SCIENTIFIC ARTICLE

The effect of different doses of esmolol on hemodynamic, bispectral index and movement response during orotracheal intubation: prospective, randomized, double-blind study

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KEYWORDS
Depth of anesthesia; Propofol; Intubation; Bispectral index; Esmolol

Abstract
Objectives: A prospective, randomized and double-blind study was planned to identify the optimum dose of esmolol infusion to suppress the increase in bispectral index values and the movement and hemodynamic responses to tracheal intubation.

Materials and methods: One hundred and twenty patients were randomly allocated to one of three groups in a double-blind fashion. 2.5 mg kg⁻¹ propofol was administered for anesthesia induction. After loss of consciousness, and before administration of 0.6 mg kg⁻¹ rocuronium, a tourniquet was applied to one arm and inflated to 50 mm Hg greater than systolic pressure. The patients were divided into 3 groups; 1 mg kg⁻¹ h⁻¹ esmolol was given as the loading dose and in Group Es50 50 μg kg⁻¹ min⁻¹, in Group Es150 150 μg kg⁻¹ min⁻¹, and in Group Es250 250 μg kg⁻¹ min⁻¹ esmolol infusion was started. Five minutes after the esmolol has been begun, the trachea was intubated; gross movement within the first minute after orotracheal intubation was recorded.

Results: Incidence of movement response and the ΔBIS max values were comparable in Group Es250 and Group Es150, but these values were significantly higher in Group Es50 than in the other two groups. In all three groups in the 1st minute after tracheal intubation heart rate and mean arterial pressure were significantly higher compared to values from before intubation (p < 0.05). In the study period there was no significant difference between the groups in terms of heart rate and mean arterial pressure.

Conclusion: In clinical practise we believe that after 1 mg kg⁻¹ loading dose, 150 μg kg⁻¹ min⁻¹ iv esmolol dose is sufficient to suppress responses to tracheal intubation without increasing side effects.

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PALAVRAS-CHAVE
Profundidade da anestesia; Propofol; Intubação; Índice bispectral; Esmolol

Efeito de diferentes doses de esmolol sobre a resposta hemodinâmica, BIS e resposta de movimento durante a intubação orotraqueal: estudo prospectivo, randômico e duplo-cego

Resumo
Objetivo: Estudo prospectivo, randômico e duplo-cego planejado para identificar a dose ideal de perfusão de esmolol para suprimir o aumento dos valores do BIS e os movimentos e respostas hemodinâmicas à intubação traqueal.

Materiais e métodos: 120 pacientes foram randomicamente alocados um dos três grupos, usando o método duplo-cego. Propofol (2,5 mg kg⁻¹) foi administrado para indução da anestesia. Após a perda da consciência e antes da administração de rocurônio (0,6 mg kg⁻¹), um torniquete foi aplicado a um braço e insuflado a 50 mmHg acima da pressão sistólica. Os pacientes foram divididos em três grupos: uma dose de 1 mg kg⁻¹ h⁻¹ de esmolol foi administrada como carga e perfusão de 50 µg kg⁻¹ min⁻¹ de esmolol foi iniciada no Grupo ES50, 150 µg kg⁻¹ min⁻¹ no Grupo ES150 e 250 µg kg⁻¹ min⁻¹ no Grupo ES250. Cinco minutos após o início da perfusão, a traqueia foi intubada; o total de movimentos no primeiro minuto após a intubação orotraqueal foi registrado.

Resultados: A incidência da resposta de movimentos e os valores máximos de ΔBIS foram comparáveis nos grupos ES250 e ES150, mas esses valores foram significativamente mais elevados no Grupo ES50 que em outros dois grupos. Nos três grupos, os valores de frequência cardíaca e pressão arterial média foram significativamente maiores no primeiro minuto pós-intubação, comparados aos valores pré-intubação (p<0,05). Não houve diferença significativa entre os grupos em relação à frequência cardíaca e pressão arterial média durante o período de estudo.

Conclusão: Na prática clínica, acreditamos que após uma dose com carga de 1 mg kg⁻¹, uma dose de 150 µg kg⁻¹ min⁻¹ de esmolol IV é suficiente para suprimir a resposta à intubação traqueal sem aumentar os efeitos colaterais.

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Introduction

During anesthesia induction tracheal intubation is one of the most intensive noxious stimuli and can induce hemodynamic and movement responses and increase the bispectral index (BIS). Hemodynamic changes due to tracheal intubation, similar to changes due to other surgery-related stimuli such as anesthesia and skin incisions, are often transient. However, in patients with coronary artery disease, hypertension (HT) or with a history of cerebrovascular disease, a possible increase in hemodynamic parameters may cause myocardial ischemia, arrhythmia, infarction or cerebral bleeding. The close relationship of tachycardiac heart rate (HR) to myocardial ischemia has suggested the use of β-adrenergic receptor blockers for the suppression of the hemodynamic response to tracheal intubation.1-3

During anesthesia primarily for the treatment of HT and tachycardia β1 adrenoceptor antagonists are indicated, which have been proven in clinical studies to have a role in pain modulation. While the mechanism is unknown, esmolol infusion is known to suppress the BIS increase and movement response linked to tracheal intubation compared to placebo. However no study was found on the relationship between the effects of esmolol at different infusion doses. The hypothesis of this study is that the responses to tracheal intubation of increased movement and BIS will be suppressed due to the antinociceptive effect of esmolol in a dose-linked fashion, causing a reduction in BIS increase and movement after tracheal intubation. To test this hypothesis and identify the optimum infusion dose to suppress BIS increase and movement response, along with hemodynamic response, to tracheal intubation, a prospective, randomized and double-blind study was designed.

Methods

After receiving Dokuz Eylül University, Faculty of Medicine Clinical Trials Local Ethics Committee approval and informed patient consent this prospective, randomized, double-blind study was completed. One hundred and twenty adult patients in ASA I-II risk groups, between the ages of 18 and 65, undergoing elective surgery, apart from head, neck and cardiac surgery, were enrolled in the study.

Patients with predicted difficult intubation or airway management, body mass index > 30 kg/m², HR < 60 beats min⁻¹, systolic arterial pressure (SAP) < 100 mmHg, cardiac diseases, diabetes mellitus, renal failure, liver failure, COPD, asthma, reactive airway disease, symptomatic gastroesophageal reflux, patients with neuropsychiatric or neurological diseases, pregnant and lactating patients, patients with a history of use of opioids, tricyclic antidepressants, benzodiazepines, anticonvulsants, clonidine, β-adrenergic receptor blockers, or alcohol abuse, and patients with a history of allergic reaction to the study drugs were excluded.

No drugs were administered for preoperative medication. Anesthesia was administered after 18 G intravenous preparation of 10 mL kg⁻¹ 0.9% NaCl with fluids through a vascular
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access cannula opening. After being taken to the operating table 6 L/min oxygen was administered through a mask. In all patients, non-invasive blood pressure, electrocardiogram (ECG), pulse oximetry, and esophageal temperature after intubation were monitored. Baseline values for HR, non-invasive mean arterial pressure (MAP) and peripheral oxygen saturation (SpO₂) were recorded. After standard monitoring, patients were monitored with the A-2000 BIS XP device (Aspect Medical Systems, Newton, MA, USA). Measured control BIS values were recorded after contact testing was completed.

After pre-oxygenation to induce anesthesia 2.5 mg kg⁻¹ propofol (1% PropofolR, Fresenius, Austria) was applied for 20 s and 8 mg kg⁻¹ h⁻¹ propofol infusion was started. After loss of eyelash reflex in patients, manual end-tidal CO₂ (ETCO₂) 35–40 mm Hg was maintained by inhalation of 100% O₂ through the mask (Fig. 1). Movement response to tracheal intubation was assessed by the isolated forearm technique. For this purpose, after loss of consciousness, the cuff on the arm without the IV was inflated. After systolic blood pressure of 50 mm Hg was reached, rocuronium 0.6 mg kg⁻¹ dose was given for muscle relaxation. After 5 min of infusion of propofol, all patients were given 1 mg kg⁻¹ esmolol (BreviblocR Eczacibaşı, Baxter, USA) loading dose in 15 mL total volume 0.9% NaCl solution. Patients were randomly (sealed envelope method) allocated to three groups and after 1 min, study medication was administered by an anesthesiologist aware of the medication amount. The dose was calculated for each patient by a 50 mL syringe (10 mg/mL) perfusor; Group Es50 (n = 40) 50 mg kg⁻¹ min⁻¹ esmolol; Group Es150 (n = 40) 150 mg kg⁻¹ min⁻¹ esmolol; and Group Es250 (n = 40) 250 mg kg⁻¹ min⁻¹ infusion of esmolol. After 5 min of esmolol infusion, an anesthesia assistant blind to the amount of study drug administered intubated the patients. Five minutes after intubation esmolol infusion was terminated. In the study period, anesthesia was maintained with 8 mg kg⁻¹ h⁻¹ infusion of propofol and 50% air-O₂ mixture. At the end of the study period anesthetic management responsible for the operating theater and aware of the amount of anesthetic drugs applied to the patients left the team.

Before induction by an anesthesiologist blind to the amount of study drug (control), at 1st, 3rd and 5th minute after the start of propofol infusion, and from the start of esmolol infusion to 5 min after intubation at minute intervals, HR, MAP, BIS, and SpO₂ values were recorded. After the painful stimulus ΔBIS (difference between BIS value pre-tracheal intubation and after 5th minute post-tracheal intubation) and ΔBISmax (difference between BIS values pre-tracheal intubation and maximum value within 5th minute post-tracheal intubation) values were recorded after intubation. The time between the opening of each patient’s mouth and when the tracheal tube cuff inflated was defined as the intubation time and was recorded. Repeated intubation attempts and patients requiring more than 30 s intubation time were removed from the study. Within 1 min after intubation movement of the patient’s arm the cuff was placed on was accepted as a positive value and the air sleeve was depressurized.

During the study period, for hypotension (MAP < 60 mm Hg) first the intravenous infusion of fluid was increased and if no improvement within 5 min, 5 mg of ephedrine (Ephedrine, Haver, Istanbul, Turkey) was administered. For bradycardia (HR < 50 beats min⁻¹) 0.5 mg atropine (atropine sulfate, Haver, Istanbul, Turkey) was implemented. Side effects including hypotension, bradycardia, arrhythmia, cough, hiccup, increased airway resistance, bronchospasm, etc., were recorded. After 1 h in the recovery unit patients were asked questions such as “Do you remember any event from beginning or end of the operation?” to determine awareness of operative events and responses were recorded.

Power analysis

In the study by Menigaux et al. considering change in ΔBIS values, to reach 80% power (α = 0.05) each group should contain at least 19 patients; Guignard et al. revealed that 21 patients were required according to movement response findings. The three groups in this study contained a total of 120 patients (n = 40).

Statistics

Data were compiled using SPSS 11.0 for Windows program. To determine whether parameters had normal distribution the Kolmogorov–Smirnov test and box-plot graphics were completed. To compare mean values between the 3 groups one-way analysis of variance (one-way ANOVA) and post hoc Tukey were used. Variations within groups were analyzed using the paired-samples t-test. Non-parametric data were analyzed with the chi-square test. p < 0.05 was considered statistically significant.

Results

Between the groups there was no difference in terms of age, body weight, height, sex, ASA risk class and the tracheal intubation duration. Tracheal intubation was performed in 9–14 s (Table 1). Two patients in group Es250 were excluded from the study because of HR < 60 beats min⁻¹ after induction, and 1 patient was excluded due to difficult intubation. The data from a total of 117 patients were analyzed.

In all three groups after propofol induction and 5 min infusion duration there was no significant difference in HR compared with baseline. From the second minute of esmolol infusion until before tracheal intubation, the HR was significantly decreased according to the baseline (p < 0.05) in all 3 groups (Fig. 2). In all three groups in the 1st minute after tracheal intubation HR was significantly higher compared to values from before intubation (p < 0.05). After propofol induction, in Group Es150 after one minute, and in Group Es250 and Group Es50 after 3 min, MAP was significantly
reduced compared to basal values in the period before tracheal intubation ($p < 0.05$). In the 1st minute after tracheal intubation in all three groups MAP was significantly higher compared to values before intubation ($p < 0.001$) (Fig. 3). In the study period there was no significant difference between the groups in terms of HR and MAP.

BIS values in the first minute after induction of propofol reached the minimum value (Fig. 4). After tracheal

Table 1 Demographic data and LTI duration (mean ± standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Es250 ($n = 38$)</th>
<th>Group Es150 ($n = 39$)</th>
<th>Group Es50 ($n = 40$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>36.63 ± 10.55</td>
<td>40.12 ± 9.66</td>
<td>37.20 ± 9.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.16 ± 10.55</td>
<td>68.39 ± 12.23</td>
<td>66.90 ± 10.84</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.37 ± 7.64</td>
<td>168.36 ± 8.47</td>
<td>166.75 ± 8.62</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>37/1</td>
<td>39/0</td>
<td>40/0</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>27/11</td>
<td>27/12</td>
<td>30/10</td>
</tr>
<tr>
<td>LTI duration (s)</td>
<td>10.47 ± 1.47</td>
<td>10.89 ± 1.13</td>
<td>10.30 ± 1.02</td>
</tr>
</tbody>
</table>
intubation in the 1st and 2nd minutes BIS values in all three groups showed a significant increase compared to values from before tracheal intubation (p < 0.05). There was no significant difference between all three groups in terms of BIS values during the study period. When the Groups are compared based on the average value ΔBIS and ΔBISmax there was no significant difference between Groups Es250 and Es150, but both groups had significantly lower values than Group Es50 (p < 0.05) (Table 2). Comparing the groups in terms of movement response to tracheal intubation, there was no significant difference between Group Es250 (50%) and Group Es150 (56%) but Group Es50 (87.5%) was significantly higher than the other two groups (Table 3).

No hypotension, bradycardia, arrhythmia, cough, hiccup, bronchospasm, or increased airway resistance was observed in any patient. None of the patients indicated any intraoperative awareness in the postoperative period. BIS, HR and MAP during the pre-induction period were also similar in all 3 groups.

Discussion

This study shows that in patients anesthetized with propofol, esmolol suppressed awareness reactions, shown by movement and BIS, to tracheal intubation, in a dose-linked fashion.

Due to the short active duration of esmolol, bolus and infusion protocol, constant plasma concentration and tracheal intubation with anesthetic agents were chosen to assess more clearly the effect on BIS values, hemodynamic and movement response. Group Es250 were given an infusion dose known in the literature to suppress the BIS response;14,15 Group Es150 were given a dose that has been shown to be effective in the treatment of intra-operative HT and tachycardia16,17 and Group Es50 were given the lowest infusion dose proposed to suppress the hemodynamic response.1,20

In induction, comparisons have been made on the suppression of the hemodynamic response to tracheal intubation between different doses of esmolol, as infusion or

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Average change in ΔBIS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Group Es250 (n = 38)</td>
</tr>
<tr>
<td>ΔBIS</td>
<td>2.86 ± 2.64*a</td>
</tr>
<tr>
<td>ΔBISmax</td>
<td>4.73 ± 4.37*a</td>
</tr>
</tbody>
</table>

* p < 0.05 (compared to Group Es50)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Motion response in the groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Group Es250 (n = 38)</td>
</tr>
<tr>
<td>Movement</td>
<td>19 (50%)a</td>
</tr>
<tr>
<td>No movement</td>
<td>19 (50%)a</td>
</tr>
</tbody>
</table>

a p < 0.05 (compared to Group Es50).
bolus, placebo or with different drug groups (nicardipine, lidocaine, alfentanil, fentanyl, etc.).\textsuperscript{16,21-27} Additionally, no consensus has been reached on the optimum dose, administration method and timing.\textsuperscript{2,3} In a meta-analysis study evaluating the effectiveness of esmolol on hemodynamic changes induced by tracheal intubation by Figueredo and Garcia-Fuentes,\textsuperscript{4} esmolol suppressed the adrenergic response to tracheal intubation independent of dose and it was reported that after a loading dose of 500 μg kg\textsuperscript{-1}, within 4 min 200–300 μg kg\textsuperscript{-1} min\textsuperscript{-1} continuous infusion dose was the most efficient protocol. Johansen et al.\textsuperscript{11} administered propofol/N\textsubscript{2}O/morphine anesthesia with esmolol and, reported a dose-independent slight increase in HR and blood pressure after tracheal intubation. In this study, similar to previous studies, after tracheal intubation in all three groups an increase in HR and MAP independent of dose was found compared to values before intubation in all three groups.\textsuperscript{2,12,14}

A short-term effective β\textsubscript{1} adrenergic receptor blocker, ONO-1101 in increasing infusion doses, significantly suppressed the SAP increase linked to tracheal intubation, however it was reported that it increased the incidence of hypotension.\textsuperscript{23} Similarly, Figueredo and Garcia-Fuentes\textsuperscript{4} in a meta-analysis study, found esmolol administered with induction agents and especially opioids, caused a dose-linked increase in hypotension and bradycardia incidence before tracheal intubation. Together with this in the period before intubation in the placebo group there was a 2.6% reduction in MAP while the esmolol group had a 10.1% decrease in MAP. Similarly in our study, in all three groups, the decline in MAP from the beginning of propofol infusion continued after addition of esmolol infusion until the period prior to tracheal intubation. Although there is no statistically significant difference between groups; compared with baseline in all 3 groups before tracheal intubation (Group Es250: 17%, Group Es150: 15%, and Group Es50: 11.2%) there was a significant decrease in MAP. However hypotension (MAP < 60 mmHg) or bradycardia (HR < 50 beats min\textsuperscript{-1}) was not observed in any patient.

Many studies on the effect of esmolol on the hemodynamic response to tracheal intubation have used succinylcholine as a muscle relaxant.\textsuperscript{21-27} Administration of propofol with succinylcholine has caused significant bradycardia\textsuperscript{29} and fasciculations due to succinylcholine have been suggested to have an adverse affect on monitoring BIS.\textsuperscript{30} For these reasons we chose rocuronium in our study. Rocuronium’s vagolytic effect\textsuperscript{31} may have prevented the expected bradycardia and hypotension due to propofol and esmolol administration and contributed to ensuring stable hemodynamics. This situation we believe is additionally affected by not using opioids for induction.

As described by Prys Roberts and Kissin, to determine the depth of anesthesia, voluntary movement response to a specific type of painful stimulus is the most appropriate concept. Anesthesia depth is a pharmacodynamic measurement that includes the interaction of the two medication groups (hypnotic and analgesic agents) that form the basis of clinical anesthesia.\textsuperscript{32} Inhibition of the cerebral cortex by hypnotics results in clinical loss of consciousness and reduction in BIS values (or on EEG). The basic effect of analgesics is inhibition of the subcortical structures and spinal cord weakening the communication of painful stimuli to the cortex. As a result clinical consciousness levels and movement response reduce. In spite of the sedative effects of opioids suppressing the cortex, “unconsciousness” is only formed by hypnotics at the cortical level. “Lack of response” is formed by the interactions of analgesics and hypnotics at both cortical and subcortical levels.\textsuperscript{32}

Guignard et al.\textsuperscript{17} in patients under propofol anesthesia in steady-state conditions found that in the absence of painful stimuli remifentanil infusion did not change BIS values before tracheal intubation; however it reduced the increase in BIS values (ΔBIS), hemodynamic and movement responses to tracheal intubation in a dose-linked manner. For this reason in evaluating the analgesic component of anesthesia after painful stimuli they concluded ΔBIS values may be as sensitive as hemodynamic changes. Berkenstadt et al.\textsuperscript{33} reported that bolus administration of esmolol did not change BIS values in the absence of painful stimuli. Menigaux et al.\textsuperscript{14} in patients anesthetized with propofol and Oda et al.\textsuperscript{15} in anesthesia with 1 MAC sevoflurane with esmolol infusion, similar to opioids, found there was no significant effect on the BIS values before tracheal intubation, however increase in ΔBIS values linked to tracheal intubation and hemodynamic response and movement decreased. Kawaguchi et al.\textsuperscript{35} studied short-term effect landiolol, a β\textsubscript{1} adrenoreceptor antagonist, during steady state conditions of propofol anesthesia, and similar to remifentanil, reported a suppression in the increased entropy response (response entropy = RE and situation entropy = SE, reflective of nociceptive and hypnotic levels in general anesthesia) to tracheal intubation in the form of nociceptive response RE and RE−SE response reductions. In our study similar to previous studies,\textsuperscript{14,15} in the absence of painful stimuli after esmolol infusion and before intubation there was no reduction in BIS values in all three groups. This result shows that in the absence of painful stimuli esmolol does not affect BIS during general anesthesia. Thus it can be said that esmolol alone has no anesthetic effect. In contrast, a steady-state conditions study by Johansen\textsuperscript{29} on addition of esmolol infusion to propofol/alfentanil anesthesia, showed BIS decreased while cerebral cortical activity was suppressed and burst suppression was caused. However this study did not examine surgical stimuli and also opioids were used.

After esmolol infusion cortical EEG suppression and MAC reduction shows that esmolol infusions have different pharmacologic effects during anesthesia, because cortical suppression and MAC are anatomically separate in animals.\textsuperscript{33} After tracheal intubation in Group Es250 and Group Es150, ΔBIS values and incidence of movement response were significantly reduced compared to Group Es50. Johansen et al. in a study on propofol/N\textsubscript{2}O anesthesia with morphine premedication reported propofol’s C\textsubscript{50} values (minimum effective plasma concentration to suppress movement due to skin incision in 50% of patients) reduced linked to dose of esmolol infusion.\textsuperscript{11} In the same group, esmolol infusion alone did not reduce isoflurane MAC values (the concentration that suppresses movement response to skin incision in 50% of patients); however alfentanil infusion alone caused a dose-linked reduction in MAC values (25%), while alfentanil infusion with high-dose esmolol added, increased MAC values (43%).\textsuperscript{11} In both these studies opioids, known to
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affect movement response were used, and the movement response to the more submaximal painful stimuli of skin incision, compared to tracheal intubation, was evaluated. It is not possible to definitively comment on the effect of esmolol on the movement response to painful stimuli based on these two studies. The results of the present study are in accordance with those of previous studies, though the effect of esmolol on BIS and movement response is shown to be dose linked. During propofol anesthesia in the absence of painful stimuli esmolol does not affect BIS and in the presence of painful stimuli suppresses ΔBIS values and movement response in a dose-linked manner, affecting BIS value increases and movement response to tracheal intubation in a similar manner to esmolol and opioids.\textsuperscript{14,15,17}

The mechanism behind the effect of esmolol on BIS and movement response is not clear. The first mechanism proposed to explain this effect is that esmolol has a central anti-nociceptive effect. Another mechanism may be pharmacokinetic interactions with propofol and/or opioids.

Painful stimuli travel through the spinal cord to the brain stem, reticular formation and thalamus and from there are transmitted to the cerebral cortex where the EEG response forms.\textsuperscript{8,14} β-Adrenergic receptors are known in various regions of the reticular activating system and basal forebrain, especially in the medial septal. In this region, β-adrenoceptor agonist infusion increases EEG activity and the behavioral symptoms of wakefulness in animals; in contrast β-adrenoceptor antagonist infusion is shown to suppress the EEG response.\textsuperscript{14} Specific β₁-adrenoceptor antagonist, ONO-1101, was reported to reduce the pain behavior after intrathecal injections of formalin.\textsuperscript{14} Clinical studies show esmolol changes EEG response to painful stimuli and reduces the increase in BIS.\textsuperscript{14,15} This brings to mind the possibility that esmolol’s effects on BIS may be similar to the reduction in β-adrenoceptor block due to pain response increasing central catecholamine concentration. However, the fact that short-acting esmolol is hydrophilic and cannot pass the blood–brain barrier does not fully support this idea. Therefore, further studies are needed on the role of esmolol in central modulation of pain.

The other mechanism to explain the effect of esmolol on BIS and movement response is pharmacokinetic interactions with propofol and/or opioids.\textsuperscript{11,12} Johansen, in steady-state conditions propofol/alfentanil anesthesia, found that while esmolol infusion did not affect the plasma concentrations of propofol and alfentanil or pharmacokinetics, BIS values decreased and reversible burst suppressions occurred.\textsuperscript{35} Orme et al.\textsuperscript{36} found esmolol infusion did not significantly reduce propofol's \(C_{50}\)-value or change the plasma concentration of propofol. We did not use opioids in our study. However as propofol concentration was not measured we cannot eliminate potential pharmacokinetic interactions with esmolol. In light of these data the mechanism for esmolol’s effects on BIS and the movement response is not fully understood.

In conclusion, in patients anesthetized with propofol 250 and 150 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) esmolol infusion after 1 mg kg\(^{-1}\) loading dose reduce the increase in BIS values and the movement response linked to tracheal intubation in a dose-linked manner compared to 50 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) iv infusion. Considering the results of this study, it is concluded that in clinical practise to suppress the responses to tracheal intubation 1 mg kg\(^{-1}\) loading dose followed by 150 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) iv esmolol infusion may be used without increasing dose-linked side effects.\textsuperscript{37}

Conflicts of interest

The authors declare no conflicts of interest.

References