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Effect of Different Doses of Dexmedetomidine Combined With Desflurane on Recovery of Protective Airway Reflexes

Yue Yin, Li Zhang, ZhangGang Xue and XiaoGuang Zhang*

Department of Anesthesiology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

*Corresponding author: XiaoGuang Zhang, Department of Anesthesiology, Zhongshan Hospital, Fudan University, Shanghai 200032, China, Tel: +86 13641995733; E-mail: zhangxg@fudan.edu.cn

Abstract

Objective: Studies about effects of anesthetics on protective airway reflexes after extubation are of great clinical significance. To date, the effect of dexmedetomidine on airway reflexes is not quite clear. Accordingly, we designed the present study and examined whether increasing dose of dexmedetomidine would delay recovery of protective airway reflexes.

Methods: 120 patients undergoing surgeries under general anesthesia with laryngeal mask airway (LMA) were randomly allocated to receive 1.0 µg/kg dexmedetomidine (Group D1), 0.5 µg/kg dexmedetomidine (Group D2), 0.25 µg/kg dexmedetomidine (Group D3) or normal saline (NS, Group C). All the patients received dexmedetomidine or saline about 1 h before the termination of surgery. Time from the discontinuation of desflurane until first response to command (T1) was recorded. Two minutes after the patient responded appropriately to command, he or she was asked to swallow 20 ml of clear water. Time from first response to command until first demonstrated ability to swallow (T2), and time from discontinuation of desflurane until first demonstrated ability to swallow (T3) were recorded. Systolic blood pressure (SBP) and heart rate (HR) were recorded during the operation and right after emergence. Besides, Ricker sedation-agitation scale (RSAS) after emergence and adverse effects were recorded.

Results: T3 of patients in Group D3 (8.1 ± 2.2 min) was significantly shorter than those in Group D2 (9.4 ± 2.1 min, P=0.045) and Group D1 (9.9 ± 2.6 min, P=0.004). In a linear regression model, T3 correlated only with Group, patients in Group D3 recovered airway reflexes faster than those in Group D1 (P=0.002). SBP of patients in Group D1, D2 and D3 were significantly lower than those in Group C during emergence (P<0.01, respectively). HR of patients in Group D1 and Group D2 were lower than NS during emergence (P<0.01, P<0.05, respectively).

Conclusion: Dexmedetomidine of 0.25 µg/kg allows an earlier return of protective airway reflexes than dexmedetomidine of 1 µg/kg and may effectively control cardiovascular responses during emergence.

Introduction

Patients may still suffer from impaired protective airway reflex during early recovery period even after meeting the commonly accepted extubation criteria. Even a slight of impairment of intact protective reflexes after extubation is dangerous for patients with multiple comorbidities such as abnormal gastrointestinal motility, neurologic and pulmonary disease.

Dexmedetomidine is a potent and highly selective α2 adrenoceptor agonist with sympatholytic, sedative, analgesic and anxiolytic properties, which has been described as a useful and popular adjunct in many clinical scenarios [1]. In a previous study, Guler et al. [2] reported that dexmedetomidine 0.5 µg/kg was associated with attenuation of both the prevalence and severity of airway and circulatory reflexes during emergence from anesthesia, without prolonged recovery. When being administered as a total intravenous anesthetic agent, dexmedetomidine may lead to upper airway obstruction and a chin lift is necessary [3]. It is also reported that dexmedetomidine in healthy volunteers produces dose-dependent

sedation and decreases lower esophageal sphincter pressure (LESP) [4,5]. Therefore, whether the application of dexmedetomidine will result in delayed recovery of protective airway reflexes or increased risk of regurgitation and aspiration is still a question. Accordingly, we designed the present study to test the effect of different doses of dexmedetomidine on protective airway reflexes during emergence.

Methods

This study was approved by the Ethics Committee of Zhongshan Hospital Fudan University (Approval No: B2013-136) and written informed consent was obtained from all subjects participating the trial. The study was registered prior to the patient enrollment at Chinese Clinical Trial Registry (ChiCTR-TRC-14004208, Date of registration: 2014-01-25). Between July 2014 and November 2014, we enrolled 120 patients, aged 18-70 years, BMI 18-26 kg/m² and ASA physical status I-II, who underwent less invasive surgeries for which a laryngeal mask airway (LMA) was the planned method of airway management. After getting the written informed consent the day before surgery, the patient was asked to swallow 20 ml of clear water in a 60° upright sitting position. The patient who can swallow the water once without coughing or drooling, and no water remained in the oropharynx was

judged as passing the test (grade 1). Those who swallowed 20 ml water more than once, coughed or drooled were deemed as failing the test (grade 2) [6,7]. Exclusion criteria included a history of neuromuscular disorder; previous pharyngeal, upper gastrointestinal or nasal surgery; diabetes, asthma or cardiopulmonary disease; dysphagia, dysphonia, impaired gastric emptying or failing the swallow test. Patients were randomly allocated to receive 1.0 µg/kg dexmedetomidine (Group D1, n=30), 0.5 µg/kg dexmedetomidine (Group D2, n=30), 0.25 µg/kg dexmedetomidine (Group D3, n=30) or normal saline (NS) (Group C, n=30) by computer-generated random numbers. Dexmedetomidine or NS was prepared by a nurse anesthetist who did not participate in data collection. Dexmedetomidine was diluted with NS in 20 ml and administered about 1 h before the end of surgery within 15 min, while the control group received volume-matched NS as placebo. The attending anesthetist and the patients were blinded to group assignment. The investigator in charge of collecting data and performing the swallow test was kept blinded to the group allocation.

No premedication was given before operation. Electrocardiography, heart rate, non-invasive blood pressure, end-tidal carbon dioxide ($EtCO_2$), pulse oxygen saturation (SpO_2) and bispectral index (BIS) were monitored. In consideration of that desflurane does not affect the recovery speed of airway reflex, we chose desflurane as maintenance anesthetics [6]. However, desflurane is not suitable for induction because of its pungency, so we used sevoflurane induction and switched to desflurane after the LMA placement. Anesthesia was induced with 8% sevoflurane in conjunction with 100% oxygen by face mask and LMA (Ambu® AuraOnce™) was inserted. LMA size was determined by the quick reference guide from the company. After LMA insertion, sevoflurane was discontinued and anesthesia was maintained with desflurane and the inhaled concentration was modulated to maintain BIS at 35-55. Spontaneous respiration was maintained throughout the entire procedure. Fentanyl was titrated in 10 µg increments to maintain the respiratory rate at 12-14 breaths per min. All patients received dexmedetomidine or NS about 1 h before the termination of surgery. To decrease the airway stimulation during the emergence as much as possible, LMA was removed under deep anesthesia (BIS 35-55) immediately at the end of the procedure and then desflurane was terminated. A nasopharyngeal airway was inserted to prevent upper airway obstruction during emergence. The investigator tapped the patient's shoulder and called his/her name every 30s after termination of desflurane. As soon as the patient responded to command 'open your eyes' or 'squeeze my hands', time from termination of desflurane until first response was recorded as T1 (recovery of consciousness) and then the level of agitation was evaluated by Ricker sedation-agitation scale (RSAS) [8]. 2 min after consciousness recovery, the swallow test was performed and the recovery grade of airway reflexes was recorded. If the patient failed the swallow test, he or she was asked to repeat the test at 6,14,22 and 30 min until successfully completion of the test. Time from recovery of consciousness to successfully completion of swallow test was recorded as T2; and time from desflurane termination until passing the swallow test was defined as T3 (equals T1+T2). Besides, adverse events were recorded. During the procedure, hypotension was treated with ephedrine and bradycardia was treated with atropine.

To estimate the required sample size, a pilot study (0.25 µg/kg dexmedetomidine, n=5) was performed and only 1 patient (1/5, 20%) failed the swallow test at 2 min after being awake. We hypothesized that increasing doses of dexmedetomidine would delay recovery of protective reflexes, with α value of 0.05 and a power of 80%, Cochran-Armitage test was used to calculate the sample size. Finally, we decided

that 30 patients per group were required. Statistical analyses were performed using Statistical Product for Social Sciences (SPSS) software 19.0. Comparison of measurement data was made by one-way analysis of variance (ANOVA), LSD test was applied to compare measurement outcomes in pairs. Categorical data were compared using the chi-square test. Multiple linear regression analysis was applied to examine the influences of other confounding factors on recovery of airway reflexes. A probability (P) value<0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled in the study, 30 for each group. Demographic and baseline characters including age, gender, BMI, ASA class, dosage of fentanyl (µg/kg/min), type of surgery, time from administration of dexmedetomidine until surgery conclusion (t1) were not statistically different among all groups (Table 1).

	Group D1	Group D2	Group D3	Group C	P
Sex (male/female)	16/14	15/15	12/18	15/15	0.753
Age (y)	51.8 ± 13.6	49.5 ± 12.3	47.0 ± 14.4	48.3 ± 15.0	0.587
ASA (I-II)	24/6	26/4	25/5	21/9	0.405
BMI (kg/m²)	22.3 ± 2.4	22.5 ± 2.6	22.7 ± 2.5	23.2 ± 2.3	0.524
*Dosage of fentanyl (µg/kg/min)	0.022 ± 0.012	0.027 ± 0.014	0.025 ± 0.012	0.024 ± 0.010	0.474
Orthopedic surgery	17 (57%)	19 (63%)	18 (60%)	21 (70%)	0.579
Urinary surgery	10 (33%)	5 (17%)	7 (23%)	7 (23%)	
Gynecologic surgery	3 (10%)	6 (20%)	5 (17%)	2 (7%)	
t1 (min)	60.1 ± 12.7	60.1 ± 11.3	59.8 ± 12.4	56.8 ± 11.1	0.656

Table 1: Patient Characteristics (n=30). Values are expressed as mean ± standard deviation, or as absolute numbers. *Considering that fentanyl was associated with weight and anesthetic time, we calculated the total dose of fentanyl/weight/anesthetic time (µg/kg/min) as 'dosage of fentanyl'. Abbreviations: ASA: American Society of Anesthesiologists; BMI: Body Mass Index. Group D1: receive 1 µg/kg dexmedetomidine. Group D2: receive 0.5 µg/kg dexmedetomidine. Group D3: receive 0.25 µg/kg dexmedetomidine. Group C: receive normal saline.

All the patients completed the swallow test without severe complications such as aspiration, hypoxia or laryngospasm. At 2 min after being awake, 18 patients in Group D1, 22 in Group D2, 26 in Group D3, and 22 in Group C passed the swallow test respectively (P=0.141). All the patients passed the swallow test at 6 minutes after being awake. Time from discontinuation of desflurane until first response (T1) were not statistically different among four groups (P=0.263). Time from discontinuation of desflurane until first ability to swallow (T3) was shorter in patients given 0.25 µg/kg dexmedetomidine (8.1 ± 2.2 min (mean ± SD)), compared with those were given 0.5 µg/kg dexmedetomidine (9.4 ± 2.1 min, P=0.045) and 1 µg/kg dexmedetomidine (9.9 ± 2.6 min, P=0.004) (Figure 1).

Multivariate regression analysis was performed to confirm effect of dexmedetomidine on recovery of airway reflexes and eliminate any other confounding factor. Time from discontinuation of desflurane until first ability to swallow (T3) represented the time from discontinuation of inhaled anesthetics to full recovery of airway reflex. In a linear regression model, we defined T3 (y) as dependent variable, Group allocation (D1, D2, D3, C), dosage of fentanyl (µg/kg/min), age, BMI and ETAC (end tidal anesthetic concentration) as independent variable. Dummy variable Group was included in the multiple linear regression analysis, patients in Group D2, D3, C were compared with those in Group D1. The result showed that T3 correlated only with Group, patients in Group D3 and Group C recovered airway reflexes faster than those in Group D1 ($P=0.002$, $P=0.025$, respectively) (Table 2). Baseline heart rate (HR) and systolic blood pressure (SBP) were similar in all groups. SBP of patients receiving dexmedetomidine were significantly lower than NS during emergence ($P<0.01$, respectively). HR of patients receiving 1 µg/kg dexmedetomidine and 0.5 µg/kg dexmedetomidine were lower than NS during emergence ($P<0.01$, $P<0.05$). Hypotension happened more frequently in patients given dexmedetomidine. Patients in Group D3 underwent less bradycardia than those in Group D1 and D2 ($P<0.05$). Patients receiving dexmedetomidine had significantly lower end tidal anesthetic concentrations (ETAC) of desflurane compared to NS ($P<0.01$). RSAS scores were statistically different among four groups ($P=0.021$), patients in Group C was associated with higher RSAS scores than those in Group D1 ($P<0.05$).

T3	Coefficient	95% confidence interval	P
Group			
D2	-0.794	-2.077~0.490	0.223
D3	-2.159	-3.475~-0.842	0.002
C	-1.683	-3.152~-0.214	0.025
Age (year)	-0.007	-0.043~0.029	0.697
BMI (kg/m2)	0.135	-0.057-0.328	0.167
Dosage of fentanyl (µg/kg/min)	32.022	-6.495~70.540	0.102
ETAC	2.094	-2.020~6.209	0.315

Table 2: Multiple linear regression accounting for Group, Age, BMI, Dosage of fentanyl and ETAC *vs.* Airway reflex recovery time (T3). Group was applied as Dummy variable in the multiple linear regression analysis; patients in Group D2, D3, C were compared with those in Group D1.
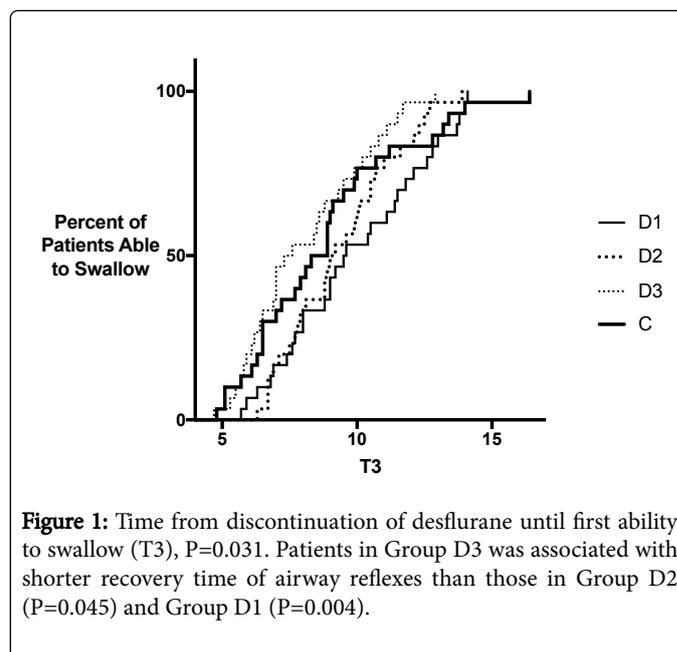

Figure 1: Time from discontinuation of desflurane until first ability to swallow (T3), $P=0.031$. Patients in Group D3 was associated with shorter recovery time of airway reflexes than those in Group D2 ($P=0.045$) and Group D1 ($P=0.004$).

Discussion

Dexmedetomidine is a potent and highly selective α_2 adrenoceptor agonist with sedative, amnestic, sympatholytic and analgesic properties, which is widely applied during the whole perioperative period and in the intensive care unit (ICU) [1]. Despite profound sedative properties, dexmedetomidine has limited respiratory depression effects [9]. A previous study indicated that dexmedetomidine 0.5 µg/kg could attenuate airway and circulatory reflexes on emergence from anesthesia in intraocular surgery, without prolonged recovery [2]. Dexmedetomidine sedation (1 µg/kg) was used for awake fiber optic intubation (AFOI) with fewer adverse reactions and more satisfaction [10,11]. Nevertheless, when being used as an intraoperative anesthetic adjuvant, whether dexmedetomidine could delay the airway reflex recovery which is crucial for patients' safety during emergency period has not been elucidated.

Mahmoud et al. [12] found that in children with no obstructive sleep apnea (OSA), the dynamic changes in nasopharyngeal and retroglossal area with respiration were marginally greater for high dose (3 µg/kg) than for low dose (1 µg/kg) dexmedetomidine, although no subject exhibited any clinical evidence of airway obstruction. It is also reported that infusion of dexmedetomidine (0.6 ng/ml, 1.2 ng/ml, 2.4 ng/ml) in healthy volunteers produces dose-dependent sedation and increased sedation decreases lower esophageal sphincter pressure (LESP), and whether regurgitation and aspiration would accompany was unknown [4,5]. Thus, we designed the present study to estimate airway safety of dexmedetomidine and its effect on recovery of airway reflexes following extubation.

Results of the present study show that dexmedetomidine 0.25 µg/kg allows an earlier return of protective airway reflexes than dexmedetomidine of 1 µg/kg. Delayed return of airway reflexes might be associated with dose-dependent sedation of dexmedetomidine. RSAS scores of patients in Group C were higher than those in Group D1, which meant sedation was deeper in patients receiving dexmedetomidine 1 µg/kg. Sundman et al. [13] found that sub hypnotic concentrations of propofol, isoflurane and sevoflurane caused

an increased incidence of pharyngeal dysfunction with penetration of bolus (10 ml) to the larynx, thus rendering the patient at an increased risk for aspiration during recovery. And there was a strong correlation between sedation and frequency of pharyngeal dysfunction. Results from Eastwood et al. [14] showed that increasing depth of propofol anesthesia was associated with increased collapsibility of the upper airway and decreased airway reflexes. This was associated with a profound inhibition of activity of the genioglossus muscle, the major dilator muscle of the upper airway. It seemed that this dose-related inhibition was the result of depressed central respiratory output to upper airway dilator muscles, and inhibitory neurotransmitters-amino butyric acid (GABA) might be the key factor. Dexmedetomidine's acting site is in locus coeruleus (LC). Central nervous system (CNS) stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the LC in the brainstem play a prominent role in the sedation and anxiolysis. Furthermore, decreased noradrenergic output from the LC allows for increased firing of inhibitory neurons, most importantly the GABA system [9,15]. Thus, we hypothesize that this dose-related effect of dexmedetomidine on depressed airway reflexes is the result of upper airway muscle dysfunction mediated by CNS and GABA system. However, some patients in Group C who didn't receive any dexmedetomide still had delayed return of protective airway reflexes. For those patients, ETAC and RSAS were highest among four groups, and they might not being totally awake and sedative when accepted the swallow test, so we cannot exclude the effect of sub hypnotic concentrations of desflurane on suppressing the airway reflexes during recovery. Patients in Group D3 received less dexmedetomidine and desflurane; two drugs may cause the synergistic effect on adequate sedation and satisfactory airway reflexes recovery.

Patients in Group C had statistically higher SBP and HR almost the entire duration of the procedure. HR and SBP of patients receiving dexmedetomidine tended to be lower than placebo during emergence. The hemodynamic data were consistent with previous studies [1]. Bradycardia and hypotension are the most common side effects of dexmedetomidine. In our study, hypotension happened more frequently in Group D1, D2, D3 than Group C (P<0.05, respectively), almost 20% patients receiving dexmedetomidine underwent hypotension during procedure.

Dexmedetomidine 0.25 µg/kg resulted in less bradycardia than 0.5 µg/kg and 1 µg/kg (P<0.05, respectively). In summary, dexmedetomidine provided smooth and hemodynamically stable emergence, and dexmedetomidine 0.25 µg/kg resulted in less adverse events.

Our study had several limitations. First, the criteria of judging recovery of airway reflexes is subjective and with low sensitivity. We adopted the approach of swallowing 20 ml water, on basis of Mckay's method [6,7]. And there are several other methods as reported. Aksu et al. [16] compared the influence of dexmedetomidine versus fentanyl on airway reflexes by means of incidence and severity of cough as extubation quality. Sundman et al. [13] observed the difference in the activity of the pharyngeal muscles with penetration of bolus to the larynx by using fluoroscopy and simultaneous solid state videomanometry. Erb et al. [17] elicited respiratory reflex responses by spraying distilled water onto the laryngeal mucosa and observed incidence of laryngospasm by fiberoptic bronchoscope. Although studies about the effect of anesthetics on recovery of airway reflexes are of great clinical significance, lack of uniform and reliable method is still the main problem. Second, our sample size may be insufficient.

Before the study, we hypothesized that recovery time of airway reflexes prolonged by increasing dose of dexmedetomidine. However, the result was 'not linear', and the sample size we calculated before might be insufficient. Therefore, we will enlarge the sample size and improve the study design based on the existing research results.

Conclusion

Dexmedetomidine of 0.25 µg/kg allows an earlier return of protective airway reflexes than dexmedetomidine of 1 µg/kg with effective cardiovascular responses control during emergence.

Conflicts of Interest

None

Clinical Trial Number

ChiCTR-TRC-14004208

Registry URL

http://www.chictr.org.cn

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