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ORIGINAL ARTICLE

Effect of remifentanil on cardiovascular and bispectral index responses following the induction of anesthesia with midazolam and subsequent tracheal intubation

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Abstract
Purpose We examined the hypothesis that remifentanil decreases the bispectral index (BIS) as well as blunts cardiovascular responses to tracheal intubation during anesthesia with midazolam.
Methods Sixty patients were randomly allocated to three groups according to the dose of remifentanil—0.1 (S), 0.2 (M), or 0.5 (L) μg kg^{-1} min^{-1}, respectively. Infusion of remifentanil was started 5 min before the induction of general anesthesia with midazolam 0.2 mg/kg in all groups. Following the administration of vecuronium 0.1 mg/kg, the trachea was intubated 5 min after induction, and the infusion rate of remifentanil was then reduced to 0.05 μg kg^{-1} min^{-1} in all groups. Mean arterial blood pressure (MAP), heart rate (HR), BIS, and 95% spectral edge frequency (SEF95) were measured until 10 min after tracheal intubation.
Results Infusion of remifentanil alone before the induction of anesthesia did not affect the hemodynamic or electroencephalographic parameters. MAP was significantly decreased after induction in all groups of patients ($P < 0.01$), with no differences among the three groups, while it was significantly increased after tracheal intubation in the patients of groups S and M, but not in those of group L. The HR did not change after induction in any of the groups, but it was also significantly increased after tracheal intubation of group S and M patients, although not in those of group L. The BIS decreased after induction, and both the BIS and SEF95 were significantly lower in group L patients than in those of group S ($P < 0.01$). All patients were unconscious after induction, and none complained of intraoperative awareness.
Conclusion In our patient cohort, remifentanil 0.5 μg kg^{-1} min^{-1} effectively decreased the BIS after the induction of general anesthesia with midazolam 0.2 mg/kg and suppressed the increase of MAP and HR in response to subsequent laryngoscopy and tracheal intubation.

Keywords Bispectral index · Electroencephalogram · Midazolam · Remifentanil · Spectral edge frequency

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Introduction

Remifentanil is a short-acting opioid commonly used in combination with intravenous and volatile anesthetics for the induction and maintenance of general anesthesia. It is known to be effective in blunting cardiovascular responses to noxious stimuli [1–3]. Maintaining hemodynamic stability and the depth of anesthesia is crucially important during the induction of general anesthesia and subsequent tracheal intubation. Remifentanil decreases the concentration of propofol required for loss of consciousness [4], suggesting that it has an hypnotic effect and possibly influences the bispectral index (BIS), an electroencephalographic (EEG) parameter indicative of the depth of anesthesia [5]. Although several studies have examined the

effects of remifentanil on the BIS during general anesthesia [1–4, 6, 7], the results have been inconsistent and controversial. Differences in underlying conditions, such as concurrently administered anesthetics, depth of anesthesia, and the presence of noxious stimuli, may account for these inconsistencies.

Midazolam, a benzodiazepine derivative, is used in combination with opioids for the induction of general anesthesia, particularly in patients with compromised cardiac function and in those undergoing cardiovascular surgery because its sympatholytic effect is smaller than that of propofol [8–11]. Its effects on the EEG are characterized by an increase of the high frequency bands power, in sharp contrast with those of propofol [12, 13]. Although there are a large number of reports on the effect of remifentanil on the BIS during anesthesia with intravenous agents [1–4, 6, 7], most of these are associated with studies performed with propofol, and the effect of remifentanil on BIS during induction and after tracheal intubation under general anesthesia with midazolam remains unclear. Since large inter-individual differences exist in the effect site as well as the plasma concentrations of midazolam [12, 13], which would affect EEG responses during anesthesia, examining the effect of remifentanil on the EEG during anesthesia with midazolam is of clinical importance. In the study reported here, we examined the hypothesis that remifentanil would decrease the BIS as well as blunt cardiovascular responses to tracheal intubation during anesthesia with midazolam.

Materials and methods

The study protocol was approved by the human investigation committee of Osaka City University Hospital (Osaka, Japan). Sixty patients undergoing elective orthopedic surgery and who provided informed consent were randomly allocated (by means of computer-generated allocation table) to three groups according to the dose of remifentanil (0.1, 0.2, or 0.5 $\mu g\ kg^{-1}\ min^{-1}$). One of the authors (Y. I.) allocated the patients and operated the syringe pump. Patients with an abnormal electrocardiogram (ECG), with cardiovascular, respiratory, or psychological disease, or with predicted difficulty in tracheal intubation were excluded. Other exclusion criteria included old age (>70 years old), a regular use of beta adrenoceptor antagonists, hypnotic medication, drug or alcohol abuse, and morbid obesity with body mass index >30 kg/m^2.

Premedication was not used. After arriving at the operating rooms, an intravenous (i.v.) catheter was inserted and lactated Ringer's solution 500 ml was infused rapidly for fluid loading. Patients were monitored with a three-lead ECG, SpO_2, and non-invasive arterial pressure measurements at 1-min intervals. After the baseline measurement, infusion of remifentanil at 0.1, 0.2, or 0.5 $\mu g\ kg^{-1}\ min^{-1}$ was started 5 min before the induction of general anesthesia in the patients of groups S, M and L, respectively. After induction with midazolam 0.2 mg/kg, the patient's name was repeatedly called while his/her shoulders were shaken. After the loss of consciousness had been confirmed, vecuronium bromide 0.1 mg/kg was administered i.v.; the trachea was intubated 5 min after induction. The lungs were mechanically ventilated to maintain an end-tidal carbon dioxide tension between 35 and 40 mmHg. After intubation, the infusion rate of remifentanil was reduced to 0.05 $\mu g\ kg^{-1}\ min^{-1}$ in all groups. Anesthesia in all cases was performed by staff anesthesiologists of our department who were blinded to the group allocation. Ephedrine 5 mg or nicardipine 0.5 mg was administered when the mean arterial blood pressure (MAP) fell to <60 mmHg or increased >120 mmHg, respectively.

The operation was started after completion of the procedures described above. Anesthesia was maintained with sevoflurane and remifentanil, and the BIS was around 40–50 during the operation. At the end of operation, the neuromuscular blockade was reversed, the endotracheal tube was removed, and the patients were transferred to the recovery room. They were interviewed by a blinded observer as soon as they were oriented to time, place, and person, between 2 and 4 h postoperatively, and on the next day in the ward. Questions were asked the patients following the format of a standardized interview. These questions included "What was the last thing you remember before you went to sleep for your surgery?", "What was the first thing you remember after surgery?", "Can you remember anything in between these two periods?", and "Did you have any dreams during anesthesia?" following a standardized interview.

Blood pressure and heart rate (HR) were recorded automatically by an anesthesia information system (ORSYS; Philips Electronics Japan, Tokyo, Japan). EEG data were continuously observed by a monitor (BIS XP ver. 4.0, A-2000 monitor 3.23; Aspect Medical Systems, Newton, MA) using BisSensor strips with four electrodes (Aspect Medical Systems). All binary data packets, which contained raw wave data, BIS, and 95% spectral edge frequency (SEF95), were recorded on a personal computer (LB500/J2; NEC Corp, Tokyo, Japan) using a computer software program (Bispectrum Analyzer) developed by our group [14]. Hemodynamic and EEG parameters were analyzed independently by two of the authors (W. M. and K. T.), both of whom did not participate in the administration of anesthesia in this study. MAP, HR, and EEG parameters, BIS, and SEF95 were compared among the three groups at baseline, before the infusion of midazolam 0.2 mg/kg, before laryngoscopy, and 1, 2, 3, 4, 5, and 10 min after tracheal intubation.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical analyses were performed using Sigma Stat ver. 3.0 (Systat Software, San Jose, CA) and SAS statistical software, release 9.1 (SAS Institute, Cary, NC). The number of patients was determined by power analysis based on our preliminary study. In that study, the mean BIS in group S before laryngoscopy was 65 ± 6. Assuming a type I error protection of 0.05 and a power of 0.90 for detecting a 10% difference in BIS, 19 patients were required in each group. Categorical data were compared using chi-square tests. Age, weight, and height among the three groups were examined by one-factor analysis of variance (ANOVA). Differences in MAP, HR, and SEF95 throughout the experiments among the three groups were examined using ANOVA for repeated measurements. We subsequently examined the changes in these parameters within the same study group from baseline to 10 min after the induction of anesthesia, and differences among the three groups at the same time points were subjected to the Scheffé test, taking into account the number of measurements. As BIS at baseline was between 94 and 98 for all patients, it was compared only with the value before tracheal intubation. The number of patients requiring ephedrine and nicardipine among each of the three groups was examined using the Fisher's exact test, followed by Tukey's multiple comparisons. The doses of ephedrine and nicardipine were compared by Kruskal–Wallis test followed by the Steel–Dwass test for multiple comparison. $P < 0.05$ was considered statistically significant.

Results

All patients completed the study period. No differences were found in patients' characteristics, baseline hemodynamics, or EEG parameters among the three groups (Table 1; Figs. 1, 2). Infusion of remifentanil alone before the induction of general anesthesia did not affect MAP, HR, BIS, or SEF95 in any group (Figs. 1, 2). No changes were detected in raw EEG data, as characterized by low-voltage, high-frequency waves (Fig. 3). After the induction of anesthesia with midazolam, all patients lost consciousness, did not respond when called by name or shaken by the shoulder, and had an assessment of alertness/sedation (OAA/S) score of 1 within 2 min. No patients complained of intraoperative awareness.

The MAP significantly decreased after induction in all groups ($P < 0.01$), with no differences seen among the three groups before laryngoscopy (Fig. 1a), but it significantly increased after tracheal intubation compared with before laryngoscopy in groups S and M ($P < 0.01$ for both). In group L, MAP was not increased after intubation compared with before laryngoscopy, and it was significantly lower than in the patients of group S 1 and 2 min after tracheal intubation ($P < 0.01$). Overall changes of MAP in group L were significantly different from those in group S ($P = 0.02$). The HR did not change after induction (Fig. 1b), but it also significantly increased after tracheal intubation in groups S and M ($P < 0.01$), but not in group L. The HR in group L was significantly lower than that in group S 1 and 2 min after tracheal intubation ($P < 0.05$). In contrast to the MAP, there were no differences in overall changes of HR among the patients of the three groups. Ephedrine 5–20 mg was only used in five patients of group L. Both the frequency of use and the dose of ephedrine were significantly higher in group L patients than in those in groups S and M ($P < 0.01$ for all, Table 1). Nicardipine was used in one and four patients in groups M and S, respectively, and the mean dose was 1.0 mg in both groups. There were no differences in the frequency or the dose of nicardipine among the three groups.

Apparent EEG amplitude was increased in all patients after the induction of anesthesia. The EEG frequency in patients of group L was slower than that in the patients of group S and M before laryngoscopy. It increased thereafter, and the EEG was similar among the three groups 10 min after tracheal intubation (Fig. 3). BIS also decreased in all groups after induction, whereas it did not change after tracheal intubation compared to its value before laryngoscopy (Fig. 2a). The BIS was significantly lower in group L than in group S before laryngoscopy and 1 min after tracheal intubation ($P < 0.01$ for both), but it was not

Table 1 Patients' characteristics and the number of patients required ephedrine and nicardipine

Study characteristics	Group S	Group M	Group L
Patient characteristics			
Age (years)	61 ± 13	63 ± 13	66 ± 12
Weight (kg)	63 ± 10	57 ± 9	60 ± 11
Height (cm)	160 ± 9	158 ± 8	158 ± 7
Sex (male/female)	7/13	7/13	9/11
ASA I/II	8/12	6/14	6/14
Number of patients required			
Ephedrine	0	0	5**
Nicardipine	4	1	0

Patients randomly assigned to groups denoted S, M, and L were administered remifentanil at 0.1, 0.2, or 0.5 μg kg^{-1} min^{-1}, respectively

Data are expressed as mean ± standard deviation (SD) of 20 experiments

There are no significant differences among the three groups except for the number of patients who required ephedrine

** $P < 0.01$ compared with groups S and M

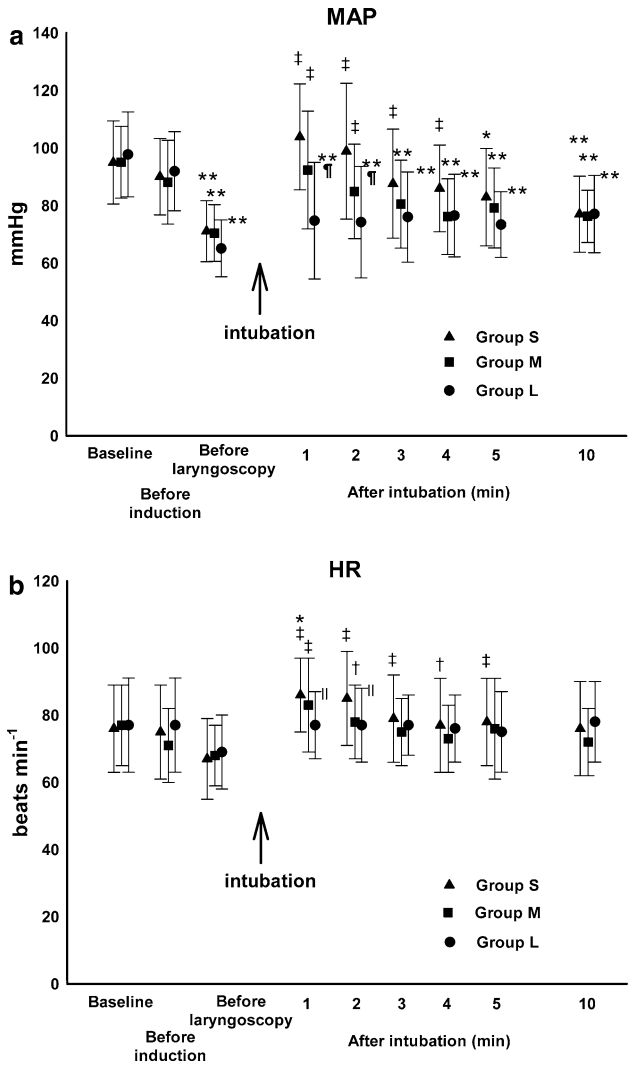

Fig. 1 Mean arterial blood pressure (*MAP*) (**a**) and heart rate (*HR*) (**b**) in patients receiving remifentanil 0.1 (*group S*), 0.2 (*group M*), and 0.5 μg kg^{-1} min^{-1} (*group L*) ($n = 20$, each group). Continuous infusion of remifentanil was started 5 min before the induction of general anesthesia with 0.2 mg/kg of midazolam. Tracheal intubation was performed 5 min after induction, and the infusion rate of remifentanil was then reduced to 0.05 μg kg^{-1} min^{-1} in all groups. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with baseline, $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$ compared before laryngoscopy within the same study group, $^{\|}P < 0.05$, $^{\P}P < 0.01$ compared with group S at the same time point

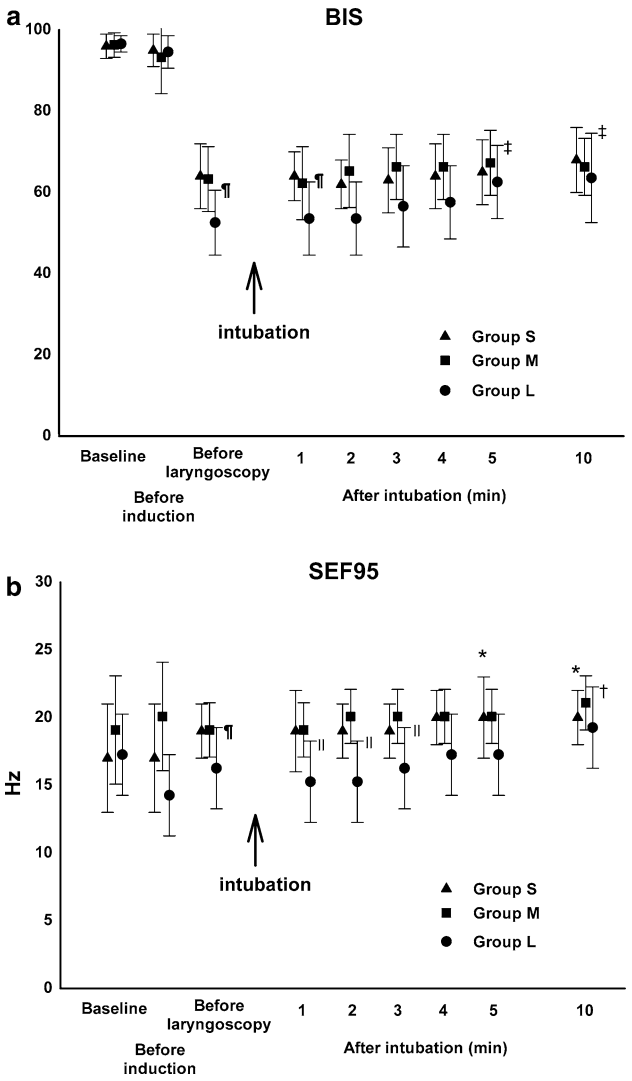

Fig. 2 Bispectral index (*BIS*) (**a**) and 95% spectral edge frequency (*SEF95*) (**b**) in patients receiving remifentanil 0.1 (*group S*), 0.2 (*group M*), and 0.5 μg kg^{-1} min^{-1} (*group L*) ($n = 20$, each group). Continuous infusion of remifentanil was started 5 min before the induction of general anesthesia with 0.2 mg/kg of midazolam. Tracheal intubation was performed 5 min after induction and then the infusion rate of remifentanil was reduced to 0.05 μg kg^{-1} min^{-1} in all groups. $^{*}P < 0.05$ compared with baseline, $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$ compared before laryngoscopy within the same study group, $^{\|}P < 0.05$, $^{\P}P < 0.01$ compared with group S at the same time point

different 2 min after tracheal intubation and thereafter. The BIS did not change during the first 10 min after tracheal intubation in group S or M; in group L, the BIS was significantly increased 5 and 10 min after tracheal intubation compared with before laryngoscopy ($P < 0.01$), and it was not different from that for group S or M patients. There were significant differences in the overall changes of BIS between groups S and L ($P < 0.001$). SEF95 was significantly lower in group L than in group S both before laryngoscopy ($P = 0.01$; Fig. 2b) and 1–3 min after tracheal intubation ($P < 0.05$). There were no differences among the three groups 4–10 min after tracheal intubation. There were significant differences in the overall changes of SEF95 between groups S and L ($P < 0.001$).

Discussion

We have shown that both BIS and SEF95 were significantly lower and the increases in MAP and HR following

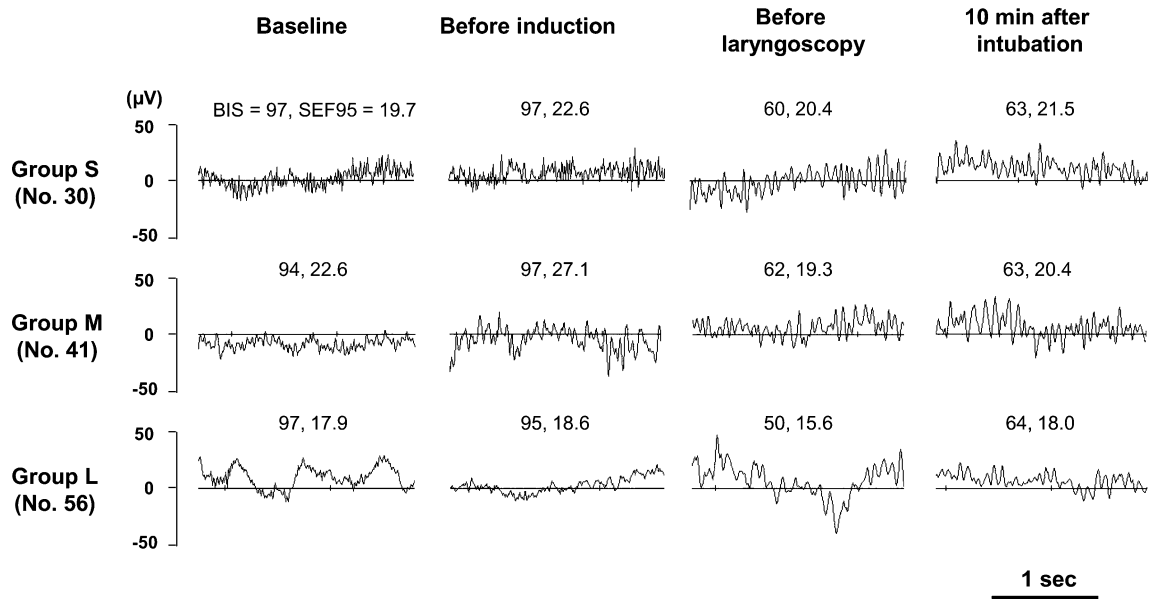

Fig. 3 Electroencephalogram obtained during induction and after tracheal intubation. The electroencephalogram (EEG) at baseline, 5 min after starting the infusion of remifentanil (before the induction of general anesthesia), before laryngoscopy, and 10 min after tracheal intubation is shown with the corresponding bispectral index (*BIS*) and 95% spectral edge frequency (*SEF95*) values. The EEG was measured by the BIS monitor and recorded on a personal computer using a computer software program developed by our group [14]

tracheal intubation were significantly smaller in those patients receiving remifentanil 0.5 μg kg^{-1} min^{-1} than in those receiving lower doses. These results suggest that remifentanil increased the depth of the anesthesia, as indicated by the decrease in EEG frequency and BIS, in addition to suppressing the sympathetic response to tracheal intubation after the induction of anesthesia with midazolam.

Among the various researchers that have studied BIS during anesthesia with remifentanil [1–4, 6, 7], Guignard et al. [1] showed that remifentanil suppressed the increase of BIS in response to tracheal intubation in a dose-dependent manner, but it did not affect BIS before laryngoscopy. These results suggest that remifentanil is effective for blunting the increase of BIS only in the presence of noxious stimuli. Another study showed that bolus infusion of remifentanil 1 μg/kg did not suppress the increase of BIS in patients with preeclampsia during anesthesia induced with thiopental 4 mg/kg, even though it did suppress the increase of blood pressure and HR [2]. Unfortunately, neither of these studies examined other EEG parameters that could potentially affect the BIS.

In contrast to the results of these earlier studies, we found that BIS was decreased by remifentanil in a dose-dependent manner after induction and that it did not increase following tracheal intubation. This difference may result from the relatively high BIS value in our patients, which was due to the predominant EEG waves in the high-frequency band, as shown by the mean SEF95 of around 20 Hz. In our study, the mean BIS values before laryngoscopy in patients receiving remifentanil 0.1 or 0.2 μg kg^{-1} min^{-1} were approximately 65, which is comparable with those obtained during the infusion of propofol alone at plasma or effect site concentrations of 2–3 μg/ml, and they decreased after the start of remifentanil infusion [6, 7]. On the other hand, supplementary infusion of remifentanil during general anesthesia, when the BIS values were 40–50, may not further decrease BIS [1, 2]. In our study, remifentanil 0.5 μg kg^{-1} min^{-1} was effective than smaller doses for maintaining EEG frequency, a predominant index of the depth of anesthesia, at lower levels, as shown in Fig. 3, resulting in lower SEF95 and BIS values. These results are consistent with those reported previously [7].

Previous studies have shown that both blood pressure and HR are decreased by remifentanil used in association with propofol for the induction of general anesthesia [15]. In our study, remifentanil alone did not affect the MAP or HR prior to induction in our study, as reported previously [16], suggesting that remifentanil may augment the cardiovascular suppressant effects of concurrently administered agents rather than cause these effects on its own. Increases in MAP and HR after tracheal intubation were suppressed by remifentanil 0.5 μg kg^{-1} min^{-1}, suggesting that this dose was enough to suppress cardiovascular responses to tracheal intubation. The estimated effect site concentration of remifentanil 10 min after starting infusion at 0.5 μg kg^{-1} min^{-1}, which was the time when tracheal intubation was performed in our study, reached 70–80% of the steady state concentration and was approximately

11 ng/ml [17]. This is comparable with levels known to be effective for suppressing the increase of BIS as well as blood pressure and HR during anesthesia with propofol [1].

Ephedrine was required in five patients receiving remifentanil 0.5 μg kg^{-1} min^{-1} during induction and before tracheal intubation, but not in patients receiving a lower dose of remifentanil. Although ephedrine may have increased the HR, there were no differences in HR before laryngoscopy among the patients of three groups, suggesting that the possible increase in the HR caused by ephedrine would have been suppressed by remifentanil in patients receiving remifentanil 0.5 μg kg^{-1} min^{-1}. The HR was significantly increased after tracheal intubation in patients receiving remifentanil 0.1 or 0.2 μg kg^{-1} min^{-1}, which may be an effect of the nicardipine used for controlling blood pressure.

Midazolam has less of a cardiac sympatholytic effect and induces smaller hemodynamic changes than propofol, and it has been used for the induction of general anesthesia with opioids [8, 11]. Although numerous studies have examined the effects of midazolam on the EEG [5, 12, 13], few studies have examined the effects of midazolam used with opioids in this context [9, 10]. The EEG after the induction of anesthesia with midazolam is characterized by low-voltage, high-frequency waves associated with relatively high BIS values [12, 18].

In this study, the BIS was >60 during anesthesia induced with midazolam and remifentanil 0.1 or 0.2 μg kg^{-1} min^{-1}, which is higher than the range assessed to be adequate for surgery [19]. Although previous studies have indicated that awareness with recall is unlikely when the BIS value is <60 [20], results of more recent studies suggest the lack of a definite relationship between the occurrence of intraoperative awareness and BIS values >60 [21]. Despite relatively high BIS values, none of our patients complained of awareness, which is consistent with the results of other studies in which no patients complained of awareness during anesthesia with midazolam and fentanyl for a coronary artery bypass graft, even when the BIS was >60 [10]. Other studies have also shown that the incidence of intraoperative awareness is lower in patients receiving midazolam before the induction of general anesthesia than in those who do not receive it [22, 23], suggesting that midazolam has a good amnesic effect and ability to prevent intraoperative awareness. However, we cannot completely eliminate the possibility that intraoperative awareness did occur. Sandin et al. [24] repeated the post-operative interviews three times and noted that intraoperative recall was highly identified at the final interview performed 7–14 days after the operation.

There are several limitations to our study. First of all, plasma concentrations of midazolam or remifentanil were not measured, or the effect site concentrations of midazolam were not maintained at stable levels, and the interaction of these agents remains unknown. However, since BIS was stable before laryngoscopy and after tracheal intubation in patients receiving remifentanil 0.1 or 0.2 μg kg^{-1} min^{-1} initially, the effect site concentration of midazolam would also have been stable, and the significant differences in the BIS among the three groups would have resulted from the different dose of remifentanil. The observed increases in both the BIS and SEF95 after the infusion rate of remifentanil had been decreased from 0.5 to 0.05 μg kg^{-1} min^{-1} also support this hypothesis. Secondly, a control group with only midazolam, without opioids, was not included, and the absolute effect of remifentanil on the BIS in the presence of only midazolam is not clear. Since intense stimuli, such as laryngoscopy and tracheal intubation, under anesthesia will induce a remarkable sympathetic response following induction with only midazolam, the procedure is not only potentially hazardous but may be ethically unacceptable. Third, we did not induce anesthesia with lower or higher doses of midazolam, and the effect of remifentanil on EEG parameters at different doses of midazolam was not studied. However, in our preliminary study, there were no differences in the BIS between patients receiving midazolam 0.2 mg/kg and those receiving 0.3 mg/kg, and a midazolam dose <0.2 mg/kg was insufficient for the induction of anesthesia.

In summary, we have shown that remifentanil 0.5 μg kg^{-1} min^{-1} effectively increased the depth of anesthesia after the induction of general anesthesia with midazolam 0.2 mg/kg and suppressed sympathetic responses to subsequent laryngoscopy and tracheal intubation.

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Conflict of interest statement None.

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