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Research Article

Dextromethorphan reduced fentanyl induced cough and stress hormones release. A randomized double blind controlled study

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Abstract *Background:* The previous reports demonstrated variable changes in stress hormones profile when different NMDA receptor antagonists were administered and this study traced the effect of dextromethorphan premedication as an NMDA antagonist on postoperative neuro-endocrine response. As dextromethorphan is a known central antitussive agent, this study also evaluated its effect on fentanyl induced cough reflex.

Methods: Sixty female patients ASA class I, undergoing posterior vaginal repair surgeries under general anesthesia were studied. Patients were allocated to one of two groups: Dextromethorphan group in which the patients received oral dextromethorphan 60 mg and Placebo group in which the patients received 20 ml of water for injection orally 60 min prior to surgery. The incidence of cough was calculated following fentanyl 2 μg/kg administration and the severity was assessed by using cough assessment scale. Stress hormones were collected before surgery and again at 1 and 12 h postoperatively and compared. The appearance of adverse reactions was reported.

Results: The incidence of reflex fentanyl cough was lower in dextromethorphan group 13% (4 patients) in comparison to placebo 36% (11 patients). Two patients developed mild and two

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moderate forms in the DEX group in relation to six mild, four moderate, and one severe cough form in the control group. The stress hormones were significantly higher at 1 and 12 h postoperatively in both groups in comparison to its preoperative values. However, at 1 h postoperatively, ACTH, epinephrine, and growth hormone values were significantly low in the dextromethorphan group (59.5 ± 21.7 pg/ml, 144.4 ± 11.4 pg/ml, and 3.7 ± 0.8 ng/ml, respectively) relative to the control group (72.2 ± 21.9 pg/ml, 159.6 ± 19.7 pg/ml, and 4.4 ± 1.2 ng/ml, respectively) but these changes became insignificant at 12 h.

Conclusion: Premedication with 60 mg dextromethorphan reduced the rise in stress hormones at 1 h postoperatively. Also, the use of dextromethorphan decreased the incidence and severity of fentanyl induced cough.

1. Introduction

It was believed that reflex cough may occur following fentanyl administration and that cough may range from simple to sudden explosive coughing attacks with unwanted outcomes [1]. Several studies have been tried to reduce reflex coughing by the use of different techniques and variable pharmacological interventions. The use of the huffing maneuver, a forced expiration against open glottis, prior to fentanyl administration [2] and even both the dilution of fentanyl to 10 μg/ml or the slow speed of its injection reduced the incidence and severity of fentanyl induced cough [3]. As bronchoconstriction was blamed to play a role in the mechanism of reflex cough, salbutamol, beclomethasone, sodium chromoglycate, and terbutaline exhibited an effective control when given 15 min before the fentanyl injection [4,5]. In addition, a variety of preemptive drugs including lidocaine, ephedrine [6], ketamine [7], clonidine [8], and priming doses of vecuronium [9] have succeeded in that field.

Also, the stress response to surgery was believed to affect the hypothalamo–pituitary–adrenal axis leading to disturbance in the stress hormone profile and increase in the incidence of perioperative morbidity [10]. The previous studies attempted to reduce the neurohormonal response and consequently its morbidity incidence by the modification of anesthetic practice and postoperative pain management. In conjunction to the application of peripheral and neuroaxial analgesic maneuvers, still the preemptive medications such as alpha 2 agonists [11] and opioids [12] demonstrate an effective intervention for the control of surgical stress. The glutamate receptors were believed to have an effective role in the neuroendocrine response regulation and the previous animal and human studies found that the blockade of NMDA receptors (subtype of glutamate receptors) by MK-801 [13], ketamine [14], and magnesium sulfate [15] altered in different ways the neuroendocrine response to tissue trauma. That was clear by tracing the effects of both ketamine and MK-801 on prolactin levels. Ketamine administration increased the prolactin values and on the other hand MK-801 decreased its levels [13,14].

Dextromethorphan is a NMDA receptor antagonist, which was used for a long period of time as a central cough sedative medicine and effective analgesic adjuvant in the process of postoperative pain management. The antitussive effect was attributed to its structural component of the codeine analog 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 [16,17].

For these two effective actions, this study traced the efficacy and safety of dextromethorphan premedication with 60 mg 1 h prior to surgery on both the postoperative stress hormones profile and the fentanyl induced cough reflex.

2. Methods

Following approval from the local ethics committee and obtaining informed written consents from patients who participated in this study; the study was conducted on 60 female patients, ASA physical status I and undergoing posterior vaginal repair surgeries under general anesthesia. The study was done in Dar Al Shifa hospital in Kuwait in the period between December 2008 and February 2010.

Patients were excluded from this study if associated with a history of smoking, chronic cough, bronchial asthma, chronic obstructive lung diseases, or recent upper respiratory tract infection within the previous 2 weeks. Also, they were not included if presented with significant medical diseases (ASA physical status > I), more than 90 kg, or experiencing the intake of analgesic anti-inflammatory drugs, steroids, angiotensin converting enzyme inhibitors ACE, anti-psychiatric agents, or bronchodilator drugs.

In the preoperative anesthesia visit, the patients were told about the oral administration of the study drugs before shifting to operation theater. Also they were instructed about the blood sampling for hormonal profile 2 h before surgery and again at 1 and 12 h following the procedure.

In this study, the 60 female patients were allocated to two equally divided groups (30 patients in each) by using the closed envelop technique. The groups were selected according to the type of administered drug as follows:

- Dextromethorphan group (DEX group): in which the patients received dextromethorphan 60 mg (Dextrokuf; Kuwait Saudi Pharmaceutical industries Co., S.A.K.) 60 min prior to the surgery (1 ml of Dextrokuf = 3 mg of dextromethorphan).
- Control group (Placebo group): in which the patients received 20 ml of water for injection 60 min prior to the surgery.

The medications were prepared by a blind nurse according to the instructions written in a closed envelop and these drugs were administered 1 h before the surgery.

On arrival at the operation theater, the basic monitors were attached to the patients including electrocardiogram, pulse oximetry, and noninvasive blood pressure. The patients in

both groups received fentanyl 2 μg/kg over a period of 2 s. Following fentanyl injection, the patients were observed over a period of 1 min for both the incidence and severity of cough similar to the previous studies [1–8]. The number of patients who developed reflex coughing (incidence) and their percentage were calculated and compared between both the groups. Also, this study was designed to follow the same scale used for cough severity assessment in the study of Lin et al. [1], in which mild = 1–2 coughs, moderate = 3–5 coughs and severe = more than 5 coughs.

The anesthesia was standardized in the two groups in which the induction was continued by propofol 2 mg/kg and cisatracurium 0.15 mg/kg to facilitate orotracheal intubation. Anesthesia was maintained with sevoflurane 1% in O_2/N_2O mixture (50%:50%) and incremental doses of muscle relaxant guided by the peripheral nerve stimulator. For adequate intraoperative as well as early postoperative analgesia and proper hemostatic control, 15 ml of lidocaine–epinephrine (1:400.000) was infiltrated vaginally by the surgeon. The sevoflurane was titrated to keep the intraoperative hemodynamic data within 20% of its preinduction values. At the end of procedure, sevoflurane was discontinued and the residual neuromuscular blockade was antagonized with neostigmine and atropine. Following the hospital protocol for postoperative analgesia in patients undergoing posterior vaginal repair surgeries, non-steroidal anti-inflammatory drugs are usually used, so diclofenac 100 mg suppository was inserted before shifting to postanesthesia care unit (PACU) and again 10 h later.

In this study, the intraoperative as well as early postoperative hemodynamic profile in PACU, including mean arterial blood pressure and heart rate, were collected every 10 min and compared between the studied groups. When modified Aldrete score reached above or equal to 9, the patients in PACU were shifted to the ward.

Also, the study was designed to trace the effect of dextromethorphan premedication on the postoperative stress hormones assay as a measure for its suggested modulatory effect on surgical stress. The withdrawal of blood samples were done in the morning 2 h before surgery and again at 1 and 12 h postoperatively. Blood samples were collected into two different tubes; plain tubes for measuring serum Adreno-corticotropine hormone (ACTH) and growth hormone (GH) levels and EDTA tubes for epinephrine analysis. Within 2 h of blood withdrawal the samples were centrifuged and frozen at −70 °C. Both ACTH and growth hormones were measured by radioimmunoassay (RIA) technique while plasma levels of epinephrine were determined by high-performance liquid chromatography (HPLC) with electrochemical detection (ECD) from plasma ethylenediamine tetraacetic acid (EDTA) by using the ClinRep® device (Merc/Recipe, Munich, Germany). The base-line hormonal values in the two studied groups were compared to each other and to the readings in the postoperative period. Also, the hormonal levels 1 h following the end of procedure and again at 12 h postoperatively in the dextromethorphan treated group were compared to their levels in the control group at the same time intervals.

If any patient developed adverse reactions, such as vomiting, somnolence, respiratory distress, drowsiness, hallucination, blurred vision, skin rashes, or itching was documented and compared.

Table 1 Demographic data in the two studied groups [mean ± standard deviation (SD)].

	Dextromethorphan group (n = 30)	Placebo group (n = 30)
Age (yrs)	33 ± 4.1	35.1 ± 4.1
Weight (kg)	68.4 ± 8.5	70.3 ± 7.4
Duration of surgery (min)	60 ± 8.7	57.5 ± 8.5

No significant differences between the two groups.

3. Statistical analysis

The sample size was calculated by using ACTH blood levels as the primary outcome of this study. The α-error level was fixed at 0.05 and the power was set at 90%. The mean ± standard deviation of the cases and that of the control was estimated similar to that in the study of Ledowski and his colleagues [10]. Data were expressed as mean ± standard deviation (SD) or number (%). Comparison between groups was done by using the student's t-test. Nominal data were analyzed using the Chi square test. P values < 0.05 were considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 13 for Microsoft Windows.

4. Results

The demographic data in the two groups were comparable as regards to age, weight, and duration of surgery (Table 1).

Following fentanyl administration, the number of patients who developed reflex fentanyl coughing was less in the dextromethorphan DEX treated group [4 patients (13%)] when compared to the patients in the control group [11 patients (36%)] (Table 2).

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

	Dextromethorphan group (n = 30)	Placebo group (n = 30)
Incidence of fentanyl cough	4 (13.3%)*	11 (36.6%)
No. of patient with mild cough	2 (50%)	6 (54.5%)
No. of patients with moderate cough	2 (50%)	4 (36.3%)
No. of patients with severe cough	0 (0%)	1 (3.3%)

No. = number.
* Significantly different when compared to placebo group (P < 0.05).

By using a special assessment scale to measure the severity of the fentanyl induced cough, the patients in the two groups were significantly different when the cough was categorized into mild, moderate, and severe forms. In dextromethorphan premedicated group, two cases out of four were showing a mild degree of cough in comparison to six patients in the placebo group. Also, two patients were estimated as having moderate cough in DEX group when compared to four patients in the placebo group. Furthermore, one case in the placebo treated group was considered as the severe form (Table 2).

The measured stress hormones (ACTH, epinephrine, and growth hormones) were significantly different in the two studied groups.

The base-line hormonal values did not differ significantly between the two groups but the values were significantly lower in comparison to the readings at 1 and 12 h.

At 1 h postoperatively, the ACTH, epinephrine, and growth hormone levels in the dextromethorphan treated group were significantly lower than in the control group. However, at 12 h, no significant differences were detected between the two studied groups.

When the hormonal levels were traced and compared at 1 and 12 h postoperatively, no significant differences were measured in the dextromethorphan treated group. On the other hand, ACTH, epinephrine, and growth hormones were significantly lower in placebo at 12 h when compared to the readings at 1 h postoperatively (Figs. 1–3).

The use of dextromethorphan in this study was not associated with serious side effects. Only four patients developed postoperative vomiting in dextromethorphan group in comparison to three patients in the placebo group and were treated by I.V. ondansetron. The hemodynamic profile was statistically insignificant at the various time intervals in the studied groups.

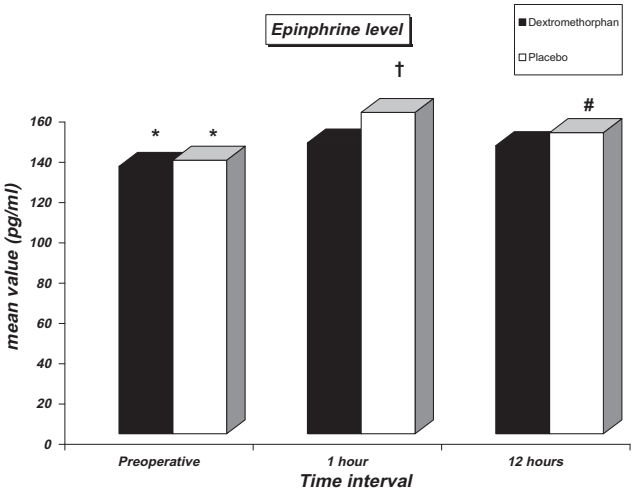

Figure 1 Epinephrine levels between the studied groups. (*) Significantly different when compared to the values at 1 and 12 h postoperatively ($P < 0.001$). (†) Significantly different compared to the dextromethorphan group at 1 h ($P = 0.0002$). (#) Significantly different compared to the values at 1 h ($P = 0.023$).

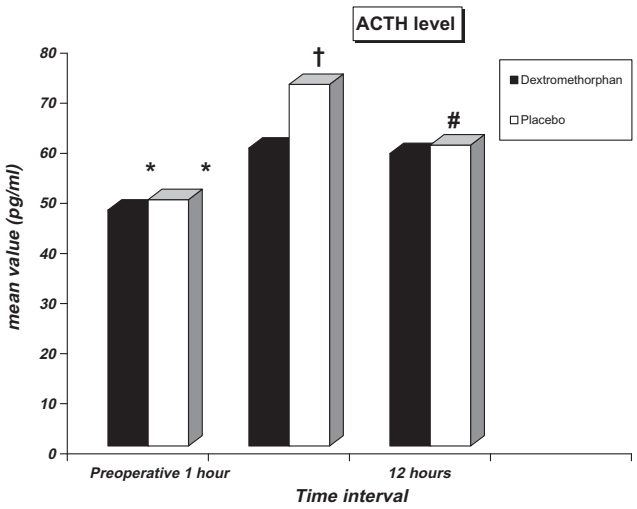

Figure 2 ACTH levels between the studied groups. (*) Significantly different when compared to the values at 1 and 12 h postoperatively ($P < 0.0001$). (†) Significantly different when compared to the dextromethorphan group at 1 h ($P = 0.01$). (#) Significantly different when compared to the values at 1 h ($P = 0.0006$).

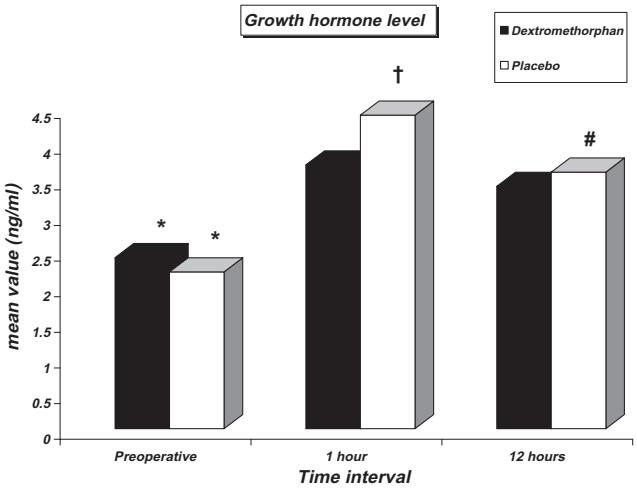

Figure 3 Growth hormone levels between the studied groups. (*) Significantly different when compared to the values at 1 and 12 h postoperatively ($P < 0.0001$). (†) Significantly different when compared to the dextromethorphan group at 1 h ($P = 0.005$). (#) Significantly different when compared to the values at 1 h ($P = 0.002$).

5. Discussion

The premedication with dextromethorphan 60 mg 1 h prior to the induction of general anesthesia reduced not only the incidence of fentanyl induced cough but also the degree of that cough when it was assessed by a special scale used in previous studies [1–8]. The number of patients who developed cough decreased effectively to four patients (13.3%) when dextromethorphan was used (two mild and two moderate cough) in

comparison to 11 patients (36.6%) in the placebo treated group (six mild, four moderate, and one severe cough). In this study, the well-known central antitussive action of dextromethorphan and the elevation of the cough threshold without inhibition of ciliary activity [17] could explain its successful effect on the incidence and severity of reflex fentanyl cough.

Several reports participated in that field in-order to decrease the cough response to fentanyl injection and exhibited controversial results. Coinciding with the results in our study, Ambesh and his colleagues [2] demonstrated a decrease in the incidence of fentanyl cough into 4% in the cases using huffing maneuver in relation to 32% in the control group. In the huffing maneuver group, no patients developed severe form of coughing while 12% was categorized as the moderate to severe form of cough in the other group. Also, Lin and his colleagues [6] proved that both lidocaine 2 mg/kg and ephedrine 5 mg succeeded to reduce fentanyl reflex cough with little hemodynamic changes in the ephedrine group. In accordance to these findings, intravenous premedication with clonidine 2 μg/kg significantly decreased the cough which occurs after fentanyl administration (17.3% in clonidine pretreated patients versus 38.7% in control group). That effect was associated with mild reduction in heart rate and blood pressure [8]. Similar to that, Yeh and his colleagues [7] used small dose of preemptive ketamine 0.15 mg/kg one minute prior to fentanyl injection and showed a significant reduction in the incidence of fentanyl induced cough (7.2%) when compared to the use of saline injection (21.6%). Because the bronchospasm was considered as a contributing factor in that cough response, also Agarwal et al. [4] and Lui et al. [5] demonstrated that bronchodilators, steroids, and mast cell stabilizers, such as salbutamol, terbutaline, beclomethasone, and sodium chromoglycate played an effective interventional role.

On the contrary, propofol 0.6 mg/kg in the study of Lin and his colleagues [6] failed to reduce the cough incidence. Similarly, 0.01 mg/kg intravenous atropine was not considered as a prophylactic preventive measure [5]. Although ketamine administration in the study of Yeh et al. [7] was associated with reduction in the incidence of fentanyl induced cough but it did not change the severity of that cough significantly.

The shortage and difficulty in finding dextromethorphan parenteral preparations directed this study to use the more available oral syrup formulae. In order to find an effective and safe dextromethorphan oral dose, the previous reports were closely revised and it was found that the dextromethorphan was ranging between 0.5 mg/kg and 150 mg [16]. In this study, the dose of 60 mg was selected within this safe, effective, and recommended range.

The stress response to surgery was believed to augment the adreno-hypophyseal hormones release and to enhance the sympathetic nervous system activity [10]. Although, the type of anesthesia was found by some authors to be an effective modulatory factor for surgical stress response [19] but still others did not show any correlation between the depth of anesthesia and perioperative stress hormones release [10]. During surgical intervention, tissue trauma is the main stimulus which initiates the hyperalgesic responses with activation of hypothalamo–hypophyseal–adrenal axis [10] and, therefore, preventive analgesia; before surgical stimulation may be considered as an effective modulating factor for that stress response [16].

After tissue injury, the excitatory neurotransmitter glutamate with other chemical mediators were released for initiation of pain cascade and regulation of its associated hemodynamic and hormonal stress responses. Glutamate was believed to interact with its target NMDA and non-NMDA receptors [20]. The previous studies included a variety of NMDA receptor antagonists and monitored their effects on stress hormones release.

It was believed that ACTH is a sensitive measure to the severity of surgical trauma and the associated stress response. Similarly, both epinephrine and growth hormones are secreted in response to adrenal and pituitary stimulation by the tissue mediators [21].

In this study, dextromethorphan as a NMDA receptor antagonist was used for premedication of patients 1 h prior to the surgery. Dextromethorphan 60 mg succeeded to decrease the rise in epinephrine, ACTH, and growth hormones release at 1 h in the postoperative period when compared to the preemptive use of placebo. At 12 h postoperatively, no significant differences were detected between the two groups as regards the hormonal profile.

Although the vagina was infiltrated thoroughly with epinephrine–lidocaine solution in all studied patients but dextromethorphan treated patients showed a significant decrease in the stress hormones levels more than the patients in the other group. This could be explained by the effective multimodal antagonistic action of dextromethorphan hydrobromide on NMDA receptors which played an important role in the block of pain cascade and stress hormones release. The long duration of dextromethorphan hydrobromide action from 3 to 8 h [17] enabled its use as an oral premedicant drug.

Similar results occurred in the previous reports which studied the effect of other NMDA antagonists on neuroendocrine regulation. The use of MK-801 (dizocilpine) in the study of Zelena and his colleagues [13] decreased the level of prolactin in response to foot shock stimulus in a rat model. Coinciding with that, the NMDA antagonist cis-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755) reduced the rise in prolactin values following suckling stimulation in rats and that effect was abolished by NMDA injection [22]. Similarly and in laparoscopic cholecystectomy patients, magnesium sulfate 50 mg/kg immediately given before pneumoperitoneum reduced the levels of epinephrine, norepinephrine, and ADH hormones without altering the plasma rennin and cortisol values [15]. Also when was administered in a monkey model, ketamine exerted an inhibitory action on hypothalamo–adrenal axis and consequently decreased the ACTH and cortisol secretion [23]. Even when combined to either ropivacaine or bupivacaine in caudal analgesia, ketamine not only prolonged the duration of analgesia but also reduced the cortisol level [24].

Contradictory to these results, ketamine administration in the study of Hergovich et al. [14] demonstrated a significant rise in stress hormones levels including prolactin and cortisol. Also, memantine intake in healthy human volunteers did not affect neither plasma prolactin nor serum cortisol values [14]. In surgical intensive care patients, ketamine/midazolam and ketamine/propofol combinations resulted in a significant increase in both ADH and norepinephrine plasma values [25]. In order to compare between the effects of S^+ ketamine and the racemic mixture on serum catecholamine and cortisol levels, Doenicke and his colleagues [26] found that both drugs exhibited a stimulatory effects on the hormonal secretion with rise in epinephrine, norepinephrine, and cortisol serum levels. The norepinephrine levels were higher in the racemic mixture

than the S^+ isomer and that claimed to be responsible for the increase in the hemodynamic outcome in the racemic group.

Although the mechanism of action of MK-801 (dizocilpine), memantine, and CGS 19755 was attributed to their antagonistic activity on NMDA receptors [13,14,22] but magnesium in addition to that was believed to have a direct inhibitory effect on both catecholamine secretion and vasoconstriction induced by vasopressin [15]. With the exception of one animal study [23], many authors believed that the rise in stress hormones level following intravenous ketamine use may be related to the direct sympathetic nervous system activation [25,26]. On the other hand, 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 [23]. The dextromethorphan effect in our study may be related to the blockade of NMDA receptors and consequently the hyperalgesic response.

The use of dextromethorphan in this study was not associated with significant perioperative adverse events. Only vomiting occurred in a few number of patients in the two studied groups. The premedication with 60 mg dextromethorphan was not accompanied by drowsiness, hallucination, blurred vision, skin rashes, itching, or hemodynamic disturbances. These results were going in hand with those of previous studies [16–18].

In spite of using a small sample size in this study, the results were in favor with dextromethorphan premedication. A larger sample size, multi-central research, and dose response methodology may be needed in the future studies.

6. Conclusion

Premedication with 60 mg dextromethorphan 1 h prior to the surgery reduced not only the rise in stress hormones release (epinephrine, ACTH, and growth hormone) at 1 h postoperatively but also the incidence and severity of fentanyl induced cough.

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