

Esmolol prevents movement and attenuates the BIS response to orotracheal intubation[†]

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Background. Beta-adrenergic agonists enhance behavioural and electroencephalographic arousal reactions. We explored whether adding esmolol, a short-acting β_1 -adrenoceptor antagonist, to propofol anaesthesia modified the bispectral index (BIS) during induction of anaesthesia and orotracheal intubation.

Methods. Fifty patients were randomly allocated, in a double-blind fashion, to receive esmolol 1 mg kg^{-1} followed by $250 \mu\text{g kg}^{-1} \text{ min}^{-1}$ or saline (control). Esmolol or saline was started 6 min after a target-controlled infusion (TCI) of propofol (effect-site concentration $4 \mu\text{g ml}^{-1}$). After loss of consciousness, and before administration of vecuronium 0.1 mg kg^{-1} , a tourniquet was applied to one arm and inflated to 150 mm Hg greater than systolic pressure. Eleven minutes after the TCI began, the trachea was intubated; gross movement within the first min after orotracheal intubation was recorded. BIS was recorded at 10-s intervals. Mean arterial pressure (MAP) and heart rate were measured non-invasively every min.

Results. There were no intergroup differences in BIS, heart rate or MAP before laryngoscopy. BIS increased significantly after orotracheal intubation (compared with the pre-laryngoscopy values) in the control group only, with a maximum increase of 40 (SD 18)% vs 8 (11)% in the esmolol group ($P < 0.01$). Maximum changes in heart rate [45 (19)% vs 23 (14)%] and MAP [62 (24)% vs 45 (23)%] with orotracheal intubation were also significantly greater in the control group than in the esmolol group. More patients in the control than in the esmolol group moved after orotracheal intubation (23 vs 12, $P < 0.01$).

Conclusion. Esmolol not only attenuated haemodynamic and somatic responses to laryngoscopy and orotracheal intubation, but also prevented BIS arousal reactions in patients anaesthetized with propofol.

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Noxious stimulation during general anaesthesia causes various reactions, including movement, sympathetic nervous system stimulation, and arousal reactions that may be detected on the electroencephalogram (EEG).^{1–3} For example, laryngoscopy and orotracheal intubation increase the bispectral index (BIS), as well as haemodynamic variables.² Both BIS and the haemodynamic responses to noxious stimulation are attenuated by opiate administration.^{1,2} These results suggest that BIS monitoring can help to detect inadequate analgesia during general anaesthesia.

Esmolol, a short-acting β_1 -adrenoceptor antagonist, produces dose-dependent attenuation of the adrenergic response to laryngoscopy and orotracheal intubation.⁴ However, previous studies assessing the effectiveness of

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esmolol in blunting the haemodynamic alterations induced by laryngoscopy and orotracheal intubation failed to monitor electrical activity of the brain. Only a few studies have evaluated the effect of interaction between β -adrenoceptor antagonists and anaesthetics on BIS.^{5,6} They raised the possibility that esmolol administration may mask inadequate anaesthesia.

It is also known that esmolol decreases the amount of anaesthesia required to prevent movement in response to skin incision.^{7,8} Although a correlation between BIS and movement has been observed under some circumstances,⁹ no relationship has been observed in other studies.^{10,11} A poor relationship between movement and BIS is understandable since EEG measures cortical activity, whereas movement in response to noxious stimulation originates in the spinal cord.¹² Our purpose was therefore to determine whether preventing haemodynamic responses during laryngoscopy and orotracheal intubation with esmolol simultaneously ameliorates somatic and BIS arousal reactions.

Materials and methods

After approval from the Medical Ethics Committee of the Hôpital Ambroise Pare, we obtained written informed consent from 50 patients. All were ASA physical status I or II, aged 18–70 yr, and scheduled for elective non-cranial surgery. Exclusion criteria included neurological, cardiac or metabolic disease, chronic hypertension, asthma or reactive airway disease, cardiovascular or β -blocker medication, routine use of analgesics or hypnotic medication, drug or alcohol abuse, and obesity (>130% of ideal body weight).

Patients were assigned randomly, in a double-blind fashion, to one of two groups (25 patients per group): control or esmolol. Group allocations were based on computer-generated codes. The hospital pharmacist prepared suitable syringes for each patient: a 10-ml syringe containing either isotonic sodium chloride (saline) or esmolol 100 mg in saline for the initial bolus, and a 50 ml syringe containing either saline or esmolol 250 mg diluted in saline for the continuous infusion. Patients and personnel involved in patient management and data collection were unaware of the group assignment.

Figure 1 shows the time line for the study protocol. No sedative premedication was given. After preoxygenation, the subjects were anaesthetized with i.v. propofol. The patients were manually ventilated to maintain end-tidal carbon dioxide concentration between 30 and 35 mm Hg until laryngoscopy and orotracheal intubation; subsequently, they were mechanically ventilated with oxygen 40%. Propofol was administered via a computer-assisted infusion device (Fresenius Vial Medical, Brezins, France) using a program written in Visual Basic[®] 5 (Microsoft Corporation, Redmond, OR, USA) by one of the investigators (BG). The pharmacokinetic set published by Marsh and colleagues¹³ was used to estimate target effect-site concentrations of

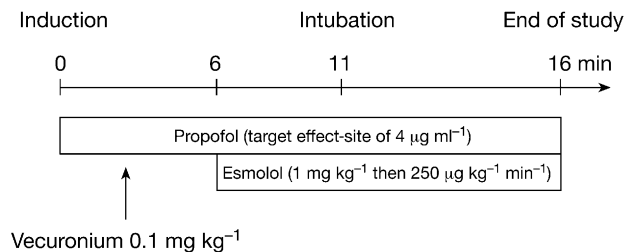


Fig 1 Details of study.

propofol. The plasma effect-site equilibrium rate constant (K_{eo}) value used for propofol was 0.638 min^{-1} .¹³ Propofol was administered to a target effect-site concentration of $4 \mu\text{g ml}^{-1}$ (i.e. 2 mg kg^{-1} bolus followed by $225 \mu\text{g kg}^{-1} \text{ min}^{-1}$) during the entire study period.

The isolated-arm technique was used to evaluate patient movement after administration of the neuromuscular blocking agent.² After loss of consciousness, an arm tourniquet was inflated to 150 mm Hg above systolic pressure; vecuronium 0.1 mg kg^{-1} was then given. Six minutes after the propofol target-controlled infusion (TCI) began, the esmolol group was given a bolus of esmolol 1 mg kg^{-1} , followed by an infusion of $250 \mu\text{g kg}^{-1} \text{ min}^{-1}$. The control group was given a comparable volume of saline. The trachea was intubated 11 min after the start of the propofol infusion. The same investigator (CM) performed the laryngoscopy and orotracheal intubation in every patient, while a second investigator (BG) noted the duration of laryngoscopy and orotracheal intubation, defined as the time from mouth opening until inflation of the tracheal tube balloon. This second examiner also assessed patient movement in response to laryngoscopy and orotracheal intubation. A positive response was defined as gross purposeful movement of the arm with the tourniquet attached within 1 min of orotracheal intubation. Hypotension was defined as a mean arterial pressure (MAP) $<60 \text{ mm Hg}$ and bradycardia as heart rate $<50 \text{ beats min}^{-1}$. The study ended 16 min after starting the propofol.

Before induction of anaesthesia, silver/silver chloride pre-gelled electrodes (Aspect Medical Systems, Natick, MA, USA) were applied to the left and right frontal (Fp1 and Fp2) regions and referred to a vertex electrode (Cz). We confirmed that electrode impedance was $<2000 \Omega$. The EEG was recorded continuously using an Aspect A-1000 EEG monitor (Aspect Medical Systems, Natick, MA, USA), which also continuously computed the BIS (revision 3.3). A BIS value was generated every 10 s. Arterial pressure and heart rate were measured non-invasively every minute using a Cardiacap monitor (Datex, Helsinki, Finland), and acquired simultaneously with the EEG using multi-serial interfaces between the monitors and a personal computer. All acquired data were stored on disk for subsequent analysis.

The BIS values given are the mean of six measurements taken at each data point. The recordings were taken before

induction; before the start of esmolol or saline; 1, 3 and 5 min (pre-laryngoscopy) after the start of the esmolol infusion; and 1, 2 and 5 min after orotracheal intubation.

Changes in BIS, heart rate and MAP with orotracheal intubation (Δ BIS, Δ HR and Δ MAP, respectively) were defined as the differences between the pre-laryngoscopy values and the maximal value obtained for each variable within the first 5 min after orotracheal intubation.

On the first postoperative day, patients were asked whether they recalled any intraoperative events.

Statistical analysis

All statistical analyses were performed using Statview (Version 5.0, SAS Institute Inc., Cary, NC, USA). Physical characteristics, durations of laryngoscopy and orotracheal intubation, and maximum Δ BIS, Δ HR and Δ MAP during the 5 min following orotracheal intubation were evaluated using analysis of variance (ANOVA). The BIS, heart rate and MAP at each time point in each group and Δ BIS, Δ HR and Δ MAP from baseline were analysed using ANOVA and repeated-measures ANOVA. To evaluate the stability of the BIS recordings, the coefficients of variation of the BIS values obtained within the 1-min periods were calculated for each individual.

Fisher's exact test was used to compare the proportion of patients with movement in each group. When a difference in proportions was found between the groups, pair-wise comparisons were performed. Results are presented as mean (SD); $P < 0.05$ was considered statistically significant.

Table 1 Physical characteristics of the control and esmolol groups. Data are mean (SD or range)

	Control <i>n</i> =25	Esmolol <i>n</i> =25
Age (yr)	36 (18–54)	37 (19–53)
Weight (kg)	71 (15)	68 (16)
Height (cm)	172 (11)	173 (10)
Sex (m/f)	18/7	15/10
Intubation duration (s)	37 (21)	47 (28)

Table 2 Bispectral index (BIS), heart rate and mean arterial pressure (MAP) for the control (*n*=25) and esmolol (*n*=25) groups. Values are mean (SD). * $P < 0.001$ vs pre-esmolol value; † $P < 0.05$, ‡ $P < 0.001$ vs pre-laryngoscopy values; § $P < 0.05$, ¶ $P < 0.001$ vs control group. OTI=oro-tracheal intubation

	BIS		Heart rate		MAP	
	Control	Esmolol	Control	Esmolol	Control	Esmolol
Pre-induction	97 (1)	97 (1)	71(11)	70 (13)	86 (14)	88 (12)
Pre-esmolol	44 (6)	44 (8)	68 (9)	68 (11)	81 (17)	83 (14)
Pre-laryngoscopy	45 (6)	43 (6)	69 (7)	64 (11)	79 (15)	77 (14)
1 min after OTI	61 (10) ‡ *	43 (7) ¶	96 (18) ‡ *	75 (8) ‡ ¶	130 (26) ‡ *	109 (16) ‡ §
2 min after OTI	53 (10) ‡	41 (9) ¶	83 (14) ‡	70 (9) † ¶	109 (22) ‡	97 (18) ‡ §
5 min after OTI	47 (9)	40 (6) ¶	74 (13)	67 (11) §	90 (16)	86 (15)

Results

No significant differences were found between the esmolol and control groups with respect to age, weight, height, sex ratio or the duration of laryngoscopy and orotracheal intubation (Table 1). BIS, heart rate and MAP during the pre-induction period were also similar in the two groups (Table 2).

In all patients, BIS values obtained within each 1-min period before laryngoscopy were stable, with a coefficient of variation that did not exceed 10%. BIS values, heart rate and MAP did not differ significantly between the two groups before laryngoscopy (Table 2). Furthermore, BIS values remained stable from injection of esmolol or saline to laryngoscopy, with a coefficient of variation of less than 15% in each patient (Fig. 2).

Laryngoscopy and orotracheal intubation were associated with a significant increase in BIS (compared with the pre-laryngoscopy values) in the control group only (Table 2 and Fig. 2), with a maximal increase of 40 (SD 18)% (range 6–90%), compared with 8 (11)% (range 0–48%) in the esmolol group ($P < 0.01$; Fig. 3).

Maximum Δ HR and Δ MAP after orotracheal intubation from pre-stimulus values were significant ($P < 0.05$) for both groups; however, these changes were significantly greater in the control group (MAP: 62 (SD 24)% vs 45 (23)%, $P < 0.01$; heart rate: 45 (19)% vs 23 (14)%, $P < 0.05$; Fig. 3). More patients moved in response to laryngoscopy and orotracheal intubation in the control group (23 of 25) than in the esmolol group (12 of 25) ($P < 0.01$). Δ BIS, Δ HR and Δ MAP did not correlate with the presence or absence of movement in the esmolol group (Fig. 3). Neither hypotension nor bradycardia was noted in either group. None of the patients reported recall of intraoperative events when questioned on the first postoperative day.

Discussion

Esmolol is clinically effective in attenuating adrenergic responses to a number of noxious intraoperative stimuli, including laryngoscopy and orotracheal intubation.⁴ The present study demonstrated that esmolol not only attenuated the haemodynamic and gross motor responses to laryngoscopy and orotracheal intubation, but also prevented arousal

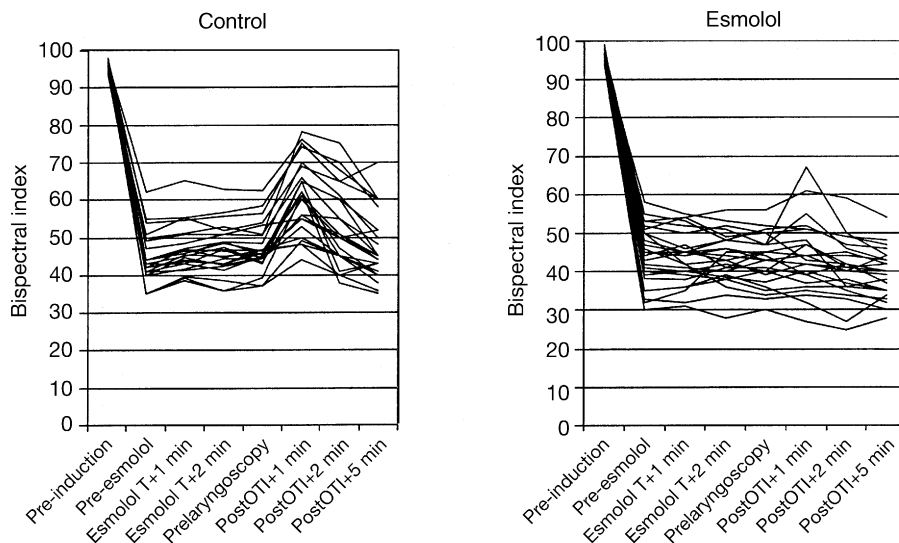


Fig 2 Individual bispectral index values: before induction; 1 min before esmolol, 1, 3 and 5 mins (pre-laryngoscopy) after the start of esmolol infusion; and 1, 2 and 5 min after orotracheal intubation (OTI).

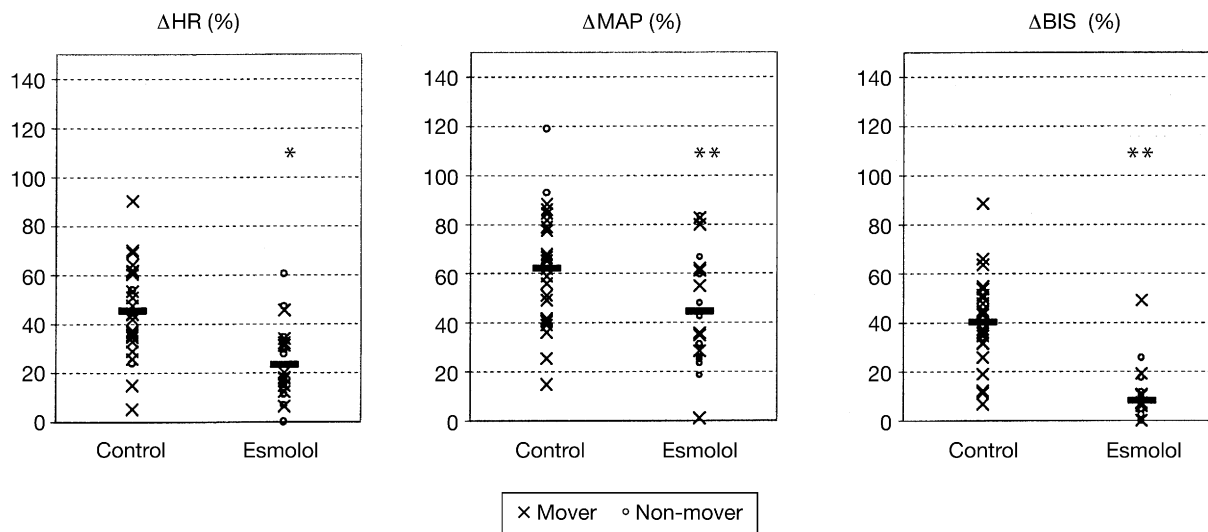


Fig 3 Maximum changes of heart rate (Δ HR), mean arterial pressure (Δ MAP), and bispectral index (Δ BIS) after orotracheal intubation expressed as percentage of values recorded before laryngoscopy in the control and esmolol groups. Each symbol represents an individual patient. The horizontal bars denote mean values for each variable. * $P < 0.05$; ** $P < 0.01$ vs control group.

reactions, as indicated by attenuated BIS increases after the stimulation of laryngoscopy and orotracheal intubation. Our current data support those we reported previously with high-dose remifentanyl.² Together, these findings suggest that esmolol and opioids similarly influence BIS during propofol anaesthesia.

There is a dose-dependent risk of hypotension and bradycardia before laryngoscopy when esmolol is combined with anaesthesia induction agents.⁴ However, the esmolol regimen used in the present study did not result in any deleterious haemodynamic effects. We did not use opioids, which may have decreased heart rate and MAP before laryngoscopy in other studies.^{4,14} Compared with earlier reports,^{4,14} esmolol was more effective in this study in

controlling tachycardia than the pressor response to laryngoscopy and orotracheal intubation. This difference is consistent with the different mechanisms involved in each response: bradycardia results from a direct cardiac effect of esmolol whereas hypotension results from a gradual decrease in renin release.¹⁵ As might be expected, the time required to obtain 90% of the maximum decrease in heart rate (4.8 min) is far shorter than that for the same decrease in MAP (42 min).¹⁵

Esmolol decreased the incidence of movement in response to laryngoscopy and orotracheal intubation. These results are consistent with reports that esmolol reduces the propofol concentration required to prevent movement in response to skin incision.⁷ In that study,

propofol was combined with nitrous oxide and morphine premedication.⁷ Interaction between any of the anaesthetic components, specifically with nitrous oxide or morphine and esmolol, may have caused the effect. In fact, the same group found that esmolol had no effects on isoflurane minimum alveolar concentration (MAC) alone, but that MAC was decreased when esmolol was given along with alfentanil, suggesting a possible potentiation of opioid action by esmolol.⁸ That study only evaluated movement and haemodynamic responses to skin incision. In contrast, our current study indicates that propofol combined with esmolol alone, at a similar dose to that used by Johansen and co-workers,⁸ blunted nociceptive reactions to laryngoscopy and orotracheal intubation, including changes in BIS, as well as the autonomic and somatic responses. It is unclear whether our results are inconsistent with those of Johansen and co-workers⁸ because there were differences in the design and anaesthetic regimens between the two studies. However, our results are consistent with two other studies, each of which demonstrated that esmolol can be used as an alternative to opioids for maintaining haemodynamic,^{6,16} and BIS⁶ stability during general anaesthesia.

Addition of esmolol to general anaesthesia with propofol did not affect BIS before laryngoscopy. This observation suggests that esmolol does not modify BIS during general anaesthesia when substantial sympathetic activation is unlikely. It seems likely that esmolol has no anaesthetic effect *per se*; instead, it acts mainly via β -adrenergic block and is thus effective only during sympathetic activation. These results are consistent with a recent study reporting that the propofol blood concentration preventing response to command was unaltered by esmolol.¹⁷ In contrast, Johansen¹⁸ showed that esmolol suppressed the EEG, with a decrease in BIS and an increase in the burst suppression ratio during propofol/alfentanil anaesthesia. However, in the latter study,¹⁸ surgical stimuli were not controlled and it seems likely that esmolol blunted the adrenergic response to them.

Our results and previous studies^{5,6} clearly indicate that β -adrenoceptor antagonists not only block cardiovascular stress responses after noxious stimulation, which could mask inadequate anaesthesia, but also increase the antinociceptive component of anaesthesia. The mechanism for this effect remains unclear. One explanation may be a central antinociceptive effect of β -adrenoceptor block. Consistent with this hypothesis is the finding that i.v. esmolol¹⁹ decreases nociceptive behaviour in rats after formalin injection, as did intrathecal ONO 1101,²⁰ another β_1 -adrenoceptor antagonist. Noxious stimulation is transmitted through the spinal cord, the brainstem reticular formation and the thalamus to the cerebral cortex, where it evokes an EEG arousal response. Beta-adrenoceptors are present in various parts of the reticular activating system, particularly the medial septal region of the basal forebrain.²¹ Infusion of β -adrenoceptor agonists into this region elicits enhancement of behavioural and EEG indices of waking in

animals.²¹ Conversely, infusion of β -adrenoceptor antagonists decreases EEG indices of arousal.²¹ Similarly in humans, infusion of isoprenaline²² or epinephrine²³ causes clinical signs of arousal associated with an increase in BIS.²³ Additionally, BIS levels are significantly correlated with plasma norepinephrine concentrations after oral diazepam premedication.²⁴ This finding suggests that the noxious stimulation of laryngoscopy and orotracheal intubation increases central catecholamine concentrations, and that esmolol prevents the increase in BIS in response to laryngoscopy and orotracheal intubation by blocking β -adrenoceptors within the reticular formation. However, the pharmacokinetics of esmolol do not entirely support this hypothesis. Esmolol is hydrophilic, as is atenolol;²⁵ and like atenolol, it probably does not readily cross the blood-brain barrier.²⁶ The brain:plasma ratio for esmolol is unknown, but it was found to be 0.20 for atenolol, compared with 26 and 50, respectively for the lipophilic β -adrenoceptor antagonists, propranolol and oxprenolol.

Another explanation may be an alteration of the pharmacokinetics of propofol by esmolol. Doses of esmolol similar to those we used were not found to change the performance of the propofol TCI device in two studies,^{7,18} whereas it increased the bias and reduced the inaccuracy of the TCI device in another.¹⁷ Our finding, that BIS values before laryngoscopy were similar in the two groups, does not support this theory. In addition, esmolol has been shown to control intraoperative nociceptive responses during desflurane anaesthesia in a similar way to a comparative group that received desflurane and an opioid in the anaesthetic regimen.⁶ In another study, patients β -blocked with atenolol required less fentanyl and isoflurane than unblocked control patients to produce similar BIS values.⁵ However, we did not measure propofol concentrations and thus cannot eliminate a potential pharmacokinetic interaction with esmolol. Moreover, esmolol, by attenuating the haemodynamic responses to laryngoscopy and orotracheal intubation, may have prevented the increase in cardiac output that would normally lead to redistribution of blood flow, with a resultant fall in the effect-site concentration of propofol and an increase in BIS. Thus, the exact mechanism of action of esmolol in blocking the BIS response to noxious stimulation is not understood.

In conclusion, esmolol had no significant effect on BIS before laryngoscopy and orotracheal intubation in patients anaesthetized with propofol. However, it not only attenuated the haemodynamic responses, but also prevented movement and BIS increases in response to laryngoscopy and orotracheal intubation. These results suggest that esmolol may produce a clinically important antinociceptive effect.

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