Rev Bras Anestesiol. 2014;64(5):343–349

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Intraoperative esmolol infusion reduces postoperative analgesic consumption and anaesthetic use during septorhinoplasty: a randomized trial

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Received 17 August 2013; accepted 31 October 2013
Available online 2 February 2014

KEYWORDS
Analgesia;
Bispectral index;
Esmolol;
Morphine

Abstract
Background and objectives: Esmolol is known to have no analgesic activity and no anaesthetic properties; however, it could potentiate the reduction in anaesthetic requirements and reduce postoperative analgesic use. The objective of this study is to evaluate the effect of intravenous esmolol infusion on intraoperative and postoperative analgesic consumptions as well as its effect on depth of anaesthesia.
Methods: This randomized-controlled double blind study was conducted in a tertiary care hospital between March and June 2010. Sixty patients undergoing septorhinoplasty were randomized into two groups. History of allergy to drugs used in the study, ischaemic heart disease, heart block, bronchial asthma, hepatic or renal dysfunction, obesity and a history of chronic use of analgesic or β-blockers were considered cause for exclusion from the study. Thirty patients received esmolol and remifentanil (esmolol group) and 30 patients received normal saline and remifentanil (control group) as an intravenous infusion during the procedure. Mean arterial pressure, heart rate, and bispectral index values were recorded every 10 min. Total remifentanil consumption, visual analogue scale scores, time to first analgesia and total postoperative morphine consumption were recorded.
Results: The total remifentanil consumption, visual analogue scale scores at 0, 20 and 60 min, total morphine consumption, time to first analgesia and the number of patients who needed an intravenous morphine were lower in the esmolol group.
Conclusions: Intravenous infusion of esmolol reduced the intraoperative and postoperative analgesic consumption, reduced visual analogue scale scores in the early postoperative period and prolonged the time to first analgesia; however it did not influence the depth of anaesthesia.

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0104-0014
http://dx.doi.org/10.1016/j.bjane.2013.10.015

PALAVRAS-CHAVE
Analgesia;
Índice bispectral;
Esmolol;
Morfina

Infusão intraoperatória de esmolol reduz o consumo pós-operatório de analgésicos e o uso de anestésico durante a septorrinoplastia: estudo randômico

Resumo
Justificativa e objetivos: esmolol é conhecido por não ter atividade analgésica e propriedades anestésicas; porém, pode potenciar a redução da necessidade de anestésicos e reduzir o uso de analgésicos no pós-operatório. O objetivo deste estudo foi avaliar o efeito da infusão de esmolol por via intravenosa sobre o consumo de analgésico durante os períodos intraoperatório e pós-operatório, bem como seu efeito sobre a profundidade da anestesia.
Métodos: este estudo randômico, controlado e duplo-cego foi conduzido em um hospital terciário entre março e junho de 2010. Foram randomicamente divididos em dois grupos 60 pacientes programados para serem submetidos à septorrinoplastia. História de alergia aos medicamentos usados no estudo, isquemia cardíaca, bloqueio cardíaco, asma brônquica, insuficiência hepática ou renal, obesidade e história de uso crônico de analgésicos ou β-bloqueadores foram os critérios de exclusão. Trinta pacientes receberam esmolol e remifentanil (grupo esmolol) e 30 receberam soro fisiológico e remifentanil (grupo controle) via perfusão intravenosa. Pressão arterial média, frequência cardíaca e valores do índice bispectral foram registrados a cada 10 minutos. Consumo total de remifentanil, escores da escala visual analógica, tempo para a primeira analgesia e consumo total de morfina no pós-operatório foram registrados.
Resultados: o consumo total de remifentanil, os escores da escala visual analógica nos minutos 0, 20 e 60, o consumo total de morfina, o tempo para a primeira analgesia e o número de pacientes que precisaram de morfina intravenosa foram menores no grupo esmolol.
Conclusões: esmolol em infusão intravenosa reduziu o consumo de analgésicos tanto no intraoperatório quanto no pós-operatório, reduziu os escores da escala analógica visual no pós-operatório imediato e prolongou o tempo para a primeira analgesia; contudo, não influenciou a profundidade da anestesia.

Introduction

Esmolol is an ultra-short-acting, cardioselective β_1-receptor antagonist. It is effective in blunting adrenergic responses to perioperative stimuli, including tracheal intubation,[1] intraoperative events caused by decreasing anaesthetic depth,[2] and tracheal extubation.[3] Esmolol is known to have no analgesic activity and no anaesthetic properties.[4] However, previous studies have shown that esmolol could potentiate the reduction in anaesthetic requirements during propofol,[5] or volatile-based anaesthesia.[6] In a previous study it was suggested that esmolol infusion reduced the intraoperative use of fentanyl, decreased haemodynamic responses and reduced postoperative morphine consumption.[7] Esmolol also decreased nociception in a variety of experimental settings, suggesting the potential to decrease the intraoperative anaesthetic requirements.[8] In animals esmolol provided analgesia and a reduction of cardiovascular responses to pain in the absence of anaesthesia.[9] However the role of esmolol in pain modulation remains to be established.

This prospective, randomized, double-blind, placebo controlled study was designed to assess the effect of perioperative esmolol upon analgesic consumption and depth of anaesthesia in patients undergoing septorhinoplasty surgery.

Methods

Patients

After approval by the Institutional Ethics Committee, patients' written informed consents were obtained. The study took place in a tertiary hospital between March and June 2010. Patients of American Society of Anesthesiologists (ASA) physical status I–II, ages 18–65 years old and undergoing septorhinoplasty were enrolled in this study. Patients were selected randomly by using computer-generated random numbers and divided into two groups (esmolol vs. control). Exclusion criteria included allergic history to any of the drugs used in the study, ischaemic heart disease, heart block, bronchial asthma, hepatic or renal dysfunction and obesity (body mass index ≥ 30) and a history of chronic use of analgesic or β-blocking agents. No patients were excluded from the study according to these criteria. Patient recruitment to the study was started upon calculation of the sample size using the University of Iowa's sample size calculator. At 95% confidence level $(1-\alpha)$ and power $(1-\beta)$ of 80%, ratio of cases to control 1:1, we enrolled 30 cases for the study group while 30 cases were required as controls.

Anaesthesia

All patients were informed about the visual analogue scale (VAS; 0 = no pain, 10 = worst imaginable pain), the verbal rating scale (VRS; 0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = severe pain, 4 = excruciating pain) and the patient-controlled IV analgesia device before surgery. Patients were not premedicated before surgery. All patients were monitored with bispectral index (BIS) in addition to standard monitorization.

Patients in the esmolol group received a loading dose of esmolol (0.5 mg kg^{-1} in 30 mL normal saline) followed by an infusion of esmolol (0.05 mg kg^{-1} min^{-1}) while patients in the control group received the same volume of normal saline for loading dose and continuous infusion.

General anaesthesia was induced in all patients with propofol (2.5 mg kg^{-1}) and a mixture of oxygen and air (50–50%). After induction, an infusion of remifentanil (0.05–0.5 μg kg^{-1} min^{-1}) was started in both groups. Vecuronium bromide (0.1 mg kg^{-1}) was administered to maintain muscle relaxation and for tracheal intubation. Sevoflurane at an end-tidal concentration of 2 MAC in air/oxygen mixture was used for the maintenance of anaesthesia. To determine the depth of anaesthesia, BIS monitoring was used in addition to autonomic or somatic signs and changes in mean arterial pressure (MAP) or heart rate (HR). A BIS value between 40 and 60 was targeted since it was accepted as an adequate level of anaesthesia at which recall was prohibited.[10]

The depth of anaesthesia was assessed. (1) An increase in MAP and HR of more than 20% from baseline for more than 1 min; (2) autonomic signs (e.g. mydriasis, flushing, lacrimation); (3) somatic signs (e.g. purposeful eye movements, grimacing, swallowing); and (4) BIS values greater than 60 were considered as inadequate depth of anaesthesia. The remifentanil dose was titrated to increase the depth of anaesthesia in the presence of at least one of these signs. Data were recorded 1 min before induction, immediately after induction, 1, 3 and 5 min after intubation and at 10 min intervals during surgery. During surgery, the quality of the surgical field was evaluated every 10 min by the same surgeon, who was blinded to the study, using an evaluation scale for bleeding of the surgical field (Table 1). At the completion of surgery, all infusions were discontinued.

Table 1 Evaluation scale for bleeding of surgical field.

0 No bleeding
1 Slight bleeding – no suctioning of blood required
2 Slight bleeding – occasional suctioning required. Surgical field not threatened
3 Slight bleeding – frequent suctioning required. Bleeding threatens surgical field a few second after suction removed
4 Moderate bleeding – frequent suctioning required. Bleeding threatens surgical field directly after suction removed
5 Severe bleeding – constant suctioning required. Bleeding appears faster than can be removed by suction. Surgical field severely threatened and surgery impossible

The neuromuscular block was antagonized with neostigmine (0.05 mg kg^{-1}) and atropine (0.01 mg kg^{-1}). The times to emergence from anaesthesia (extubation, eye opening and response to simple verbal stimuli), duration of surgery and total remifentanil consumption were recorded. An anaesthetist who was blinded to the study groups conducted the entire course of anaesthesia. Intraoperative bradycardia and hypotension were defined as a HR lower than 45 beats/min and a MAP value less than 50 mm Hg, respectively. Patients experiencing bradycardia or hypotension were treated with atropine (0.5 mg) or intermittent ephedrine (5 mg).

Blinding was achieved by requesting an anaesthetist who was not involved in the study to prepare the infusion solutions for each patient according to the computer-generated random numbers and groups determined at the beginning of the study. The solutions were labelled with the patients' names only. The patient name, number and the solution prepared were recorded by this anaesthetist. The solutions were then given to the anaesthetist administering the anaesthesia.

Postoperative management and evaluations

All patients were transferred to the postanaesthesia care unit (PACU) after surgery and observed for 3 h. Pain intensity was evaluated using both VAS and VRS. Patients, whose VAS scores were $\geq$3 at any time, received an IV morphine infusion (0.1 mg/kg of loading dose, 1 mg on demand, 5 min of lock-out time) by a PCA device. VAS and VRS scores, morphine consumption, time to first analgesia and side effects such as sedation, nausea, vomiting, and respiratory depression were recorded at the indicated time intervals. The sedation level was recorded according to a four-point scale (0 = awake and alert, 1 = mildly sedated, easy to arouse, 2 = moderately sedated but can be aroused, 3 = deeply sedated, difficult to arouse). Vomiting was treated with metoclopramide IV (10 mg). Respiratory depression was defined as a ventilatory frequency of less than 8 per minute. The Aldrete score was evaluated to determine the time to discharge from the PACU. At the end of 3 h, patients with an Aldrete score of $\geq$9 were discharged from the PACU after being directed to take perioral (P.O) naproxen sodium for analgesia, if needed. At the time of discharge, all patients were asked two questions: (1) what was the last thing you remember after entering the operating room? and (2) do you recall anything from your operation?; to determine if they recalled any intraoperative events. Time to discharge from the hospital was recorded. The anaesthetist who observed the patients during surgery also observed the patients in the PACU. Both patients and observers were blind with respect to treatment groups. On the second day after surgery, patients were interviewed by telephone to evaluate the pain intensity and analgesic requirement after discharge.

Statistical analysis

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) version 11.5 programme (SPSS Inc., Chicago, IL, USA). The Shapiro Wilks' test was used to determine normal distribution for continuous variables. All the continuous variables were

Table 2 Patient and surgical characteristics.

	Control group ($n = 30$)	Esmolol group ($n = 30$)	p-Value
Age (yr)	29.1 (9.5)	27.4 (7.9)	0.445
Gender (F/M)	19/11	21/9	0.584
Weight (kg)	61.8 (11.8)	60.7 (8.7)	0.691
Height (cm)	169 (8.9)	167 (6.6)	0.328
ASA (I/II)	27/3	29/1	0.612
Duration of surgery (min)	109 (35.1)	97 (27.8)	0.148
Duration of anaesthesia (min)	126.6(36.9)	111 (29)	0.093
T Remifentanil used (mg)	1.6 (1.3)	0.8 (0.5)	0.004[a]
The emergence times (min)			
Extubation	4.5 (2.3)	5.3(2)	0.568
Opening eyes	5.3 (2.4)	6 (2.1)	0.602
Response to orders	6 (2.4)	6.3 (2)	0.856

Values are mean (SD) or number.
[a] $p < 0.05$; statistically significant.

presented as median and standard deviation. The ordinal variables were presented as median (inter-quartile range) and categorical variables were presented as percentage (%). The mean values of groups were compared using Student's t or Mann–Whitney U tests. Repeated SAP, DAP, MAP, SpO_2 and HR values were compared using the Bonferroni multiple comparisons test within the groups and between groups. Variance analysis was used for repeated measurements. Because repeated variables showed significant change, the measurement time causing this change was determined for categorical comparisons using Chi-squared and Fisher's exact tests. The Mann–Whitney U test was used to compare nonparametric variables. Statistical significance was set at $p < 0.05$.

Results

All 60 patients enrolled in the study were evaluated for statistical analysis and all the analyses were performed according to the original groups. All patients were evaluated for the analgesic and anaesthetic effects of esmolol and no patients were excluded after randomization. Patient characteristics, duration of surgery and anaesthesia, quantity of remifentanil used, the emergence times from the end of anaesthesia for the two groups are shown in Table 2. Remifentanil used during anaesthesia was significantly lower in the esmolol group ($p = 0.004$). There were no differences in patient characteristics, duration of anaesthesia and surgery and the emergence times from the end of anaesthesia between two groups.

The MAP during anaesthesia is shown in Fig. 1. There was no significant difference between two groups with regard to MAP during anaesthesia. The MAP showed fluctuations from baseline value in both groups.

The HR during anaesthesia is shown in Fig. 2. The HR at 70th, 80th and 90th minutes after intubation was higher in the esmolol group ($p = 0.035$, $p = 0.027$ and $p = 0.017$, respectively). The HR was generally higher during surgery in the esmolol group but it was not statistically significant. The HR showed fluctuations from baseline value in both groups.

The BIS values are shown in Fig. 3. There were no significant differences between two groups with regard to BIS values during anaesthesia. There were also no significant differences from the baseline value in both groups.

VAS and VRS scores are shown in Figs. 4 and 5, respectively. The VAS and VRS scores were significantly lower in the esmolol group at 1 and 20 min and 1 h after anaesthesia ($p = 0.001$, $p = 0.034$ and $p = 0.016$, respectively for VAS scores; $p = 0.033$, $p = 0.016$ and $p = 0.022$, respectively for VRS scores).

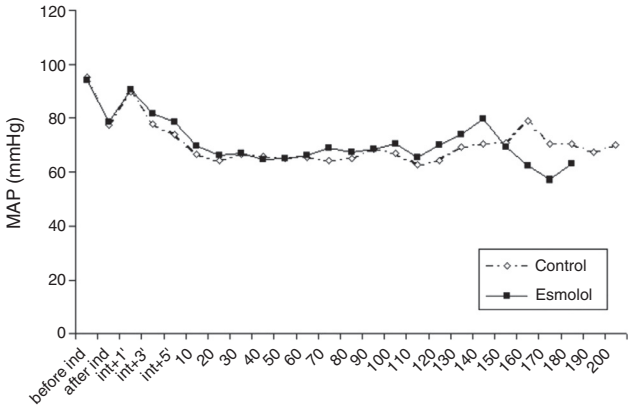

Figure 1 MAP (mm Hg) during anaesthesia.

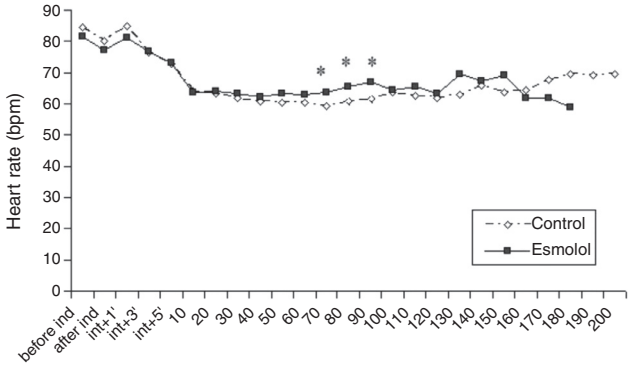

Figure 2 HR (beats min^{-1}) during anaesthesia. *$p < 0.05$; significant inter-group differences.

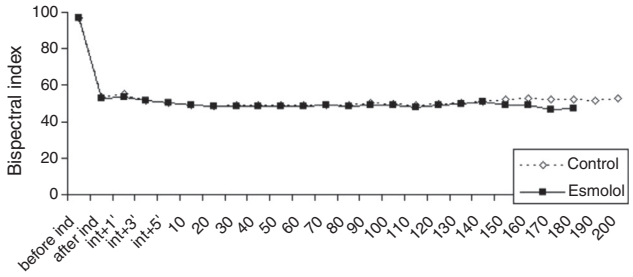

Figure 3 BIS values during anaesthesia.

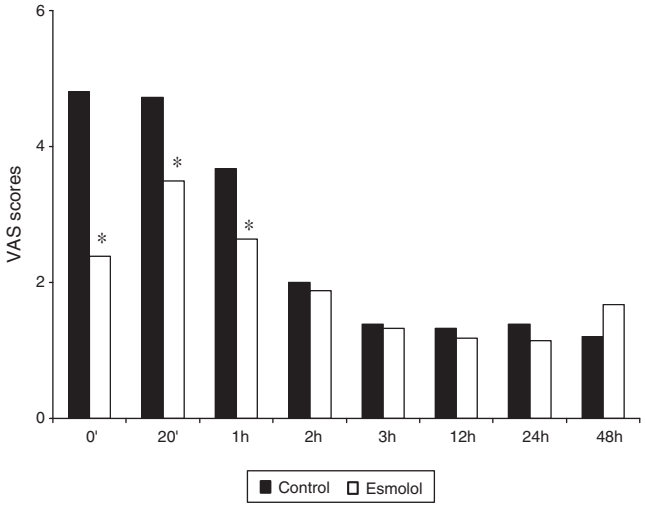

Figure 4 VAS scores in the postoperative period. *$p < 0.05$; statistically significant.

Time to first analgesia and discharge from PACU, Aldrete scores, quantity and percentage of IV morphine and analgesic used after discharge and the incidence of side effects in both groups are shown in Table 3. Time to first analgesia was significantly longer in the esmolol group ($p = 0.001$). Total morphine consumption and the number of patients who received IV morphine were significantly lower in esmolol group ($p = 0.011$ and $p = 0.005$, respectively).

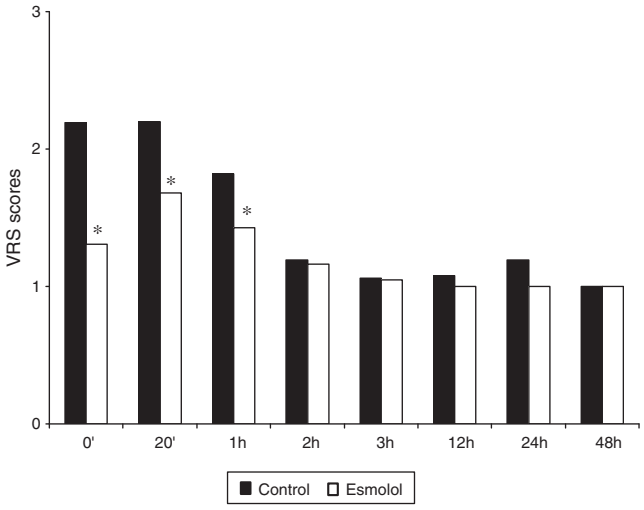

Figure 5 VRS scores in the postoperative period. *$p < 0.05$; statistically significant.

Discussion

In this study we found that esmolol shows a postoperative analgesic effect when administered intraoperatively in septorhinoplasty patients. Esmolol reduced the postoperative VAS and VRS scores, together with elongating the time to first analgesia and reducing both the total IV morphine consumption and the number of patients who needed morphine. Also, the amount of remifentanil used during anaesthesia was significantly lower in the esmolol group.

Previous studies focused on the effect of β-blocker usage upon anaesthesia and postoperative pain management have suggested that β-antagonists reduce anaesthetic requirements during anaesthesia[5] and inhalation anaesthetic minimum alveolar concentration (MAC),[6] and improve early postoperative recovery.[11]

The specific mechanism by which β-blockade potentiates the analgesic effect of an opioid remains controversial. Inhibitory G protein-coupled receptor agonists act upon postsynaptic inhibition via G protein-coupled potassium channels or via the pre-synaptic inhibition of

Table 3 Patients' data in postoperative period.

	Control group ($n = 30$)	Esmolol group ($n = 30$)	p-Value
Time to first analgesia (min)	43.8 (60.8)	108 (81.6)	0.001[a]
Morphine used (mg)	12.9 (8.7)	7.1 (8.4)	0.011[a]
Morphine usage (%)	86.7	53.3	0.005[a]
Time to discharge (min)	202.8 (38)	189.5 (11.5)	0.071
Aldrete score (9/10)	4/26	3/27	0.688
Analgesic at home (tablets)	3.6 (2.5)	2.6 (2.2)	0.92
Analgesic at home (%)	80	73.3	0.542
Side effects			
Nausea	8	6	0.542
Vomiting	4	4	1.000
Sedation scores (0/1)	4/26	2/28	0.389

Values are mean (SD) or number.
[a] $p < 0.05$; statistically significant.

neurotransmitter release through the regulation of voltage-gated Ca^{2+} channels; such a pathway underlies the nociceptive effect of clonidine.[12] Hageluken and colleagues demonstrated that β-adrenergic antagonists activated G-proteins in isolated cell membranes and it was suggested that this was the mechanism of central analgesia.[13]

Esmolol has been postulated to reduce anaesthetic requirements via a direct antinociceptive property in a variety of experimental studies, suggesting the potential to decrease the intraoperative anaesthetic requirements.[8,14] In animals esmolol provided analgesia and reduction of cardiovascular responses to pain in the absence of anaesthesia.[9]

Another mechanism that may significantly contribute to the anaesthetic-sparing involves decreased excitatory stimulation of central nervous system effector sites of hypnosis and somatic response. In this case, peripheral interruption of β-adrenergic autonomic pathways decreases afferent input and anaesthetic requirements.[15] The clinical utility of this effect was demonstrated by Zaugg et al.[11] in a study with elderly surgical patients undergoing non-cardiac surgery. Pre- and postoperative atenolol and high dose intraoperative atenolol decreased requirements for intraoperative fentanyl and postoperative morphine. Chia et al.[7] suggested that perioperative esmolol administration reduced the intraoperative use of isoflurane and fentanyl as well as reducing morphine consumption for 3 days postoperatively in patients undergoing abdominal total hysterectomy.

Several studies have suggested that sympatholytic drugs may be alternative to opioids in treating acute intraoperative haemodynamic responses. It was reported that in elderly patients undergoing noncardiac surgery, perioperative β-blockade with atenolol improved haemodynamic stability, reduced the opioid analgesic requirement and contributed to a faster early recovery.[11] In a previous study, it was suggested that perioperative β-antagonist administration was an alternative to remifentanil in maintaining intraoperative stable haemodynamics with similar side effects.[16] This was also the case in our study, with no statistically significant difference between groups with respect to intraoperative HR and MAP, demonstrating that esmolol successfully replaced a role classically performed by remifentanil.

Some studies suggested that administration of esmolol attenuated the cardiovascular response to perioperative stimuli. Miller et al.[1] suggested that a bolus dose of esmolol combined with a low dose of narcotic resulted in effective control of haemodynamic response to tracheal intubation. In different studies, it was demonstrated that a single bolus dose of esmolol effectively attenuated HR and systolic blood pressure increases produced by laryngoscopy and tracheal intubation.[17,18]

Similar to these studies, esmolol attenuated haemodynamic responses to perioperative stimuli such as tracheal intubation, incision and extubation and there were no differences between groups in our study with respect to haemodynamic responses.

Adequate depth of anaesthesia as indicated by the BIS was achieved in a group of elderly patients, using high dose atenolol and a restricted amount of anaesthesia.[11] In parallel to this study despite remifentanil requirements being significantly lower, anaesthesia was still adequate as indicated by BIS in the esmolol group and no recall was seen in either of the groups in our study. Also, noxious stimuli during general anaesthesia causes an increase in BIS as well as tachycardia, hypertension and movement.[19,20] Previous studies assessing the effectiveness of esmolol in blunting the haemodynamic responses induced by tracheal intubation failed to monitor electrical activity of the brain. Only a few studies have evaluated the effect of interaction between β-adrenergic antagonists and anaesthetics on BIS.[11,16] In 2001 Johansen suggested that perioperative infusion of esmolol decreased BIS values and increased burst suppression ratio.[21] In 2002, Menigaux and colleagues suggested that esmolol attenuated haemodynamic and somatic responses to laryngoscopy and orotracheal intubation, and also prevented BIS arousal reactions in patients anaesthetized with propofol.[22] In our study esmolol prevented BIS increases in response to noxious stimuli including tracheal intubation, incision and tracheal extubation as well as blunting haemodynamic responses in relation to these stimuli. Only one patient in both groups demonstrated significant tachycardia and hypertension associated with an increase in BIS. The clinical importance of this finding is that esmolol may have the potential to replace anaesthetic drugs that are given for the sole purpose of blunting haemodynamic responses.

Titration of anaesthetics to HR and blood pressure without administration of β-adrenergic antagonists may lead to prolonged recovery from anaesthesia as a result of 'relative overdosing' with administered anaesthetics and/or analgesics. Faster recovery from anaesthesia was reported in patients receiving propranolol.[23] It was shown that the extubation time and recovery in the PACU were significantly faster in patients treated with intra- or perioperative atenolol.[11] In contrast to these studies, there were no differences in extubation time and recovery from anaesthesia between groups in our study. In these studies the patients were under chronic β-adrenergic antagonist treatment in the preoperative period or high dose atenolol was administered intraoperatively. However none of our patients were receiving β-adrenergic antagonists chronically and esmolol was not administered in high dose, suggesting a relationship between the chronicity of use of β-adrenergic antagonists and the time to recovery from anaesthesia.

There are some limitations to this study. The patients in the esmolol group received remifentanil as an analgesic during the operation. BIS values were recorded to determine wakefulness of patients. Although BIS values during surgery were similar between groups, analgesia is a different concept from anaesthesia. The esmolol administered to patients may have partially masked the classical hypertension and tachycardia responses that are associated with pain. However, analgesic administration was not omitted in the esmolol group, despite being consumed at a lower dose.

In conclusion, esmolol reduced intraoperative remifentanil and postoperative morphine consumption; but it had no effect on depth of anaesthesia. We suggested that esmolol may possess analgesic properties, and because it is capable of effectively controlling tachycardia and hypertension during surgery, it may also demonstrate the benefit of providing a faster recovery with fewer side effects for patients undergoing ambulatory surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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