.22
Odds ratio	OR	0.12
Attributable risk	AR	(−)0.40, or (−)40%
Preventive fraction	PF	0.78, or 78%

difference was determined between the two groups in terms of moderate and severe cough (p=0.026 and p=0.028, respectively). Time to onset of cough was shorter in Group H (1.0±2.4 sec) than in Group C (3.0±3.3 sec) (p=0.001). RSS between the two groups measured when patients were taken to the operating room differed statistically in favor of Group H (p<0.0001) (Table 2). Comparison of the groups using four -cell crosstab revealed absolute risk reduction of -0.4, relative risk reduction of -0.78 and number needed to treat -2.5 when patients were given hydroxyzine compared to the control group (Table 3).

Discussion

Hydroxyzine HCL is an H1 receptor antagonist and is frequently used orally for premedication prior to interventional procedures in pediatric patients [14]. This study represents the first investigation of the effect of hydroxyzine used as a preoperative sedative on fentanyl -induced cough. The results show it is highly effective in reducing the incidence and severity of cough.

Fear of the hospital environment and particularly of surgery, stress created by separation from parents and awareness of painful and invasive procedures and psychological trauma and anxiety are significant problems in pediatric cases. The use of premedication is therefore very important in these. Several drugs are used for this purpose [15]. Due to the anxiolytic, sedative and secretion -reducing effects of hydroxyzine HCL and the fact it is available in syrup form, it is widely used alone or in combination with other medications for premedication in pediatric cases [15,16]. In addition, since it is an H1 receptor we used it on the basis that it may be effective against cough caused by opioids used during induction of anesthesia. One study of mice suggested that fentanyl leads to cough by increasing histamine secretion in the airways [7]. However, other mechanisms regarding fentanyl -induced cough have also been suggested, such as fentanyl inhibiting central sympathetic outflow, causing vagal predominance, and thus leading to cough and bronchoconstriction and bronchospasm [4,5,17]. In addition, 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 [18-20]. One study reported that fentanyl may cause cough by stimulating irritant receptors in intratracheal smooth muscles [4]. Opioids have also been reported to lead to cough by causing the release of histamine, leukotrienes and other inflammatory mediators from mast cells in the lungs [21,22]. One study claimed that while morphine and meperidine have a high histamine release capacity, fentanyl and remifentanil have no effect on histamine release [23]. In a mouse study, Kamei et al. [19] reported that fentanyl caused cough by increasing levels of citric acid, which induces cough, and significantly increasing histamine concentrations in broncheoalveolar lavage fluid in the airways. However, irrespective of the mechanism involved, the tussive effect is disturbing and may give rise to undesired consequences [3-6]. The prevalence and severity of such cough varies depending on the dose administered, the rate of administration, the concentration, the vascular access involved and the age of the patient [1,8,9,24,25].

In one study the authors concluded that the association between fentanyl -induced cough and age might be attributed to younger patients having a higher irritant receptor activity level and that this may contribute to the incidence of cough [26] In another study involving children aged between 4 and 10 years, fentanyl was administered through the peripheral vein in a 2 -3 μg kg -1 iv bolus, and a cough reflex of 43.5% was observed 1. In addition similar to our study, prospective, another study was carried in children aged between 2 and 14 years, and fentany given 1μg kg -1 dose and cough frequency was observed 46.3%, and fentanyl given 2 μg kg -1 and cough frequency was emerged at 60% 24. In these two studies, however, atropine was used before the administration of fentanyl and this may have affected the level of cough. Yeh et al. 4 injected 1.5μg kg -1 fentanyl over 5 sec and observed a fentanyl -induced cough level of 21.6%. Lin et al. [26] administered 2.5μg kg -1 fentanyl iv over 2 sec and observed a high incidence of cough, at 65%. The levels reported in studies vary considerably. In our study, in which 2μg kg -1 fentanyl was administered in 3 sec, we observed an incidence of fentanyl -induced cough of 51.1%.

Various methods and drugs are used to prevent the resulting cough reflex. Methods such as the rate of administration of fentanyl, the concentration and the location of the vascular access have been used as non -drug techniques [8,9,27]. Kim et al. [27] administered remifentanil at a dose of 1.5 μg kg -1 in 30, 45 and 60 sec to child patients aged 3 -12 undergoing general anesthesia. The observed incidences of cough were 33.3%, 17.9% and 5.0%, respectively.

A large number of drugs are used in the prevention of fentanyl -induced cough (ephedrine, beclomethasone, β2 -receptor agonists, H1 receptor antagonists, ketamine, clonidine, lidocaine, midazolam, and propofol). All these drugs exhibit bronchorelaxant effects on airway smooth muscle [4,5,10,11,26]. Lidocaine, one of the most widely used of these drugs, has been shown to reduce airway reactiveness, possibly via mechanically and chemically induced airway reflexes [17]. Pandey et al. showed that the administration of 2 μg kg -1 lidocaine 1 min before fentanyl iv reduced the incidence of cough from 65% (control group) to 14% 3. Pheniramine maleate, another effective drug and H1 receptor, has been reported to be very effective against fentanyl -induced cough and to reduce the incidence from 20% to 2.5% [10,11]. Our findings are parallel to these studies, and oral hydroxyzine administered at a dose of 1 μg kg -1 in the

preoperative period was as effective as lidocaine and pheniramine in preventing fentanyl -induced cough.

We therefore used hydroxyzine HLC syrup, an antihistaminic frequently used in the sedation of pediatric patients undergoing surgical procedures, to prevent fentanyl -induced cough. Hydroxyzine was highly effective in terms of both the incidence and severity of fentanyl -induced cough. All coughs in Group H were mild, while in Group C 15.6% were moderate and 11.1% were severe. When the groups were compared using four -cell crosstab, premedication with hydroxyzine emerged as very useful in preventing fentanyl -induced cough (number needed to treat:(-2.5). The sedation effectiveness of hydroxyzine HCL used in premedication in child patients was significantly better compared with the control group. The ratio of patients who one scores the RSS was 82.2% in Group C and 28.9% in Group H. This was an important finding for the sedation effect of hydroxyzine HCL used in premedication.

Conclusion

Premedication with 1 μg kg -1 hydroxyzine HCL suppressed both the incidence and severity of fentanyl -induced cough during general anesthesia induction and had a sedative effect on child patients. Further studies might now be performed with different dosages for both reduce the fentanyl -induced cough and see the sedation effect of hydroxyzine.

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