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ORIGINAL INVESTIGATION

Effects of lidocaine and esmolol on hemodynamic response to tracheal intubation: a randomized clinical trial☆

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KEYWORDS
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Laryngoscopy;
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Tachycardia

Abstract
Introduction and objectives: Although lidocaine is widely used to prevent cardiovascular changes resulting from laryngoscopy and orotracheal intubation, it is still unclear whether there are more efficacious drugs. This study aimed to compare the beta-blocker esmolol with lidocaine regarding the effects on hemodynamic response after orotracheal intubation.
Methods: The study has a prospective, randomized, double-blind, superiority design, and assessed 69 participants between 18 and 70 years of age, ASA I-II, scheduled for elective or emergency surgery under general anesthesia with orotracheal intubation. Participants were randomly allocated to receive 1.5 $mg.kg^{-1}$ esmolol bolus followed by 0.1 $mg.kg^{-1}.min^{-1}$ esmolol infusion (n = 34) or 1.5 $mg.kg^{-1}$ lidocaine bolus followed by 1.5 $mg.kg^{-1}.h^{-1}$ lidocaine infusion (n = 35). We recorded changes in heart rate, arterial blood pressure and incidence of adverse events.
Results: Post-intubation tachycardia episodes were significantly less frequent in the esmolol group (5.9% vs. 34.3%; Relative Risk (RR) 0.17; 95% Confidence Interval (95% CI) 0.04–0.71; Number Needed to Treat (NNT) 3.5; $p = 0.015$. After orotracheal intubation, mean heart rate was significantly lower in the esmolol group (74.5 vs. 84.5, $p = 0.006$). Similar results were observed in the subsequent 3 and 6 minutes (75.9 vs. 83.9, $p = 0.023$ and 74.6 vs. 83.0, $p = 0.013$, respectively).
Conclusion: Esmolol was a safe and more effective intervention to reduce incidence of tachycardia and control heart rate immediately after tracheal intubation when compared to lidocaine.

☆ Study conducted at the Anesthesiology Department, Hospital de Base do Distrito Federal, Brasília, DF, Brazil.

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Introduction

Most patients undergoing general anesthesia require laryngoscopy and tracheal intubation. These maneuvers elicit stimuli resulting in sympathetic activation and catecholamine release, leading to cardiovascular changes such as tachycardia, arterial hypertension, and arrhythmias. These responses, as well as the resulting hemodynamic consequences, can cause severe arrhythmias, myocardial ischemia, and cerebrovascular events.[1]

To mitigate the sympathetic response and prevent cardiovascular reflexes during laryngoscopy and tracheal intubation, several agents have been used perioperatively, such as opioids,[2,3] N-Methyl-D-aspartate (NMDA) receptor antagonists,[4] alpha-2 agonists,[1,5] beta-blockers,[6,7] and local anesthetics such as lidocaine.[4,8] Despite the lack of current consensus on the best pharmacological strategy, intravenous lidocaine is the most commonly used agent, as it prevents electrocardiographic changes such as tachycardia, hypertension, increased intraocular and intracranial pressure resulting from laryngoscopy and tracheal intubation. In addition, when systemically administered, lidocaine suppresses airway reflexes.[4,9] Therefore, lidocaine is also used to reduce cough reflex in the perioperative period.[8]

Adverse effects related to excessive sympathetic stimulation can also be controlled by administration of beta-blockers. In fact, beta-adrenergic antagonism enables greater control of cardiac rhythm, myocardial oxygen consumption and blood pressure, preventing cardiovascular events.[3] Previous investigations indicate that esmolol, a cardio selective $beta_1$ receptor antagonist, with an ultrashort action, can help prevent hemodynamic changes in response to tracheal intubation.[10] However, few studies compared the efficacy of esmolol versus lidocaine in preventing cardiovascular changes in patients undergoing laryngoscopy and tracheal intubation, and there is still no consensus on the dose to be administered.

Thus, this study aimed to compare the effects of intravenous administration of esmolol with lidocaine regarding the incidence of perioperative tachycardia in patients undergoing laryngoscopy and orotracheal intubation during general anesthesia.

Methods

Study design

This is a prospective, randomized, double-blind clinical trial with active comparators, conducted at the Hospital de Base do Distrito Federal (Brasilia, Brazil). The clinical trial was approved by the local Research Ethics Committee (Foundation for Education and Research in Health Sciences – FEPECS, Brasília, DF, Brazil) and registered on Plataforma Brasil (http://aplicacao.saude.gov.br/plataformabrasil) under CAAE nº 88800118.9.0000.5553, opinion nº 2.740.009, of June 27, 2018, and registered on ClinicalTrials (NCT03612492). After participants were duly informed about the details of the study protocol, the written informed consent was obtained. Data were collected between July 2018 and January 2019.

Participants

Patients scheduled for elective or emergency surgery under general anesthesia with orotracheal intubation were recruited for the study. Inclusion criteria were age between 18 and 70 years and ASA (American Society of Anesthesiologists) physical status I to II. We excluded patients with suspected difficult airway management, body mass index above 35 $kg.m^{-2}$, patients who received regional anesthesia, patients with pulmonary, cardiac, hepatic, renal or neurological disorders, on use of illicit drugs, using beta-blocker preoperatively, patients who required two or more laryngoscopy attempts, or patients who refused to participate in the study.

Randomization, allocation, confidentiality, and blinding

A computer-generated simple randomization list was created using the randomizer.org platform, with an allocation ratio of 1:1. Patients considered eligible who agreed to participate in the study received anonymous unique identifiers randomly allocated to one of two groups: esmolol or lidocaine. The allocation list was kept confidential throughout the allocation process as the list was managed by a single investigator not involved with patient clinical care. This investigator prepared the syringes (bolus syringe and infusion syringe) with the intervention of interest and loaded the infusion pump with the syringe with a predetermined infusion rate, which was directly delivered to the operating room.

Due to the nature of the treatment, all patients were unaware of the therapy during the intervention period. Likewise, those responsible for acquiring intraoperative data were blinded as to the allocation of groups. The blinding of researchers involved in participant clinical care was maintained by delivering same-volume visually identical syringes and unidentifiable infusion pumps to the operating room.

Interventions

At anesthesia induction, in the control group patients received a lidocaine intravenous bolus dose of 1.5 $mg.kg^{-1}$ and maintenance infusion of 1.5 $mg.kg^{-1}.h^{-1}$, while in the intervention group patients received an esmolol intravenous bolus dose of 1.5 $mg.kg^{-1}$ and maintenance infusion of 0.15 $mg.kg^{-1}.min^{-1}$. Drug administration started concurrently with anesthesia induction and lasted throughout the study period.

All patients were submitted to standard monitoring. After venipuncture all patients received Intravenous (IV) premedication with midazolam (0.05 $mg.kg^{-1}$). The studied drug IV infusion pump was initiated, and anesthetic induction was performed with the IV injection of the study ''bolus syringe'', followed by fentanyl (2 $mcg.kg^{-1}$), propofol (2 $mg.kg^{-1}$) and rocuronium (1 $mg.kg^{-1}$). Anesthesia was maintained with sevoflurane 1 CAM.

We performed assessments at six determined moments: T1, upon operating room admission; T2, two minutes after administration of IV midazolam; T3 after anesthesia induction (duration of 3 minutes); T4, after orotracheal intubation

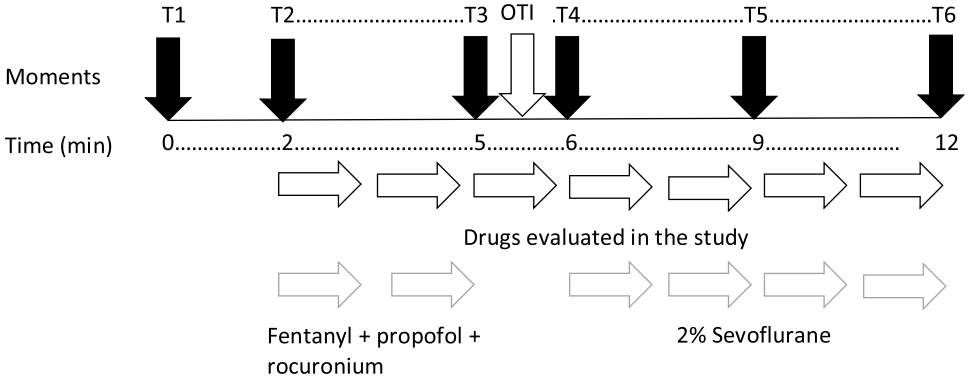

Figure 1 Times and moments of participant assessments. T1: Admission to operating room; T2: 2 minutes after IV administration of midazolam; T3: 3 minutes after induction of anesthesia; T4: 1 minute after Orotracheal Intubation (OTI); T5: 3 minutes after OTI; T6: 6 minutes after OTI.

(duration of 1 minute); T5, three minutes after orotracheal intubation; T6, six minutes after orotracheal intubation (Fig. 1).

Heart rate and blood pressure were continuously monitored. Hypertension was defined as Systolic Blood Pressure (SBP) above 120% of baseline value or above 140 mmHg, while hypotension was defined as SBP below 80% of baseline value or below 90 mmHg. Tachycardia was defined as Heart Rate (HR) above 20% of baseline or above 100 beats/min. Absolute bradycardia was defined as HR less than 50 beats.min^{-1}. The following treatments were offered: atropine 0.5 mg for bradycardia, ephedrine 5 mg for hypotension, and clonidine 1 mcg.kg^{-1} for hypertension and/or tachycardia.

Outcomes

The primary outcome was the incidence of tachycardia during laryngoscopy and orotracheal intubation. Secondary outcomes were changes in heart rate, mean and systolic blood pressure, incidence of hypertension, hypotension, bradycardia, and other adverse events.

Sample size

Recruitment began after sample size was calculated by the Laboratory of Epidemiology and Statistics of Instituto Dante Pazzanese de Cardiologia (http://www.lee.dante.br) based on a previous pilot study carried out in our service. The pilot study was carried out assessing the same doses used in patients assigned to receive lidocaine to identify adequacy of intubation conditions and incidence of adverse events. Thirty-three patients in each group would be required to detect a 30% difference in the proportion of tachycardia after intubation (10% in the esmolol group and 40% in the lidocaine group), with a type 1 error of 5% and a power of 80%. Considering the likelihood of follow-up flaws or exclusion of patients, we decided to enroll 40 patients into each group.

Statistical analysis

Linearity and normality of variable distribution were checked using histograms, normal probability plots, residual scatter plots, and the Shapiro-Wilk test. Student's *t*-test with Satterthwaite correction and Wilcoxon-Mann-Whitney's non-parametric *U*-test were used to compare differences between groups for the variables showing approximately normal and asymmetric distribution, respectively. Categorical data frequency was compared using Fisher's exact test or the chi-square test, as appropriate. Results were presented as mean (Standard Deviation, SD), mean difference along with 95% Confidence Interval (95% CI), or median (Interquartile Range, IQR). Dichotomous data were presented as absolute number (percentage), Relative Risk (RR) with 95% confidence interval, and Number Needed to Treat (NNT). Because of the irregular pattern of the functions observed, the Area Under the Curve (AUC) and the positive incremental Area Under the Curve (piAUC) were calculated by the trapezoidal rule. PiAUC is the area under the curve above the baseline value. A p-value < 0.05 was considered significant. Statistical analyses were performed using SPSS for Macintosh (Statistical Package for the Social Sciences, Chicago, IL, USA) version 20.0 and Stata 14 (StataCorp, College Station, TX, USA).

Results

Eighty patients were recruited for the study. Of these, six patients were excluded for not meeting all inclusion criteria (n = 5), or due to previous use of beta-blockers (n = 1). The remaining patients were randomly allocated to the esmolol (n = 37) or lidocaine (n = 37) group. Subsequently, five patients were excluded from the study due to unanticipated difficult orotracheal intubation (n = 4, two in the esmolol group and two in the lidocaine group), or due to bronchospasm after tracheal intubation (n = 1, esmolol group). Thus, a total of 69 patients were included in the final analysis of the study, 34 patients in the esmolol group and 35 in the lidocaine group (Fig. 2).

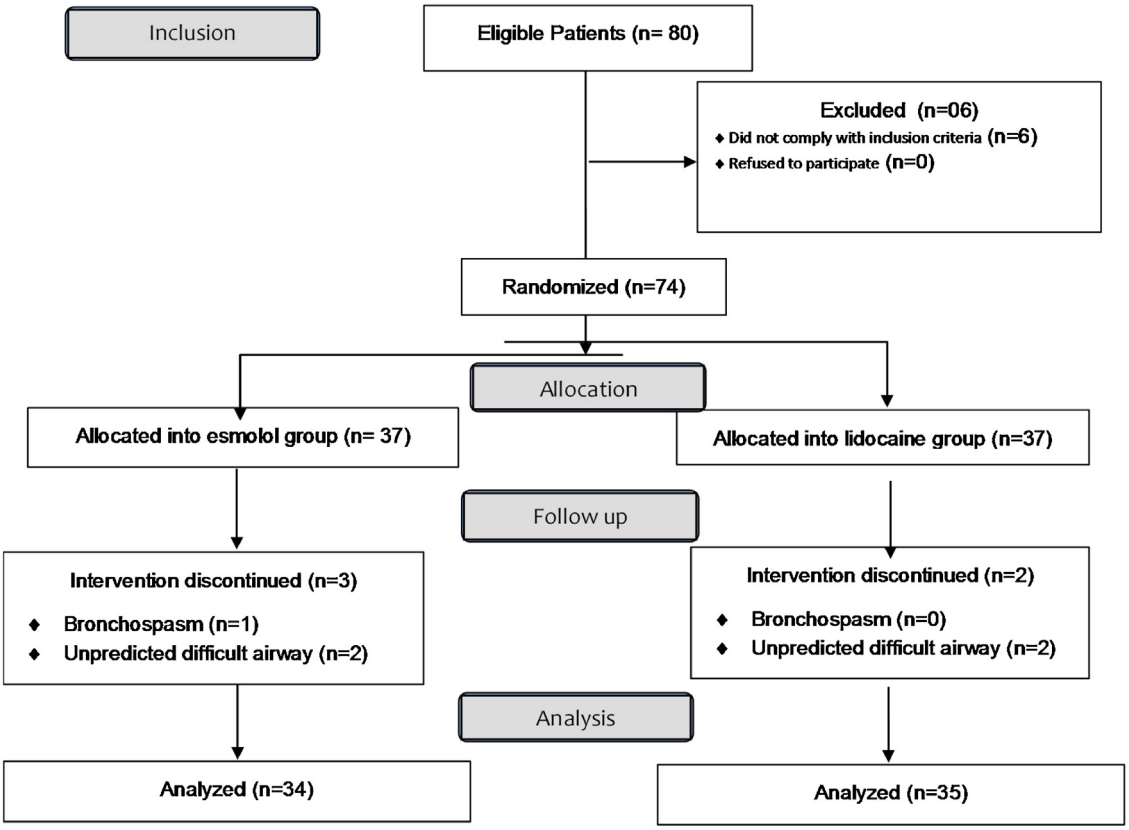

Figure 2 Randomization flowchart.

Table 1 Demographic data.

	Esmolol Group (n = 34)	Lidocaine Group (n = 35)	*p*
Age, years (mean, SD)	46.4 (14.3)	47.8 (14.5)	0.698
Weight, kg (mean, SD)	72.9 (12.4)	73.1 (16.8)	0.962
Height, cm (mean, SD)	167 (10)	165 (10.7)	0.529
Male, n (%)	16 (47.1)	14 (40)	0.554
ASA, n (%)			0.947
I	8 (23.5)	8 (22.9)	
II	26 (76.5)	27 (77.1)	
HBP, n (%)	12 (35.3)	8 (22.9)	0.262
DM2, n (%)	5 (14.7)	0 (0)	0.096
Elderly n (%)	9 (26.5)	11 (31.4)	0.651
Obesity, n (%)[a]	4 (11.8)	8 (22.9)	0.238
Surgery Type, n (%)			0.752
Elective	29 (85.3)	28 (80)	
Emergency	5 (14.7)	7 (20)	

ASA, American Society of Anesthesiologists; DM2, type 2 Diabetes Mellitus; SD, Standard Deviation; HBP, High Blood Pressure.
[a] Obesity was defined by body mass index higher than 30 $kg.m^{-2}$.

The groups were homogeneous regarding demographic data (Table 1).

Primary outcome

At the time of intubation, the esmolol group had a lower incidence of tachycardia (5.9% vs. 34.3%; RR = 0.17; 95% CI 0.04 to 0.71; NNT = 3.5; $p = 0.015$).

Secondary outcomes

Esmolol group patients had a lower incidence of coughing or movement, hypertension and arterial hypotension compared to the lidocaine group, however, without statistical significance (Table 2). All patients who had hypotension were treated with ephedrine. The only patient in the esmolol group who had bradycardia did not need atropine, as he did not have hypotension.

Table 2 Response to tracheal intubation.

	Esmolol Group (n = 34)	Lidocaine Group (n = 35)	RR	95%CI	*p*
Tachycardia (n/%)	2/5.9	12/34.3	0.17	(0.04 a 0.71)	0.015[a]
Bradycardia (n/%)	1/2.9	0/0	3.08	(0.13 a 73.21)	0.485
Cough or movement (n/%)	2/5.7	4/11.8	0.51	(0.10 a 2.62)	0.424
Arterial hypertension (n/%)	1/2.9	2/5.7	0.51	(0.05 a 5.41)	0.580
Arterial hypotension (n/%)	16/47.1	17/48.6	0.97	(0.59 a 1.58)	0.900

Categorical variables are shown as absolute numbers and percentages (assessed by OR).
RR, Relative Risk; 95% CI, 95% Confidence Interval.
[a] $p < 0.05$ was considered significant.

After laryngoscopy and tracheal intubation (T4), mean heart rate was approximately 12% lower in the esmolol group compared to the lidocaine group ($p = 0.006$). Similar results were observed in moments T5 and T6 (3 and 6 minutes after tracheal intubation, respectively), when mean heart rate was approximately 10% lower (in both moments) in the esmolol group compared to the lidocaine group ($p = 0.023$ and $p = 0.013$, respectively) (Supplement Table S1).

Figure 3 summarizes results of the Area Under the Curve (AUC) regarding heart rate. Although the esmolol group demonstrated an AUC lower than the overall heart rate, this variable did not reach statistical significance. The positive incremental Area Under the Curve (PiAUC) was statistically significant ($p = 0.017$).

Mean arterial pressure values were lower in the esmolol group right after tracheal intubation: 65.8 (15.4) vs. 75.5 (19.8) mmHg, $p = 0.027$. At other moments after tracheal intubation, mean arterial pressure remained lower in the esmolol group, but without significance (Supplement Table S2). AUC and PiAUC were comparable (Fig. 4). No difference was observed regarding systolic blood pressure or its AUC (Supplement Table S3 and Supplement Fig. S4).

Discussion

This study revealed that the incidence of tachycardia during laryngoscopy and orotracheal intubation was lower in patients receiving esmolol bolus of 1.5 $mg.kg^{-1}$ followed by esmolol infusion at 0.15 $mg.kg^{-1}.min^{-1}$ when compared to those who received lidocaine. It is noteworthy that the incidence of adverse events such as hypertension and hypotension, coughing or movement did not differ between patients receiving esmolol or lidocaine.

Regarding the primary outcome, incidence of tachycardia, our findings were consistent with previous studies reporting the efficacy of esmolol in blunting the cardiovascular response to laryngoscopy and orotracheal intubation.[11–14] However, it is important to emphasize that our study contributes to this knowledge using a single protocol. In fact, whereas previous studies used a bolus dose of esmolol, our study used a loading dose (1.5 $mg.kg^{-1}$) followed by a maintenance dose (0.15 $mg.kg^{-1}.min^{-1}$). According to Efe et al.,[15] continuous infusion doses of esmolol (0.5 $mg.kg^{-1}.min^{-1}$) provide better hemodynamic stability for patients with coronary artery disease undergoing coronary artery bypass graft compared to bolus doses (1.5 mg. kg^{-1}). The authors underlined the safety and effectiveness of the doses they studied in patients with limited cardiac reserve, even at doses above those recommended in the literature. Although we used a distinct protocol of administration, our study revealed a maximum fall in heart rate immediately after tracheal intubation, as well as in the 3rd and 6th consecutive minutes, comparable to studies that used bolus doses of esmolol.[12–14]

Hemodynamic response to airway handling results from reflex sympathetic hyperactivity. According to Shribman et al.,[16] while tracheal intubation mainly elevates heart rate, laryngoscopy predominantly causes an increase in blood pressure. The authors advocate that laryngoscopy produces a balanced stimulus between cardioaccelerator fibers and vagal response. On the other hand, tracheal intubation produces less vagal stimulation, thus generating a proportionally higher increase in the incidence of tachycardia. These changes were chiefly described in the first minute after tracheal intubation and may have caused reflex sympathetic hyperactivity and consequently increased myocardial oxygen consumption.[17] In our study, we observed that heart rate and mean blood pressure levels in the first minute after intubation in the esmolol group were lower than in the lidocaine group, and within safe levels in both groups.[12,14] However, no change was detected in the mean arterial pressure at the other moments of assessment after tracheal intubation. Singh et al.[3] compared the effects of esmolol and lidocaine on hemodynamic changes and, as opposed to our results, they observed better control of blood pressure levels (mean, systolic and diastolic blood pressure), in addition to the effects on heart rate in the esmolol group immediately after and up to 5 minutes after tracheal intubation. However, this disagreement can be explained because they used a higher dose (2 $mg.kg^{-1}$) in their study.

Since we did not observe hemodynamic changes, arrhythmias or bronchospasm episodes, another important finding of our study was that the esmolol administration protocol used was associated with the absence of serious adverse events. Although these results agree with most reports employing bolus administration of esmolol,[11,13,14,18] it is important to underline that Korpinen et al. found a trend towards episodes of intraoperative hypotension and bradycardia in elderly patients in which the combination of propofol and esmolol was used.[12] Despite the possibility of these events being related to the use of beta-blockers, our study, as well as findings reported by Gulabani et al.,[1] do not support this hypothesis.[1,12]

Movement or coughing are also considered adverse events related to laryngoscopy and orotracheal intubation. While Panti et al.[9] reported that intravenous lidocaine reduces cough resulting from these procedures, very few studies

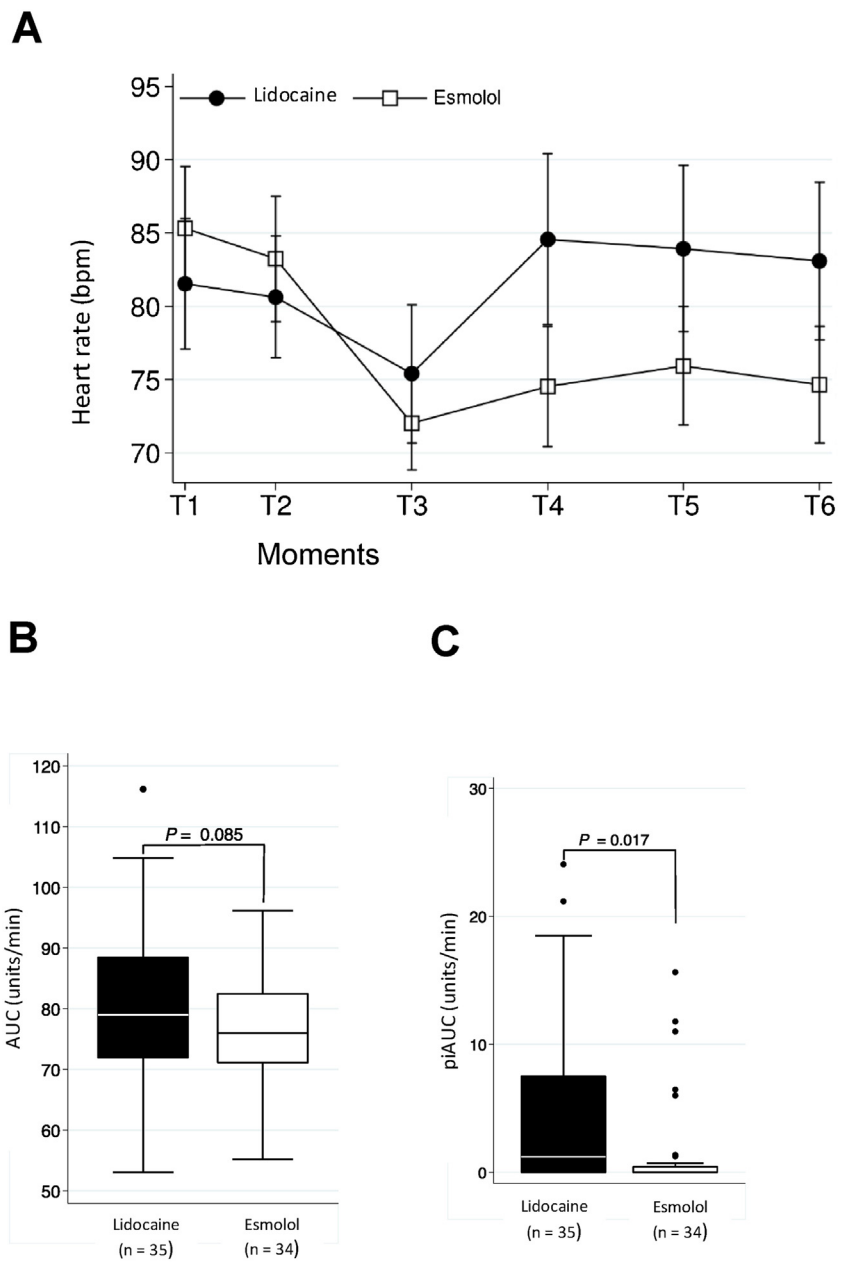

Figure 3 Effects of intravenous administration of esmolol and lidocaine on heart rate. (A) Variation of heart rate over time. Both the (B) Area Under the Curve (AUC,) and the (C) positive incremental Area Under the Curve (piAUC) were calculated by trapezoidal integration of heart rate measurements over time.

evaluated the efficacy of esmolol to prevent these events. Shende et al.[19] did not find superiority in intubation conditions (mandibular relaxation, coughing, patient movements, and vocal cord movements) in patients that received esmolol and metoprolol. In our study, patients who received esmolol had a lower occurrence of coughing or movement, however, there was no statistical difference between the groups. This finding is anticipated, as there is still no concrete evidence of the interference of beta-blockers in neuromuscular blockade.

The present study has some limitations that need to be highlighted. First, our randomized clinical trial was not stratified by elective and emergency surgery between the groups studied. Second, we did not assess variations in the QT interval and did not measure the levels of catecholamines, acute-phase proteins and interleukins in patients, which would provide more reliable results on hemodynamic responses and metabolic stress related to tracheal intubation.[20] Third, the group of patients receiving esmolol may have shown a greater tendency toward hypotension or bradycardia, as it had a greater number of diabetic patients. However, this group of patients did not present a higher incidence of cardiac autonomic neuropathy or preoperative signs of dysautonomia.[21] Excluding patients previously taking beta-blockers and patients with coronary artery disorder can also be identified as a poten-

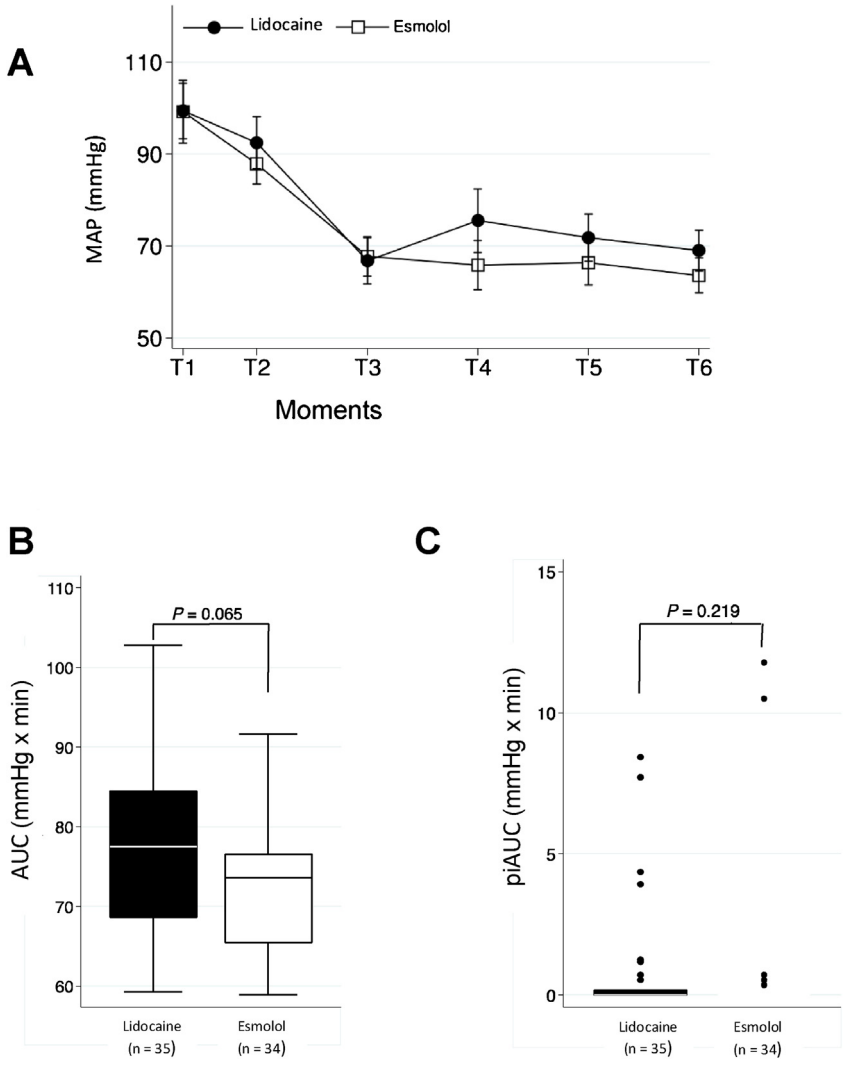

Figure 4 Effects of intravenous administration of esmolol and lidocaine on mean arterial pressure. (A) Variation of mean arterial pressure over time. Both the (B) Area Under the Curve (AUC), and the (C) positive incremental Area Under Curve (piAUC) were calculated by trapezoidal integration of mean arterial pressure measurements over time.

tial limitation, for the current guideline on cardiovascular assessment indicates that these patients would benefit more from intraoperative beta-adrenergic antagonism.[21] Furthermore, the unfavorable outcomes resulting from tachycardia and arterial hypertension are critical in patients with coronary artery disease, which makes it essential to control these variables.[17] Studies have revealed an increased incidence of perioperative myocardial infarction when there are episodes of hypertension or intraoperative heart rate is higher than 110 beats per minute.[12,16] In our study, patients who received lidocaine had a higher incidence of hypertension, but without statistical difference, probably because the incidence was relatively low (5.7%) and the sample size was not estimated to consider this objective. Thus, it is possible that using esmolol may be more beneficial to patients with cardiovascular disease, nonetheless further investigation is required to test this hypothesis.

The data presented in this study suggest that the esmolol 1.5 mg.kg^{-1} bolus administration before general anesthesia induction, followed by maintenance infusion of 0.15 mg.kg^{-1}.min^{-1} secured better heart rate management immediately after tracheal intubation, with a lower risk of tachycardia when compared to lidocaine.

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Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.01.014.

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