Optimal dose of remifentanil for the prevention of hemodynamic responses during induction of anesthesia with desflurane

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Background: This study was designed to determine the optimal dose of remifentanil single bolus for the prevention of cardiovascular disturbance due to both a rapid increase in desflurane concentration and stimulation by intubation.

Methods: One hundred three adult patients were enrolled in this prospective, double-blind, randomized study. Before anesthesia induction, all patients received normal saline (control) or one of the following 3 doses of remifentanil: 1.0 μg/kg of remifentanil (remifentanil 1.0), 1.5 μg/kg of remifentanil (remifentanil 1.5), and 2.0 μg/kg of remifentanil (remifentanil 2.0). After induction with propofol and rocuronium, 1.3 minimal alveolar concentration of desflurane with oxygen was administered via a face mask. Heart rate (HR) and mean blood pressure (MBP) were recorded before remifentanil administration, and 1, 2, and 3 min after inhalation of desflurane, as well as 0, 1, 2, and 3 min after intubation. The proportions of patients with hemodynamics that maintained within ± 25% of preinduction values (MBP and HR proportion) were calculated.

Results: MBP and HR were lower in the 3 remifentanil groups than in the control group throughout the study period. The MBP proportion was higher in remifentanil 1.0 group than in control group. The HR proportion was higher in the 3 remifentanil groups than in control group.

Conclusions: A single bolus injection of remifentanil (1.0–2.0 μg/kg) may be effective in alleviating adverse hemodynamic changes induced by both desflurane inhalation and tracheal intubation. Especially, administration of remifentanil 1.0 μg/kg maintained more stable blood pressure compared to the control group throughout the study period. (Anesth Pain Med 2015; 10: 104-109)

Key Words: Desflurane, Hypertension, Intubation, Remifentanil, Tachycardia.

INTRODUCTION

Desflurane has a low blood/gas partition coefficient that makes induction and emergence more rapidly. However, a rapid increase in desflurane concentration produces cardiovascular stimulation during an induction period [1]. This can exacerbate hemodynamic changes due to endotracheal intubation. It is especially dangerous to patients with cardiovascular or cerebrovascular disease. Cardiovascular stimulation produced by desflurane can be attenuated by using opioids, β-blockers, and α2-agonists [2-5]. However, the drug with a long duration of action may cause hypotension during the period without stimulation after endotracheal intubation.

Remifentanil is a selective μ-opioid receptor agonist that has a rapid onset and short duration of action [6,7]. Its pharmacokinetic profile is effective in preventing cardiovascular stimulation during induction of anesthesia with desflurane.

This study was designed to determine the optimal dose of remifentanil single bolus for the prevention of cardiovascular disturbance due to both a rapid increase in desflurane concentration and stimulation by endotracheal intubation.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board of Eulji hospital and written informed consents to our prospective, double-blind, randomized study from patients, we enrolled patients with American Society of Anesthesiologists (ASA) physical status I aged between 20–60 years in this study. The patients were scheduled for elective surgery under general anesthesia. Patients with cardiovascular disease, respiratory...
disease, neurologic diseases, endocrine disease, or obesity (body mass index > 30 kg/m²) were excluded from the study. To be equally stimulated during intubation, patients in anticipation of difficulty in endotracheal intubation (Mallampati score > 3, thyromental distance > 6 cm, or mouth opening < 3.5 cm) were excluded. Patients with resting blood pressure ≥ 140/90 mmHg at a preanesthetic visit were also excluded.

A total of 120 patients were randomly allocated to 4 groups using a computerized randomization table: Those who received normal saline (control group), those who received 1.0 μg/kg of remifentanil (remifentanil 1.0 group), those who received 1.5 μg/kg of remifentanil (remifentanil 1.5 group), and those who received 2.0 μg/kg of remifentanil (remifentanil 2.0 group). Remifentanil doses were titrated by using lean body mass [8]. The minimal alveolar concentration (MAC) of desflurane was adjusted for age group [9]. Standard MAC values are those for patients at the age of approximately 40 years. The equation is MAC/MAC₄₀ = 1.32 × 10⁻⁰.₀₀₀₃₀₃₅Age or a 6.7% decrease in MAC per decade. One MAC in the twenties were 7.6 vol%. Those in the thirties, forties, and fifties were 7.1, 6.6, and 6.1 vol%, respectively.

All patients were premedicated with diazepam (7 mg, P.O.) 1 hour before surgery and hydrated with Ringer’s lactated solution as appropriate rate for body weight and duration of fasting during perioperative period. Heart rate, pulse-oximetric findings, noninvasive blood pressure, electrocardiographic findings, capnographic findings, and end-tidal desflurane concentration were monitored. Preoxygenation (O₂ 8 L/min) via a face mask was done for 3 minutes, and patients received normal saline or one of the 3 different remifentanil doses (1.0, 1.5, and 2.0 μg/kg) over 30 seconds with intravenous administration of propofol (2 mg/kg). After loss of consciousness, rocuronium (0.8 mg/kg) was injected. Simultaneously, 1.3 MAC of desflurane with O₂ 8 L/min was administered via a face mask. To minimize air leakage and the difference in the increasing rate of desflurane, an oropharyngeal airway was inserted in each patient, and the triple maneuver was applied. Mechanical ventilation (tidal volume, 10 ml/kg; respiratory rate, 10 breaths/min) was employed via a tightly fitted face mask by using both hands. Intubation was attempted 3 minutes after the start of inhalation of desflurane. Heart rate, blood pressure, and end-tidal desflurane concentration were recorded before remifentanil administration, and 1, 2, and 3 minutes after inhalation of desflurane, as well as immediately, 1, 2, and 3 minutes after endotracheal intubation (Fig. 1). In each group, the proportions of patients with hemodynamic values that maintained within ± 25% of preinduction values were calculated.

SPSS (Ver.18.0, SPSS Inc., Chicago, IL, USA) was used to analyze data, and Sigma plot (Ver.12.3, SYSTAT software Inc., San Jose, CA, USA) was used to determine the sample size. The Chi-square test and Fisher’s exact test were used for categorical hemodynamic data. Repeated measured ANOVA with Tukey test for post hoc analysis were used to evaluate continuous hemodynamic data and the difference between the individual groups. One-way ANOVA and the Chi-square test were used to compare differences in demographic data between the groups. Bonferroni correction was applied for adjustment of P value for multiple tests. P value of < 0.05 was considered significant. A sample size of > 25 for each group was needed to have an 80% power (β = 0.20) of detection of about 40% increase in the proportion of patients maintaining stable hemodynamics within ± 25% of preinduction values (α = 0.05) on the basis of the preliminary study. Values are expressed as means ± SD, means ± SE, or numbers of patients.

RESULTS

A total of 120 patients were screened in this study. Five patients were excluded because of the failure of intubation at the first attempt with a direct laryngoscope or more than 1 minute of delay in the completion of intubation. Twelve patients were also excluded because blood pressure on arrival at the operation room was higher than 140/90 mmHg. Finally, 103 patients completed this study.

There were no significant differences between the 4 groups in demographic data, initial blood pressure, heart rate (Table 1),
Table 1. Demographic and Hemodynamic Data

|                      | Control (n = 27) | Remifentanil 1.0 (n = 26) | Remifentanil 1.5 (n = 25) | Remifentanil 2.0 (n = 25) |
|----------------------|------------------|---------------------------|---------------------------|---------------------------|
| Age (yr)             | 40.4 ± 11.8      | 42.6 ± 11.5               | 40.0 ± 12.0               | 41.8 ± 11.9               |
| Gender (M/F)         | 11/16            | 17/9                      | 15/10                     | 13/12                     |
| Height (cm)          | 166.1 ± 9.4      | 166.3 ± 8.9               | 166.7 ± 11.9              | 165.2 ± 9.1               |
| Weight (kg)          | 62.8 ± 10.3      | 69.6 ± 12.2               | 68.2 ± 10.6               | 66.9 ± 11.9               |
| Initial BP (mmHg)    |                  |                           |                           |                           |
| Systole              | 124.3 ± 14.0     | 129.0 ± 14.4              | 129.8 ± 11.4              | 127.8 ± 13.6              |
| Diastole             | 75.8 ± 10.4      | 75.9 ± 9.1                | 77.4 ± 10.6               | 78.9 ± 11.7               |
| Initial HR (beats/min) | 70.0 ± 13.3     | 71.6 ± 12.0               | 70.8 ± 10.1               | 74.0 ± 16.3               |
| Complication (n)     |                  |                           |                           |                           |
| Hypotension          | 0                | 1                         | 1                         | 1                         |
| Bradycardia          | 0                | 0                         | 1                         | 1                         |

Values are the mean ± SD or the number of patients. BP: blood pressure, HR: heart rate.

DISCUSSION

This study demonstrated that a single bolus injection of
Fig. 3. Values are mean ± SE. (A) Changes in mean blood pressure. The 3 remifentanil groups show lower blood pressure values than the control group throughout the study period. However, there are no significant differences between the 3 remifentanil groups. In control group, mean blood pressure is significantly increased in 0 min and 1 min after intubation compared with its preinduction value. In remifentanil groups, mean blood pressure is significantly decreased before intubation and increased after intubation but there is no significant difference with preinduction value. On the x-axis, 0, 1, 2, and 3 minutes; 0, 1, 2, and 3 minutes after desflurane inhalation; PI 0; PI1, PI2, and PI3; 0, 1, 2, and 3 minutes after intubation. Control: group who received normal saline, remifentanil 1.0, 1.5 and 2.0: groups who received 1.0, 1.5 and 2.0 μg/kg of remifentanil. *P < 0.05 compared with its preinduction value (Bonferroni corrected). (B) Changes in heart rate. The 3 remifentanil groups show lower heart rates than the control group throughout the study period. However, there are no significant differences between the 3 remifentanil groups. In control group, heart rate is higher in all observation period compared with its preinduction value but in remifentanil groups, heart rate is not increased in 0, 1, 2 and 3 minutes after desflurane inhalation. On the x-axis, 0, 1, 2, and 3 minutes; 0, 1, 2, and 3 minutes after desflurane inhalation; PI 0, PI1, PI2, and PI3; 0, 1, 2, and 3 minutes after intubation. Control: group who received normal saline, remifentanil 1.0, 1.5 and 2.0: groups who received 1.0, 1.5 and 2.0 μg/kg of remifentanil. *P < 0.05 compared with its preinduction value (Bonferroni corrected).

Fig. 4. (A) Changes in categorical blood pressure during anesthesia induction. The proportion of patients with mean blood pressure maintain within ± 25% of the preinduction values is significantly higher those in the remifentanil 1.0 group than the control group. Control: group who received normal saline, remifentanil 1.0, 1.5 and 2.0: groups who received 1.0, 1.5 and 2.0 μg/kg of remifentanil, MBP: mean blood pressure. *P < 0.05 compared to the control group (Bonferroni corrected). (B) Changes in categorical heart rate during anesthesia induction. The proportion of patients with heart rate that maintain within ± 25% of the preinduction values is significantly higher those in the 3 remifentanil groups than in the control group. Control: group who received normal saline, remifentanil 1.0, 1.5 and 2.0: groups who received 1.0, 1.5 and 2.0 μg/kg of remifentanil, HR: heart rate. *P < 0.05 compared to the control group (Bonferroni corrected).
remifentanil effectively alleviated adverse changes in both blood pressure and heart rate induced by desflurane inhalation and tracheal intubation. Remifentanil (1.0, 1.5, and 2.0 μg/kg) effectively reduced the fluctuation in blood pressure throughout the study period. In particular, remifentanil (1.0 μg/kg) could maintain more stable blood pressure than control group.

Desflurane causes sympathetic activation, with hypertension, tachycardia, and increased plasma catecholamine levels when its inhalation concentration is rapidly increased [1]. Many drugs have been used to attenuate these disadvantages. Fentanyl, esmolol, and clonidine blunt transient cardiovascular responses to a rapid increase in desflurane concentration [2]. Labetalol attenuates hemodynamic responses induced by tracheal intubation and desflurane induction [4]. Mean blood pressure was significantly lower when using propofol than that when using thiopental sodium as an induction agent during desflurane anesthesia [10].

Remifentanil is one of the most widely used drugs for blunting hemodynamic responses induced by desflurane. Target-controlled infusion of remifentanil effectively blocks hemodynamic responses to tracheal intubation during induction of anesthesia with desflurane. The EC50 values of remifentanil that blocks hemodynamic responses to tracheal intubation during induction of anesthesia with 1 MAC desflurane are 3.7 ng/ml in adults [3] and 3.4 ng/ml in children [11]. The effect-site remifentanil concentration of 3.3 ng/ml is useful for blunting hemodynamic responses in 95% of patients when 2.0 mg/kg of propofol induction is followed by 3% desflurane inhalation [12]. The effect-site remifentanil concentration of 4 ng/ml was required to alleviate the response by 5 min exposure of 1.7 MAC of desflurane inhalation [13]. Higher concentration of desflurane induces a greater sympathetic stimulation [14,15] and could be required more dose of remifentanil to control increasing BP and HR after desflurane inhalation. Our study was designed using the clinical dose of desflurane with single bolus injection of remifentanil. Although remifentanil has been used through continuous infusion with pump in many cases, a single bolus injection of remifentanil is a convenient method, without requiring additional equipment. Because remifentanil has a rapid onset of action and a short latency to peak effect [6,7,16], bolus injection followed by desflurane inhalation could be useful for preventing hemodynamic changes. Our results demonstrated that this simple method could be appropriate for control of blood pressure during induction of anesthesia with desflurane. However, this method may be inadequate for control of heart rate increased by intubation. Heart rate still increased more than 25% relative to the preinduction value in 64-80% patients in the 3 remifentanil groups. It is thought that the timing of intubation is beyond the peak effect time of remifentanil. The half-life of the central compartment of remifentanil is only 0.71-0.74 minutes [17]. Thus, plasma remifentanil concentration may be inadequate to prevent an increase in heart rate due to intubation. To alleviate this response, remifentanil bolus shortly before intubation could be useful. After the study was completed, we collected additional data. With remifentanil 1 μg/kg initially, boosting dose of remifentanil 0.5 μg/kg was administrated in 30 seconds before intubation. Although limited in that data was too small (male, n = 5; female, n = 5) and not randomized, we found out that heart rate was better maintained within ±25% of pre-induction value (7/10). A further study to confirm the optimal time and dose of remifentanil bolus injection is needed. In addition, concomitant use of other agents such as labetalol, esmolol and clonidine might be helpful.

A limitation of our study is that only ASA I patients were included in our study. The sympathetic activation of desflurane and being followed by hemodynamic disturbance may be more dangerous in patients with cardiovascular disease. Accordingly, we could not include these patients in control as well as remifentanil groups. Further studies for response of remifentanil use and desflurane inhalation in elderly patients or patients with cardiovascular disease are needed. Interestingly, hemodynamic changes induced by desflurane inhalation in patients with hypertension [18] or diabetic autonomic neuropathy [19] are similar to those in normal subjects.

Another limitation is that changes in blood pressure and heart rate that maintained within ±25% of the baseline values were used for this study. Generally, changes that maintain within ±20% of the baseline blood pressure and heart rate are accepted as safe criteria for anesthesia. However, patients should be treated when blood pressure is lower than 90 mmHg and when heart rate is less than 60 beats/min or more than 100 beats/min. We chose values that maintained within ±25% as safe criteria for anesthesia in this study.

We determined the doses of remifentanil according to lean body mass. The pharmacokinetic parameters of remifentanil are more closely related to lean body mass than to total body weight [20]. Because we excluded obese patients (body mass index > 30 kg/m²) from the study, calculation of doses by lean body mass seems to be imperatively necessary. However, it is recommended that remifentanil doses be calculated by
lean body mass to prevent obese patients from remifentanil overdose.

In conclusion, the results of this study suggest that a single bolus injection of remifentanil (1.0–2.0 μg/kg) may be effective in alleviating adverse changes in blood pressure and heart rate induced by both desflurane inhalation and tracheal intubation. Especially, administration of remifentanil 1.0 μg/kg maintained more stable blood pressure compared to the control group throughout the study period.

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