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The effect of propofol infusion on minimum alveolar concentration of sevoflurane for smooth tracheal intubation

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Abstract
Purpose. This study was conducted to determine the effect of propofol infusion on the minimum alveolar concentration necessary for smooth tracheal intubation (MACEI) of sevoflurane.
Methods. Sixty-nine patients, American Society of Anesthesiologists (ASA) status I, aged 30–49 years, were randomly assigned to one of three groups according to the agents used for tracheal intubation ($n = 23$ for each group): the SP group, in whom the intubation was attempted under sevoflurane plus propofol infusion; the S group, tracheal intubation under sevoflurane alone; and the P group, tracheal intubation under propofol infusion alone. Anesthesia was induced with propofol 2.5 mg·kg^{-1} i.v. bolus. Prior to the tracheal intubation attempt, propofol infusion, 10 mg·kg^{-1}·h^{-1}, was given for 15 min in the SP and P groups, and sevoflurane equilibration was established in the SP and S groups. All tracheal intubation attempts were made 15 min after anesthetic induction. The end-tidal sevoflurane concentration at which tracheal intubation was attempted was predetermined by the up-and-down method (with 0.5% as a step size). MACEI was determined using a logistic regression test.
Results. The MACEI of sevoflurane was 1.73% in the SP group, and 2.99% in the S group. Laryngoscopy was not possible in the P group patients.
Conclusion. Propofol infusion reduced sevoflurane MACEI. This finding suggests that propofol would be an excellent adjuvant to use with sevoflurane for tracheal intubation.

Key words Anesthetic techniques: tracheal intubation · Anesthetics, intravenous: propofol · Anesthetics, volatile: sevoflurane

Introduction

The plasma propofol concentration that resulted in a 95% probability of no response during tracheal intubation (Cp95 intubation) to be 34.8 μg·ml^{-1}. However, with this concentration, patients experienced severe hypotension and their systolic blood pressure decreased to 70.3 mmHg [1]. Moreover, a very large dose of propofol appeared to be required, which did not seem to be practical. It is assumed that smooth tracheal intubation cannot be achieved with propofol alone at a clinically acceptable dose.

In contrast, sevoflurane alone makes smooth tracheal intubation possible, without a muscle relaxant, at a clinically acceptable dose. Previously, we reported the minimum alveolar concentration necessary for smooth tracheal intubation (MACEI) of sevoflurane to be 4.52% [2]. However, with a high concentration of sevoflurane, it takes a long time to reach equilibration between cerebral and alveolar gas tensions.

In terms of upper airway integrity, propofol is an excellent agent [3]. However, tracheal intubation with a combination of sevoflurane and propofol, without a muscle relaxant, has not yet been tried. We hypothesized that a combination of sevoflurane plus propofol would allow smoother tracheal intubation without a muscle relaxant than either agent alone. In this study, we tested the effect of propofol infusion on the MACEI of sevoflurane in patients undergoing elective surgery under general anesthesia.

Subjects and methods

The study protocol was approved by the Ethics Committee of Mito Saiseikai General Hospital, and written informed consent was obtained from each patient. Sixty-nine adult patients (American Society of Anesthesiologists [ASA] physical status I; age range, 30 to 49

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years) who were undergoing elective surgery under general anesthesia were enrolled in this study. The patients were randomly assigned to one of three groups according to the agents used for tracheal intubation ($n = 23$ for each group): the SP group, in whom tracheal intubation was attempted under sevoflurane plus propofol infusion; the S group, in whom the intubation was attempted under sevoflurane alone; and the P group, in whom the intubation was attempted under propofol infusion alone.

Blood pressure was determined indirectly, and electrocardiogram, arterial hemoglobin oxygen saturation (SpO2), and rectal temperature were continuously monitored, using a patient monitor system (BP-508; Colin, Komaki City, Aichi, Japan). Acetated Ringer's solution was infused intravenously, at the rate of $10\,ml \cdot kg^{-1} \cdot h^{-1}$ as a maintenance fluid during the study period. In all the patients, anesthesia was induced using propofol, $2.5\,mg \cdot kg^{-1}$, i.v. bolus, and a laryngeal mask airway (LMA) was inserted. In the SP and S groups, the patients were connected to an anesthesia ventilator, which delivered a tidal volume of $10\,ml \cdot kg^{-1}$ at 12 bpm in a controlled ventilation mode, and they inhaled sevoflurane of a predetermined concentration in pure oxygen. The P group patients inhaled pure oxygen under manually assisted ventilation, which was provided because of the possibility of the patient fighting against the mechanical ventilator. Breath-by-breath inspired/end-tidal sevoflurane and carbon dioxide concentrations were measured with a gas monitor (RASCAL-1, Albion Instruments, Salt Lake City, UT, USA). We employed a semiclosed anesthetic breathing system with a fresh gas flow of $6\,l \cdot min^{-1}$. For the measurement of anesthetic concentration, respiratory gases were sampled from an angle piece fitted at the distal end of the LMA. End-tidal sevoflurane concentration at laryngoscopy and tracheal intubation was predetermined by an up-and-down method (0.5% as the step size), starting with 2% (SP group) or 4% (S group). End-tidal CO_2 and rectal temperature were maintained at around 30 mmHg and 35.5°C or above, respectively.

In the SP and P groups, in addition to the induction dose, propofol, $10\,mg \cdot kg^{-1} \cdot h^{-1}$, was infused for 15 min prior to the tracheal intubation attempt. In the SP and S groups, when 90% or more of the predetermined end-tidal sevoflurane concentration had been achieved and maintained for at least 10 min under mechanical ventilation, the LMA was removed, and tracheal intubation, using a cuffed tracheal tube (Portex, 7.0-mm internal diameter [ID]), was attempted by conventional indirect laryngoscopy. The P group patients inhaled pure oxygen under manually assisted ventilation for the same period prior to the intubation attempt. All tracheal intubation attempts were made 15 min after anesthetic induction, using bolus propofol.

The patient were described as either "unresponsive" or "responsive" to laryngoscopy and tracheal intubation. When laryngoscopy was uneventful, and coughing and bucking did not occur after tracheal cuff inflation, this was considered "unresponsive". When we encountered difficulty in mouth-opening, gross purposeful muscular movements, vocal cord movements during laryngoscopy, or bucking after cuff inflation, this was considered "responsive". A single anesthesiologist, who was not blinded to the grouping, attempted all laryngoscopies and tracheal intubations, while another anesthesiologist, who was blinded to the grouping, determined the presence or absence of any responses.

Arterial blood samples were taken from the radial artery, just after the intubation attempt, for the determination of blood propofol concentration in the ten "unresponsive" patients in the SP and S groups, and in ten patients who were randomly selected from the P group. Blood samples were stored at 5°C until extraction and assay. Blood propofol concentration was determined using high-performance liquid chromatography.

Statistical analyses were done using analysis of variance (ANOVA) for differences in demographic data. Analysis of the probability of unresponsiveness versus end-tidal sevoflurane concentration, the maximum likelihood estimators of the model parameters, and goodness of fit were tested using a logistic regression test (SAS proprietary software; SAS Institute, Chicago, IL, USA), which provided the best fitting sigmoid curve. A probit test (SAS proprietary software, SAS Institute) was used to obtain 95% confidence limits. Intraoperative awareness was recorded. $P < 0.05$ was considered statistically significant. All values were expressed as means ± SD.

Results

There were no significant differences in the demographic data among the three groups (Table 1). LMA was inserted smoothly in all the patients after induction with propofol, $2.5\,mg \cdot kg^{-1}$ (i.v.). Arterial blood pressure and heart rate before induction, and before and after tracheal intubation attempts, in the SP and S groups, are shown in Fig. 1. The mean end-tidal CO_2 value for all patients was 30 ± 2 mmHg. Mean body temperature for all patients during the study was 36.1 ± 0.6°C.

The total amount of propofol administered before intubation attempts was $5.0\,mg \cdot kg^{-1}$ in the SP and P groups, and $2.5\,mg \cdot kg^{-1}$ in the S group. The responses in the 23 consecutive patients in each of the SP and S groups and the end-tidal sevoflurane concentration in oxygen are shown in Fig. 2. A finding of "responsive" was observed in all the patients in the P group. The reasons for responsiveness are listed in Table 1.

Table 1. Demographic data and reasons for responsiveness

Group	SP[a]	S[a]	P[a]
Demographic data			
Sex (M/F; *n*)	3/20	7/16	5/18
Age (years)[b]	42 ± 5	41 ± 6	39 ± 6
Height (cm)[b]	158 ± 6	160 ± 9	160 ± 9
Weight (kg)[b]	57 ± 8	58 ± 8	57 ± 7
Reasons for responsiveness			
Difficulty in mouth-opening	1	1	18
Gross purposeful muscular movements during laryngoscopy	4	3	5
Bucking after cuff inflation	6	6	0

[a] See text for explanation of groups
[b] Values are means ± SD

The dose-response curve based on the logistic regression test revealed that the median effective dose (ED50) of the end-tidal sevoflurane concentration necessary for smooth tracheal intubation was 1.73% (95% confidence limits, 1.20%–2.11%) in the SP group and 2.99% (95% confidence limits, 0.28%–3.94%) in the S group (Fig. 3). Propofol infusion reduced sevoflurane MACEI by 42%.

Mean blood propofol concentrations just after the intubation attempt were 4.18 ± 0.37 $\mu g \cdot ml^{-1}$, 0.70 ± 0.09 $\mu g \cdot ml^{-1}$, and 3.75 ± 0.61 $\mu g \cdot ml^{-1}$ for the SP, S, and P groups, respectively. There was no significant difference in propofol concentrations between the SP and P groups, but the concentrations were greater than that in the S group.

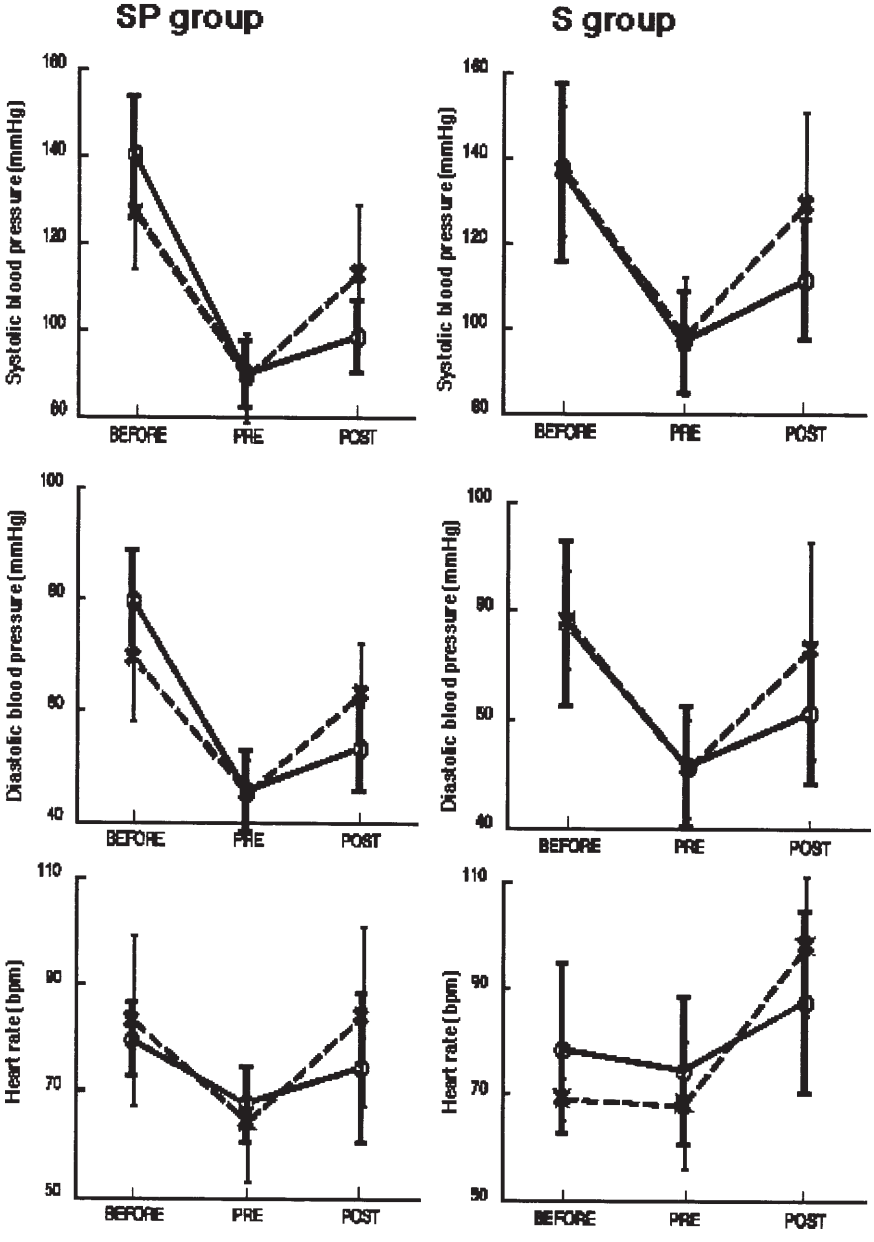

Fig. 1. Arterial blood pressure and heart rate before induction (*BEFORE*), and before (*PRE*) and after (*POST*) tracheal intubation attempts in the SP and S groups (see text for explanation of groups). Data values are means ± SD. *Continuous lines*, Unresponsive; *dashed lines*, responsive

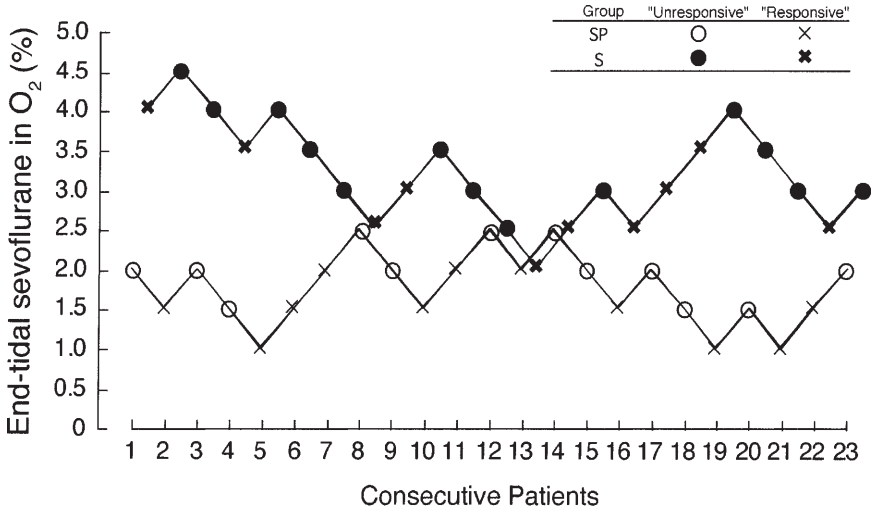

Fig. 2. Responses of the 23 consecutive patients in each of the SP and S groups in whom tracheal intubation was attempted, and the end-tidal concentrations of sevoflurane in oxygen

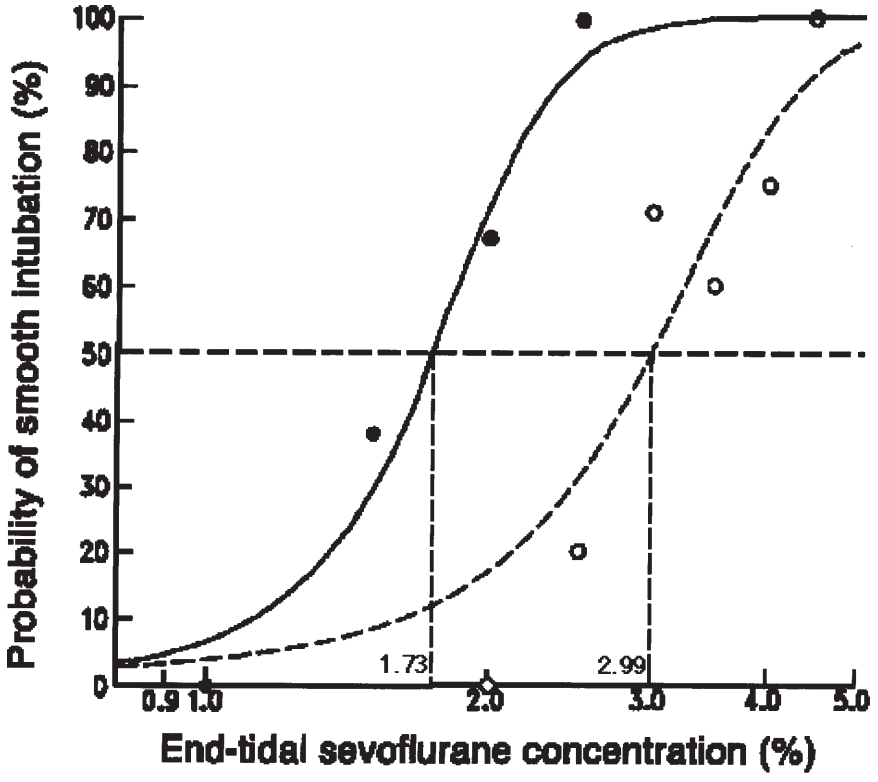

Fig. 3. Dose-response curves for sevoflurane, plotted from logistic regression analyses of individual end-tidal concentrations and the respective reactions to tracheal intubation in the SP group (*solid line* and *solid circles*) and the S group (*dashed line* and *open circles*). The concentrations at which the probability of smooth intubation was 50% were: 1.73% (95% confidence limits, 1.20%–2.11%) and 2.99% (95% confidence limits, 0.28%–3.94%) in the SP and S groups, respectively

One female patient in the SP group experienced hypotension (<70 mmHg systolic blood pressure) and was successfully treated with bolus ephedrine (10 mg, i.v.). She was excluded from the study. No patient reported awareness during the study period.

Discussion

The results of the present study show that when identical doses of propofol are utilized for anesthetic induction and subsequently administered for 15 min, the propofol reduces the MACEI of sevoflurane. Sevoflurane plus propofol infusion appears to be an appropriate combination that allows smooth tracheal intubation without a muscle relaxant.

The propofol dose in the present study maintained blood pressure and heart rate at an acceptable level prior to the intubation attempt in most patients, but kept no patients aware. In order to minimize the inhalation time to establish equilibration between cerebral and alveolar gas tensions, the anesthesia machine was

primed with 1% sevoflurane prior to induction, and positive pressure ventilation was performed via an LMA in place in the SP and S groups. Manually assisted ventilation was performed in P group patients because patient fighting against the ventilator had been observed frequently in a preliminary study.

When interaction between volatile and intravenous anesthetic agents is defined, it is important that each agent has reached its steady-state concentration [4]. The conventional method of determining the MACEI of volatile anesthetics requires that a predetermined constant end-tidal concentration of the volatile anesthetic is maintained for at least 15 min to establish equilibration among cerebral, arterial blood, and alveolar gas tensions before tracheal intubation is attempted [2,5–8]. All determinations in this study were made at a slightly shorter time-phase than that used in previous studies. Because sevoflurane has a low blood-gas partition coefficient [9], the cerebral concentration of sevoflurane increases more rapidly than that of other volatile anesthetics. So, we believe that equilibration among cerebral, arterial blood, and alveolar gas tensions is established before tracheal intubation is attempted. Blood propofol concentration is known to reach a steady state quickly. When propofol was infused for 15 min after the bolus injection, blood propofol concentration rapidly reached a steady state [10,11]. It is probable that, in the present study, tracheal intubation was attempted after sevoflurane and propofol had reached their steady-state concentrations.

The plasma propofol concentration that facilitated smooth tracheal intubation (Cp95 intubation) was reported to be 34.8 $\mu g \cdot ml^{-1}$ [1], which value was about ten times higher than that in our present study. Propofol, 500 mg, as a single bolus injection, supplemented by fentanyl and intravenous lidocaine, facilitated smooth tracheal intubation in only 15% of patients, but caused coughing and/or bucking in 70% of patients [12]. These findings suggest that smooth tracheal intubation can be attained only when a large dose of propofol is administered, but in such circumstances, there is a risk of severe hypotension. As was seen in the P group in this study (blood propofol concentration, $3.75 \pm 0.61 \mu g \cdot ml^{-1}$), propofol alone did not even allow laryngoscopy. The results of the present study suggest that the inhalation of sevoflurane at low concentrations, in addition to the use of propofol, permits smooth tracheal intubation, and it is not necessary to treat the small hemodynamic changes that occur before and after intubation. Previously, we reported that, for sevoflurane, MACEI was greater than MAC [2]. However, in the present study, the sevoflurane MACEI in the SP group patients, 1.73%, was close to the sevoflurane MAC, 1.71%, reported by Katoh and Ikeda [13]. In the present study, the sevoflurane MACEI in the S group patients, 3.42%, was significantly less than the sevoflurane MACEI, 4.52%, previously determined without adjuvant in our department [2]. This suggests that the propofol induction dose affects MACEI even 15 min after induction. These findings confirm that propofol is not a strong analgesic, but that it is an excellent adjuvant for tracheal intubation.

There are some limitations to this study. First, arterial blood samples for the determination of blood propofol concentration were taken after the intubation attempt, and blood propofol concentration may be influenced by the stress of the intubation attempt. Second, blood propofol concentration was determined only in those who were "responsive", and it is possible that blood propofol concentration may differ between "unresponsive" and "responsive" patients. Finally, the step size for sevoflurane was 0.5%, and this may have affected the final MACEI values. However, these limitations do not seem to have affected the principal results of this study; namely, the effect of propofol on MACEI reduction.

In conclusion, propofol infusion reduced the MACEI of sevoflurane in patients undergoing elective surgery. Propofol used for anesthetic induction reduced MACEI even 15 min after induction. These results of this study suggest that propofol would be an excellent adjuvant to use with sevoflurane for tracheal intubation.

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