

Original Article

The effect of dexmedetomidine on remifentanyl-induced difficulty in mask ventilation: a randomized clinical trial

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Abstract: Background: The ultra-short onset time of remifentanyl has many advantages during induction of anesthesia. However, it can also induce difficult mask ventilation due to chest wall rigidity. This study evaluated the effect of dexmedetomidine infusion on remifentanyl-induced difficult mask ventilation. Methods: Sixty patients, aged 18-65 years (ASA class I, II), were enrolled and provided informed consent. Prior to propofol injection, each patient received an infusion of 1 µg/kg dexmedetomidine or saline (control group) for 10 min. The baseline difficulty of mask ventilation was evaluated after intravenous injection of propofol (2 mg/kg). Two minutes after propofol injection, patients received a bolus dose of remifentanyl (1 µg/kg) and mask ventilation difficulty was reassessed. Difficulty of mask ventilation was evaluated using a modified scoring system and vital signs were recorded throughout the study period. Results: The incidence of difficult mask ventilation was significantly lower in the dexmedetomidine than in the control group (36.7% vs. 70.0%, p -value = 0.02). Vital signs were more stable in the dexmedetomidine than in the control group during the study period. Conclusion: Dexmedetomidine (1 µg/kg) infusion can significantly reduce the incidence of difficult mask ventilation induced by a bolus dose of remifentanyl (1 µg/kg).

Keywords: Dexmedetomidine, remifentanyl, muscle rigidity/chemically induced, muscle rigidity/prevention & control, opioid/adverse effects

Introduction

Dexmedetomidine (DEX), an α_2 adrenergic agonist, has anesthetic sparing, analgesic, anxiolytic and sympatholytic effects [1]. Recently, DEX has been used as an adjuvant agent due to its anesthetic/opioid sparing effect. Small intravenous doses of DEX (1 µg/kg or 0.5 µg/kg) have been reported to reduce the incidence of hypotension during induction and to blunt cardiovascular responses during endotracheal intubation.

Remifentanyl (REMI) is an ultra-short acting opioid with a context sensitive half time of 3 min regardless of infusion time [2]. Its $T_{1/2} k_{e0}$ is 0.75 min, making the time for equilibration between plasma and effect site extremely short [3]. REMI is widely used for balanced anesthesia and can efficiently reduce the minimum alveolar concentration of inhalation agents. However, REMI shares the side effects of all other

synthetic opioids, including chest wall rigidity (CWR), which has been reported in 5-8% [4] to 100% [5, 6] of patients. CWR during induction of anesthesia can cause difficult mask ventilation, increase central venous pressure, induce acid-base disturbances [7], increase intra-abdominal pressure during laparoscopy [8], and may even cause hypoxemia [9].

Few studies have assessed the ability of pretreatment with neuromuscular blocking agents [10] or benzodiazepines [11] to reduce opioid induced CWR. DEX has also been reported to reduce opioid induced rigidity in rats [12]. To date, however, no clinical study has assessed the effects of DEX on REMI induced CWR. This prospective, randomized, double blind study was designed to evaluate the effects of DEX pretreatment on REMI induced CWR during induction of general anesthesia. We hypothesized that 1 µg/kg DEX could sufficiently attenuate CWR from a REMI bolus injection during induction of anesthesia.

Materials and methods

Patient population

This study included ASA class I/II patients, aged 18-65 years. Patients were excluded if they had BMI > 30 kg/m²; any type of neuromuscular disorder; history of antidepressant medication; pregnancy; known side effects to opioids; alcohol dependency (> 3 times per week); smoking history, craniotomy state; history of cardiac surgery, hypertension, or congestive heart failure (left ventricular ejection fraction < 50%); anticipated difficulty with airways (e.g. Mallampati class 3/4, short neck, mandible prognathism, previous upper airway surgery, chromosomal abnormality, or rheumatoid arthritis); or hypersensitivity to DEX. This study was approved by the hospital's institutional review board (2013-08-014), and all patients provided written informed consent.

The total number of patients was calculated based on a previous study, in which 45% of patients experienced CWR after a target controlled infusion of REMI (effect site concentration 4 ng/ml) [13]. Assuming that DEX would reduce 10% CWR incidence, and with an alpha error of 0.05 and a beta error of 0.2, a sample size of 30 patients per group was calculated.

Patients were randomized into a DEX and a control group using random allocation software. A randomization table was generated by one researcher (Park), resulting in a label printed with only the allocation number. The table and label were given to the anesthesia nurse, who prepared the experimental drug (DEX or saline) according to the table and attached the label to the syringe. The drug was infused into the patient by another anesthesia nurse. A second researcher (Noh), who was blinded to drug allocation, assessed the CWR and difficulty in mask ventilation. Data were collected by a web-based electronic data capture system (REDCap™).

All patients received anesthetic pretreatment with midazolam 2 mg and glycopyrrolate 0.2 mg. Patient monitoring (ECG, pulse oximeter, NBP) was started when the patient entered the operating room. Vital signs were checked and each patient received DEX 1 µg/kg (as a 4 µg/ml solution) or an identical volume of normal saline via a syringe pump for 10 minutes. Vital signs were assessed after 10 min infusion peri-

od, followed by administration of a bolus dose of REMI (1 µg/kg, as a 50 µg/ml solution). Patients were asked about any discomfort 1 min later, vital signs were assessed, and propofol 2 mg/kg was administered 2 min later. Mask ventilation was evaluated before injecting rocuronium 0.7 mg/kg 2 min later. Endotracheal intubation was performed 2 min after rocuronium injection and vital signs were recorded.

The rigidity or difficulty of mask ventilation has categorized into 4 grades [14, 15]. This scale has been modified, with category 1 defined as no difficulty of mask ventilation and normal ETCO₂ waveform; category 2 as slight difficulty of mask ventilation, but normal ETCO₂ waveform; category 3 as difficult mask ventilation and abnormal ETCO₂ waveform; and category 4 as unable to perform mask ventilation and no detectable ETCO₂ waveform.

Rescue protocol

If mask ventilation was impossible (category 4), rocuronium (1.2 mg/kg) was administered, followed immediately by endotracheal intubation.

Significant vital sign changes during medical treatment were defined as a 40 beat/min reduction in HR (bradycardia) and a 50 mmHg reduction in MBP (hypotension). Patients with bradycardia were injected with atropine 0.5 mg, and patients with hypotension received repeated injections of phenylephrine 50 µg until MBP increased 50 mmHg.

Data management

Study data were collected and managed using REDCap electronic data capture tools at the Department of Anesthesiology and Pain Medicine Laboratory of Chungnam National University Hospital [16]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Statistical methods

Normality was tested with the Shapiro-Wilk test and homoscedasticity with Bartlett's test for

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Table 1. Demographic data

	Control (n = 30)	DEX (n = 30)	P
Age, yr	40.7 ± 12.4	40.9 ± 14.5	0.954
Height, cm	162.7 ± 8.7	162.5 ± 9.2	0.943
Weight, kg	60.2 ± 10.3	56.5 ± 7.3	0.117
BMI, kg/m ²	22.7 ± 3.0	21.5 ± 2.6	0.083
Sex (M/F)	12/18	12/18	1

Values are shown as mean ± SD or number of patients. There were no significant differences between the groups. DEX: dexmedetomidine group.

Table 2. Frequency (percentage) of patients in the control and dexmedetomidine groups according to modified category

	Control	DEX	P
Category			0.056
1	9 (30.0%)	19 (63.3%)	
2	9 (30.0%)	4 (13.3%)	
3	8 (26.7%)	6 (20.0%)	
4	4 (13.3%)	1 (3.3%)	

Values are given as numbers of patients (%). DEX: dexmedetomidine group.

Table 3. Frequency (percentage) of rigidity

	Control	DEX	P
Rigidity			0.019
No	9 (30.0%)	19 (63.3%)	
Yes	21 (70.0%)	11 (36.7%)	

Values are given as numbers of patients (%). DEX: dexmedetomidine group.

continuous variables. Data were compared by independent t-tests when all statistical conditions were met. Welch's test was used only when normality was verified and the Kruskal-Wallis when both conditions were not met. The incidence of rigidity was compared using the chi-square test or Fisher's exact test, and the significance of hemodynamic changes was verified using a mixed effects model. To compare both groups at multiple points and changes between periods, periodical data were obtained and analyzed separately. The D interval was defined as the interval from baseline to immediately before propofol injection, the P interval as the interval from immediately before propofol injection to immediately before endotracheal intubation, and the T interval as the interval from immediately before endotracheal intubation before to 2 min after endotracheal intubation. Maximum likelihood was used as the parameter estimation method using the R sta-

tistical package (3.1.0). The lme4 package was used for mixed effect modeling, and significance was tested with the lmerTest package.

Results

The study enrolled 60 patients, 30 in each group. Demographic data and categorical distribution were similar in the two groups (**Tables 1, 2**). The incidence of CWR was significantly higher in the control than in the DEX group (70% [21/30] vs. 36.7% [11/30], $P = 0.02$) (**Table 3**). CWR was 33.3% (95% CI 6.2% to 60.4%) lower in the DEX than in the control group.

There were no significant changes in MBP during the D interval ($P = 0.104$) or between the two groups ($P = 0.170$). Although there were no differences in heart rate in the control group ($P = 0.32$), heart rate decreased significantly from baseline in the DEX group during the D interval ($P = 0.000$) and was significantly lower than the change observed in the control group during this interval ($P = 0.000$) (**Figures 1, 2**).

Both the DEX ($P = 0.000$) and control ($P = 0.000$) groups showed significant reductions in MBP during the P interval, although the decrease was significantly lower in the DEX group ($P = 0.019$). Heart rate decreased significantly in the control ($P = 0.022$) but not the DEX ($P = 0.6$) group during the P interval, with the rate of reduction also differing significantly in the two groups ($P = 0.047$) (**Figures 1, 2**).

During the T interval, MBP increased significantly in both the control ($P = 0.000$) and DEX ($P = 0.000$) groups, although the increase was significantly lower in the DEX group ($P = 0.015$). Pulse was also significantly increased in both the control ($P = 0.000$) and DEX ($P = 0.000$) groups, with the increase significantly lower in the DEX group ($P = 0.038$) (**Figures 1, 2**).

Although no patient experienced severe hypotension ($MBP < 50$ mmHg), two patients developed bradycardia (< 40 beats/min). Bradycardia in both patients was relieved by a single bolus dose of atropine 0.5 mg after endotracheal intubation.

Discussion

These results showed that pretreatment with DEX 1 µg/kg could reduce the incidence of REMI-induced rigidity, as well as significantly

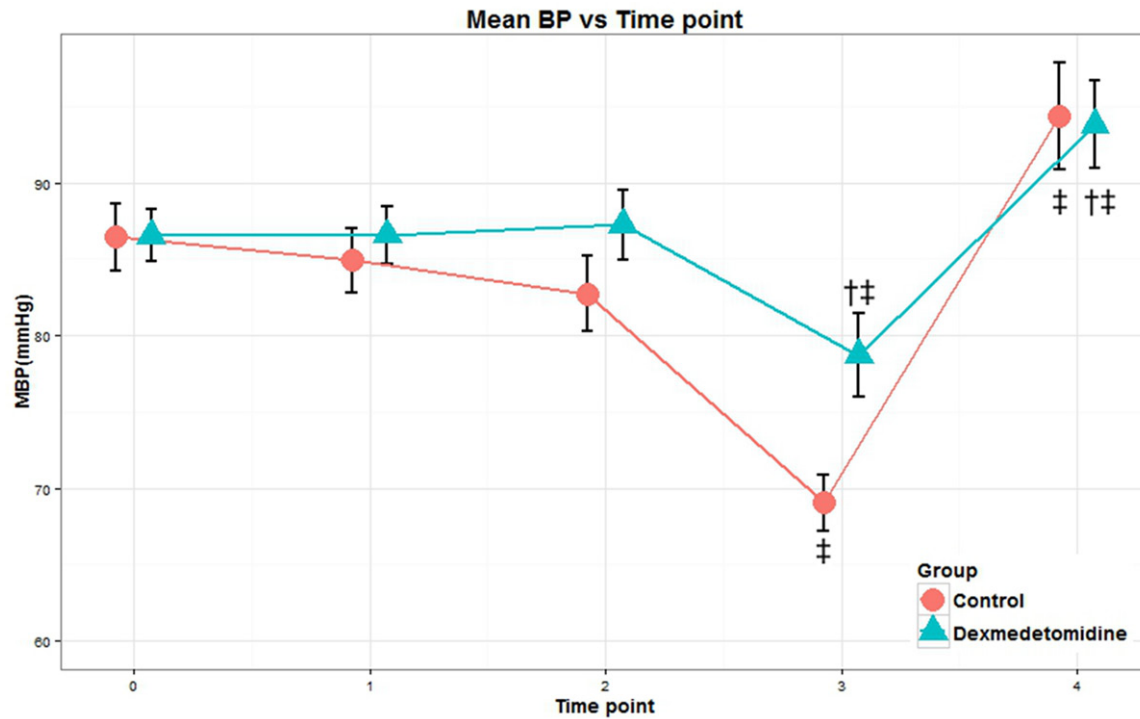


Figure 1. MBP at specific time points in the control and dexmedetomidine groups. Time point 0: baseline (before dexmedetomidine infusion); time point 1:10 minutes after dexmedetomidine infusion; time point 2:2 minutes after remifentanyl bolus injection; time point 3:2 minutes after propofol injection; time point 4: time of endotracheal intubation. Values are presented in mean $\pm$ standard error of mean. * $P < 0.05$, $\ddagger P < 0.01$ compared with baseline or previous value; $\dagger P < 0.05$, $\S P < 0.01$ compared with the control group.

reducing the incidence of difficult mask ventilation after REMI injection. Similarly, DEX pretreatment was found to efficiently reduce alfentanil induced muscle rigidity in rats [12, 17]. Other studies also suggested a relationship between opioid induced rigidity and α_2 adrenergic receptors (A2R) by showing that central A2R antagonists (atipamezole, idazoxan) intensified alfentanil-induced muscle rigidity [12, 18]. Yohimbine, another A2R antagonist, also increased rigidity after fentanyl injection [19]. The effect of DEX on muscle rigidity has been shown to be dose dependent [17]. Unlike DEX, a central acting A2R agonist, peripheral A2R agonists do not reduce the incidence of muscle rigidity [12].

Specific brain regions and various neurotransmitters have been shown to be involved in opioid induced rigidity. Brain mapping and pharmacological studies have found that the pontine raphe nucleus is the most important region for rigidity [20-22]. Denervation of coeruleospinal tract (CST) neurons, or intravenous or intrathecal injection of the α_1 blocker prazosin, has been shown to reduce rigidity, linking nor-

epinephrine with rigidity [23-25]. Glutamate [26, 27], serotonin [28] and dopamine [29] have been reported to be involved in coeruleospinal neurotransmission. Unlike mu opioid receptors, which mediate muscle rigidity, activation of the kappa1 and delta1 opioid receptors has been shown to attenuate rigidity [30].

Although clinical studies have reported conflicting results, other agents, such as neuromuscular blocking agents, benzodiazepine, and naloxone, have also been shown to prevent muscle rigidity. Although pretreatment with pancuronium but not diazepam (0.15 mg/kg) was reported to reduce the severity and incidence of fentanyl (30 μ g/kg) induced rigidity [14], another study reported that pretreatment with diazepam (5 mg) or midazolam (2.5 mg) but not atracurium (40 μ g/kg) efficiently attenuated opioid induced rigidity [11]. In a more recent study, priming with rocuronium or vecuronium reduced the incidence of rigidity [10].

The mechanism behind muscle rigidity and difficult mask ventilation remains unclear. A study using EMG found that alfentanil increased

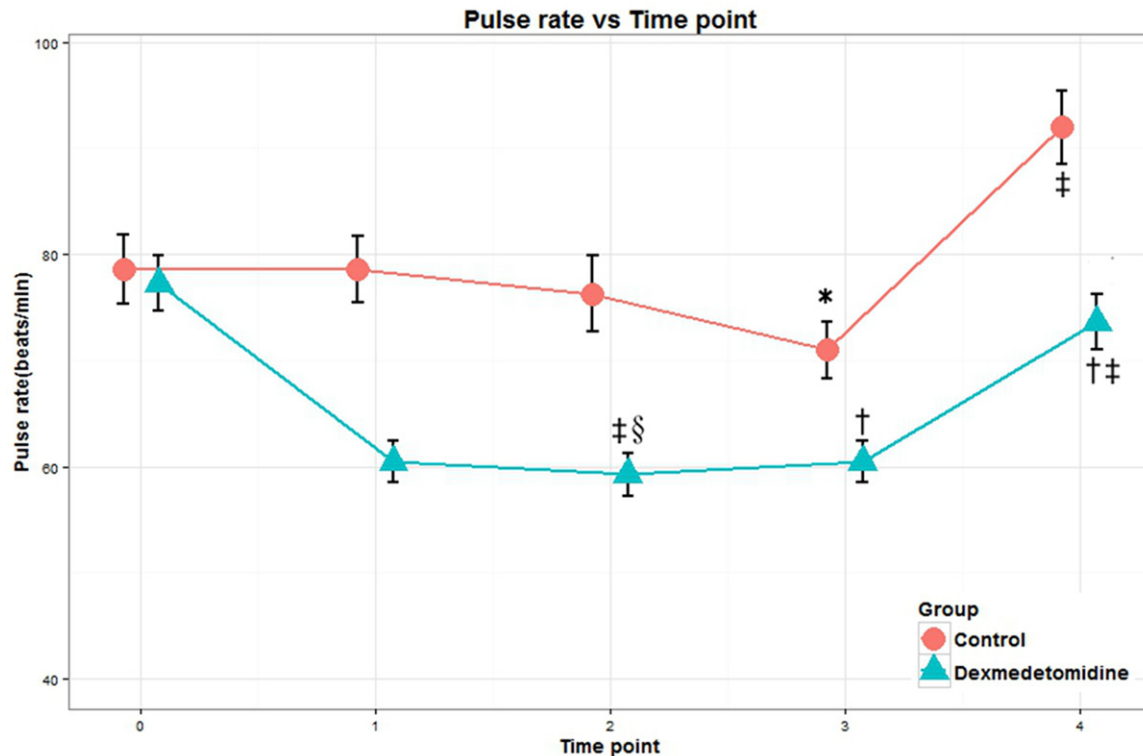


Figure 2. Pulse rates at specific time points in the dexmedetomidine and control groups. Time point 0: baseline (before dexmedetomidine infusion); time point 1:10 minutes after dexmedetomidine infusion; time point 2:2 minutes after remifentanyl bolus injection; time point 3:2 minutes after propofol injection; time point 4: time of endotracheal intubation. Values are presented in mean $\pm$ standard error of mean. * $P < 0.05$, ‡ $P < 0.01$ compared with baseline or previous value, † $P < 0.05$, § $P < 0.01$ compared with the control group.

intercostal/rectus abdominis muscle tone. In cases of severe rigidity, cervical movement was shown to be nearly impossible [7]. Closure of glottic and supraglottic tissues was observed after sufentanil injection via fiberoptic bronchoscopy [31]. Another study using fiberoptic bronchoscopy in patients with fentanyl induced difficult mask ventilation reported the occurrence of truncal rigidity and/or glottic closure [32].

Opioid induced CWR has been shown to be related to the infusion rate of the drug. Although a 5 min infusion of REMI 0.2~0.25 $\mu\text{g/kg/min}$ did not induce CWR [33], 45% of patients developed CWR after a TCI infusion of effect site concentration 4 ng/ml [13].

DEX prevents hypotension during induction of general anesthesia by activating A2Rs in resistant vessels [34]. Patients in the present study also showed more stable blood pressure after DEX infusion. DEX has also been found to reduce pulse rate due to sympatholysis and baroreflex from vasoconstriction [34, 35]. The

combination of DEX plus REMI would therefore further reduce pulse rate. However, severe bradycardia (< 40 beats/min) was observed in only two patients and the average pulse rate in the DEX group was above 50/min.

This study had several limitations. Unlike studies using EMG or passive movement of the extremities to objectively assess the level of rigidity, this study evaluated only the difficulty of mask ventilation. Another limitation was that muscle rigidity was evaluated after a bolus injection of REMI, not after a target controlled infusion.

In conclusion, pretreatment with DEX 1 $\mu\text{g/kg}$ can effectively reduce the incidence of difficult mask ventilation after a bolus injection of REMI (1 $\mu\text{g/kg}$).

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Disclosure of conflict of interest

None.

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