Effect of midazolam pretreatment on desflurane $\text{MAC}_{\text{BAR}}$ at an effect−site concentration of remifentanil 1.0 ng/ml

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Background: The goal of this prospective study was to determine the effect of midazolam pretreatment on the desflurane requirement for blunting the sympathetic response after surgical incision (minimum alveolar concentration blockade of adrenergic responses, $\text{MAC}_{\text{BAR}}$) when desflurane is combined with a target-controlled concentration of remifentanil at 1 ng/ml.

Methods: Sixty-five patients aged 30 to 60 years with American Society of Anesthesiologists physical status of I or II who were undergoing general anesthesia for thyroidectomy were registered for this study. The patients were randomly allocated to receive either 30 $\mu$g/kg of midazolam (Group M) or isovolemic saline (Group C) intravenously before anesthetic induction. All patients were anesthetized with propofol, rocuronium, desflurane and remifentanil at a target-controlled effect-site concentration of 3 ng/ml at intubation followed by 1 ng/ml throughout the study. Sympathetic responses to surgical incision were determined 10 minutes after stabilization of end-tidal desflurane and target-controlled remifentanil concentrations. The predetermined end-tidal desflurane concentrations and $\text{MAC}_{\text{BAR}}$ for each group were determined using an up-and-down sequential allocation technique.

Results: The $\text{MAC}_{\text{BAR}}$ of desflurane with 1 ng/ml remifentanil concentration was 7.1 and 6.8% without and with midazolam pretreatment, respectively, using Dixon’s up-and-down method ($P = 0.755$).

Conclusions: Midazolam administered intravenously before anesthetic induction does not impact the $\text{MAC}_{\text{BAR}}$ of desflurane with an effect-site concentration of remifentanil 1.0 ng/ml. (Anesth Pain Med 2015; 10: 27-31)

Key Words: Desflurane, Midazolam, Minimum alveolar concentration, Remifentanil.

INTRODUCTION

Desflurane is a widely used inhalation agent because of its rapid anesthetic induction and emergence. These characteristics of desflurane are a direct result of its low blood/gas partition coefficient, making it possible to precisely control the anesthetic depth due to the low solubility of desflurane in tissue [1]. However, high concentrations of desflurane which blocks the adrenergic response for surgical incision during inhalation anesthesia might increase sympathetic activity and cause transient increases in the arterial blood pressure and heart rate. Ultimately, this may compromise myocardial oxygenation in the presence of coronary artery disease [2]. Many studies have been performed using fentanyl, remifentanil, and clonidine to reduce the $\text{MAC}_{\text{BAR}}$ of desflurane [3-6].

Midazolam, frequently used for premedication before surgery to reduce anxiety and induce sedation and amnesia, reportedly decreases the minimum alveolar concentration to prevent movements in response to a noxious stimulus in 50% of the population (MAC) [7]. However, the effect of midazolam on the $\text{MAC}_{\text{BAR}}$ has yet to be studied.

The aim of this study was to assess whether injection of midazolam before anesthetic induction can reduce the $\text{MAC}_{\text{BAR}}$ of desflurane with an effect-site concentration of remifentanil 1.0 ng/ml.

MATERIALS AND METHODS

The Institutional Ethics Committee of our hospital approved this study, and written informed consent was obtained from all patients. Sixty-five patients aged 30–60 years with an American Society of Anesthesiologists physical status of I or II who were undergoing general anesthesia for thyroidectomy were registered for this study. The patients were randomly allocated to receive either 30 $\mu$g/kg of midazolam (Group M) or isovolemic saline (Group C) intravenously before anesthetic induction. All patients were anesthetized with propofol, rocuronium, desflurane and remifentanil at a target-controlled effect-site concentration of 3 ng/ml at intubation followed by 1 ng/ml throughout the study. Sympathetic responses to surgical incision were determined 10 minutes after stabilization of end-tidal desflurane and target-controlled remifentanil concentrations. The predetermined end-tidal desflurane concentrations and $\text{MAC}_{\text{BAR}}$ for each group were determined using an up-and-down sequential allocation technique.

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Conclusions: Midazolam administered intravenously before anesthetic induction does not impact the $\text{MAC}_{\text{BAR}}$ of desflurane with an effect-site concentration of remifentanil 1.0 ng/ml. (Anesth Pain Med 2015; 10: 27-31)
Society of Anesthesiologists physical status classification class of I or II who were scheduled for thyroidectomy under general anesthesia were enrolled in the study. Patients who were allergic to midazolam or remifentanil; pregnant; taking benzodiazepines, opioids, or antipsychotic drugs; obese (body mass index of > 30 kg/m²); hypertensive; or currently using any medications that might affect the cardiovascular system or block the adrenergic responses to surgical incision were excluded.

Using a computer-generated random number table (Random Allocation Software, version 1.0), the patients were randomly allocated to one of two groups. For the patients in Group M, 30 μg/kg of midazolam was injected intravenously before anesthetic induction. For the patients in Group C, isovolemic normal saline was injected intravenously before anesthetic induction.

All patients were transferred to the operating room without premedication. Standard monitoring was used throughout the study, including noninvasive arterial pressure monitoring, electrocardiography, and pulse oximetry. Spectral entropy values were also monitored in all patients.

Before anesthetic induction, 30 μg/kg of midazolam was administered to the patients in Group M, and isovolemic normal saline was administered to the patients in Group C. Anesthetic induction was then performed by intravenous administration of propofol at 1.5 mg/kg with remifentanil at a target-controlled effect-site concentration of 3 ng/ml using a Marsh model of a commercial target-controlled infusion pump (Orchestra® Base Primea; Fresenius Vial, Brezins, France). Rocuronium at 0.6 mg/kg was then injected to facilitate tracheal intubation. Next, the lungs were ventilated with desflurane in a 50% oxygen and air mixture, and the remifentanil concentration was reduced to 1 ng/ml throughout the study. The mechanical ventilation was adjusted to maintain a tidal volume of 8 ml/kg and an end-tidal carbon dioxide value of 30-35 mmHg. The designated end-tidal concentration of desflurane was maintained for at least 10 min [8,9].

The heart rate (HR) and mean arterial blood pressure (MAP) were recorded before induction of anesthesia, 2 and 1 min before skin incision, at skin incision, and at 1 min intervals during the first 5 min after surgical incision. Spectral entropy values were also recorded at the same time points. The preincision value was defined as the mean value of the 2- and 1 min measurements before skin incision. If the MAP decreased enough to require administration of a vasoactive agent prior to skin incision (MAP < 50 mmHg), the patient was withdrawn from the study and the same concentration of desflurane was used for the following patient.

The Dixon’s up-and-down method was used to determine the MACBAR [10]. The response of the preceding patient determined the concentration of the inhalational agent given to the succeeding patients in each group. We arbitrarily started the patients in both groups at a 6.0% end-tidal concentration of desflurane (corresponding to 1 MAC according to the age of the studied population). If the response of the preceding patient in that group was positive (either HR or MAP increased by ≥ 15% above the preincision value), the end-tidal concentration given to the next patient was increased by 0.5%. If the response was negative (neither HR nor MAP increased by ≥ 15%), the end-tidal concentration given to the next patient was decreased by 0.5%. The mean of seven independent crossovers of the responses provided the MACBAR for each group.

During the study, patients were excluded if their MAP dropped below 50 mmHg or their HR dropped below 45 beats/min.

Statistical analysis was performed with IBM SPSS Statistics 20.0 (IBM, Armonk, NY, USA). Student’s t-test, the χ² test, and Fisher’s exact test were used to compare differences between the two groups. The MACBAR of desflurane was calculated from the mean of the midpoints of pairs of concentrations from consecutive patients in which a positive response was followed by a negative response according to the up-and-down method [10]. The Dixon’s up and down method needs at least six pairs for statistical analysis [10,11]. The study was continued until seven pairs of successful-failed MACBAR had occurred.

A P value of < 0.05 was considered to be statistically significant. Data are presented as means ± SDs.

RESULTS

Sixty-five patients were randomized into each group. Five patients were excluded from the study because their MAP fell below 50 mmHg (one in Group C and four in Group M); in these cases, a vasoactive drug was immediately injected. Therefore, data from the remaining 60 patients were included for analysis (Fig. 1). The demographic and baseline characteristics were comparable in both groups (Table 1). The time of midazolam injection to skin incision in Group M ranged from 13 to 17 minutes.

Fig. 2 and 3 depict the individual responses to skin incision according to the up-and-down sequence. The MACBAR of
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Fig. 1. Flow diagram of the patients. Sixty-five patients were randomized for the study; five patients (one from Group C and four from Group M) were eliminated due to low blood pressure. Group C: control group, Group M: midazolam pretreatment group.

Table 1. Demographic Data and Operation Characteristics

|                      | Group C (n = 26) | Group M (n = 34) |
|----------------------|------------------|------------------|
| Age (yr)             | 43.4 ± 9.7       | 43.6 ± 9.0       |
| Sex (M/F)            | 9 (35) / 17 (65) | 7 (21) / 27 (79) |
| Height (cm)          | 164.4 ± 8.0      | 163.0 ± 7.6      |
| Weight (kg)          | 61.7 ± 9.7       | 59.8 ± 10.8      |
| BMI (kg/m²)          | 22.8 ± 3.0       | 22.3 ± 2.5       |
| ASA physical class (II/III) | 20 (77) / 6 (23) | 31 (91) / 3 (9) |
| Preoperative HR (beats/min) | 67.1 ± 12.3   | 72.6 ± 15.9 |
| Preoperative MAP (mmHg)  | 107.6 ± 16.6    | 110.0 ± 13.7    |
| Mean HR before skin incision (beats/min) | 70.9 ± 16.5  | 76.8 ± 13.9    |
| Mean MAP before skin incision (mmHg)  | 75.8 ± 15.8     | 78.0 ± 13.7    |

Data are expressed as mean ± SD, median (IQR) or number (%). Group C: control group, Group M: midazolam pretreatment group. BMI: body mass index, MAP: mean arterial pressure, HR: heart rate. There is no significant difference between the two groups.

desflurane with an effect-site concentration of remifentanil at 1 ng/ml was 7.1 ± 1.8% in Group C and 6.8 ± 1.6% in Group M (P = 0.755).

DISCUSSION

Our study demonstrated that 30 μg/kg of midazolam pretreatment fails to decrease the MACBAR of desflurane with
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Fig. 2. Responses of 26 consecutive patients to skin incision according to the up-and-down sequence in Group C with a 1 ng/ml target effect-site concentration of remifentanil. The end-tidal concentration of desflurane with 1 ng/ml remifentanil required to block the adrenergic response in 50% of the patients was 7.1 ± 1.8%.

Fig. 3. Responses of 34 consecutive patients to skin incision according to the up-and-down sequence in Group M with a 1 ng/ml target effect-site concentration of remifentanil. The end-tidal concentration of desflurane with 1 ng/ml remifentanil required to block the adrenergic response in 50% of the patients was 6.8 ± 1.6%.

1 ng/ml remifentanil concentration, although it is known to decrease the MAC value of desflurane [7].

Midazolam is a short-acting benzodiazepine that is widely used because of its hypnotic and anxiolytic properties [12]. Furthermore, benzodiazepines decrease the amount of desflurane required to produce anesthesia [7]. In a previous investigation, premedication with midazolam at 25 μg/kg decreased the MAC of desflurane to 4.9 ± 0.9% and that at 50 μg/kg decreased it to 4.9 ± 0.5% from 5.9 ± 0.6% in patients 31-65 years of age [7]. However, the effects of midazolam pretreatment on the MACBAR of desflurane have not been studied. Therefore, we hypothesized that premedication with midazolam can reduce the MACBAR of desflurane. However, our results suggest that midazolam pretreatment has no impact on the MACBAR of desflurane.

One possible explanation for the absence of a correlation between the MACBAR of desflurane and midazolam pretreatment is the mechanism of action of midazolam. This drug has hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle-relaxing properties by acting as an agonist of gamma-aminobutyric acid (GABA) receptors [12,13]. However, it has no analgesic properties compared with other drugs such as opioids or clonidine; those are known to attenuate sympathetic activity due to tracheal intubation, surgical incision, or ketamine anesthesia [3-6,14]. Taittonen et al. [14] investigated whether clonidine or midazolam premedication could attenuate the perioperative responses during ketamine anesthesia and concluded that midazolam does not prevent the ketamine-induced increase in catecholamine concentrations, nor does it attenuate the catecholamine response to surgery. However, clonidine did decrease the preoperative and postoperative plasma catecholamine concentrations due to its analgesic, indirectly sedating, and muscle-relaxing effects.

Daniel et al. [3] reported that fentanyl augments the blockade of the sympathetic response to incision produced by desflurane, and Dedola et al. [4] reported that remifentanil decreases the MACBAR of desflurane in the presence and absence of N2O. The analgesic effect of opioids is well known to inhibit the ascending transmission of nociceptive information from the dorsal horn of the spinal cord [13].

The effect of midazolam on the hemodynamic system could be considered another difference between it and the aforementioned drugs. Hemodynamic alterations induced by anesthetic agents are mediated through their effects on the sympathetic nervous system. Most general anesthetics, including benzodiazepines, decrease sympathetic activity in humans. The predominant hemodynamic change is a slight reduction in the arterial blood pressure secondary to a decrease in the systemic vascular resistance [12]. However, the effect of midazolam on sympathetic nervous system activity has been studied in patients without stimulation. Samuelson et al. [15] reported that anesthetic induction with midazolam did not blunt the hemodynamic response to intubation in patients with ischemic heart disease and that the stresses of surgery are not blocked by midazolam.

Our results are consistent with a previous investigation.
showing that propofol did not attenuate the cardiovascular response to the stimulus provided by a rapid increase in the desflurane concentration [16]. This is because the mechanism of action of propofol is quite similar to that of midazolam (both acting at the GABA\textsubscript{A} receptor, leading to an increased frequency of chloride ion channel opening) [13]. On the other hand, most opioids reduce sympathetic tone while enhancing parasympathetic tone and this is primarily mediated by the central nervous system [13]. Moreover, \(\alpha\)-agonists have direct effects on the sympathetic nervous system, decreasing the HR and systemic blood pressure [13].

Our study has several limitations. First, the lack of direct determination of plasma concentrations of midazolam can be considered as an important shortcoming of the study. However, intervals between midazolam injection and skin incision have slight variation (13 to 17 minutes). Second, we increased the desflurane end-tidal concentration according to the Dixon’s up-and-down method, but the high concentration of desflurane itself might have affected the sympathetic activity. A previous study reported that acutely increasing the inspired concentration of desflurane from 7.2 to 10.9\% led to massive sympathetic activation, hypertension, and tachycardia, and that these responses began to abate 7-8 min after initiating desflurane [17,18]. Thus, when the patient was ventilated with desflurane at a concentration above 7.0\%, the sympathetic activation might have resulted in marked hypertension and tachycardia.

In conclusion, midazolam at 30 \(\mu\)g/kg administered intravenously before anesthetic induction did not impact the MAC\textsubscript{BAR} of desflurane with 1 ng/ml remifentanil. This finding suggests that another drug is necessary to block the hemodynamic response to surgical incision, even when midazolam premedication has been administered.

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