Brazilian Journal of Anesthesiology 2023;73(4):426–433

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Efficacy of a single dose of esmolol to prevent extubation-related complications during emergence from anesthesia: a randomized, double-blind, placebo-controlled trial

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Received 15 October 2020; accepted 28 August 2021
Available online 21 September 2021

KEYWORDS
Esmolol;
Hypertension;
Tachycardia;
Tracheal extubation

Abstract
Background: Few trials have examined the efficacy of esmolol to attenuate hemodynamic and respiratory responses during extubation. However, the most appropriate dose of esmolol and an optimal protocol for administering this beta-blocker are uncertain.
Methods: Ninety patients ASA physical status I, II, and III (aged 18–60 years) scheduled to procedures with general anesthesia and tracheal extubation were selected. Patients were randomized into esmolol and placebo group to evaluate the efficacy and safety of a single bolus dose of esmolol (2 $mg.kg^{-1}$) on cardiorespiratory responses during the peri-extubation period. The primary outcome was the rate of tachycardia during extubation.
Results: The rate of tachycardia was significantly lower in esmolol-treated patients compared to placebo-treated patients (2.2% vs. 48.9%, relative risk (RR): 0.04, 95% confidence interval (95% CI) = 0.01 to 0.32, $p = 0.002$). The rate of hypertension was also significantly lower in the esmolol group (4.4% vs. 31.1%, RR: 0.14, 95% CI 0.03 to 0.6, $p = 0.004$). Esmolol-treated patients were associated with higher extubation quality compared to patients who received placebo ($p < 0.001$), with an approximately two-fold increase in the rate of patients without cough (91.1%) in the esmolol group compared to the placebo group (46.7%). The rate of bucking was approximately 5-fold lower in the esmolol group (8.9% vs. 44.5%, respectively, RR: 0.20 (95% CI, 0.1 to 0.5, $p = 0.002$, with an NNT of 2.8).
Conclusion: A single bolus dose of esmolol is an effective and safe therapeutic strategy to attenuate cardiorespiratory responses during the peri-extubation period.

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https://doi.org/10.1016/j.bjane.2021.08.012

Introduction

Tracheal extubation is a critical step during anesthetic care when cardiovascular and respiratory decompensations can occur, such as tachycardia, hypertension, arrhythmias, myocardial ischemia, bronchospasm, or laryngospasm.[1,2] These potentially fatal complications related to extubation result from stimulation of the larynx, trachea, and bronchi, which increase the release of catecholamines. As a result, detailed monitoring of the cardiovascular stress response to extubation may be necessary, especially in high-risk patients.[3,4] Importantly, it has been demonstrated that the incidence of respiratory complications can be higher after extubation than during the induction of anesthesia or tracheal intubation.[1]

While several strategies have been employed to control the cardiovascular and respiratory responses to airway manipulation during the intubation period,[5–7] no standard therapy or guidelines have been established to prevent hemodynamic responses during the peri-extubation period. It has long been recognized that pharmacological strategies, such as local anesthetics, N-methyl D-aspartate (NMDA) antagonists, alpha-2 agonists, and beta-blockers can significantly reduce the rate of serious outcomes related to tracheal intubation.[5–9] In this respect, the prophylactic use of beta-blockers in the peri-extubation period has suggested a potential intervention to attenuate cardiovascular responses and decrease unfavorable events such as the reflexes of airway manipulation.[9]

Esmolol is a unique selective β1-adrenoceptor antagonist leading to reduced heart contractility, slowed atrioventricular conduction and increased atrioventricular refractoriness, which ultimately results in decreased myocardial oxygen demand.[10] Besides its cardioselectivity, this beta-blocker has become an attractive therapeutic choice in the peri-extubation period due to its rapid onset of action as well as its effects with a short duration. However, few trials have assessed whether the administration of esmolol could improve patient safety and outcomes after extubation.[11–13] Therefore, in this study, we examined the hypothesis that the administration of esmolol can reduce the incidence of cardiorespiratory responses during the peri-extubation period. Thus, this randomized trial aimed to evaluate the efficacy and safety of a single dose of esmolol (2 $mg.kg^{-1}$) infused over 2 minutes to attenuate cardiovascular and respiratory responses during the period of tracheal extubation.

Methods

Trial design

This is an investigator-initiated, double-blind, placebo-controlled trial (allocation ratio 1:1) conducted at the Hospital de Base, a tertiary hospital in Brasília, Brazil. The trial was registered at ClinicalTrials.gov (NCT04264286). Patients were recruited from February 2020 through July 2020. Ethical approval for the study was granted by the Fundação de Ensino e Pesquisa em Ciências da Saúde (FEPECS, Brasília, Brazil), with record number 3.732.847, on 28 November 2019, and registered in the Brazil platform (http://aplicacao.saude.gov.br/plataformabrasil) under the number CAAE 22078619.6.0000.8153. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

We randomly assigned 90 eligible patients to esmolol or placebo. Patients were eligible for inclusion in the trial if they were between 18 and 60 years of age with American Society of Anesthesiologists (ASA) physical status I to III. Patients scheduled to urgent or elective procedures with general anesthesia and tracheal extubation were selected. All medical specialties were evaluated.

Patients were excluded from the study if there was any contraindication or history of hypersensitivity to esmolol. Other exclusion criteria were: patients with atrioventricular block in any degree, cardiac arrhythmias, heart failure, kidney disease, a body mass index (BMI) $\geq 35\ kg.m^{-2}$, and history of asthma. Besides, we excluded patients in whom neuraxial block was performed before anesthetic induction, users of beta-blockers or calcium channel blockers, and the patients whose tracheal extubation would take place outside the operating room (e.g., in the intensive care unit [ICU]).

Procedures and interventions

Patients were identified and underwent clinical assessments according to the center's local standard practice, which included triage history, noninvasive blood pressure monitoring, oxygen saturation (SpO2), and body (tympanic) temperature measurements, assessment of bispectral index (BIS) values, and electrocardiogram recording. Patients were monitored with an A-2000 BIS monitoring system (Aspect Medical Systems, Inc., Newton, MA), and received either sevoflurane or propofol that were titrated to maintain BIS between 40 and 60. Neuromuscular monitoring was performed by acceleromyography with the recording of four sequential 50 mA stimuli (TOF-Watch® SX). Venoclysis was performed at the discretion of the anesthesiologist, based on the anesthetic needs of each participant. Midazolam (0.05 $mg.kg^{-1}$) was administered intravenously at the patient's arrival to the operating room.

Patients were maintained under general anesthesia after intubation, at the discretion of the anesthesiologist. After surgery, when the train-of-four (TOF) count was $\geq$2 responses, the dose of all anesthetics was reduced and sugammadex (2 $mg.kg^{-1}$) was used to reverse deep neuromuscular blockade. When the T4/T1 ratio exceeded 90%, anesthetics were discontinued, and the study interventions (esmolol or placebo) were infused over two minutes (two minutes before extubation). Extubation was performed after postoperative neurological assessment indicating spontaneous respiration, eye-opening, and/or voluntary movements.

For the patients in the esmolol group, a solution of 2 $mg.kg^{-1}$ diluted in 20 ml was used, while for the placebo group 0.9% saline solution (20 ml) was applied.

Vital measurements such as heart rate (HR) and systolic blood pressure (SBP) were evaluated at multiple time points: T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion (after one minute of

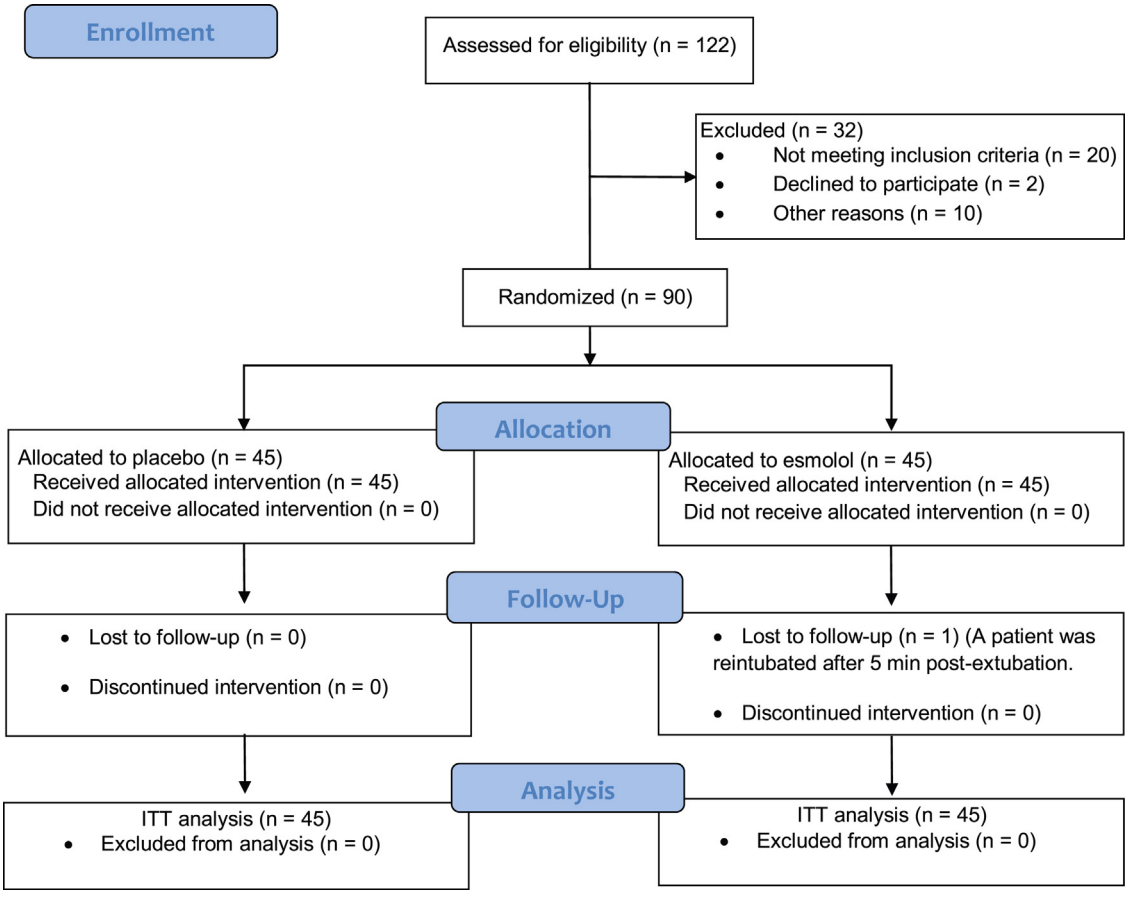

Figure 1 Flow diagram of participants through the trial. ITT denotes intention-to-treat.

the infusion); T_2: End of infusion (at the end of infusion); T_3: Extubation (during extubation); T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

The quality of extubation was assessed using a 5-point numeric rating scale with lower scores representing better quality of extubation: 1 = no coughing, 2 = minimal coughing (1 or 2 coughing episodes) or transient cough in response to the removal of the tube that resolved with extubation, 3 = moderate coughing (3 or more coughing episodes lasting up to 5 seconds), 4 = severe coughing (4 or more coughing episodes lasting more than 5 seconds) and symptoms of labored breathing, and 5 = serious coughing with laryngospasm.[13]

Bradycardia cases were managed by a bolus dose of atropine 0.5 mg intravenous, whereas clonidine 1 $mcg.kg^{-1}$ was used to control hypertension and/or tachycardia. Patients that developed hypotension were administered ephedrine (5 mg). In the case of laryngospasm, treatment consisted of the administration of 100% oxygen with positive pressure. Unresponsive cases were further treated with intravenous administration of 0.25 $mg.kg^{-1}$ of succinylcholine. All patients were given oxygen (concentration of 100% at 5 $l.min^{-1}$ via standard face mask.

According to the hospital standard care guidelines, all patients received metamizole (2 g) [except when any allergy was reported], parecoxib (40 mg), or tenoxicam (40 mg) [except in cases of contraindication to anti-inflammatory drugs], and morphine or tramadol for postoperative analgesia at the end of the surgical procedure and before extubation. Opioid choice was at the discretion of the anesthesiologist according to the patient's profile and surgical size. While we verified that all patients received adequate analgesia at the end of the surgery, individual records were not acquired.

Outcomes

The primary outcome was the rate of patients with tachycardia during and after extubation. Secondary outcomes were the rate of hypertension, bradycardia, hypotension, coughing, bucking, extubation quality scores, and variations in SBP and HR levels and adverse events. Hypertension was defined as SBP above 120% of the baseline value or >140 mmHg, while hypotension was defined as SBP below 80% of baseline value or <90 mmHg. Tachycardia was defined as HR above 120% of the baseline value or >100 bpm. Absolute bradycardia was defined as HR less than 50 bpm. The incidence of hypertension, hypotension, tachycardia, bradycardia, and adverse events were recorded throughout the study period.

Sample size

Sample size calculations were based on a pilot cross-sectional study, which found a prevalence of 45% of

tachycardia among patients undergoing surgical procedures at our center. Thus, assuming a type-I error (alpha) of 5% (two-tailed), 38 patients in each group were randomized to detect a reduction of 35% percentage points in the rate of tachycardia in the esmolol group compared to placebo (45% vs. 10%) with 90% power. The final sample size was increased by a further 15% (90 patients in total, 45 participants in each group) to allow potential dropouts.

Randomization and allocation concealment

We used a computer-generated, centrally concealed randomization sequence. Furthermore, we employed syringes sequentially numbered and packaged in opaque and sealed containers. Specifically, syringes containing esmolol or placebo were centrally prepared, pre-coded based on the randomization list, and sent sequentially to the operating room immediately before administration. Blinding occurred at the level of patients, surgery staff and outcome assessors. Both drug and placebo solutions were identical in appearance, volume, viscosity, and odor and were prepared by an investigator no involved in recruitment or patient care.

Statistical analysis

Results are summarized as mean (standard deviation), number (percentage), and relative risk (RR) with a 95% confidence interval (95% CI). Dichotomous and categorical variables were compared with chi-square tests. The Student's *t*-test was used to compare the treatment groups with respect to continuous variables. We used linear mixed-effects models to investigate the effect of esmolol and placebo on blood pressure and heart rate levels over time. Time and treatment groups were considered fixed-effects and were treated as categorical variables. Interaction terms between time and treatment group were used in addition to a random intercept for each patient. All statistical analyses were based on an intention-to-treat (ITT) principle, in which all patients randomized were included in the analyses, regardless of protocol deviations or actual treatment received. A p-value < 0.05 (two-tailed) was considered statistically significant. We also estimated the number of patients who needed to be treated to prevent one event (NNT) as the reciprocal of the risk difference between the esmolol and placebo groups. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Macintosh (Chicago, IL, USA) and Stata 14 (College Station, Texas, USA).

Results

A total of 122 patients were screened in this randomized trial. Of these, 32 did not meet the eligibility criteria (Fig. 1). Thus, 90 patients were assigned to either the esmolol group (n = 45 participants) or the placebo group (n = 45 participants). The mean age was 46.7 years (range 18 to 70 years), 53 participants (58.9%) were female, and the study sample had an average BMI of 24.8 $kg.m^{-2}$ (range 16 to 32.3 $kg.m^{-2}$). As shown in Table 1, central randomization generated groups well balanced in terms of prognostic factors and demographic characteristics. Moreover, the distribution of surgical procedures across different specialties was comparable between the groups, and no medical specialty was seriously over-represented in the study sample. Perioperative care measures were also similar between groups (Table 2).

Table 1 Participant demographics, clinical baseline characteristics and perioperative care measures.

Variable	Placebo (n = 45)	Esmolol (n = 45)
Age (years), mean (SD)	44.2 (15.1)	49.2 (12.8)
Height (meters), mean (SD)	1.65 (0.1)	1.67 (0.1)
Weight (kg), mean (SD)	68.9 (10.3)	68.7 (9.7)
BMI ($kg.m^{-2}$), mean (SD)	25.1 (3.5)	24.4 (2.5)
Female, n (%)	29 (64.4)	24 (53.3)
ASA, n (%)		
I	9 (20.0)	10 (22.2)
II	24 (53.3)	27 (60.0)
III	12 (26.7)	8 (17.8)
Hypertension, n (%)	13 (28.9)	20 (44.4)
Diabetes, n (%)	7 (15.6)	11 (24.4)
Obesity, n (%)	4 (8.9)	2 (4.4)
Type of surgery, n (%)		
Elective	40 (88.9)	39 (86.7)
Urgency	5 (11.1)	6 (13.3)
Medical specialty, n (%)		
Bronchoesophagology	4 (8.9)	0
Maxillofacial surgery	4 (8.9)	4 (8.9)
Head and neck surgery	5 (11.1)	1 (2.2)
Coloproctology	1 (2.2)	3 (6.7)
General surgery	8 (17.8)	7 (15.6)
Mastology	3 (6.7)	4 (8.9)
Neurosurgery	5 (11.1)	6 (13.3)
Oncological surgery	5 (11.1)	3 (6.7)
Orthopedics	2 (4.4)	1 (2.2)
Otorhinolaryngology	3 (6.7)	6 (13.3)
Thoracic surgery	4 (8.9)	5 (11.1)
Urology	0	3 (6.7)
Vascular surgery	1 (2.2)	2 (4.4)

ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

A patient in the esmolol group was reintubated after 5 minutes because of a seizure event, whereas a patient in the placebo group was given clonidine for the management of a serious hypertensive episode. However, both patients were included in the ITT analysis.

Primary outcome

The rate of tachycardia was 48.9% in the placebo group (22 of 45 patients), as compared with 2.2% (1 of 45 patients) in the esmolol group (relative risk [RR], 0.04; 95% confidence interval [CI], 0.01 to 0.3; $p = 0.002$) (Table 2), with an NNT of 2.1.

Table 2 Perioperative care measures.

Variable	Placebo (n = 45)	Esmolol (n = 45)	p[a]
General anesthetic (anesthesia maintenance), n (%)			
Sevoflurane	29 (64.4)	24 (53.3)	0.28
Propofol	16 (35.6)	21 (46.7)	
Opioid supplement to general anesthesia, n (%)			
Fentanyl (induction and maintenance)	15 (33.3)	16 (35.6)	0.82
Fentanyl (induction) and remifentanil (maintenance)	30 (66.7)	29 (64.4)	
Duration of anesthesia, mean (SD), min	215.8 (104.5)	222.3 (94.1)	0.76
Operative time, mean (SD), min	163.3 (91.4)	171.3 (89.0)	0.68

[a] Continous variables were tested by t-tests. Categorical variables were tested via chi-squared tests.

Table 3 Primary and secondary outcomes.

	Placebo (n = 45)	Esmolol (n = 45)	RR (95% CI)	p-value
Primary outcome				
Tachycardia, n (%)	22 (48.9)	1 (2.2)	0.04 (0.01 to 0.3)	0.002[a]
Secondary outcomes				
Bradycardia, n (%)	0	1 (2.2)	3.00 (0.1 to 71.7)	0.50
Hypertension, n (%)	14 (31.1)	2 (4.4)	0.14 (0.03 to 0.6)	0.007[a]
Hypotension, n (%)	0	5 (11.1)	11.0 (0.6 to 193.0)	0.10
Quality of extubation, n (%)				
No coughing	21 (46.7)	41 (91.1)	1.95 (1.4 to 2.7)	< 0.001[a]
Minimal coughing	14 (31.1)	3 (6.7)	0.31 (0.1 to 0.9)	0.003[a]
Moderate coughing	8 (17.8)	1 (2.2)	0.20 (0.03 to 1.3)	0.01[a]
Severe coughing	0	0	–	–
Serious coughing with laryngospasm	2 (4.4)	0	0.20 (0.01 to 4.1)	0.30
Safety outcomes				
Bucking, n (%)	20 (44.4)	4 (8.9)	0.20 (0.1 to 0.5)	0.002[a]
Laringoespasm, n (%)	2 (4.4)	0	0.20 (0.01 to 4.1)	0.30
Broncoespasm, n (%)	1 (2.2)	0	0.33 (0.01 to 8.0)	0.50

RR denotes relative risk. 95% CI denotes 95% confidence interval. For 2 × 2 tables with zero events in a cell, a continuity correction was applied by adding 0.5 to each cell.
[a] $p < 0.05$ was considered statistically significant. Results are based on chi-square tests.

Secondary outcomes

Fewer patients in the esmolol group than in the placebo group developed hypertension (RR, 0.14; 95% CI, 0.03 to 0.6, with an NNT of 3.1). However, the rate of bradycardia or hypotension did not differ significantly between the two groups.

A significant difference in heart rate levels between esmolol and placebo was found from extubation (T_3) to 10 minutes after extubation (T_7) (Fig. 2 and Table 4). Patients who received esmolol had, on average, heart rate levels approximately 20% lower compared to patients who received placebo. Similar results were observed for systolic blood pressure levels, which were approximately 12% lower in patients that received esmolol compared to patients that received placebo between time points T_3 and T_7 (Fig. 2 and Table 4).

Esmolol-treated patients were associated with a higher quality of extubation compared to patients who received placebo (chi-squared test, $p < 0.001$), with an approximately two-fold increase in the rate of patients without cough (91.1%) in the esmolol group compared to the placebo group (46.7%) (Table 3).

Safety

One patient in the esmolol group was reintubed due to seizure episode. This event was considered unrelated to the study drug by the treating clinical team. The rate of bucking was approximately 5-fold lower in the esmolol group compared to placebo (8.9% vs. 44.5%, respectively, RR: 0.20 (95% CI, 0.1 to 0.5, $p = 0.002$, with an NNT of 2.8). The overall rate of laryngospasm and bronchospasm was low in the study population, with two episodes of laryngospasm and only one episode of bronchospasm, all in the placebo group (Table 3).

Discussion

In this randomized trial, treatment with esmolol resulted in a significantly lower rate of tachycardia and hypertension compared to placebo. Analyses considering the trajectory of systolic blood pressure and heart rate levels over time confirmed the findings of the primary outcome, indicating that esmolol offers persistent effects for up to 10 minutes after extubation.

In the present trial, we examined the efficacy of esmolol 2 mg.kg^{-1} in a single dose to attenuate the hemodynamic response to extubation. Other drugs have been used to control hemodynamic changes to endotracheal intubation and extubation. For instance, Bostan et al. investigated the effects of esmolol (1 mg.kg^{-1}), fentanyl (1 μg.kg^{-1}), and lidocaine (1 mg.kg^{-1}) during laryngoscopy, intubation, and extubation. Esmolol treatment was associated with significantly lower systolic and diastolic blood pressure and heart rate levels compared to the other drugs, primarily in the first, third, and fifth minutes after extubation. Nonetheless, the rates of tachycardia and hypertension were not investigated.[14] Shrestha et al. also compared esmolol to lidocaine 1 mg.kg^{-1} in relation to their hemodynamic effects on extubation.[15] The authors observed that a higher dose of esmolol (1.5 mg.kg^{-1}) offered better control of heart rate than lidocaine at the moment of oropharyngeal suctioning and at 1 minute after extubation. Additionally, esmolol-treated patients displayed lower SBP levels during oropharyngeal aspiration, extubation, and 3 minutes after extubation. In contrast to the results reported by Bostan et al.,[14] esmolol at the dose of 1.5 mg.kg^{-1} failed to control heart rate levels during or after the first minute post-extubation. Similar results were observed for SBP levels, which were indistinguishable between the esmolol and lidocaine groups after the third minute of post-extubation. By using a higher dose of esmolol, our results are in partial agreement with those findings and complement those previous findings demonstrating the efficacy and adequate safety profile of a higher dose of esmolol in achieving longer hemodynamic stability during the peri-extubation period.

Of note, while a single dose of esmolol 2 mg.kg^{-1} infused over 2 minutes was administered in our trial, our results are consistent with those reported Alkaya et al. who compared esmolol (infused over 10 minutes at a dose of 0.2 μg.kg^{-1}.min^{-1}) to placebo in the prevention of hemodynamic responses to tracheal extubation after craniotomy.[11] Lower levels of SBP were observed in the esmolol group during extubation and 1, 3, and 5 minutes after extubation. There was also evidence for lower heart rate levels in the esmolol group compared to the placebo-treated patients 10 minutes after extubation. Thus, our results may indicate that the strategy employed in our trial not only facilitates administration but also augments adherence by anesthesiologists, without jeopardizing clinical outcomes.

The safety of beta-blockers to blunt hemodynamic response after extubation has been discussed previously.[16–18] In a head-to-head trial examining beta-blockers only, Prajwal et al. compared the hemodynamic effects of esmolol (an ultra-short-acting β-blocker) at a dose of 1.5 mg.kg^{-1} to labetalol (a nonselective β-antagonist with α1-antagonist activity with a longer half-life) at a dose of 0.25 mg.kg^{-1}.[16] This trial showed that labetalol promoted a lower heart rate at 5 and 15 minutes after extubation, with no significant difference compared to esmolol during extubation or in the first initial minutes post-extubation. Esmolol-treated patients, on the other hand, displayed significantly lower SBP levels in the second and third minutes after extubation than patients treated with labetalol. Nonetheless, for SBP levels, no difference between these two beta-blockers was detected during extubation and at 4 and 5 minutes after extubation. According to the authors, labetalol might be more effective at controlling heart rate levels, whereas esmolol might be more effective at controlling blood pressure levels. A major limitation of that trial was that the rates of tachycardia or hypertension were not assessed.[16] Overall, our trial corroborates the notion that treatment with esmolol 2 mg.kg^{-1} offers a significant control of blood pressure and heart rate levels, and may be associated with a lower risk of adverse events than other longer-life beta-blockers, such as atenolol or metoprolol.[17,18]

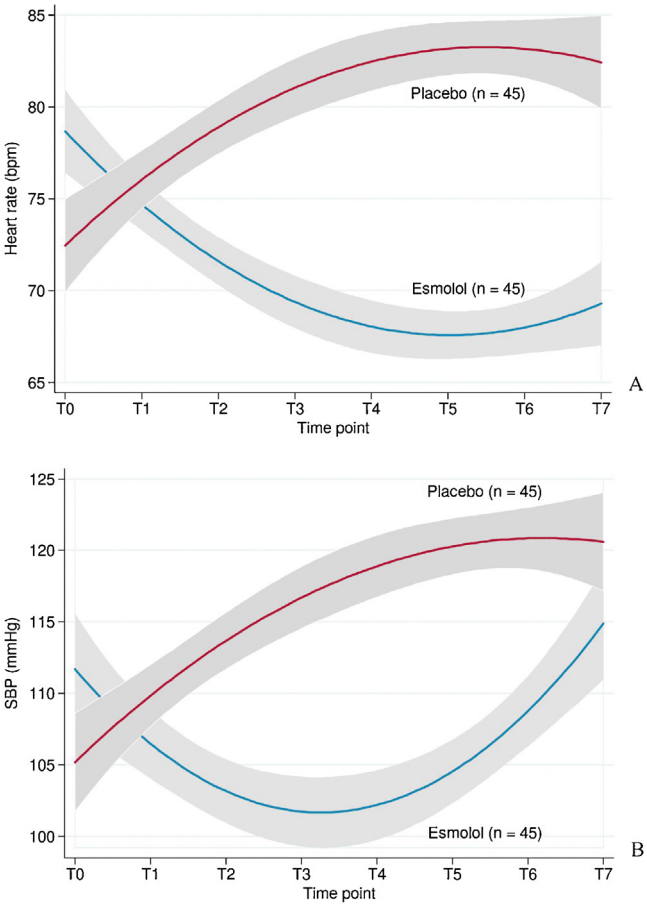

Figure 2 Prediction plots for heart rate (panel A) and systolic blood pressure (panel B). A quadratic model was used to represent graphically the trajectory of systolic blood pressure (SBP) and heart rate levels over time. Results are displayed as predicted means (lines) and approximate 95% confidence intervals (shaded areas). The esmolol group is represented by blue lines, whereas the placebo group is represented by red lines. T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion; T_2: End of infusion (at the end of infusion); T_3: Extubation; T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

Regarding the optimal doses of esmolol, a previous placebo-controlled trial in patients undergoing lumbar disc herniation surgery tested the effect of esmolol using a bolus dose of 0.5 mg.kg^{-1} followed by a dose maintenance interval of 0.1 (experimental group 1) or 0.2 mg.kg^{-1}.min^{-1} (experimental group 2) until the 10th minute after extubation.[19] Although the authors did not report any difference between the placebo and esmolol groups in the hemodynamic

Table 4 Heart rate and systolic blood pressure levels during the peri-extubation period.

Variable	Placebo (n = 45)	Esmolol (n = 45)	Mean difference (95% CI)	*p*-value
Heart rate, mean (SD), bpm				
T_0	74.3 (10.2)	77.8 (10.1)	3.83 (-0.2 to 7.9)	0.06
T_1	74.7 (10.8)	74.7 (9.3)	0.37 (-3.7 to 4.4)	0.96
T_2	74.8 (10.7)	70.7 (9.2)	-3.62 (-7.7 to 0.4)	0.08
T_3	86.1 (10.3)	71.2 (8.7)	-13.5 (-17.6 to -9.5)	< 0.001[a]
T_4	85.0 (9.6)	68.7 (9.4)	-14.6 (-18.6 to -10.5)	< 0.001[a]
T_5	84.0 (9.2)	65.4 (7.7)	-16.8 (-20.9 to -12.8)	< 0.001[a]
T_6	84.2 (9.6)	65.4 (7.6)	-17.7 (-21.8 to -13.7)	< 0.001[a]
T_7	83.1 (8.2)	71.2 (7.5)	-11.1 (-15.2 to -7.1)	< 0.001[a]
Systolic blood pressure, mean (SD), mmHg				
T_0	108 (13.4)	110.4 (15.1)	2.47 (-3.6 to 8.6)	0.43
T_1	107.6 (13.1)	107.5 (14.3)	-0.18 (-6.3 to 5.9)	0.95
T_2	108.3 (12.9)	102.9 (13.6)	-5.40 (-11.5 to 0.7)	0.08
T_3	120.4 (14.5)	104.9 (15.6)	-15.5 (-21.6 to -9.4)	< 0.001[a]
T_4	121.0 (16.2)	101.7 (17.5)	-19.2 (-25.3 to -13.1)	< 0.001[a]
T_5	119.4 (14.3)	101.0 (17.4)	-18.4 (-24.5 to -12.3)	< 0.001[a]
T_6	121.7 (13.1)	108.5 (17.1)	-13.3 (-19.5 to -7.2)	< 0.001[a]
T_7	119.4 (12.1)	116.3 (14.6)	-3.14 (-9.3 to 3.0)	0.31

Mean differences and 95% confidence intervals (95% CI) are marginal predictions based on the mixed-effects models. T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion ; T_2: End of infusion (at the end of infusion); T_3: Extubation; T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

[a] $p < 0.05$ was considered statistically significant. Results are based on mixed-effects models.

response in the initial minutes, the rate of hypertension was notably lower in patients treated with esmolol. In that trial, there was evidence of dose-response effects, with faster recovery times observed in patients who received the highest dose of the beta-blocker. Thus, it is possible that the dose of esmolol is a critical factor in attenuating the response to extubation, with smaller doses being less effective compared to higher doses, even when associated with a continuous maintenance dose.

In line with the abovementioned observations, another trial found that a high dose of esmolol (2 $mg.kg^{-1}$ in bolus) reduced systolic blood pressure during extubation, but that a lower dose (1 $mg.kg^{-1}$ in bolus) was insufficient to prevent the incidence of hypertension.[12] Our trial adds further evidence suggesting that a single large dose of esmolol might be an optimal strategy to attenuate the increases in heart rate and systolic blood pressure levels simultaneously.

Concerning the most suitable administration protocol, a previous trial indicated that the proportion of patients without cough and with normal breathing was higher in the esmolol group (2 $mg.kg^{-1}$) compared to the placebo group.[11] In contrast to that trial, in which a dose of esmolol of 2 $mg.kg^{-1}$ via a 10-minute infusion was used, our trial used a 2-minute infusion protocol. Thus, our findings strengthen the hypothesis that the suppressive effects of esmolol on airway reflexes during the peri-extubation period could be independent of administration protocol.

Further investigations would be valuable in determining how the respiratory effects are mediated by esmolol. It is conceivable that a higher dose of esmolol is sufficient to inhibit cough triggering mechanisms via blockage of ion channels. The majority of the vagal afferent nerves responsible for triggering the cough reflex are composed of unmyelinated C fibers,[20] and the afferent nerve endings are found in abundance in the mucosa and the walls of the upper airways to the proximal bronchioles.[21] These fibers express a variety of receptors and ion channels that trigger coughing when activated, with the onset and spread of action potentials in afferent sensory nerves being mediated by voltage-dependent sodium channels.[22] A preclinical study investigated the properties of ultra-short-acting β1 blockers, and demonstrated that esmolol can block voltage-dependent sodium channels in sensory neurons in a dose-dependent manner.[23] Another study also showed that esmolol can inhibit L-type calcium channels, which would have an additional effect on fast sodium channels, being responsible for suppressing the conduction of the action potential.[24]

Some limitations of this trial should be considered. First, for safety concerns, we excluded patients with coronary artery disease and those who had been prescribed beta-blockers. Thus, the generalizability of our results can be limited. Second, our trial was underpowered to detect uncommon or rare adverse events. Third, we were unable to follow-up patients to examine the impact of esmolol treatment on postoperative pain levels, recovery time, and hospital length of stay. Fourth, we enrolled both emergency and elective cases, used different agents for postoperative analgesia, and the trial protocol did not specify the time intraoperative administration of analgesic agents. All these aspects could introduce clinical and methodological heterogeneity, causing our estimates to be less precise. Fifth, we included patients undergoing different surgical procedures, making the study conclusions more pragmatic than trials conducted within a single medical specialty. However, although the distribution of surgeries within medical spe-

cialties was similar between esmolol-treated patients and placebo-treated patients, it is possible that the specific type of surgeries differed slightly between the groups. However, the randomization was performed with adequate computer-generated methods and allocation concealment, decreasing the risk of selection biases. Finally, our trial may be underpowered to detect the effects of esmolol on the secondary outcomes. However, our study can serve as the basis for further investigations appropriately designed to elucidate the effects of esmolol on respiratory outcomes.

Conclusion

Altogether, our findings indicate that a single bolus dose of esmolol (2 mg.kg^{-1}) infused over 2 minutes is effective and safe to attenuate cardiovascular and respiratory responses in the period of peri-extubation. Our results suggest that esmolol has great potential to be included as a standard therapy during extubation.

Financial support and sponsorship

None.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Assistance with the study: We would like to thank all colleagues in the Anesthesiology Department of the Hospital de Base do Distrito Federal, especially Dr. Nadja Glória Correa Graça for supporting the study.

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