

Optimal Concentration of Sevoflurane to Prevent Cardiovascular Depression after Induction of General Anesthesia with Remifentanyl and Propofol

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Abstract

Background: We examined the optimal concentration of sevoflurane to prevent cardiovascular depression after induction of general anesthesia with remifentanyl and propofol.

Methods: Seventy-five adult patients were randomized to one of three groups (n = 25). Midazolam (0.025 mg/kg) and remifentanyl (0.5 µg/kg/min) were administered to all patients, followed by propofol (1.0 mg/kg) and rocuronium (0.6 mg/kg) after 2 min. The lungs were ventilated manually with sevoflurane and oxygen via a tightly fitted face mask. The trachea was intubated when end-tidal sevoflurane concentration reached 1%, 1.5%, and 2% in each group, respectively. Three min after the start of administration, remifentanyl was decreased to 0.25 µg/kg/min. The effect-site concentration of remifentanyl was 6.0 ng/ml for 4 min after it was started. Hemodynamic variables were recorded from before induction of anesthesia to 15 min after tracheal intubation.

Results: There were no serious adverse events such as severe bradycardia or asystole. Relative change of mean arterial pressure after induction of general anesthesia in the end-tidal sevoflurane 1% group was smaller than that of the end-tidal sevoflurane 1.5% and end-tidal sevoflurane 2% groups.

Conclusion: An end-tidal sevoflurane concentration of 1% was sufficient when general anesthesia was induced with an effect-site concentration of remifentanyl of 6.0 ng/mL and propofol of 1 mg/kg.

Keywords: Sevoflurane; Cardiovascular depression; Induction of general anesthesia

Abbreviations: ASA PS: American Society of Anesthesiologist Physical Status; ET_{Sevo}: End-tidal sevoflurane; HR: Heart Rate; ET_{CO₂}: End-tidal carbon dioxide; MAP: Mean Arterial Pressure; SD: Standard Deviation

Introduction

Remifentanyl is widely used with midazolam [1], propofol [2-6], or sevoflurane [7-9] for induction of general anesthesia. Albertin et al. reported that the effect-site concentration of remifentanyl was 6.0 ng/ml for blunting the sympathetic response to tracheal intubation in 95% of adult patients [10]. However, the use of remifentanyl in anesthetic combinations such as sevoflurane and propofol may cause cardiovascular depression through their interaction, as manifested by symptoms such as severe bradycardia and asystole [11-14]. Remifentanyl decreases the concentration of propofol required for loss of consciousness [15]. Overdosing of anesthetics at the induction of general anesthesia is associated with the risk of cardiovascular depression [16]. Previous studies have assessed the optimal concentrations for inducing loss of consciousness and calculation of the minimum alveolar concentration following administration of remifentanyl in combination with sevoflurane or propofol at the induction of general anesthesia [7,9,10]. However, the optimal concentration of sevoflurane, which does not affect hemodynamics, has not yet been quantified in combination with remifentanyl and propofol during induction of general anesthesia. The purpose of this study was to examine the optimal concentration of sevoflurane to prevent cardiovascular depression after induction of general anesthesia with remifentanyl and propofol.

Materials and Methods

The study design was randomized, prospective, and unblinded. After obtaining approval from the ethics committee and informed consent, 75

adult patients were enrolled in the study. The patients were American Society of Anesthesiologist physical status (ASA PS) I-II and were undergoing supine elective surgery with general anesthesia at Osaka Koseinenkin Hospital between September and November 2009. Patients who were allergic to any of the anesthetic agents used in this study, and those with an anticipated difficult airway were excluded from the study. Patients were randomly assigned into one of three groups with an end-tidal sevoflurane (ET_{Sevo}) concentration of 1% (ET_{Sevo} 1% group), 1.5% (ET_{Sevo} 1.5% group) or 2% (ET_{Sevo} 2% group) according to a computer-generated random number sequence (n=25 per group).

None of the patients received pre-medication. Standard monitoring was applied, including electrocardiography, non-invasive blood pressure, heart rate (HR), end-tidal carbon dioxide (ET_{CO₂}), ETSevo, and pulse oximetry (BP-608 Evolution II; Omron Colin, Tokyo, Japan). Following baseline measurements, all patients received a 0.025 mg/kg bolus of midazolam intravenously. Next, remifentanyl was immediately administered at the rate of 0.5 µg/kg/min. Three min later, the infusion rate was decreased to 0.25 µg/kg/min, which was maintained throughout the course of the study. Effect-site concentration of remifentanyl was simulated at 6.0 ng/ml

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for 4 min after the start of remifentanyl (Tivatrainer™ copyright to Frank Engberts; Leiden, Netherlands). The dose of remifentanyl was decreased based on ideal body weight in obese patients (body mass index > 25). Two min after the start of remifentanyl administration, propofol (1 mg/kg) was administered, followed by rocuronium (0.6 mg/kg) to facilitate tracheal intubation. After loss of consciousness, the lungs were ventilated manually with sevoflurane and 100% oxygen via a tightly fitted face mask. The vaporizer dial was set to deliver a concentration twice that of the target ET_{Sevo} concentration (e.g., 2% for the ET_{Sevo} 1% group). The trachea was intubated when ET_{Sevo} reached the designated concentration for each group (i.e., 1%, 1.5%, and 2%, respectively). After tracheal intubation, the lungs were mechanically ventilated with ET_{Sevo} at 1% and 33% oxygen in an air mixture at a tidal volume of 8–10 ml/kg, and the respiratory rate was adjusted to maintain ET_{CO_2} between 35 mmHg and 40 mmHg (Figure 1). A semi-closed system with a fresh gas flow of 6 L/min was used throughout the study period. Mask ventilation and tracheal intubation were performed by a single experienced anesthesiologist (N. K.).

All hemodynamic variables were recorded at the following seven time points: before induction of anesthesia (T0, baseline); immediately before tracheal intubation (T1); immediately after tracheal intubation (T2); 3 min after tracheal intubation (T3); 5 min after tracheal intubation (T4); 10 min after tracheal intubation (T5); and 15 min after tracheal intubation (T6). Mean arterial pressure (MAP) and HR were calculated as relative values (%) with respect to T0 (100%). If HR fell below 40 beats/min, atropine sulfate 0.5 mg was administered. A fall in systolic blood pressure to below 80 mmHg was treated with ephedrine 5 mg. We recorded the frequency of ephedrine and atropine use during the first 15 min after tracheal intubation.

Statistics

Sample size was calculated based on our pilot study for the measurements of MAP at T2. The mean value of MAP in the pilot study was 71 mmHg for the ET_{Sevo} 1% group and 58.9 mmHg for the ET_{Sevo} 2% group, and the standard deviation (SD) was defined as 9.6 mmHg. Analysis indicated that 16 patients would be required in each group to detect a 12.1 mmHg difference in change in MAP ($\alpha=0.05$ and $\beta=0.2$). To compensate for nonevaluable patients, we planned to enrol 25 patients per group. Sex, ASA PS, and frequency of using ephedrine and atropine were analyzed using Yate's 2x3 chi-square test. The following values were expressed as mean \pm SD and analyzed using non-repeated measures analysis of variance, followed by the Student-Newman-Keuls test for multiple comparisons: age, height, weight, body mass index, and relative values of MAP and HR

with respect to T0. Statistical analysis was performed using Excel 2007 (Microsoft, Redmond, Washington, U.S.A.) with the add-in software ystat 2008 (Shinya Yamazaki, Koriyama, Japan). All tests of significance were two-sided and values of $P < 0.05$ were considered significant.

Results

A total of 75 patients were randomized. Five patients were excluded. The reasons for exclusion were leakage of intravenous drip and repeated intubation attempts. Hence, 23 patients in the ET_{Sevo} 1% group, 24 patients in the ET_{Sevo} 1.5% group, and 23 patients in the ET_{Sevo} 2% group completed the study protocol (Figure 2). Patient characteristics and induction data did not differ significantly between groups (Table 1). The relative value of MAP at T1 in the ET_{Sevo} 1.5% ($59.8 \pm 9.9\%$; $P < 0.01$) and ET_{Sevo} 2% ($56.3 \pm 11.2\%$; $P < 0.01$) groups were lower than that in the ET_{Sevo} 1% group ($68.4 \pm 9.9\%$). The relative value of MAP at T2 in the ET_{Sevo} 2% group ($64.3 \pm 12.0\%$; $P < 0.01$) was lower than that in the ET_{Sevo} 1% ($82.6 \pm 15.1\%$) and ET_{Sevo} 1.5% ($75.6 \pm 15.5\%$) groups. The relative value of MAP at T3 in the ET_{Sevo} 2% group ($61.2 \pm 11.1\%$; $P < 0.05$) was lower than that in the ET_{Sevo} 1% ($72.6 \pm 16.8\%$) and ET_{Sevo} 1.5% ($70.1 \pm 13.3\%$) groups (Figure 3). The relative values of HR did not differ between the groups at any point (Figure 4). There were no serious adverse events such as severe bradycardia or asystole. In the post-operative interviews of patients, none admitted to awareness during anesthesia.

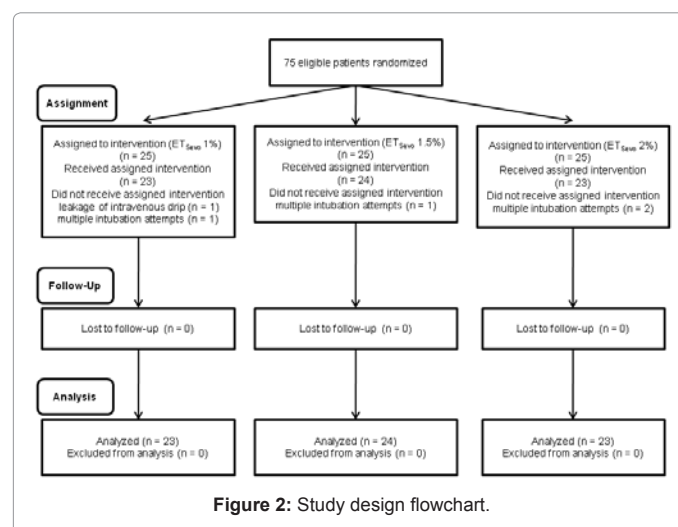


Figure 2: Study design flowchart.

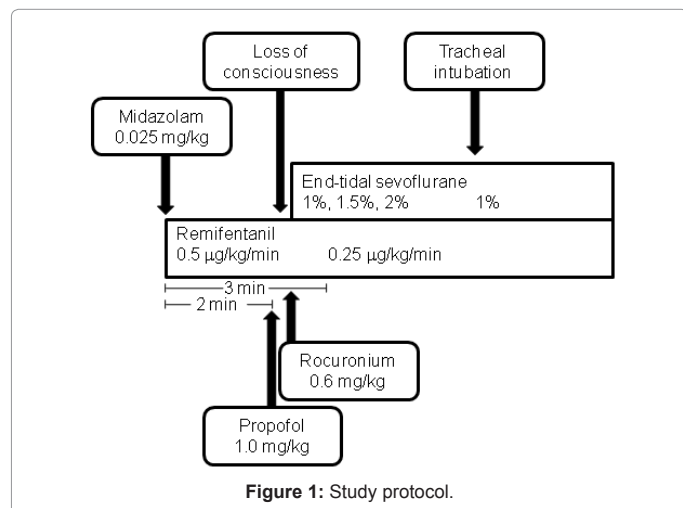


Figure 1: Study protocol.

	ET_{Sevo} 1% (n = 23)	ET_{Sevo} 1.5% (n = 24)	ET_{Sevo} 2% (n = 23)
Age (years)	45.6 \pm 14.7	48.5 \pm 16.0	50.1 \pm 13.1
Height (cm)	163.7 \pm 8.3	160.8 \pm 8.8	160.0 \pm 9.1
Weight (kg)	61.0 \pm 9.3	57.3 \pm 8.3	58.4 \pm 9.7
Body mass index (kg/m ²)	22.8 \pm 3.6	22.1 \pm 2.9	22.8 \pm 2.9
Gender (male/female)	9/14	9/15	6/17
ASA PS (I/II)	15/8	13/11	13/10
Frequency of using ephedrine (use/no use)	6/17	6/18	12/11
Frequency of using atropine (use/no use)	0/23	0/24	0/23

Data are expressed as mean \pm standard deviation. ASA PS: American Society of Anesthesiologist physical status

Table 1: Patient characteristics and induction data.

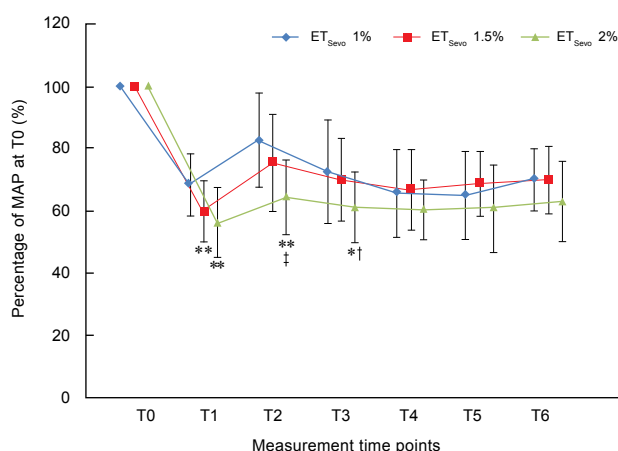


Figure 3: Changes in MAP relative values. MAP was calculated as a relative value (%) with respect to T0 (100%). Values are expressed as mean \pm standard deviation. * $P < 0.05$, ** $P < 0.01$ compared with the ET_{Sevo} 1% group; † $P < 0.05$, ‡ $P < 0.01$ compared with the ET_{Sevo} 1.5% group. MAP: mean arterial pressure; ET_{Sevo}: end-tidal sevoflurane; T0: before induction of anesthesia (baseline); T1: immediately before tracheal intubation; T2: immediately after tracheal intubation; T3: 3 min after tracheal intubation; T4: 5 min after tracheal intubation; T5: 10 min after tracheal intubation; T6: 15 min after tracheal intubation.

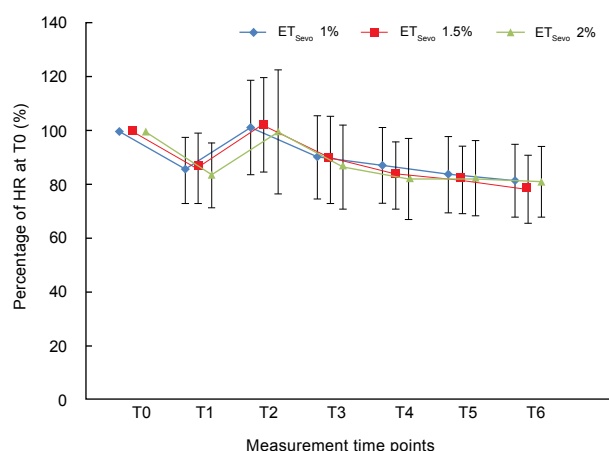


Figure 4: Changes in HR relative values. HR was calculated as a relative value (%) with respect to T0 (100%). Values are expressed as mean \pm standard deviation. There was no significant difference between the groups. HR: heart rate; ET_{Sevo}: end-tidal sevoflurane; T0: before induction of anesthesia (baseline); T1: immediately before tracheal intubation; T2: immediately after tracheal intubation; T3: 3 min after tracheal intubation; T4: 5 min after tracheal intubation; T5: 10 min after tracheal intubation; T6: 15 min after tracheal intubation.

Discussion

The results of this study demonstrated that the change in MAP from before induction of anesthesia was smaller in the ET_{Sevo} 1% group than in the ET_{Sevo} 1.5% and 2% groups. In all groups, no significant increase was observed in blood pressure or HR after tracheal intubation compared to before induction of anesthesia. This indicated that cardiovascular responses to tracheal intubation were blunted even with an ET_{Sevo} of 1% with an effect-site concentration of remifentanyl of 6.0 ng/ml and propofol of 1 mg/kg. The results also revealed that an ET_{Sevo} concentration of 1% is sufficient

during induction of general anesthesia and concentrations of 1.5% and 2% are associated with greater fluctuation in blood pressure. Thus, a minimal dose of anesthetics is required as long as a sufficient amount of opioid is given to suppress response to the stimulation of tracheal intubation, as in the present setting. Overdosing should be avoided since it may cause a marked decrease in blood pressure. No significant difference was found in the frequency of use of ephedrine. However, given that hypotension was observed in all groups, questions have remained regarding optimal ET_{Sevo} concentration. Tivatrainer™ simulations showed that the adequate effect-site concentration of propofol was not obtained if the anesthetic protocol of the present study was applied without subsequent sevoflurane. Sevoflurane or another general anesthetic is necessary to prevent awareness during tracheal intubation. It was hypothesized that reducing ET_{Sevo} concentration to 1% or less may reduce the incidence of post-intubation hypotension, but this hypothesis was not investigated for the same reason. Further studies based on a protocol involving the prophylactic use of vasopressors are thus needed to explore a combination of drugs that does not cause hypotension.

A limitation of the present study is that the attending anesthesiologists were not blinded to the treatment assignment. However, we thought it was dangerous if the attending anesthesiologist is not able to see the vaporizer dial and end-tidal sevoflurane concentration on the monitor. This study data was analyzed by another anesthesiologist who was not familiar with the details of this study. Thus we see very little possibility of this study design influencing the analysis of result. Another limitation is that we did not evaluate the objective loss of consciousness by examining, for example, the bispectral index value. Application of the bispectral index might reduce the risk of awareness. We used midazolam for its amnestic effect, as demonstrated in a clinical trial of remifentanyl [17]. Midazolam might contribute to the prevention of awareness in this study.

In conclusion, ET_{Sevo} concentration of 1% was sufficient to prevent cardiovascular depression when general anesthesia was induced with an effect-site concentration of remifentanyl of 6.0 ng/mL and propofol of 1 mg/kg.

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