J Anesth (2003) 17:154–160
DOI 10.1007/s00540-003-0168-6

Journal of
Anesthesia

Original articles

Comparison of adjuvant anesthetics for propofol induction

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Abstract
Purpose. Fentanyl was compared with nitrous oxide/sevoflurane as an adjuvant anesthesia to propofol during induction.
Methods. Two-hundred sixty-three patients of American Society of Anesthesiologists physical status 1 or 2 undergoing minor surgery were randomly divided into two groups. Group F patients (n = 125) received 2 μg·kg^{-1} fentanyl and 1.8 mg·kg^{-1} propofol, and were ventilated by mask with oxygen. Group S patients (n = 138) received 1.8 mg·kg^{-1} propofol, followed by inhalation of 4% sevoflurane in N_2O (4 l·min^{-1}) and oxygen (2 l·min^{-1}) by mask. The trachea was intubated exactly 2, 3, 4, or 5 min after injection of 0.1 mg·kg^{-1} vecuronium, and the conditions of endotracheal intubation were scored according to the patients' responses to laryngoscopy and endotracheal intubation. Systolic blood pressure (SBP) and heart rate (HR) were measured before and after endotracheal intubation. The cost of anesthetics was also calculated.
Results. No significant differences in SBP were observed between the groups throughout the induction period. HR did not change from preanesthetic values in group F. In contrast, HR in group S patients increased by 9–18 beats·min^{-1} (bpm) after inhalation of N_2O/sevoflurane and further increased by 17–21 bpm following endotracheal intubation. Significant differences in HR were noticed between the groups ($P < 0.001$). The conditions of endotracheal intubation were similar in the two groups and were satisfactory when mask ventilation exceeded 3 min. Fentanyl was less expensive than sevoflurane/N_2O anesthesia when mask ventilation exceeded 3 min.
Conclusion. From the standpoints of hemodynamics and drug cost, fentanyl is preferable to N_2O/sevoflurane inhalation as an adjuvant to propofol during induction, because mask ventilation for more than 3 min was required for satisfactory endotracheal intubation.

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Received: July 8, 2002 / Accepted: March 25, 2003

Key words Anesthetics · Propofol · Fentanyl · Nitrous oxide · Sevoflurane · Muscle relaxant · Vecuronium · Anesthesia induction · Endotracheal intubation · Cost of anesthetics

Introduction

Nondepolarizing muscle relaxants are favorable in facilitating endotracheal intubation to minimize the risks associated with succinylcholine [1]. One of the drawbacks of using nondepolarizing muscle relaxants during induction is their slow onset of action. For example, an average of 3.8 min is necessary to achieve sufficient muscle relaxation for endotracheal intubation after administration of 0.07 mg·kg^{-1} of vecuronium [2]. Drugs of faster onset, such as rocuronium or rapacuronium, are not yet available in Japan. During anesthesia induction using vecuronium, therefore, some adjuvant anesthesia to the induction agent is appropriate, because the plasma concentration of the agent would be too low to inhibit sympathetic hyperactivity in response to endotracheal intubation.

Opioids are frequently used for this purpose because they potently suppress circulatory responses to endotracheal intubation [3]. Sevoflurane may also be useful because it does not elicit hyperdynamic circulation, even when high concentrations are inhaled via a mask [4]. It may also have an advantage over fentanyl because volatile anesthetics can augment neuromuscular block by vecuronium [5,6], although some anesthesiologists express concern about its use during induction of anesthesia via a mask due to the risk of contaminating the operating room with trace concentrations of waste anesthetics [7]. However, no study has compared opioids and inhalation agents as adjuvant anesthetics to an induction agent.

In the present study, the authors compared i.v. fentanyl with N_2O/sevoflurane inhalation after induc-

tion of anesthesia with propofol from the standpoint of the patients' reaction to laryngoscopy and endotracheal intubation. We also evaluated the effects of both techniques on the cost of anesthetics. We hypothesized that although fentanyl injection would alleviate hyperdynamic circulation in response to endotracheal intubation, N_2O/sevoflurane anesthesia could enhance the neuromuscular blockade induced by vecuronium, resulting in more satisfactory intubating conditions than with fentanyl.

Materials and methods

This study was performed in the Sapporo Medical University Hospital after institutional approval and informed consent from each patient had been obtained. Two hundred sixty-three American Society of Anesthesiologists physical status 1 or 2 patients without cardiovascular disease who were undergoing minor surgery were included in this study. Those patients who were anticipated to have difficult airways and for whom mask ventilation was contraindicated were excluded from the study. Premedication consisted of 2 to 3 mg of midazolam and 0.5 mg of atropine 30 min before anesthesia induction. In the operating room, the patients were randomly assigned to group F or S, depending on the anesthesia technique, and further divided into four subgroups (eight groups in total), depending on the duration of mask ventilation from vecuronium injection to endotracheal intubation. Group F patients (n = 125) received fentanyl 2 $\mu g \cdot kg^{-1}$, followed 3 min later by propofol 1.8 $mg \cdot kg^{-1}$ (containing 0.2% lidocaine) for induction. After the patients fell asleep, vecuronium 0.1 $mg \cdot kg^{-1}$ was given. This group of patients was ventilated with 100% oxygen at a flow rate of 6 $l \cdot min^{-1}$ via a mask throughout the induction period. Group S patients (n = 138) received the same dose of propofol for anesthesia induction, followed by inhalation of sevoflurane (4%) in N_2O (4 $l \cdot min^{-1}$) and oxygen (2 $l \cdot min^{-1}$) via a mask and i.v. injection of 0.1 $mg \cdot kg^{-1}$ vecuronium.

The trachea was intubated after exactly 2, 3, 4, or 5 min of vecuronium injection in F-2 and S-2, F-3 and S-3, F-4 and S-4, or F-5 and S-5, respectively, followed by inhalation of N_2O (66%), oxygen (33%), and sevoflurane (0.5%–1%). Endotracheal intubation was carried out by experienced anesthesiologists, and the intubation conditions were scored by an attending anesthesiologist (H.T., S.S., or Y.K.) according to the patient's responses to laryngoscopy and endotracheal intubation, as listed in Table 1. Patients whose laryngoscopy time exceeded 30 s were excluded from the study. When the patient's vocal cords were not visualized directly at the first attempt but were visualized several minutes later at the second attempt, the condition was scored as 3 for laryngoscopy and 4 for endotracheal intubation. When the patient's vocal cords were not visualized again at the second attempt, the patient's data were excluded because of difficult intubation [8].

Systolic blood pressure (SBP; oscillometric), heart rate (HR), electrocardiogram (ECG), and pulse oximetry were monitored throughout the study period and recorded at the following seven points: before fentanyl (group F only); before propofol; 1 min after propofol; and 1 min before and 1, 2, and 3 min after endotracheal intubation. Hemodynamic data for those patients whose vocal cords had not been directly visualized at the first attempt were not incorporated into the evaluation. The inspired and end-tidal concentrations of oxygen, carbon dioxide, and anesthetic agents were also monitored. At a postoperative round, all patients were asked whether they had had any signs of awareness during anesthesia.

In evaluating the cost of anesthetics, only the prices of fentanyl, sevoflurane, N_2O, and oxygen consumed before endotracheal intubation were calculated, because after intubation these prices were comparable among the groups, as were those of propofol, lidocaine, and vecuronium. We calculated the molecular weight and specific gravity of sevoflurane as 200 and 1.525, respectively.

Table 1. Conditions of laryngoscopy and endotracheal intubation [2]

Score	Laryngoscopy	Endotracheal intubation
0	Vocal cords abducted	No patient movement Good visualization
1	Vocal cords slightly adducted Fair visualization	Diaphragmatic movement on endotracheal intubation
2	Vocal cords adducted Difficult visualization	Coughing on intubation of trachea
3	Inability to visualize directly	Gross movement of the extremities and coughing with endotracheal intubation
4		Inability to intubate

Data were expressed as means ± SD. Statistical analysis was performed by the chi-squared test, analysis of variance (ANOVA) for multiple comparisons, the Mann-Whitney U-test, and the Kruskal-Wallis test when appropriate. When a significant difference was obtained by ANOVA, post hoc analysis was performed with Scheffé's test or Dunnett's test. A P value of less than 0.05 was considered to indicate statistical significance.

Results

Three patients were excluded from data collection because of difficult endotracheal intubation. In addition, six patients (one patient each in groups F-2 and S-3 and two patients each in groups S-2 and S-4) were excluded from the hemodynamic evaluation because the vocal cords were not directly visualized at the first attempt. Consequently, 260 patients were evaluated for the conditions pertaining to laryngoscopy and endotracheal intubation, and 255 patients were evaluated for hemodynamic changes.

There were no significant differences among the groups in patient characteristics, average doses of midazolam for premedication, or preanesthetic hemodynamics (Table 2). The end-tidal concentration of sevoflurane increased as the duration of mask ventilation was prolonged in group S patients (Table 2). However, it reached a plateau at 4 min of inhalation, and no further increment was observed. No patients reported any signs of awareness during anesthesia on postoperative day (POD) 1.

Figure 1 shows the conditions in response to application of the laryngoscope and endotracheal intubation in the eight groups. No significant difference was observed among group F patients with respect to the conditions of laryngoscopy ($P = 0.236$). In contrast, laryngoscopy became easier as the duration of mask ventilation was prolonged in group S patients ($P = 0.004$). The conditions of endotracheal intubation became more satisfactory as the duration of mask ventilation increased in both groups ($P < 0.001$ for each). No significant differences in conditions of either laryngoscopy or endotracheal intubation were found between the time-matched groups. More than 90% of patients received scores of ≦1 in response to endotracheal intubation when mask ventilation exceeded 3 min. The results of the condition of intubation revealed that for satisfactory intubation,

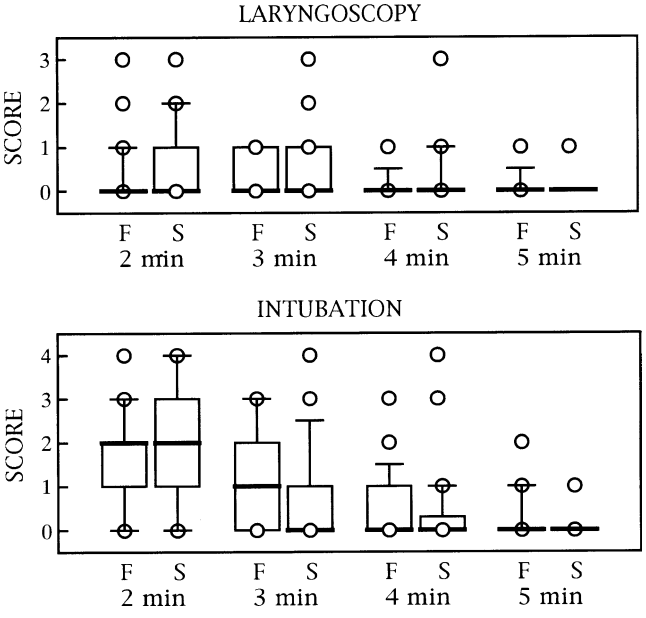

Fig. 1. Conditions of laryngoscopy and endotracheal intubation in the eight groups. Medians are shown by the *bold bars*, the 25th and 75th percentiles by the *boxes*, and the 10th and 90th percentiles by the *bars*. No significant differences were found between groups F and S. See text for details

Table 2. Patient characteristics, dose of midazolam for premedication, and end-tidal concentrations of sevoflurane at the time of laryngoscopy

Anesthetic and patient group	n	M/F	Age (yr)	Height (cm)	Weight (kg)	Midazolam (mg)	SBP (mmHg)	HR (beats·min^{-1})	ETsev (%)
Fentanyl									
F-2	31	14/17	40 ± 13	162 ± 8	58 ± 9	2.6 ± 0.4	119 ± 14	68 ± 12	—
F-3	29	13/16	38 ± 13	163 ± 9	61 ± 12	2.7 ± 0.4	123 ± 12	73 ± 21	—
F-4	31	11/20	40 ± 14	161 ± 8	59 ± 11	2.7 ± 0.3	123 ± 15	71 ± 13	—
F-5	31	18/13	39 ± 13	164 ± 10	60 ± 11	2.7 ± 0.4	121 ± 12	76 ± 17	—
N_2O/sevoflurane									
S-2	36	18/18	34 ± 13	164 ± 9	64 ± 13	2.7 ± 0.3	120 ± 15	72 ± 12	2.6 ± 0.3
S-3	30	13/17	37 ± 12	164 ± 11	62 ± 14	2.6 ± 0.4	121 ± 14	72 ± 17	3.0 ± 0.3*
S-4	33	15/18	37 ± 12	163 ± 10	61 ± 13	2.6 ± 0.3	119 ± 11	75 ± 14	3.2 ± 0.2*
S-5	38	19/19	34 ± 13	162 ± 9	60 ± 11	2.6 ± 0.4	121 ± 14	72 ± 16	3.3 ± 0.2

SBP, systolic blood pressure; HR, heart rate; ETsev, end-tidal concentration of sevoflurane
* $P < 0.001$ vs the group with the next shortest time for mask ventilation

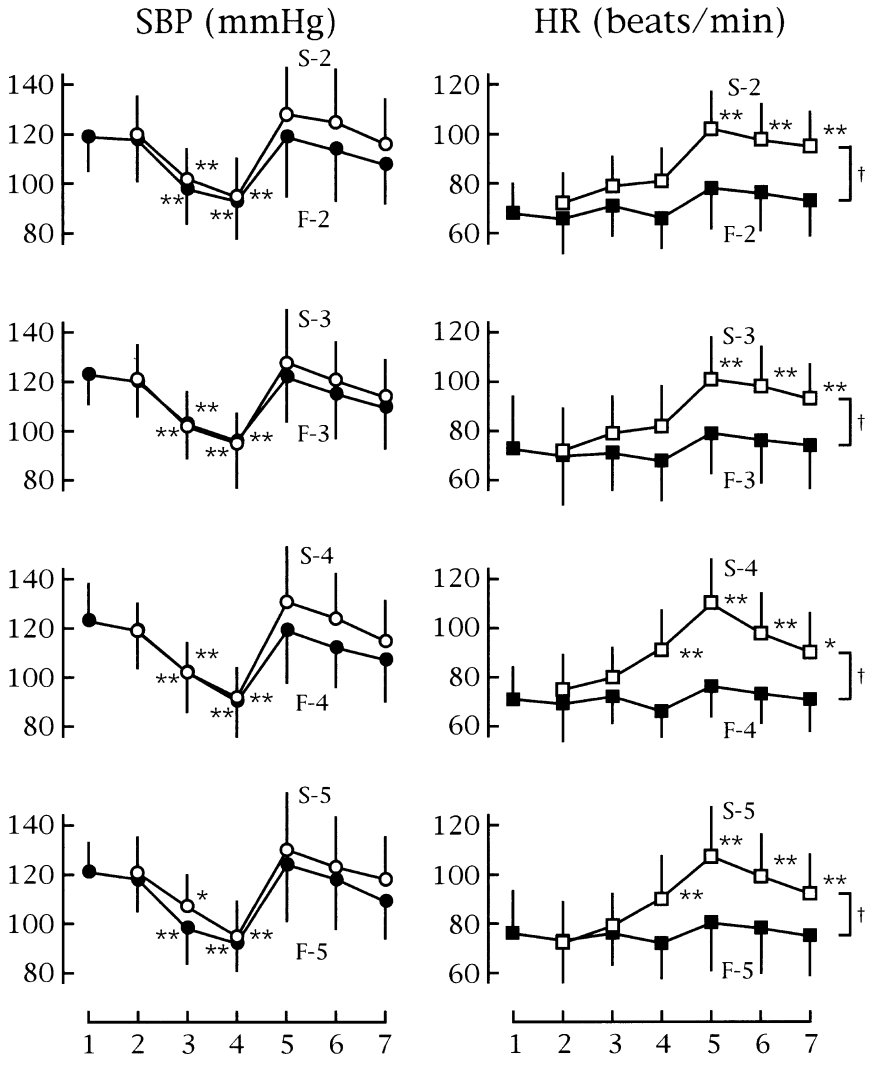

Fig. 2. Systolic blood pressure (*SBP*, **left panel**) and heart rate (*HR*, **right panel**) during induction and endotracheal intubation in the eight groups. No significant differences in SBP were observed between the time-matched groups. However, significant differences ($P < 0.001$) in HR were observed between the time-matched groups. *1* Before fentanyl, *2* before propofol, *3* 1 min after propofol, *4* 1 min before endotracheal intubation. *5*, *6*, and *7* indicate 1, 2, and 3 min after endotracheal intubation, respectively. $^{*}P < 0.05$, $^{**}P < 0.01$ vs the respective preanesthetic values. $^{\dagger}P < 0.001$ for the comparison between the groups

mask ventilation for more than 3 min after injection of vecuronium was advisable.

Fentanyl 2 μg·kg^{-1} produced nonsignificant hemodynamic changes in group F patients (Fig. 2). Propofol decreased SBP, and then endotracheal intubation increased SBP from the respective preanesthetic values in all groups. No significant differences in SBP were noted between the time-matched groups. HR did not change significantly from the preanesthetic value in group F throughout the study period (Fig. 2). In contrast, HR increased gradually after inhalation of N_2O/sevoflurane and further increased after endotracheal intubation in group S patients. Significant differences were observed in HR between groups F and S ($P < 0.001$, for each).

The costs of anesthetics in the eight groups are shown in Fig. 3. The total cost of anesthetics increased as the mask ventilation was prolonged in both groups. However, because of the prices of sevoflurane and N_2O, the total cost in group S increased more steeply than in group F with the duration of mask ventilation. Consequently, the cost of anesthetics was higher in group F than in group S when the duration of mask ventilation was ≤3 min and lower when it was ≥4 min. For group F patients whose body weight was ≤50 kg, the cost of anesthetics was less than that for group S patients, even with 3 min of mask ventilation.

Discussion

The present study showed that endotracheal intubation became more satisfactory as the duration of mask ventilation was prolonged, but no significant difference was found between fentanyl and N_2O/sevoflurane anesthesia; fentanyl or N_2O/sevoflurane anesthesia induced comparable changes in SBP after induction with propofol and endotracheal intubation; N_2O/sevoflurane anesthesia elicited an increase in HR after propofol

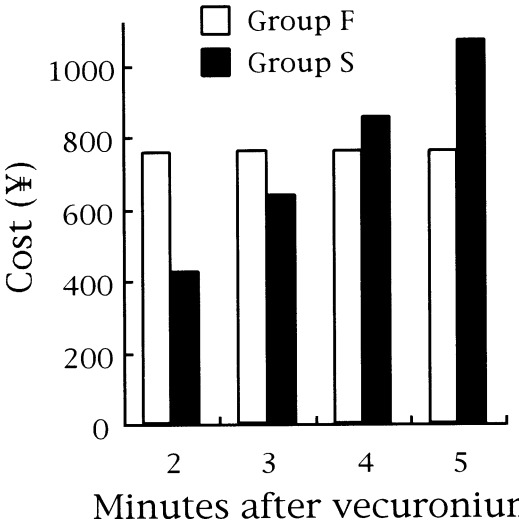

Fig. 3. Cost of anesthetics (¥) in the eight groups. The prices of fentanyl, sevoflurane, N_2O, and oxygen purchased at the Sapporo Medical University Hospital were ¥377 per 2 ml ampule, ¥108.9·ml^{-1}, ¥19.84·l^{-1}, and ¥0.24·l^{-1}, respectively. The cost of sevoflurane was calculated from Dion's equation [9]. Because the average body weight was around 60 kg in each group, we calculated the price of fentanyl on the assumption that we prepared 2 ampules for each group F patient. Therefore, ¥377 could be subtracted from the total cost for the group F patient whose body weight was ≤50 kg

induction, whereas fentanyl anesthesia did not alter HR significantly throughout the study period; and the cost of anesthetics was greater in group S than in group F when the duration of mask ventilation exceeded 3 min, which was needed for satisfactory endotracheal intubation.

Although the intubation conditions became more satisfactory as the duration of mask ventilation increased, no significant differences were observed between the respective time-matched groups. This result was contrary to our hypothesis. Because we did not use a nerve stimulator, we could not strictly evaluate the onset or extent of neuromuscular block with vecuronium in the two anesthesia techniques. However, neuromuscular blockade develops more rapidly in the airway than in the thumb after intubation doses of neuromuscular blocking drugs [10,11], so that endotracheal intubation can be accomplished earlier than has previously been advocated [12]. In addition, fentanyl can diminish airway reflexes during propofol infusion [13]. As a result, no neuromuscular blocking agent is necessary when large doses of propofol and opioids are used before endotracheal intubation [14,15]. This may partly explain why the conditions of laryngoscopy were not different within group F patients. Therefore, even if N_2O/sevoflurane anesthesia could have shortened the onset or augmented the extent of neuromuscular block by vecuronium, the total conditions pertaining to laryngoscopy or endotracheal intubation should not be different between the two anesthesia techniques. In other words, the present results indicate that 2 μg·kg^{-1} fentanyl is comparable to N_2O/sevoflurane as an adjuvant anesthetic to propofol during induction from the standpoint of intubation conditions.

The hemodynamic responses to induction and endotracheal intubation in group F patients were quite similar to those reported by Billard et al. [3]. They showed that hemodynamic changes after propofol were not modified when the propofol dose was increased from 2 to 3.5 mg·kg^{-1}. In addition, maximal preintubation hypotension occurred with a fentanyl dose of 2 μg·kg^{-1}. In the present study, SBP responses to induction and endotracheal intubation were comparable in the fentanyl and N_2O/sevoflurane groups. This is important, because blood pressure is an index of tissue perfusion and provides some indication of how the cardiovascular system is responding to anesthesia and surgical stimuli. In contrast to SBP, HR responses to induction and endotracheal intubation differed between the groups; N_2O/sevoflurane anesthesia increased HR after induction and endotracheal intubation. This result cannot be attributable to hypoxia or hypercapnia during induction, because pulse oximetry and end-tidal concentration of carbon dioxide during induction were maintained within normal limits. Therefore, N_2O/sevoflurane anesthesia may somehow induce tachycardia during mask ventilation.

Sevoflurane is not likely to induce hyperdynamic circulation by itself, even if a 2.7 minimum alveolar concentration (MAC) is inspired by mask [4]. Recently, however, Vakkuri et al. [16] reported that 8% sevoflurane in N_2O and oxygen induced tachycardia when patients received controlled ventilation via a mask. N_2O is known to enhance sympathetic activity [17–19], whereas both fentanyl and sevoflurane suppress sympathetic activity [20,21]. Furthermore, vagal activity is enhanced by fentanyl but inhibited by sevoflurane [22–24]. As a result, 2 μg·kg^{-1} fentanyl effectively suppressed tachycardia induced by endotracheal intubation, whereas 4% sevoflurane could not have inhibited tachycardia elicited by N_2O and endotracheal intubation. Therefore, our results indicate that 2 μg·kg^{-1} fentanyl is more favorable than N_2O/sevoflurane as an adjuvant anesthetic to propofol during induction, from the standpoint of hemodynamic changes.

The cost of inhalation anesthetics depends largely on the carrier gas flow rate [25]. In this study, we used a relatively high carrier gas flow rate of 6 l·min^{-1} to anesthetize our patients rapidly. This flow rate is not unusual for mask ventilation during induction of anesthesia. As a result, the cost of inhalation anesthetics increased rapidly to overcome that of fentanyl when mask ventilation

exceeded 3 min in our study. With regard to the conditions of endotracheal intubation, our results suggest that mask ventilation for more than 3 min after injection of 0.1 mg·kg^{-1} vecuronium is advisable. Consequently, fentanyl is less expensive than N_2O/sevoflurane anesthesia as an adjuvant to propofol during anesthesia induction in Japan.

There are many drawbacks to the present study. Because of the nature of the study design, we could not accomplish this investigation in a double-blinded fashion. We verified that no patients complained of having any signs of awareness during anesthesia on POD 1. However, this may not necessarily indicate that they were unconscious during anesthesia. Some additional hypnotic is usually administered before endotracheal intubation during opioid-hypnotic induction. In this context, the study might not entirely mimic the clinical situations. Postintubation hypertension would be less when an additional dose of propofol was injected in group F patients. We carried out this study in normotensive patients. Tachycardia manifested in this patient group would be of minor importance in a clinical situation. Another study involving hypertensive patients or patients with ischemic heart disease may be more valuable clinically. We used 0.1 mg·kg^{-1} vecuronium in this study; greater doses of vecuronium might alter the results. Furthermore, the effect of sevoflurane without N_2O on induction and endotracheal intubation was not examined in this study. We only calculated the cost of anesthetics at the induction period. We used N_2O and sevoflurane for maintenance of anesthesia in this study. Those two anesthetics were already delivered and accumulated in group S patients at the completion of induction. As a result, the total cost of anesthetics may not necessarily differ between the two anesthesia techniques if a lower volume of sevoflurane and N_2O were needed during the subsequent anesthesia period in group S patients than in group F.

In conclusion, the present study showed that 66% N_2O/4% sevoflurane anesthesia did not improve the conditions of endotracheal intubation after 0.1 mg·kg^{-1} vecuronium as compared with 2 μg·kg^{-1} of fentanyl. From the standpoints of hemodynamics and the cost of anesthetics during anesthesia induction and endotracheal intubation, fentanyl would be more favorable than N_2O/sevoflurane as an adjuvant to propofol induction.

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