Original Article

Pre-emptive oral dexmethorphan reduces fentanyl-induced cough as well as immediate postoperative adrenocortico-tropic hormone and growth hormone level

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Abstract

Background: Fentanyl-induced cough is not always benign and brief and can be remarkably troublesome, spasmodic, and explosive. Dextromethorphan, an opioid derivative with an antitussive action, may be effective in reducing the fentanyl-induced cough. Dextromethorphan, a N-methyl D aspartate receptor antagonist, may have some effect on diminishing the stress response to surgery. This study was undertaken to determine whether preoperative dextromethorphan could effectively attenuate its incidence, severity, and effect on postoperative stress hormone levels.

Materials and Methods: Three hundred and twenty patients of American society of anesthesiologists I-II, aged 18–60 years, undergoing elective laparoscopic cholecystectomy or appendicectomy were randomly allocated into two groups (Group C, control; Group D, dextromethorphan) consisting of 160 patients each. Patients in Group D received dextromethorphan 40 mg orally and in Group C received placebo tablets 60 minutes before induction of anesthesia. The incidence of cough was recorded for 1 minute after fentanyl injection and graded as none (0), mild (1–2), moderate (3–5), and severe (>5 cough). Blood samples were collected for estimation of stress hormone levels before surgery and again at 1 hour and 24 hours postoperatively and compared. The appearance of adverse reactions was recorded.

Results: The incidence of reflex fentanyl cough was lower in dextromethorphan group (3.9%) in comparison to placebo (59.8%). Five patients developed mild and one moderate cough in the dextromethorphan group. In the control group, 31 patients developed mild, 29 moderate, and 32 severe cough. The stress hormones were significantly higher at 1 hour and 24 hours postoperatively in both groups in comparison to its preoperative values. However, at 1 hour postoperatively, adrenocorticotropic hormone, epinephrine, and growth hormone values were significantly low in the dextromethorphan group (61.5 ± 21.1 pg/ml, 142.1 ± 11.2 pg/ml, and 3.8 ± 0.7 ng/ml) relative to the control group (73.4 ± 21.9 pg/ml, 158.9 ± 17.9 pg/ml, and 4.2 ± 1.3 ng/ml), but changes became insignificant at 24 hours postoperatively.

Conclusion: Preoperative oral dextromethorphan 40 mg decreased the incidence and severity of fentanyl induced cough and reduced the rise in stress hormones at 1 hour postoperatively.

Key words: Adreno-cortico-tropic hormone, dextromethorphan, epinephrine, fentanyl cough, growth hormone

Introduction

Intravenous administration of fentanyl during premedication induces cough, although opioid agonists are known to possess antitussive activity.[1] The reported incidence of fentanyl-induced cough (FIC) could be as high as 65% after intravenous fentanyl (2.5 μg/kg) bolus injection.[2] The vast majority of FIC are classified as benign, with rare occurrences of explosive and spasmodic coughing.[2,3] Different drugs such as terbutaline, clonidine, dexamethasone, and lidocaine and some procedures namely huffing maneuver—a forced expiration against open glottis, dilution of fentanyl to 10 μg/ml, and prolonged injection time have been tried to reduce the occurrence of reflex cough.[4-12] However, these approaches are not uniformly effective.[13]

Dextromethorphan has been used as a central cough sedative and effective analgesic adjuvant in the process

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of postoperative pain management. Dextorphan, a major metabolite of dextromethorphan, is an N-Methyl D Aspartate (NMDA) receptor antagonist producing effects similar to those of ketamine and phencyclidine.[14] The antitussive effect was attributed to its structural component of the codeine analogue, while its NMDA receptor antagonistic action was responsible for the prevention of secondary hyperalgesia, wind-up phenomenon, and consequently its analgesic outcome following tissue trauma.[15,16]

The glutamate receptors were considered to have an effect in the neuroendocrine response regulation, and the previous animal and human studies pointed that the blockade of NMDA receptors (subtype of glutamate receptors) modified the neuroendocrine response to tissue trauma in different ways.[15,16] Ketamine administration increased the prolactin level, and on the other hand, MK-801 decreased its levels.[16,17]

Our study was undertaken to evaluate the efficacy and safety of preoperative oral dextromethorphan 1 hour before induction of anesthesia on both the FIC severity and the postoperative stress hormones profile.

Materials and Methods

After approval from the Institute's Ethics Committee and obtaining written informed consent from the participants, 320 adult patients of American Society of Anesthesiologists physical status I/II, aged between 18 and 60 years scheduled for elective laparoscopic cholecystectomy, laparoscopic appendicectomy under general anesthesia were included in this prospective, randomized double-blind placebo controlled trial. Exclusion criteria were body weight exceeding 20% of ideal, history of asthma, chronic cough, upper respiratory tract infection in the previous 2 weeks, smoking, a history of bronchodilator or steroid therapy, or treatment with angiotensin-converting enzyme inhibitors or anti-psychotic drugs, impaired liver, or kidney function. Patients not completing the study and patients requiring postoperative ventilatory support were excluded from analysis, as these patients would cause bias to the results of stress response.

Based on the incidence of FIC reported in the literature (18–65%), we assumed that the expected incidence of coughing would be 40% upon administration of fentanyl in conventional manner. It was estimated that 152 subjects would be required per group in order to detect 15% absolute reduction in the incidence of coughing with 80% power and 5% probability of Type I error.

Patients were randomly allocated to either Group D ($n=160$) or Group C ($n=160$) using computer-generated randomization list generated by a statistician in a sealed envelope. Group D patients received dextromethorphan 40 mg orally (DMR 20; West Coast Pharmaceutical Works, India) 60 minutes before the surgery (one tablet of DMR 20 = 20 mg of dextromethorphan). Group C patients received two antacid tablets 60 minutes before the surgery. A blinded pharmacist prepared the sealed envelopes according to the instructions and packed the medications. All patients were monitored with standard monitoring tools—noninvasive blood pressure, electrocardiogram, and pulse oximetry. All patients were oxygenated with 6 l/min O_2 throughout the study period. Fentanyl, 2 μg/kg in 2 seconds was injected at room temperature via a T-connector for drug injection with the IV fluid running at a fast rate to minimize the dilution effect during fentanyl administration.

An independent observer who was blinded to the type of medication given to the patients observed the severity of FIC after fentanyl administration. The primary end point was FIC. Any episode of cough within 60 seconds of fentanyl administration was classified as FIC, and the severity was graded based on the number of coughing spasms (none 0, mild 1–2, moderate 3–5, and severe >5 coughs).

Propofol (1%) 2 mg/kg was administered for induction of anesthesia. One-and-a-half minutes after anesthesia induction, tracheal intubation was performed facilitated by neuromuscular blockade with atracurium 0.5 mg/kg. Anesthesia was maintained with O_2 33%, N_2O 66%, and sevoflurane 1% and incremental dose of atracurium guided by a neuromuscular monitor. At the end of procedure, sevoflurane was discontinued and the residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate. Intravenous paracetamol 1 g was administered just after induction of anesthesia and continued every 6 hours for postoperative analgesia. Patients were transferred to Post-anesthesia Care Unit (PACU) and monitored for next 24 hours. Three venous blood samples were collected at 1 hour before (baseline value) as well as 1 hour and 24 hours postoperative for stress hormone assay. Blood samples were collected into two different containers: plain vial for measuring serum adreno-corticotropic hormone (ACTH), and growth hormone (GH) levels and Ethylene-diamine-tetra-acetic acid (EDTA) vial for epinephrine analysis. Both ACTH and GHs were measured by radioimmunoassay technique, while plasma levels of epinephrine were determined by high-performance liquid chromatography. The baseline hormonal values and their postoperative values at 1 hour and 24 hours were compared among the groups and any significant change noted. Any adverse reactions, such as vomiting, somnolence,

respiratory distress, drowsiness, hallucination, blurred vision, skin rashes, or itching, were documented and compared.

Data were expressed as mean ± standard deviation or number (%). Comparison between groups was done using analysis of variance. Nominal data were analyzed using the Pearson's χ^2 test. *P*-values <0.05 were considered statistically significant. For statistical analysis, we used Statistica version 6 (Stat Soft Inc., 2001, Tulsa, OK) and SPSS Statistics version 17 (SPSS Inc., 2008, Illinois, Chicago, IL) softwares.

Results

Sixteen patients, eight from each group, were excluded from statistical analysis as they did not met the criteria (four required ventilator support in PACU or fentanyl injection could not be completed due to syringe malfunction in 12 patients). After exclusion, 304 patients, 152 in each group, were subjected to statistical analysis. The demographic profiles of the patients in both the groups were comparable about age, height, weight, and gender distribution [Table 1]. No significant difference was noted.

The incidence of cough was 91 (59.8%) in Group C compared with 6 (3.9%) in Group D [Table 2]. Furthermore, significantly more number of patient of Group C had moderate (29 patients) or severe (32 patients) FIC when compared with group D where only 1 had moderate cough [Figure 1].

The ACTH, GH, and epinephrine levels were significantly higher at 1 hour and 24 hours postoperatively in both groups

Table 1: Demographic profiles among the groups

	Group D (*n*=152)	Group C (*n*=152)
Age (years)	39 ± 12.7	38.8 ± 12.5
Weight (kg)	62.3 ± 9.6	62.4 ± 9.6
Height (cm)	164.2 ± 8.5	163.7 ± 7.5
Sex (M:F)	80:72	73:79

Table 2: Incidence and severity of fentanyl-induced cough [number (%)]

	Group D (*n*=152) %	Group C (*n*=152) %
Incidence of fentanyl induced cough	6 (3.9)*	91 (59.8)
Number of patient with no cough	146 (96.1)*	61 (40.2)
Number of patient with mild cough	5 (3.3)*	30 (19.7)
Number of patients with moderate cough	1 (0.6)*	29 (19.1)
Number of patients with severe cough	0 (0)*	32 (21)

**Significantly different when compared to Group C (P<0.00)*

Table 3: Preoperative and postoperative stress hormone levels among the groups

Group	ACTH			GH			Epinephrine		
	Preoperative	1 hour postoperative	24 hours postoperative	Preoperative	1 hour postoperative	24 hours postoperative	Preoperative	1 hour postoperative	24 hours postoperative
D	50.6 ± 18.8	61.5 ± 21.1	60.2 ± 17.8	2.7 ± 0.6	3.8 ± 0.7	3.4 ± 0.9	138.8 ± 10.8	142.1 ± 11.2	137.3 ± 11.0
C	50.8 ± 18.7	73.4 ± 21.9	62.4 ± 16.9	2.8 ± 0.6	4.2 ± 1.3	3.6 ± 0.8	138.6 ± 10.7	158.9 ± 17.9	136.4 ± 10.8
P value	0.926	0.001	0.270	0.147	0.001	0.041	0.871	0.001	0.472

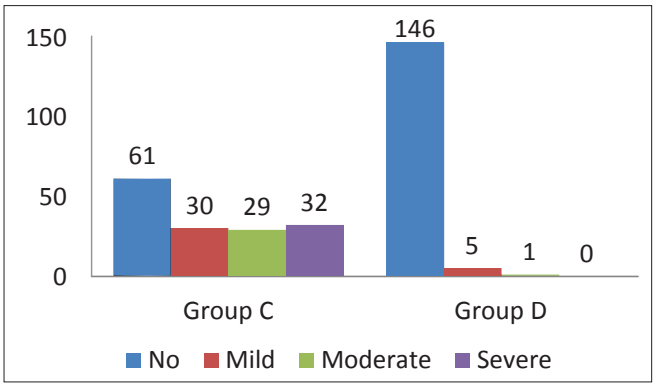

Figure 1: Incidence of fentanyl-induced cough and their grades

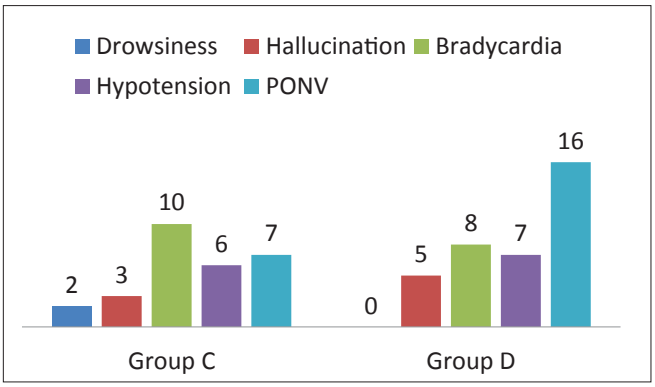

Figure 2: Incidence of adverse effects in different groups

in comparison to their preoperative values. However, at 1 hour postoperative, ACTH, epinephrine, and GH values were significantly lower in the dextromethorphan group in comparison to the control group, but these changes were not significant at 24 hours [Table 3].

The incidence of postoperative nausea vomiting (PONV) was higher in Group D. The incidence of other side effects such as hallucination, bradycardia, and hypotension was comparable in both the groups. The preoperative oral dextromethorphan 40 mg was not accompanied by drowsiness [Figure 2].

Discussion

The preoperative oral dextromethorphan 40 mg 1 hour before induction of anesthesia significantly reduces the incidence and severity of FIC and lowered the stress hormone levels at 1 hour after surgery.

There have been at least three main hypotheses proposed for the mechanism of fentanyl-induced coughing. Paintal *et al.* and Yasuda *et al.* proposed that a pulmonary chemoreflex is the likely mechanism, which is mediated either by irritant receptors (rapidly adapting receptors) or by vagal C fiber receptors (also known as J or juxtacapillary receptors) near pulmonary vessels.[18,19] Once these receptors are stimulated by fentanyl, sudden bronchoconstriction and coughing will be triggered. Substances such as histamine and neuropeptides released by action on the prejunctional μ-opioid receptors after intravenous fentanyl administration play an important role in contributing to this coughing. Benthuysen *et al.* suggest that vocal cord spasms might induce the coughing mechanism.[20]

A number of pharmacological measures have been studied in an attempt to reduce this adverse effect, with varying degrees of success. We tried with dextromethorphan. The antitussive effect was attributed to its structural component of the codeine analog. The recommended oral dose of dextromethorphan varies from 0.5 mg/kg to 150 mg.[21] We selected a dose of 40 mg. The central antitussive action of dextromethorphan and the elevation of the cough threshold without inhibition of ciliary activity could explain its successful effect in reducing the severity of reflex fentanyl cough in our study.[21]

The stress response to surgery initiated by tissue trauma is believed to stimulate the hypothalamo-pituitary-adrenal axis which in turn enhance the sympathetic nervous system activity.[15] Pre-emptive analgesia before surgical stimulation is effective in dampening that stress response.[22] The excitatory neurotransmitter glutamate along with other chemical mediators are released which initiates pain cascade and regulates hemodynamic and hormonal stress responses. Glutamate is believed to interact with NMDA and non-NMDA receptors.[23] Studies on NMDA receptors included a variety of NMDA receptor antagonists and which monitored their effects on stress hormones release. It is believed that ACTH is a sensitive marker to detect the severity of surgical trauma and the associated stress response. Epinephrine and GHs are also secreted in response to adrenal and pituitary stimulation by the tissue mediators.[24]

We used dextromethorphan for premedication of patients 1 hour before the surgery. The long duration of action (3–8 hours) of dextromethorphan warranted its use as an oral premedicant drug.[21] Dextromethorphan 40 mg decreased the rise in epinephrine, ACTH, and GH levels at 1 hour and the postoperative period when compared with the placebo group. At 24 hours, there was no significant difference detected between the two groups, with regard to the stress hormonal profile. This could be explained by the multimodal antagonistic action of dextromethorphan on NMDA receptors that inhibited the pain cascade and subsequently the stress hormones release. Similar results were reported in the studies that evaluated the effect of other NMDA antagonists on neuroendocrine regulation. In laparoscopic cholecystectomy, magnesium sulfate 50 mg/kg given before pneumoperitoneum reduced the levels of epinephrine, norepinephrine, and ADH hormones without altering the plasma rennin and

cortisol values.[25] Ketamine combined to either ropivacaine or bupivacaine in caudal analgesia not only prolonged the duration of analgesia but also reduced the cortisol level.[26]

Zelena *et al.* and Bregonzio *et al.* reported decreased level of prolactin with the use of MK-801 (Dizocilpine) and *cis*-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755), another NMDA antagonist.[15,27] Ketamine also exerted an inhibitory action on hypothalamo-adrenal axis and consequently decreased the ACTH and cortisol secretion.[28] The mechanism of action of MK-801 (dizocilpine), memantine, and CGS 19755 was attributed to their antagonistic activity on NMDA receptors, whereas magnesium in addition was believed to have a direct inhibitory effect on both catecholamine secretion and vasoconstriction induced by vasopressin.[11,13,15,17,27] The decrease in cortisol secretion following ketamine-local anesthetic caudal analgesia could be attributed to the effect of caudal analgesia itself on stress hormones release and the minimal systemic ketamine absorption.[26] The dextromethorphan effect in our study may be related to the blockade of NMDA receptors and consequently the hyperalgesic response.[29]

The limitation of our study was that we did not measure the blood levels of dextromethorphan administered.

Preoperative oral 40 mg dextromethorphan 1 hour before the surgery reduced the severity of FIC and the rise in stress hormones level (epinephrine, ACTH, and GH) during anesthesia and surgical procedures. It is suggested that a multicenter trial be conducted to determine the optimal dosage of dextromethorphan.

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