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ORIGINAL ARTICLE

Effects of pretreatment with a small dose of dexmedetomidine on sufentanil-induced cough during anesthetic induction

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Abstract
Purpose We aimed to investigate the effects of pretreatment with a small dose of dexmedetomidine on the cough caused by sufentanil during anesthetic induction.
Methods Two hundred and forty patients undergoing elective gynecological surgery under general anesthesia were randomly allocated to 4 groups ($n = 60$, each group). Dexmedetomidine 0, 0.1, 0.25, and 0.5 μg/kg was administered in 5 min to groups I, II, III, and IV, respectively, followed by the induction of general anesthesia with intravenous propofol, at a target concentration of 5 μg/ml, and sufentanil 0.5 μg/kg. The incidences and severity of cough that occurred within 1 min after the injection of sufentanil were recorded, and the incidences of cardiovascular adverse events that occurred between the administration of the dexmedetomidine infusion and 1 min after tracheal intubation were recorded.
Results The incidences of cough in group II, group III, and group IV were lower than that in group I (6.7, 5.0, and 6.7 vs. 26.7 %, $P < 0.01$), while there were no significant differences between group II, group III, and group IV. The incidences of severe sinus bradycardia in group III and group IV were higher than that in group I (18.3 and 23.3 vs. 0.0 %, $P < 0.01$), while there was no significant difference between group I and group II. There was no significant difference in the incidence of low blood pressure among the four groups.
Conclusion Dexmedetomidine at 0.10, 0.25, and 0.50 μg/kg significantly reduced the incidence of sufentanil-induced cough during anesthetic induction, with the effect being most marked for 0.10 μg/kg dexmedetomidine.

Keywords Cough · Dexmedetomidine · Opioid analgesics · Sufentanil

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Introduction

Intravenous injection of fentanyl during anesthetic induction may cause cough, which interferes with successful anesthetic induction, and in serious cases may increase intracranial pressure and intraocular pressure [1, 2]. Like fentanyl, sufentanil may also induce cough during anesthetic induction [3]. The incidence of sufentanil-induced cough was reported to reach 15.8 % in an Indian population [3]. Although sufentanil-induced cough is transient and not severe in most patients, the possibility of severity should not be ignored in patients with pneumothorax, cerebral aneurysm, brain trauma, brain hernia, open eye injury, arterial aneurysm resection, or hypersensitive airway disease. Many studies have been conducted to find approaches to suppress cough during anesthetic induction, e.g., with the pre-intravenous injection of lidocaine, ephedrine, dexamethasone, or clonidine, or the inhalation of the selective β_2 receptor agonist terbutaline [4–9]. However, these methods have their limits of range owing to drug effect onset time and side effects. Clonidine can reduce cough during anesthetic induction [7], but low blood pressure during induction limits its clinical use. Dexmedetomidine is a potent, highly selective α_2 adrenergic agonist with an activity 8 times that of clonidine. Because the pharmacological action mechanism of dexmedetomidine is similar to that of clonidine, it is presumed that dexmedetomidine may also reduce sufentanil-induced

cough during anesthesia induction. This study aimed to investigate the effects of pretreatment with a small dose of dexmedetomidine on cough caused by sufentanil during anesthetic induction, for future reference in clinical application.

Patients and methods

This study was approved by the Medical Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University, and eligible participants signed informed consents. A total of 240 women, aged 18–58 years, with body weight of 45–80 kg and American Society of Anesthesiologists (ASA) physical status I–II who were undergoing selective gynecological surgeries under general anesthesia were enrolled. Inclusion criteria were: body mass index $\leq$35 kg/m^2, no bradycardia, no upper respiratory infection during the 2 weeks before the surgery, no history of asthma, no chronic cough, and no routine use of angiotensin-converting enzyme inhibitors. Patients were randomized into four groups: group I (normal saline group), group II (0.10 μg/kg dexmedetomidine group), group III (0.25 μg/kg dexmedetomidine group), and group IV (0.50 μg/kg dexmedetomidine group) with the help of a computer-generated table of random numbers, with 60 patients in each group.

The patients did not receive premedication. After entering the operation room, the patients received routine electrocardiogram (ECG), pulse oxygen saturation (SpO_2), blood pressure (BP), heart rate (HR), and bispectral index (BIS) monitoring. After a venous pathway was established in the forearm using an 18-G IV catheter (B. Braun, Melsungen, Germany), Ringer lactate was infused at a rate of 4–6 ml/min. Before anesthetic induction, dexmedetomidine (batch 10082734; Hengrui Medicine, Jiangsu, China), at 0.10, 0.25, or 0.50 μg/kg, was added to 10 ml normal saline and this solution was infused in group II, group III, and group IV, respectively, at a steady rate of 2 ml/min, while 10 ml normal saline was infused in group I at the same rate. When the infusion was completed, a propofol target-controlled infusion (Injectomat TIVA Agilia, infusion pump; Fresenius Vial, Brezins, France) was initiated with an effect-site concentration of 5 μg/ml. When BIS had decreased to 55, the three-way infusion port that had been set up was closed, and 0.5 μg/kg sufentanil (batch 100608; Humanwell Pharmaceutical, Yichang, China) was injected over a period of 3 s. After the injection was finished, the three-way infusion port was opened again to continue infusion at the previous rate. An observer blind to the premedication given to the patients recorded the occurrence of cough 1 min after the injection of sufentanil, and the severity of the cough was graded based on its frequency. Severity was defined as: mild, 1–2 times; moderate, 3–5 times; or severe, >5 times [10]. Facial mask-assisted ventilation was performed if SpO_2 was <95 % during the observation period. Then tracheal intubation was performed under induction of 1–2 mg/kg succinylcholine. From dexmedetomidine infusion to 1 min after tracheal intubation, an intravenous injection of phenylephrine 50 μg was administered if blood pressure was low (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg), and an intravenous injection of atropine 0.5 mg was administered if severe sinus bradycardia occurred (heart rate [HR] <50 bpm). The incidences of low blood pressure and severe sinus bradycardia were recorded.

In a pilot study, we found that the incidence of sufentanil-induced cough was 28 % (14/50) following an IV bolus of sufentanil 0.5 μg/kg given over a period of 3 s in 50 patients. Therefore, we assumed that if the incidence of cough decreased to 10 %, the effect of pretreatment with a small dose of dexmedetomidine could be considered significant. To achieve 80 % statistical power with $\alpha = 0.05$, each group would need a minimum of 56 patients. We recruited 60 patients per group to allow for any dropouts. Statistical analysis was carried out using Stata 9.0 software (Stata). Quantitative data are presented as means ± standard deviation. Repeated measures analysis of variance (ANOVA) was used for intragroup comparisons, and one-way ANOVA was adopted for intergroup comparisons. The χ^2 test was employed to compare qualitative data, and the rank sum test was utilized for the comparison of ranked data. $P < 0.05$ was regarded as the significant level.

Results

There were no significant differences in age, body weight, height, or body mass index among the four groups(see Table 1).

The incidences of cough in groups II, III, and IV were lower than that in group I ($P < 0.01$), while there was no significant difference among groups II, III, and IV. There was no significant difference in the severity of cough among the four groups(see Table 2).

The incidences of severe sinus bradycardia in group I, group II, group III, and group IV were 0.0, 3.3, 18.3, and

Table 1 Comparison of general conditions among the four groups ($n = 60$)

Group	Age (years)	Body weight (kg)	Height (cm)	Body mass index (kg/m^2)
I	36 ± 10	61 ± 9	162 ± 8	23 ± 6
II	38 ± 11	58 ± 9	161 ± 7	22 ± 6
III	37 ± 9	59 ± 8	161 ± 6	23 ± 6
IV	36 ± 10	60 ± 9	161 ± 6	23 ± 7

Values are means ± SD

Table 2 Comparison of incidence and severity of cough among the four groups (%, $n = 60$)

Group	Incidence of cough	Severity of cough (n)		
		Mild	Moderate	Severe
I	16 (26.7 %)	6	5	5
II	4 (6.7 %)*	2	1	1
III	3 (5.0 %)*	1	1	1
IV	4 (6.7 %)*	1	1	2

Values are numbers (percentages)

Compared with group I, * $P < 0.01$

Table 3 Comparison of incidences of low blood pressure and severe sinus bradycardia among the four groups (%, $n = 60$)

Group	Incidence of low blood pressure	Incidence of severe sinus bradycardia
I	3 (5.0 %)	0 (0.0 %)
II	3 (5.0 %)	2 (3.3 %)
III	5 (8.3 %)	11 (18.3 %)*
IV	5 (8.3 %)	14 (23.3 %)*

Values are numbers (percentages)

Compared with group I, * $P < 0.01$

23.3 %, respectively. The incidences in group III and group IV were higher than that in group I ($P < 0.01$), and there was no significant difference between group I and group II. Each patient with bradycardia was treated with an intravenous injection of atropine 0.5 mg, and no additional dose was needed. The atropine 0.5 mg treatment was successful and helped each patient to return to the normal state rapidly. The incidences of low blood pressure in group I, group II, group III, and group IV were 5.0, 5.0, 8.3, and 8.3 %, respectively, and there was no significant difference among the four groups (see Table 3).

Discussion

Dexmedetomidine has sedative, analgesic, anti-sympathetic, and anti-shivering activities, and is able to inhibit the stress response while reducing the amounts of anesthetics and opioids used. It is able to stabilize patients' hemodynamics without causing respiratory depression. Therefore, the preoperative application of dexmedetomidine has been increasingly common. The common drug loading of this agent in clinical practice is 0.5–1.0 μg/kg, with slow intravenous injection for at least 10 min [11]. The doses used in the present study (0.10, 0.25, and 0.50 μg/kg) were lower than the common drug loading in clinical practice. The result of this study indicated that a small dose of dexmedetomidine was enough to reduce the cough caused by sufentanil during anesthetic induction. A single injection is convenient and safe for such a small dose of dexmedetomidine, without the need for an infusion pump.

The incidence and severity of cough with sufentanil are less than those with fentanyl [3], and the clinical application of sufentanil as a novel opioid has become increasingly extensive; accordingly, research on sufentanil-induced cough may have clinical significance. The mechanisms of fentanyl-induced and sufentanil-induced cough have been reported to be opioid receptors [12], reduced chest wall compliance [13], C-fiber receptors [14], irritant receptors located in the tracheobronchial mucosa [5], and the citrate in fentanyl and sufentanil injection solutions [15, 16]. Some researchers argue that the sedative effects of anesthetics may inhibit fentanyl-induced cough [17]; however, it takes 15 min for dexmedetomidine to provide sedation [18]. In the present study, the administration of 0.1 μg/kg dexmedetomidine for 5 min was enough to significantly inhibit the sufentanil-induced cough, while a sedative effect did not emerge within that time. The following factors may account for the possible mechanism of dexmedetomidine in inhibiting sufentanil-induced cough. Firstly, the ability of α_2-adrenoreceptor agonists to reverse the muscular rigidity induced by opioids in rats has been proven [19], and it is possible that the incidence of fentanyl-induced cough may be decreased by α_2-adrenoreceptor agonists via reversal of the muscular rigidity induced by fentanyl [20]. Of note, the intravenous administration of dexmedetomidine effectively blocked histamine-induced bronchoconstriction in dogs [21], and it has been demonstrated, by Sato et al. [22], that ketamine effectively reduced fentanyl-induced cough through relaxing histamine-associated tracheal smooth muscle contraction. Clonidine prevents cough while reducing blood pressure moderately [7]; however, it may cause circulatory fluctuation, whereas a short duration of dexmedetomidine infusion has no effect on blood pressure. Though the infusion of dexmedetomidine at a rate of 0.05 μg/kg/min for 5 min may increase the risk of severe sinus bradycardia during anesthetic induction, the intravenous injection of atropine 0.5 mg helps to achieve a rapid return to the normal heart rate level. Also, studies have revealed that intraoperative management with 0.50 μg/kg dexmedetomidine does not interfere with recovery time [23, 24].

The present study has its own limitations, i.e., all patients enrolled were females. However, as shown in previous studies [25], fentanyl-induced cough was not related to gender, and thus this limitation does not affect the conclusion of our study. The findings of our research indicate that dexmedetomidine may reduce sufentanil-induced cough, although further research should be carried

out to verify that this conclusion can be extrapolated to fentanyl, remifentanil, and alfentanil. Dexmedetomidine should be used cautiously in patients with sinus bradycardia before operation, owing to the effect of heart rate reduction caused by short-duration administration of this agent before anesthetic induction.

To sum up, pretreatment with 0.10, 0.25, or 0.50 μg/kg dexmedetomidine may lead to a significant reduction in the incidence of sufentanil-induced cough during anesthetic induction, with the effect being particularly marked for 0.10 μg/kg dexmedetomidine.

Conflict of interest No external funding and no competing interests are declared.

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