

The Effects of Lidocaine, Fentanyl, Nicardipine, and Esmolol on Hemodynamic and Bispectral Index Responses during Induction with Thiopental Sodium

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Background: The laryngoscopy and tracheal intubation may accompany with undesirable side effects such as hypertension, tachycardia, arrhythmia, and awareness. The aim of this study was to investigate whether the correlation between the hemodynamics and bispectral index (BIS) changes after tracheal intubation following the administration of various adjuvants to attenuate tracheal response exists or not.

Methods: The patients were randomly assigned to one of five groups (control, lidocaine, fentanyl, nicardipine, or esmolol) and the drugs were administered at preselected time before tracheal intubation. The heart rate (HR), blood pressure, rate-pressure product (RPP), BIS and the episode of BIS more than 65 ($BIS \geq 65$) were measured.

Results: There were significant differences in the mean arterial pressure and RPP between control group and other groups. The HR was the most attenuated in esmolol group. The HR and RPP was the most increased in nicardipine group except control group. There was no significant difference in the maximal BIS among the five groups. The $BIS \geq 65$ were 50% in control group and 0.3% in nicardipine group.

Conclusions: All the adjuvant drugs in the study attenuated with a various degree of the tracheal responses. However, there was no correlation between the changes of hemodynamics and BIS after the administration of various adjuvants following tracheal intubation. (Korean J Anesthesiol 2007; 53: S 7~13)

Key Words: BIS, hemodynamic response, intubation.

INTRODUCTION

Laryngoscopy and tracheal intubation may accompany hypertension, tachycardia, arrhythmia and awareness¹⁻⁴⁾ and it is well recognized that these tracheal responses are mediated by sympathetic responses. A number of pharmacologic interventions, such as local anesthetic,^{5,6)} opioids,^{7,8)} calcium channel blockers,^{9,10)} short acting β -adrenergic blockers,¹¹⁾ and their combinations¹²⁾ have been used to attenuate the reflex responses to tracheal intubation. The theoretical background of

the use of these drugs for laryngoscopy and tracheal intubation is that these adjuvant measures might attenuate the hemodynamic responses by blocking intense sympathetic discharge caused by stimulation of the upper airway.

Bispectral Index (BIS) has been proposed as a measure of the pharmacologic anesthetic effect on the central nervous system (CNS) and used as an indicator of degree of CNS depression. The numeric index directly reflects the activity of cerebral cortex.^{13,14)} BIS value more than 65 ($BIS \geq 65$) has a possibility of recall and conscious perception.¹⁴⁾ BIS may significantly increased by the laryngoscopy and tracheal intubation. However, the tracheal reflex response is mediated at the subcortical level and thus may be unrelated between hemodynamics and BIS values.¹⁵⁾ In addition, little is known that the change in BIS value immediately after tracheal intubation is directly related with the hemodynamic change.

Some drugs are known to have an effect on BIS value, even though they are not anesthetics.^{15,16)} However, there has

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been no comparison study to investigate the changes in hemodynamic and BIS responses concurrently following various adjuvant measures after laryngoscopy and tracheal intubation. We evaluated the change in hemodynamic and BIS responses simultaneously to laryngoscopy and tracheal intubation according to the administration of lidocaine (a local anesthetic), fentanyl (an opioid), nicardipine (a calcium channel blocker), and esmolol (a β -blocker), which are commonly used in clinical settings.

MATERIALS AND METHODS

After obtaining approval from the Clinical Investigation Committee and written informed consent, 150 ASA physical status I or II patients, aged 20 to 65, undergoing elective surgery requiring tracheal intubation were enrolled. The patients with cardiopulmonary disease, obesity, smoking history, expectation of difficult airway, intake of concurrent vasoactive medication, and previous adverse response to hypnotics and inhaled agents were excluded from the study. The patients' age, gender, height, and weight were recorded.

All patients were premedicated with midazolam (7.5 mg orally) the night before the operation and intramuscular 2-2.5 mg midazolam and 0.2 mg glycopyrrolate, 30 minutes before entering the operating room. After arrival in the operation room, lead II of an electrocardiogram on the patient's back and saturation via pulse oximetry (SpO_2) at patient's finger were continuously monitored. An automated blood pressure cuff was applied to the right arm to check blood pressure. Because of the relative simple operation and ethical issues, we did not use invasive arterial blood pressure monitoring. To insure uniform conditions, the same monitoring equipment was

used in all patients (M1041A, Hewlett-Packard, Germany). For preoxygenation, all patients breathed pure oxygen for 3 minutes, fresh gas flow 6 L/min, using a face mask connected to a semiclosed breathing circuit. During this period, preinduction hemodynamic data were measured and served as baseline. A 20-gauges intravenous catheter was inserted in the left forearm vein for the purpose of drug and fluid administration. Before anesthetic induction, electrodes for BIS (BISTM monitor 2000, Aspect Medical System, USA) were placed on the forehead and the baseline BIS value was recorded. The electrodes used were disposable BisSensor strips (Aspect Medical System, USA). Hemodynamic data, including heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), and BIS values were recorded from the beginning of anesthesia and at every minute after tracheal intubation. The episode of $\text{BIS} \geq 65$ during the experimental period were documented. The final values were recorded until 5 minutes after tracheal intubation. The rate-pressure product (RPP) was calculated by $\text{SBP} \times \text{HR}$.

The patients were randomly assigned to one of five groups with 30 patients in each category in a double-blind manner, depending on experimental measures. Group C was the control group. Group L patients received 2 mg/kg of lidocaine (Lidocaine HCl[®], Huons, Korea), 3 minutes before intubation. Group F patients received 2 $\mu\text{g}/\text{kg}$ of fentanyl (Fentanyl[®], Hana Pharmacy, Korea), 4 minutes before intubation. Group N patients received 30 $\mu\text{g}/\text{kg}$ of nicardipine (Perdipine[®], Dong-A Pharmacy, Korea), 2 minutes before intubation. Group E patients received 1 mg/kg of esmolol (Brevibloc[®], Jaeil Pharmacy, Korea), 90 seconds before intubation (Fig. 1). Each study drug was preset to 10 ml of the total volume mixed with normal saline. The preselected timing and doses for each

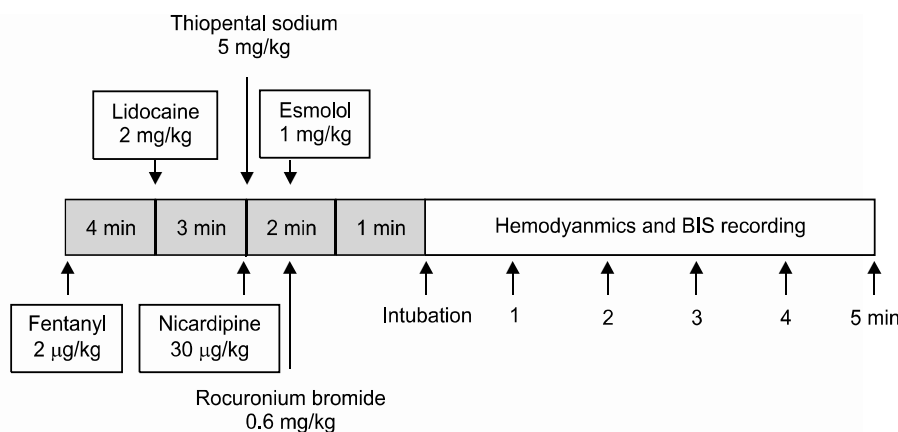


Fig. 1. Details of study. Fentanyl, lidocaine, nicardipine, and esmolol were administered at 4, 3, 2, and 1.5 min, respectively, before tracheal intubation. BIS: bispectral index.

drug were based on the previous reports.⁵⁻¹¹⁾ In each group, 10 ml of normal saline was administered at every preselected time (4 minutes, 3 minutes, 2 minutes, and 90 seconds before tracheal intubation) except for an experimental drug. The total injection volume was 50 ml in each patient and the anesthesiologist was not aware of this design when he performed laryngoscopy and tracheal intubation.

In all groups, 5 mg/kg thiopental sodium and 0.6 mg/kg rocuronium bromide were intravenously administered 2 minutes and 90 seconds before tracheal intubation, respectively, to facilitate laryngoscopy and tracheal intubation. After loss of consciousness, positive pressure ventilation using bag-valve-mask apparatus and 100% oxygen with continuous cricoid pressure was performed. Laryngoscopy and tracheal intubation were performed within 10-20 sec (T-int, time from laryngoscopy to intubation) by the same anesthesiologist who was blinded to the study drugs. Neither patient nor the anesthesiologist were aware of the experimental drugs. For safety and ethical problem, we excluded patients with HR more than 130 bpm and an SBP more than 200 mmHg or less than 80 mmHg after tracheal intubation from the study. Eliminated patients were replaced by others. After tracheal intubation, the patients were

ventilated mechanically with a tidal volume of 10 ml/kg and a fixed respiratory rate, 10 rates/min and with 2% sevoflurane in a mixture of 50% N₂O/O₂ at 4 L/min. The patient was left undisturbed for an additional 5 minutes of hemodynamic and BIS recordings, at which point the study was terminated. The occurrence of hypertension, hypotension, bradycardia, bronchospasm, and arrhythmia was noted when anesthesia was induced.

Data was presented as mean \pm standard deviation (SD). SPSS software (SPSS for windows, Release 12.0; SPSS Inc, Chicago, IL USA) was used to perform data analysis. Statistical analysis for demographic data was done by using one way-ANOVA and the incidence of episode of BIS \geq 65 was analyzed by χ^2 -test. Changes in hemodynamics were analyzed by repeated measures of ANOVA. P values $<$ 0.05 were considered statistically significant.

RESULTS

There were no significant differences in demographic data among groups (Table 1). There was no significant difference in the time from laryngoscopy to tracheal intubation among the five groups (17.8 \pm 6.1, 15.2 \pm 2.0, 14.7 \pm 1.5, 15.0 \pm 1.3 and 15.3 \pm 1.3 seconds in group C, group L, group F, group N and group E, respectively). The baseline values of HR, MAP, RPP were not significantly different among the five groups (Table 2-4). None of the patients had an abnormal ECG or an SpO₂ less than 98% during the experimentation. Eight patients were excluded due to the study's hypertensive criteria during the study (four in group C, two in group E, one in group N, and one patient in group F) and others replaced these patients.

In group C and group N, the HR increased significantly

Table 1. Demographic Data (Each n = 30)

Group	Age (yr)	Sex (M/F)	Weight (kg)	Height (cm)
Control	47.7 \pm 14.3	13/17	61.3 \pm 9.2	160.2 \pm 9.2
Lidocaine	48.0 \pm 14.1	14/16	62.1 \pm 10.8	162.2 \pm 9.4
Fentanyl	49.6 \pm 17.3	15/15	60.9 \pm 9.8	162.3 \pm 9.5
Nicardipine	43.1 \pm 14.0	17/13	61.4 \pm 11.2	161.6 \pm 9.4
Esmolol	42.2 \pm 14.1	17/13	65.3 \pm 11.2	164.3 \pm 7.5

Values are Mean \pm SD except sex (number of patients). There were no statistical differences among the five groups.

Table 2. Changes in Heart Rate (bpm) after Tracheal Intubation

Group	Baseline	Time after tracheal intubation					Repeated measures ANOVA
		1 min	2 min	3 min	4 min	5 min	
Control	77.3 \pm 15.0	100.3 \pm 15.3*	93.7 \pm 14.6*	91.0 \pm 13.9*	89.0 \pm 14.1*	88.0 \pm 13.9*	¶
Lidocaine	84.0 \pm 19.6	91.9 \pm 15.0*	86.9 \pm 15.3	83.0 \pm 15.0	80.7 \pm 14.4	81.5 \pm 14.5	§¶
Fentanyl	76.2 \pm 14.1	98.5 \pm 16.8*	93.2 \pm 16.4*	88.5 \pm 15.9	87.3 \pm 15.7*	86.8 \pm 15.0*	‡
Nicardipine	78.9 \pm 13.2	97.8 \pm 19.5*	99.0 \pm 10.6*	96.1 \pm 11.7*	92.3 \pm 12.1*	90.4 \pm 11.6*	¶
Esmolol	82.5 \pm 13.6	81.4 \pm 12.3	80.6 \pm 11.5	79.8 \pm 11.8	78.2 \pm 10.8	77.5 \pm 10.7*	† ‡ ¶

Values are Mean \pm SD. *: P $<$ 0.05 vs. baseline, †: P $<$ 0.05 vs. control, ‡: P $<$ 0.05 vs. lidocaine, §: P $<$ 0.05 vs. fentanyl, ||: P $<$ 0.05 vs. nicardipine, ¶: P $<$ 0.05 vs. esmolol.

Table 3. Changes in Mean Arterial Pressure (mmHg) after Tracheal Intubation

Group	Baseline	Time after tracheal intubation					Repeated measures ANOVA
		1 min	2 min	3 min	4 min	5 min	
Control	95.0 ± 13.2	124.6 ± 25.1*	114.9 ± 21.0*	103.8 ± 18.7*	95.5 ± 17.3	90.6 ± 15.1	† § ¶
Lidocaine	94.4 ± 16.0	105.8 ± 22.0*	97.4 ± 19.0	89.8 ± 18.6	83.9 ± 16.8*	79.6 ± 14.1*	†
Fentanyl	91.2 ± 11.4	109.4 ± 22.4*	97.9 ± 15.8*	89.9 ± 14.8	84.1 ± 13.6*	80.8 ± 12.1*	†
Nicardipine	96.7 ± 16.0	102.3 ± 17.8	96.3 ± 16.5	88.2 ± 15.3*	84.7 ± 13.1*	78.8 ± 11.5*	†
Esmolol	96.1 ± 14.6	103.1 ± 17.0*	100.9 ± 14.5*	92.6 ± 12.8	86.2 ± 12.2*	82.0 ± 10.7*	†

Values are Mean ± SD. *: P < 0.05 vs. baseline, †: P < 0.05 vs. control, ‡: P < 0.05 vs. lidocaine, §: P < 0.05 vs. fentanyl, ||: P < 0.05 vs. nicardipine, ¶: P < 0.05 vs. esmolol.

Table 4. Changes in Rate-Pressure Product ($1/10^3$ mmHg·beats/min) after Tracheal Intubation

Group	Baseline	Time after tracheal intubation					Repeated measures ANOVA
		1 min	2 min	3 min	4 min	5 min	
Control	10.1 ± 2.1	17.0 ± 3.7*	14.8 ± 3.9*	13.0 ± 3.0*	11.7 ± 2.9*	10.9 ± 2.5	† § ¶
Lidocaine	11.0 ± 3.3	13.3 ± 3.4*	11.7 ± 3.1	10.3 ± 2.8	9.2 ± 2.4*	8.8 ± 2.1*	† ¶
Fentanyl	9.9 ± 2.8	14.6 ± 3.9*	12.4 ± 3.0*	10.9 ± 2.7*	10.0 ± 2.5	9.4 ± 2.0	†
Nicardipine	10.4 ± 2.4	13.5 ± 3.7*	13.0 ± 2.5*	11.1 ± 2.6*	10.5 ± 2.0	9.7 ± 1.8*	† ¶
Esmolol	10.7 ± 2.5	11.3 ± 2.7	10.8 ± 2.2	9.9 ± 1.7*	9.1 ± 1.4*	8.6 ± 1.4*	† ‡

Values are Mean ± SD. *: P < 0.05 vs. baseline, †: P < 0.05 vs. control, ‡: P < 0.05 vs. lidocaine, §: P < 0.05 vs. fentanyl, ||: P < 0.05 vs. nicardipine, ¶: P < 0.05 vs. esmolol.

Table 5. Changes in Bispectral Index after Tracheal Intubation

Group	Baseline	Time after tracheal intubation					Repeated measures ANOVA
		1 min	2 min	3 min	4 min	5 min	
Control	95.3 ± 4.2	60.6 ± 8.7	61.5 ± 9.2	61.3 ± 4.9	58.7 ± 6.0	55.3 ± 7.6	† §
Lidocaine	93.5 ± 7.8	50.5 ± 15.9	51.7 ± 13.6	50.1 ± 12.9	48.5 ± 10.9	47.6 ± 10.2	† §
Fentanyl	92.9 ± 5.7	51.6 ± 10.1	53.6 ± 9.0	54.3 ± 0.2	51.5 ± 6.5	50.4 ± 7.2	*†
Nicardipine	94.6 ± 4.0	62.8 ± 8.6	59.5 ± 6.7	55.7 ± 6.1	54.2 ± 6.6	52.4 ± 7.4	*†
Esmolol	93.4 ± 4.7	57.8 ± 9.3	55.7 ± 8.1	52.9 ± 5.9	50.8 ± 5.4	48.7 ± 5.4	*†

Values are Mean ± SD. *: P < 0.05 vs. control, †: P < 0.05 vs. lidocaine, ‡: P < 0.05 vs. fentanyl, §: P < 0.05 vs. nicardipine, ||: P < 0.05 vs. esmolol.

compared to the baseline value until 5 minutes after tracheal intubation. In group E, however, the HR was maintained until 4 minutes and decreased at 5 minutes after tracheal intubation (Table 2). There was a significant difference in the change in HR between group C and group E.

The MAP was displayed in table 3. In group C, the MAP increased until 3 minutes after tracheal intubation and returned

to the baseline value at 4 and 5 minutes after tracheal intubation. However, the MAP decreased compared to the baseline values at 4 and 5 minutes in group L, group F, and group E, and at 3, 4, and 5 minutes in group N. There was a significant difference in overall changes of MAP between control group and other groups.

The changes in RPP are displayed in table 4. The RPP

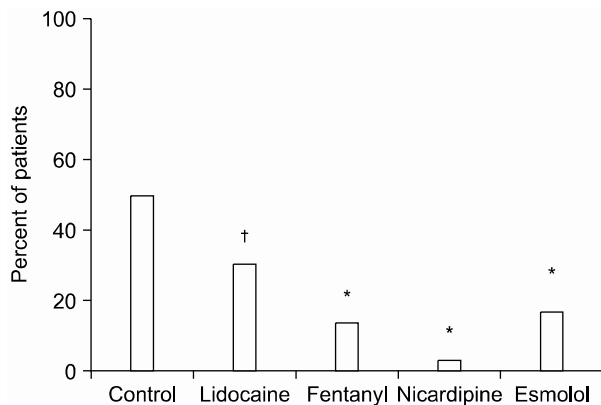


Fig. 2. Percent of patients with bispectral index more than 65 after tracheal intubation. *: $P < 0.05$ vs control, †: $P < 0.05$ vs nicardipine.

increased after tracheal intubation from 1 to 4 minutes in group C, at 1 minute in group L, from 1 to 3 minutes in group F, and from 1 to 5 minutes in group N. However, the RPP in group E were maintained at the baseline value ($10.7 \pm 2.5 \times 10^3$ mmHg·beats/min) until 2 minutes after tracheal intubation and decreased at 4 and 5 minute after tracheal intubation (9.1 ± 1.4 and $8.6 \pm 1.4 \times 10^3$ mmHg·beats/min, respectively)(Table 4). There were significant differences in the RPP between group C and the other groups.

The baseline BIS values in group C, group L, group F, group N and group E were 95.3 ± 4.2 , 93.5 ± 7.8 , 92.9 ± 5.7 , 94.6 ± 4.0 , and 93.4 ± 4.7 , respectively (Table 5). There were no significant differences in baseline BIS values and the changes in BIS after tracheal intubation among five groups. The patients who experienced episodes of $\text{BIS} \geq 65$ were evaluated (Fig. 2). In control group, 50% (15 patients) of the patients had an episode of $\text{BIS} \geq 65$. Patients who sustained the episode of $\text{BIS} \geq 65$ were 9 (30%) in group L, 4 (13.3%) in group F, 1 (3.3%) in group N, and 5 (16.7%) in group E, respectively.

DISCUSSION

The administration of lidocaine, fentanyl, nicardipine or esmolol during induction with thiopental sodium attenuated with a various degree of hemodynamic and BIS responses following tracheal intubation. However, the changes in tracheal response were not coincident with the changes in BIS responses following different adjuvants.

The unintentional awake intubation and the explicit memory of such an incident is one of the most consequential concerns during anesthetic practice. Awareness is an unpleasant and traumatic experience and has the considerable potential for morbidity, including severe emotional stress and post-traumatic stress disorder.¹⁷⁾ To our knowledge, however, little study has been performed on how adjuvants for blunting the tracheal response might be influential on the change in BIS or not. Through this study, the authors would like to find out whether the correlation between the changes in hemodynamics and BIS values exists or not following various adjuvant measures for tracheal intubation.

BIS value over 80 has been known to be associated with a high incidence of awareness and a value more than 65 is recommended for adequate sedation.^{18,19)} In our present study, the episode of $\text{BIS} \geq 65$ was regarded as the possibility of awareness as in Glass et al.²⁰⁾ In group C, the hemodynamics, including HR, MAP and RPP, were more increased than any other group and half of the patients had $\text{BIS} \geq 65$. With exception of the group C, the incidence of $\text{BIS} \geq 65$ was highest in group L (30%) and lowest in group N (3%). However, the HR and RPP in group N were more increased than all the other experimental groups. This result may suggest that the change in BIS after administration of adjuvants for suppression of tracheal response is not coordinated with the change in the hemodynamics.

Although the hemodynamic responses are the most commonly used measures to judge the depth of anesthesia, they are not precise tools for judging anesthetic depth. BIS has been widely used to identify and reduce the incidence of awareness during the anesthetic induction. BIS is highly correlated with the level of sedation and the loss of consciousness for volatile agents and most of the intravenous anesthetic agents.¹⁹⁾ BIS is a safe and simple measurement to detect the hypnotic component of anesthesia,²¹⁾ however, it may not predict the awareness reaction to intubation in surgical patients^{17,22)} and the effectiveness is still questionable. In addition, BIS value may be changed in response to drugs and stimulations such as cardiovascular or somatic responses.

A major reason for the increased risk of awakening during the anesthetic induction is the pharmacokinetic properties of the hypnotic drug that is administered as a single bolus during the induction period.²²⁾ The rapid decrease in the hypnotic effect sites concentration in combination with the stressful tracheal intubation are crucial to the development of aware-

ness.^{17,23)}

Thiopental sodium 4 mg/kg is more likely to be associated with lighter planes of anesthesia and the consequent risk of awareness than propofol 2 mg/kg after tracheal induction, if intubation is delayed or prolonged.²⁴⁾ In our study, 5 mg/kg of thiopental sodium was used as a hypnotic for tracheal intubation. Inhalational anesthetics are also known to produce dose dependent effects on BIS value. In our present study, the same dose of 2% sevoflurane was administered with adjuvants throughout the examination of all patients. The effect of sevoflurane was not a considerable factor in the study. Nakayama et al.²⁵⁾ demonstrated that the anesthesia with 2 MAC (minimum alveolar concentration) of sevoflurane without adjuvants was effective to suppress the change in BIS due to tracheal intubation. However, 2 MAC of sevoflurane did not prevent the changes in hemodynamic responses after tracheal intubation in their study.

Although the efficacy remains controversial, lidocaine has been known to have a suppressive effect on the circulatory responses due to the laryngoscopy and tracheal intubation.⁵⁾ Lidocaine, given intravenously, has an analgesic effect on the dorsal horn neurons and produces cardiovascular suppression via an effect on the CNS.²⁶⁾ In the present study, the RPP in group L increased at 1 minute and decreased at 4 and 5 minutes after tracheal intubation. In group N, the RPP increased from 1 to 3 minutes after tracheal intubation. However, the changes in BIS values were not different between group L and group N. In addition, the incidence of BIS \geq 65 was highest in group L, except in group C.

Fentanyl, an opioid, is commonly used opioid that combined with hypnotic agents to minimize the hemodynamic responses to tracheal intubation.²⁷⁾ In this study, fentanyl modified hemodynamic responses due to tracheal intubation but did not affect the BIS responses. Nicardipine, a L-type calcium channel blocker, has been known to have no effect on BIS. Hirota et al.²⁸⁾ evaluated the effect of nicardipine on BIS in hypertensive patients during general anesthesia. Clinical dosage of nicardipine did not alter the BIS during general anesthesia in their study. In our study, the incidence of BIS \geq 65 was the lowest in group N despite the most increase in RPP after tracheal intubation.

Esmolol, a short acting β 1-adrenoceptor antagonist, can be used to reduce tachycardia and blood pressure for anesthetic induction. Beta-adrenergic agonists are well known to have the effect of enhancement of behavioral and electroencephalographic

arousal reactions.²⁹⁾ Conversely, β -adrenoceptor antagonists such as isoprenaline or epinephrine decrease EEG indices of arousal.³⁰⁾ Menigaux et al.³¹⁾ reported that esmolol had not only attenuation of the hemodynamic responses but also the suppression of BIS arousal reactions due to the laryngoscopy and tracheal intubation in patients anesthetized with propofol. They used a continuous infusion of esmolol and propofol to keep the patients' BIS value below 65 during the measuring time. However, in our study, we could not find the effect that esmolol had on lowering the BIS value immediately after tracheal intubation in respect of the changes in BIS and BIS \geq 65. The difference between our result and Menigaux's result may come from the administration method and dosage of esmolol. In our study, esmolol as a bolus (1 mg/kg) was administered, however, esmolol was administered as a continuous infusion following a bolus in the Menigaux's study (1 mg/kg followed by 250 μ g/kg/min). As a result, a single bolus administration of esmolol may not be the proper dosage to stabilize the patients' BIS value.

In conclusion, all the adjuvant drugs used in this study attenuated the hemodynamic responses due to the laryngoscopy and tracheal intubation with a various degree. However, the study could not find the correlation between the changes of hemodynamics and BIS values after tracheal intubation. Appropriate adjuvant drug therapy during anesthetic induction can be used for better quality of anesthesia. Therefore, anesthesiologists should pay attention to the possibility of awareness during the laryngoscopy and tracheal intubation, resulting in one of the crucial concerns during anesthetic practice.

REFERENCES

1. Lallemand MA, Lentschener C, Mazoit JX, Bonnichon P, Manceau I, Ozier Y: Bispectral index changes following etomidate induction of general anaesthesia and orotracheal intubation. *Br J Anaesth* 2003; 91: 341-6.
2. Schneider G, Gelb AW, Schmeller B, Tschakert R, Kochs E: Detection of awareness in surgical patients with EEG-based indices-bispectral index and patient state index. *Br J Anaesth* 2003; 91: 329-35.
3. Luginbuhl M, Wuthrich S, Petersen-Felix S, Zbinden AM, Schnider TW: Different benefit of bispectral index (BIS) in desflurane and propofol anesthesia. *Acta Anaesthesiol Scand* 2003; 47: 165-73.
4. Mi WD, Sakai T, Takahashi S, Matsuki A: Haemodynamic and electroencephalograph responses to intubation during induction with propofol or propofol/fentanyl. *Can J Anaesth* 1998; 45: 19-22.

5. Tam S, Chung F, Campbell M: Intravenous lidocaine: Optimal time of injection before tracheal intubation. *Anesth Analg* 1987; 66: 1036-8.
6. Takita K, Morimoto Y, Kemmotsu O: Tracheal lidocaine attenuates the cardiovascular response to endotracheal intubation. *Can J Anaesth* 2001; 48: 732-6.
7. Splinter WM, Cervenka F: Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: effects of fentanyl, lidocaine and thiopentone. *Can J Anaesth* 1989; 36: 370-6.
8. Maguire AM, Kumar N, Parker JL, Rowbotham DJ, Thompson JP: Comparison of effects of remifentanyl and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients. *Br J Anaesth* 2001; 86: 90-3.
9. Nishikawa T, Namiki A: Attenuation of the pressor response to laryngoscopy and tracheal intubation with intravenous verapamil. *Acta Anaesthesiol Scand* 1989; 33: 232-5.
10. Mikawa K, Obara H, Kusunoki M: Effect of nicardipine on the cardiovascular response to tracheal intubation. *Br J Anaesth* 1990; 64: 240-2.
11. Helfman SM, Gold MI, DeLisser EA, Herrington CA: Which drug prevents tachycardia and hypertension associated with tracheal intubation: lidocaine, fentanyl, or esmolol? *Anesth Analg* 1991; 72: 482-6.
12. Fujii Y, Saitoh Y, Takahashi S, Toyooka H: Diltiazem-lidocaine combination for the attenuation of cardiovascular responses to tracheal intubation in hypertensive patients. *Can J Anaesth* 1998; 45: 933-7.
13. Singh H: Bispectral index (BIS) monitoring during propofol-induced sedation and anaesthesia. *Eur J Anaesthesiol* 1999; 16: 31-6.
14. Glass PS, Bloom M, Kears L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; 86: 836-47.
15. Mi WD, Sakai T, Singh H, Kudo T, Kudo M, Matsuki A: Hypnotic endpoints vs. the bispectral index, 95% spectral edge frequency and median frequency during propofol infusion with or without fentanyl. *Eur J Anaesthesiol* 1999; 16: 47-52.
16. Oda Y, Nishikawa K, Hase I, Asada A: The short-acting beta 1-adrenoreceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. *Anesth Analg* 2005; 100: 733-7.
17. Schneider G, Wagner K, Reeker W, Hanel F, Werner C, Kochs E: Bispectral index (BIS) may not predict awareness reaction to intubation in surgical patients. *J Neurosurg Anesthesiol* 2002; 14: 7-11.
18. Sie MY, Goh PK, Chan L, Ong SY: Bispectral index during modified rapid sequence induction using thiopentone or propofol and rocuronium. *Anaesth Intensive Care* 2004; 32: 28-30.
19. Edward G, Maged S, Michael J: Clinical anesthesiology. 3rd edition. New York, Mc Graw Hill, 2002, pp 114-5.
20. Glass PS, Bloom M, Kears L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; 86: 836-47.
21. Moerman N, Bonke B, Oosting J: Awareness and recall during general anesthesia. Facts and feelings. *Anesthesiology* 1993; 79: 454-64.
22. St Pierre M, Landsleitner B, Schwilden H, Schuettler J: Awareness during laryngoscopy and intubation: quantitating incidence following induction of balanced anesthesia with etomidate and cisatracurium as detected with the isolated forearm technique. *J Clin Anesth* 2000; 12: 104-8.
23. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, et al: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; 84: 891-9.
24. Struys M, Versichelen L, Byttebier G, Mortier E, Moerman A, Rolly G: Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. *Anaesthesia* 1998; 53: 4-12.
25. Nakayama M, Kanaya N, Edanaga M, Namiki A: Hemodynamic and bispectral index responses to tracheal intubation during isoflurane or sevoflurane anesthesia. *J Anesth* 2003; 17: 223-6.
26. Blair MR: Cardiovascular pharmacology of local anesthetics. *Br J Anaesth* 1975; 47: 247-52.
27. Nakayama M, Ichinose H, Yamamoto S, Kanaya N, Namiki A: The effect of fentanyl on hemodynamic and bispectral index changes during anesthesia induction with propofol. *J Clin Anesth* 2002; 14: 146-9.
28. Hirota K, Kabara S, Kushikata T, Kitayama M, Ishihara H, Matsuki A: Effects of nicardipine and diltiazem on the bispectral index and 95% spectral edge frequency. *Eur J Anaesthesiol* 2003; 20: 809-12.
29. Berridge CW, Foote SL: Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic beta-receptors within the medial septal region of the basal forebrain. *J Neurosci* 1996; 16: 6999-7009.
30. Ishiyama T, Oguchi T, Iijima T, Matsukawa T, Kashimoto S, Kumazawa T: Ephedrine, but not phenylephrine, increases bispectral index values during combined general and epidural anesthesia. *Anesth Analg* 2003; 97: 780-4.
31. Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M: Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br J Anaesth* 2002; 89: 857-62.