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ORIGINAL INVESTIGATION

Metoprolol for prevention of bucking at orotracheal extubation: a double-blind, placebo-controlled randomised trial

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KEYWORDS
Airway extubation;
Cough;
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Tachycardia and hypertension

Abstract

Background: Respiratory responses to extubation can cause serious postoperative complications. Beta-blockers, such as metoprolol, can interfere with the cough pathway. However, whether metoprolol can effectively control respiratory reflexes during extubation remains unclear. The objective of this study is to evaluate the efficacy of intravenous metoprolol in attenuating respiratory responses to tracheal extubation.

Methods: Randomized, double-blinded, placebo-controlled trial. Setting: Tertiary referral center located in Brasília, Brazil. Recruitment: June 2021 to December 2021. Sample: 222 patients of both sexes with an American Society of Anesthesiologists (ASA) physical status I–III aged 18–80 years. Patients were randomly assigned to receive intravenous metoprolol 5 mg IV or placebo at the end of surgery. The primary outcome was the proportion of patients who developed bucking secondary to endotracheal tube stimulation of the tracheal mucosa during extubation. Secondary outcomes included coughing, bronchospasm, laryngospasm, Mean Blood Pressure (MAP), and Heart Rate (HR) levels.

Results: Two hundred and seven participants were included in the final analysis: 102 in the metoprolol group and 105 in the placebo group. Patients who received metoprolol had a significantly lower risk of bucking (43.1% vs. 64.8%, Relative Risk [RR = 0.66], 95% Confidence Interval [95% CI 0.51–0.87], $p = 0.003$). In the metoprolol group, 6 (5.9%) patients had moderate/severe coughing compared with 33 (31.4%) in the placebo group (RR = 0.19; 95% CI 0.08–0.43, $p < 0.001$).

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Conclusion: Metoprolol reduced the risk of bucking at extubation in patients undergoing general anesthesia compared to placebo.

Introduction

Bucking and coughing secondary to endotracheal tube stimulation of the tracheal mucosa occur frequently after the general anesthetic recedes.[1] These reflex responses are initiated by activating irritant receptors in the tracheal mucosa, leading to a reflexive contraction of the airway smooth muscles and the stimulation of the cough reflex.[1-3] Approximately 40–70% of patients develop bucking and coughing in surgical procedures requiring general anaesthesia.[1-3] Bucking and coughing may lead to significant complications, including tachycardia, hypertension, higher intracranial and intraocular pressure (especially after craniotomies and eye procedures), wound dehiscence after laparotomy, laryngeal oedema, myocardial ischemia and increased surgical site bleeding.[1-4] In particular, cough during and after endotracheal tube removal may cause a ligature to slip or non-ligated small vessels to bleed profusely because of increased venous pressure. Thus, bucking and coughing can increase the length of hospital stay, health-related costs and mortality.[1,2,5]

Although guidelines on pharmacological methods to control hemodynamic responses to airway manipulation during the intubation period have been developed,[6] recommendations on appropriate strategies to prevent respiratory and cardiovascular responses during tracheal extubation are not fully established. Several drugs can be used to control the hemodynamic responses to airway manipulation during the extubation period, including short-acting opioids, alpha-2 agonists, local anesthetics, corticosteroids, and beta-blockers.

In this respect, beta-blockers are known to reverse sympathetic activation during acute stress, suggesting a potential role of this drug class in attenuating cardiovascular responses and decreasing the risk of harmful events after extubation.[2,7,8] We recently showed that treatment with esmolol, an ultrashort-acting intravenous beta-blocker, was associated with clinically relevant hemodynamic control after tracheal extubation, which might contribute to the reduction of respiratory reflexes such as bucking and coughing.[2] Here, we hypothesized that metoprolol, a beta-blocker with a longer half-life than esmolol, could also show favorable effects on cough and bucking after extubation. In this respect, only a few randomized trials have explored the effects of metoprolol on the cardiovascular response after extubation, and none have examined the potential beneficial respiratory effects of metoprolol, specifically in relation to bucking and coughing.[9,10]

Therefore, the main objective of this randomized, double-blinded, placebo-controlled trial was to examine whether intravenous administration of a bolus infusion of 5 mg metoprolol before extubation could reduce the risk of bucking compared to placebo.

Methods

Setting and trial design

Before providing written informed consent, all participants were informed about the study protocol and objectives. Ethical approval was provided by the Ethics Committee at the Instituto Hospital de Base do Distrito Federal (Jorge Alves de Almeida) on January 2021 (14/01/2021) (CAAE: 37700620.5.0000.8153). The trial was registered in the Brazilian Registry of Clinical Trials (RBR-3xk4qkq) and approved in May 2021 (21/05/2021). All research procedures were conducted in accordance with the Helsinki Declaration. We followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[11]

This was an investigator-initiated, randomized, double-blind, placebo-controlled trial with a 1:1 allocation ratio, at a single tertiary care hospital. Blinding occurred at the level of patients and investigators (surgery team and outcome assessors). All surgeries were performed at the Hospital de Base, Distrito Federal, Brazil.

Eligibility criteria for enrollment

Both male and female patients were eligible. We included participants aged between 18 and 80 years, with an American Society of Anesthesiologists (ASA) physical status of I, II or III, undergoing elective or urgent surgical procedures with general anesthesia using direct laryngoscopy and orotracheal extubation in the operating room.

Additionally, we used the following non inclusion criteria: participants with any contraindications or history of hypersensitivity to the study drugs, patients with coronary artery disease, atrioventricular block, cardiac arrhythmias, heart failure, chronic respiratory diseases such as chronic obstructive pulmonary disease or asthma, recent respiratory tract infection, chronic cough, current smoking, renal failure, hepatopathies, and morbid obesity (defined as a body mass index $\geq$ 40 $kg.m^{-2}$). Furthermore, we did not consider the enrollment of beta-blocker and calcium channel blocker users.

Criteria for exclusion from the trial and data analysis

Participants were excluded from the trial and data analysis if they met any of the following criteria during surgery: intraoperative hemodynamic instability (for example, hemorrhage and anaphylaxis), previous blocks in the airway region (e.g., superior laryngeal or transtracheal), procedures involving orotracheal intubation approaches other than direct laryngoscopy (e.g., videolaryngoscopy), use of atropine/

neostigmine, difficult intubation (defined as more than two attempts) and patients who required neuraxial anesthesia.

General anesthesia

All patients received routine monitoring, intravenous fluid infusions, and premedication with intravenous midazolam (0.05 mg.kg^{-1}). Induction was performed with lidocaine (1 mg.kg^{-1}), fentanyl (2 μg.kg^{-1}), propofol (2 mg.kg^{-1}), and rocuronium (0.6–1 mg.kg^{-1}). Patients were maintained under balanced general anesthesia (sevoflurane and remifentanil) or total intravenous anesthesia (propofol and remifentanil). The Bispectral Index (BIS) was kept between 40 and 60 at the discretion of the attending anesthesiologist.

The inner diameter of the endotracheal tube used was 7.5 mm for female patients and 8.0 mm for male patients. Cuff pressure was controlled at 20–25 mmHg and was monitored with a pressure gauge. After successful intubation, mechanical ventilation (tidal volume: 6–8 ml.kg^{-1}, respiratory rate: 12–18 breaths/min) was initiated, and the end-tidal carbon dioxide pressure was maintained at 35–40 mmHg.

We administered a bolus infusion of 50 μg fentanyl if Systolic Arterial Pressure (SAP) or Heart Rate (HR) levels increased by 20% or more compared to baseline values. Patients were administered ephedrine (5 mg) if Systolic Blood Pressure (SBP) levels dropped below 20% compared to baseline levels. Patients were also given atropine (0.01 mg.kg^{-1}) if HR levels fell below 50 beats per minute (bpm). At the end of the surgery, all anesthetics were discontinued.

Neuromuscular block was reversed using 2 to 4 mg.kg^{-1} of sugammadex according to the Train Of Four (TOF) values. The endotracheal tube was removed when the following parameters were met: pressure support ventilation, respiratory rate of 12–20 breaths/min, tidal volume of 6 ml.kg^{-1}, $SpO_2 \geq 95\%$, spontaneous eye-opening, voluntary movements, BIS $\geq$ 80, and a TOF > 90%. A routine oropharyngeal blind suction was performed before extubation.

Study drugs: metoprolol and placebo

According to the minimal alveolar concentration of approximately 0.5 or the expected time for the patient to wake up of 13 min (as indicated in the target-controlled infusion propofol pump), the metoprolol group received a bolus infusion of 5 mg/20 ml of metoprolol over 3 minutes. Patients randomized to the placebo group received 0.9% saline over three minutes. For both metoprolol and placebo groups, extubation was performed after postoperative neurological assessment, indicating spontaneous breathing, eye-opening, and/or voluntary movements.

Outcomes

Our primary outcome was the proportion of patients developing bucking, a clinician-assessed outcome. In our study, bucking was defined as a situation in which a patient is trying to cough and strain on an endotracheal tube and has violent expiratory contraction of skeletal muscles secondary to endotracheal tube stimulation of the tracheal mucosa.

Secondary outcomes included cough after extubation, Mean Arterial blood Pressure (MAP), Heart Rate (HR) levels, and adverse events such as bronchospasm and laryngospasm. Regardless of symptomatology, we conducted a comprehensive auscultatory examination for bronchospasm and laryngospasm in all participants post-extubation and before discharge from the operating room.

The outcomes were evaluated longitudinally at several time points: on admission, at the end of the surgery, one minute before infusion of the study drugs, during the first minute of infusion, at the end of infusion, during extubation, and at 1, 3, 5, 10, 60, and 120 min after extubation.

The incidence of arterial hypertension, hypotension, tachycardia, and bradycardia was recorded throughout the study period. After extubation, we defined hypertension as SAP $\geq$ 120% of baseline value or $\geq$ 140 mmHg and hypotension as SBP levels below 80% of the baseline value or < 90 mmHg. Tachycardia was defined as an HR $\geq$ 120% of the baseline value or > 100 bpm. Bradycardia was defined as an HR $\leq$ 50 bpm.[1,2,4]

We also examined extubation quality, which was rated using a 5-point numerical rating scale (modified Minogue scale,[12] which assesses cough quantity and time), with lower scores representing better extubation quality: 1 = No cough, 2 = Mild cough (coughing once or twice, or transient cough in response to extubation, which resolves spontaneously), 3 = Moderate cough (3 coughing episodes, lasting up to 5 seconds), 4 = Severe cough ($\geq$ 4 coughing episodes, lasting longer than 5 seconds), and 5 = Very severe cough (severe cough with laryngospasm). This outcome was assessed by the assistant anesthesiologist (blind to the treatment group) at the time of the patient's discharge from the operating room (peri-immediate extubation period, up to 10 min after extubation). The highest recorded score was used for analysis.

Sample size

Based on data from our previous randomized trial,[2] we estimated that the proportion of patients with bucking was approximately 44.4% in the placebo group. Considering a 50% relative reduction in the risk of bucking in the metoprolol group (22.2% vs. 44.4%), 204 participants (102 per group) yielded 90% power to detect this between-group difference at an alpha level of 5% (two-sided). The number of participants per group increased to 113 (226 patients in total) to allow for a 10% dropout rate.

Randomization, allocation concealment and blinding

Using a computer-generated random sequence, eligible participants were randomized 1:1 via simple randomization (www.randomizer.org). The allocation sequence was kept inaccessible to all investigators throughout patient recruitment and treatment.

The syringes were carefully prepared centrally by investigators who were not involved in patient recruitment, care, or follow-up. Specifically, syringes were consecutively numbered according to the randomization list and sent sequentially to the operating room shortly before administration.

Both study drugs had identical volumes, odors, viscosities, and appearances.

Statistical methods

The primary analysis was based on the per-protocol population, consisting of eligible participants who completed the trial according to the protocol without any major protocol deviations and did not meet any of the exclusion criteria during surgery.

We checked linearity and normality assumptions using histograms, normal probability plots, and the Shapiro-Wilk test. The Mann-Whitney test compared variables with asymmetric distributions, whereas the Student's *t*-test for independent samples examined between-group differences in variables with approximately normal distributions. Binary and categorical variables were compared by Fisher's exact or χ^2 test. Continuous variables were summarized as mean (Standard Deviation, SD), mean (95% Confidence Interval, 95% CI) or median (Interquartile Range, IQR). Binary and categorical variables were presented as absolute numbers (percentages), and associations were captured using the Relative Risk (RR) along with 95% CI. We calculated the Number Needed to Treat (NNT) to measure clinical benefit. We used a linear mixed-effects model with the restricted maximum likelihood estimator to analyze continuous outcomes with repeated measures. The model had a random intercept for each patient and explicitly considered the correlation between time points. In the fixed-effects part of the model, treatment and time were entered as categorical variables. In addition, an interaction term between treatment and time was also included. A two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 20. (Chicago, IL, USA) and Stata (version 16, StataCorp, College Station, TX, USA).

Results

Patient characteristics

From June 2021 through December 2021, we screened 226 patients (Fig. 1). Of these, 222 were included: 111 patients were randomly assigned to the placebo group, and 111 were randomly assigned to the metoprolol group.

Nine patients in the metoprolol group and 6 patients in the placebo group were excluded from the analysis (see Fig. 1 for reasons). Therefore, none of these 9 patients received an infusion of either placebo or metoprolol. Thus, the final analysis encompassed 102 patients in the metoprolol group and 105 patients in the placebo group.

The study population had a mean (SD) age of 45 (16) years, a mean (SD) body mass index of 26 (4.4) $kg.m^{-2}$, 114 participants (55%) were women, and most patients 136 (66%) had an ASA physical status II (Table 1).

Primary outcome: bucking

The primary outcome occurred in 44 of 102 patients (43.1%) in the metoprolol group and 68 of 105 patients (64.8%) in the placebo group (RR = 0.67, 95% CI 0.51 to 0.87, $p = 0.003$), resulting in an NNT of 5.

Secondary outcomes: coughing

As shown in Table 2, participants in the metoprolol group were less likely to develop moderate or severe degrees of cough after extubation than participants in the control group ($p < 0.001$ for the global test of any differences between groups). In the metoprolol group, 6 of 102 patients (5.9%) had moderate/severe coughing compared to 33 of 105 patients (31.4%) in the placebo group (RR = 0.19, 95% CI 0.08 to 0.43, $p < 0.001$, NNT = 4). No cases of very severe coughing with difficult breathing or laryngospasm were observed.

Secondary outcomes: hemodynamic changes and adverse events

Figure 2 (panel A) shows the longitudinal changes in HR levels during the perioperative period. The global joint significance test yielded a $p < 0.001$, indicating that the two groups differed significantly in their HR trajectory patterns during follow-up period under examination. On extubation, HR levels increased rapidly in the placebo group but remained relatively stable in the metoprolol group. In time point-specific analysis, the metoprolol group was associated with significantly lower HR levels than the placebo group from the period that covers the end of infusion to 2 hours after extubation. Similar patterns were observed for MAP levels, but the lowest MAP levels observed in the metoprolol group were restricted to three time points, including the extubation time up to 3 min after extubation (Fig. 2, panel B).

Ten of 102 patients (9.8%) in the metoprolol group and 77 of 105 patients (73.3%) in the placebo group developed tachycardia (RR = 0.13, 95% CI 0.07 to 0.24, $p < 0.001$, NNT = 2). There was one case of bradycardia in both trial groups.

Furthermore, patients in the metoprolol group were 64% less likely to develop hypertension than their placebo-treated counterparts (RR = 0.36, 95% CI 0.22 to 0.59, $p < 0.001$, NNT = 3). No significant differences were observed in the incidence of hypotension between the metoprolol and placebo groups (Table 2).

One case of bronchospasm occurred in the metoprolol group and none in the placebo group ($p = 0.25$). No deaths or serious adverse events related to the study drugs occurred in either group.

Discussion

Tracheal extubation is a critical step after general anesthesia, being as clinically important as intubation and the first surgical incision. From the patient's perspective, tracheal extubation can be a stressful and unsettling experience, affecting the postoperative recovery and resulting in serious complications.[5]

To the best of our knowledge, this is one of the few randomized trials investigating the action of beta-blockers on

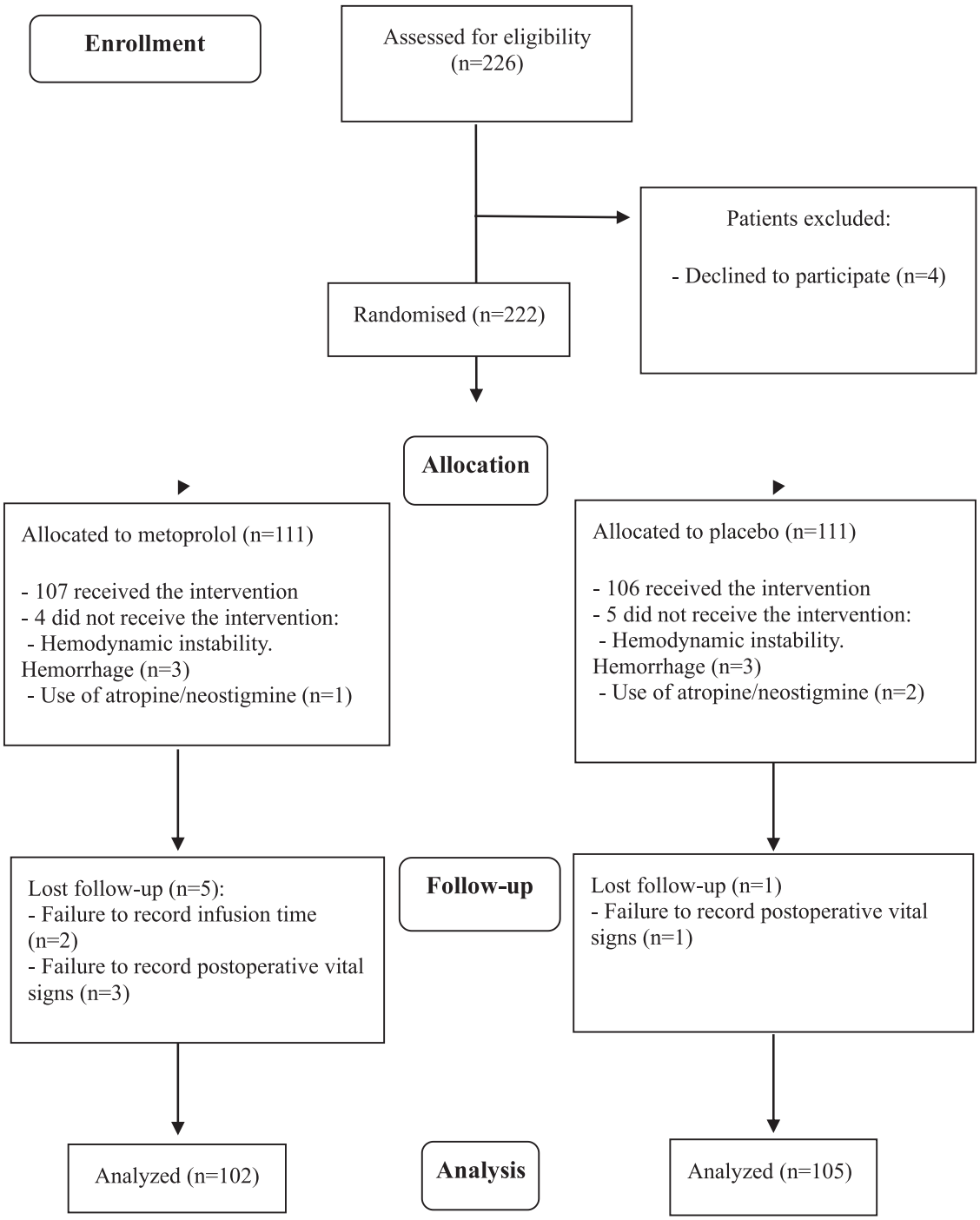

Figure 1 Consort Flow Diagram.

airway reflexes related to tracheal extubation[2,7,13-15] and the first to examine the benefits of metoprolol at extubation for a wide range of surgical procedures.

The efficacy of esmolol in reducing the risk of bucking and increasing the quality of extubation has recently been reported, as it has been shown that beta-blockers can interfere with cough pathways, decreasing their excitability during airway procedures such as orotracheal extubation.[2] In a previous randomized trial in patients undergoing abdominal surgeries, treatment with esmolol (1 mg.kg^{-1}) was associated with significantly lower heart rate and systolic blood pressure levels than treatment with placebo (saline) after tracheal extubation.[7] In another trial,[9] when metoprolol (0.02 mg.kg^{-1}), verapamil (0.05 mg.kg^{-1}), diltiazem (0.2 mg.kg^{-1}), and placebo were administered 2 min before tracheal extubation, patients treated with metoprolol showed stable heart rate

Table 1 Sociodemographic, clinical, and surgical characteristics of the study population.

	Metoprolol (n = 102)	Placebo (n = 105)
Sociodemographics		
Age (years), mean (SD)	43.6 (15.1)	47.1 (17)
Weight (kg), mean (SD)	72.6 (14.6)	69.8 (12.8)
BMI ($kg.m^{-2}$) (SD)	26.3 (4.8)	25.3 (4)
Female, (%)	53 (52)	61 (58)
Clinical characteristics		
ASA physical status, n (%)		
I	20 (19.6)	15 (14.3)
II	65 (63.7)	71 (67.6)
III	17 (16.7)	19 (18.1)
Arterial hypertension, n (%)	20 (19.6)	20 (19)
Type-II diabetes, n (%)	8 (7.8)	12 (11.4)
Obesity (BMI $\geq$ 30), n (%)	10 (9.8)	10 (9.6)
Hypothyroidism, n (%)	5 (4.9)	5 (4.8)
Hyperthyroidism, n (%)	1 (1)	1 (1)
Surgery-related characteristics		
Type of surgery, n. (%)		
Elective	77 (75.5)	72 (68.6)
Emergency	25 (24.5)	33 (31.4)
Medical specialty, n (%)		
Maxillofacial	10 (9.8)	6 (5.7)
Head and neck	8 (7.8)	6 (5.7)
General surgery	15 (14.7)	27 (25.7)
Oncological surgery	7 (6.9)	5 (4.8)
Plastic surgery	0	3 (2.9)
Thoracic surgery	2 (2.0)	0
Vascular surgery	1 (1.0)	0
Gynecology	6 (5.9)	4 (3.8)
Mastology	15 (14.7)	10 (9.5)
Neurosurgery	18 (17.6)	22 (20.9)
Ophthalmology	0	5 (4.8)
Orthopedics	5 (4.9)	3 (2.9)
Otolaryngology	12 (11.7)	6 (5.7)
Proctology	1 (1.0)	2 (1.9)
Urology	2 (2.0)	6 (5.7)
Surgical time (min), mean (SD)	151.7 (78.9)	145.5 (76.8)
Anesthesia-related characteristics		
Maintenance of anesthesia, n (%)		
Non-opioid drugs		
Sevoflurane	65 (63.7)	74 (70.5)
Propofol	37 (36.3)	31 (29.5)
Opioids		
Remifentanil	57 (55.9)	48 (45.7)

BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status; SD, Standard Deviation.
Obesity is defined as body mass index $\geq$ 30 $kg.m^{-2}$.
Arterial hypertension was defined as a diagnosis of arterial hypertension with oral antihypertensive use.
The length of surgery was defined as the time from the first incision to complete closure.

Table 2 Primary and secondary outcomes.

	Metoprolol (n = 102)	Placebo (n = 105)	RR (95% CI)	*p*
Primary outcome				
Bucking, n (%)	44 (43.1)	68 (64.8)	0.67 (0.51–0.87)	0.003
Secondary outcomes: coughing[a]				
No cough (1)	40 (39.2)	23 (21.9)	1.79 (1.16–2.77)	0.009
Mild cough (2)	56 (54.9)	49 (46.7)	1.18 (0.90–1.54)	0.24
Moderate cough (3)	3 (2.9)	27 (25.7)	0.11 (0.04–0.37)	<0.001
Severe cough (4)	3 (2.9)	6 (5.7)	0.51 (0.13–2.00)	0.34
Secondary outcomes: hemodynamic responses				
Tachycardia, n (%)	10 (9.8)	77 (73.3)	0.13 (0.07–0.24)	<0.001
Bradycardia, n (%)	1 (1)	1 (1)	0.97 (0.53–1.78)	0.93
Hypertension, n (%)	17 (16.7)	48 (45.7)	0.36 (0.22–0.59)	<0.001
Hypotension, n (%)	23 (22.5)	17 (16.2)	1.39 (0.79–2.45)	0.25
Secondary outcomes: adverse events				
Bronchospasm[b], n (%)	1 (0.5)	0	3.1 (0.13–74.9)	0.49

Modified Minogue scale: 1 = No cough, 2 = Mild cough (coughing once or twice), 3 = Moderate cough (3 coughing episodes, lasting up to 5 seconds), 4 = Severe cough (≥ 4 coughing episodes), and 5 = Very severe cough (severe cough with laryngospasm).
RR denotes relative risk. 95% CI denotes 95% Confidence Interval.
[a] $p < 0.001$ for the global test of any difference between groups (Fisher's exact test).
[b] A continuity correction (0.5) was added to each cell of a 2 by 2 table.

levels compared to baseline values. Unfortunately, none of the previous trials on metoprolol[9,10-15] analyzed the incidence of respiratory responses, such as bucking and cough, hindering a direct comparison between ours and previous findings. In our trial, no patients in the metoprolol required management for hypotension or bradycardia, indicating that metoprolol could be a safe intervention to prevent bucking and coughing after extubation.

Several other non-beta-blocker drugs have been examined to improve the quality of the peri-extubation period, with less promising results. For example, diltiazem and verapamil were associated with higher rates of hypotension and bradycardia, occasionally requiring vasopressor therapy.[9] A systematic review including 16 trials (1516 patients) revealed that intravenous lidocaine administration was associated with significant reductions in post-extubation cough (RR = 0.64; 95% CI 0.48–0.86) compared to placebo or no intervention.[4] In a randomized trial in patients undergoing thyroid surgeries, the effects of lidocaine, dexmedetomidine and placebo after extubation were compared. A significantly lower risk of cough was observed in the lidocaine group (28%) and the dexmedetomidine group (32%) than in placebo-treated patients (67%). Nevertheless, 58% of patients in the dexmedetomidine group developed bradycardia, although no cases of bradycardia were noted in the lidocaine and placebo groups.[3] A recent network meta-analysis indicated that dexmedetomidine, remifentanil, fentanyl and lidocaine were comparable in reducing the incidence of moderate and severe coughing. These four drugs were also superior to placebo or no treatment.[1] Dexmedetomidine generally blunted the tachycardia and hypertension associated with extubation compared with placebo, but was associated with a higher risk of bradycardia, particularly during infusion. By contrast, fentanyl and lidocaine had comparable hemodynamic perturbations to placebo or no treatment during extubation.[1] Trials investigating beta-blockers were not included in this meta-analysis. Overall, the accumulated evidence indicates that beta-blockers could be superior to other agents, such as opioids, local anesthetics, and calcium channel blockers in mitigating cardiorespiratory responses at extubation.[2,7,9] However, more head-to-head trials are needed to verify this hypothesis.

Our study has a few limitations. First, we did not include patients with coronary artery disease and beta-blocker users, exclusion criteria that could reduce the generalizability of our findings. Second, we enrolled patients who underwent a wide variety of surgical procedures. Given our broader inclusion criteria than previous randomized trials, our results should be interpreted as applying to the "average" surgical patient. Hence, we cannot rule out the possibility that metoprolol may have higher (or lower) efficacy than placebo in certain types of surgical procedures and patient populations. Therefore, additional surgery-specific investigations are warranted. Third, we used the Portuguese version of the Minogue scale, which has not been validated. However, the scale's relative simplicity and blinding of outcome assessors make differential detection biases unlikely, and any potential impact on our results is expected to be minimal. Fourth, our findings regarding secondary outcomes should be interpreted cautiously, as they are considered exploratory in nature. This caution is warranted because the sample size was not specifically calculated to address these outcomes, and no correction method was employed to mitigate the potential for family-wise errors.

Conclusion

In this randomized, double-blind, placebo-controlled trial, the administration of intravenous metoprolol (5 mg) reduced the risk of bucking at tracheal extubation compared to placebo. Metoprolol was well tolerated, resulting in better control of mean arterial pressure and heart rate levels during the peri-extubation period and higher extubation quality

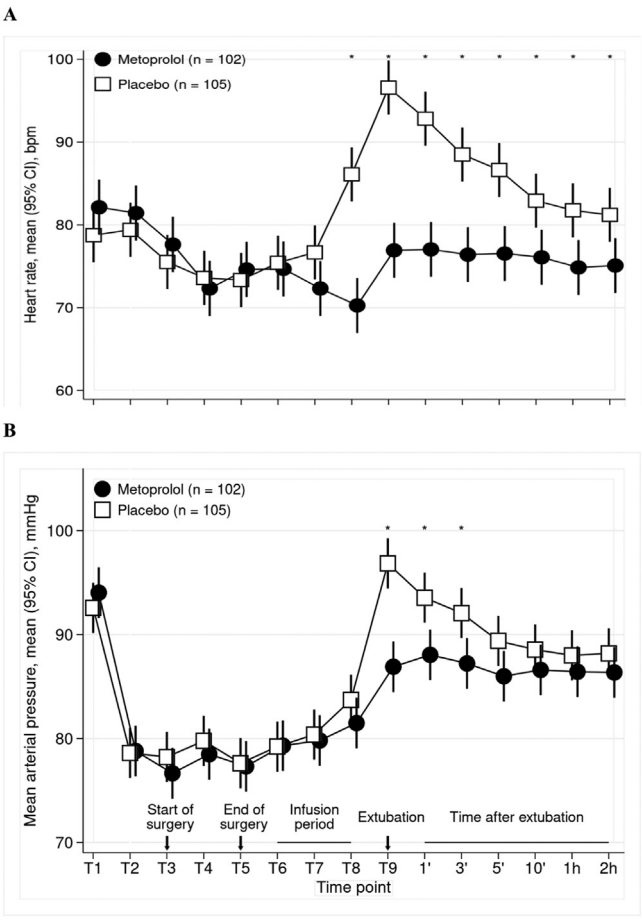

Figure 2 Trajectory of heart rate (panel A) and mean arterial pressure (panel B) levels during the perioperative period. Results are based on linear mixed-effects models. 95% CI denotes 95% Confidence Interval. *Denotes statistically significant results at two-sided α = 5% (i.e., $p < 0.05$). T1 denotes arrival at the operating room. T2 denotes the immediate period after orotracheal intubation. T4 denotes 1h after orotracheal intubation. T5 end of surgery. T6, T7 and T8 encompass the pre-infusion period, 1 min of infusion and end of infusion, respectively. 1' to 4' denote time in minutes after extubation. In Panel A, the significance levels were: T8 ($p < 0.001$), T9 ($p < 0.001$), 1' to 3' after extubation ($p < 0.001$), 4' after extubation ($p = 0.004$), 1h after extubation ($p = 0.004$) and 2h after extubation ($p = 0.01$). All the remaining time points were not statistically significant. In Panel B, the significance levels were T9 ($p < 0.001$), 1' after extubation ($p = 0.002$) and 2' after extubation ($p = 0.006$). All the remaining time points were not statistically significant.

than placebo. We found no statistically significant differences between the metoprolol and placebo groups in the incidence of bradycardia and hypotension.

Ethics approval and consent to participate

Before providing written informed consent, all participants were informed about the study protocol and objectives. Ethical approval was provided by the Ethical Committee at the Instituto Hospital de Base do Distrito Federal (Jorge Alves de Almeida Venancio) on January 2021 (14/01/2022) (CAAE: 37700620.5.0000.8153). The trial was registered in the Brazilian Registry of Clinical Trials (RBR-3xk4qkq) and approved on May 2021 (21/05/2022). https://ensaiosclinicos.gov.br/rg/RBR-3xk4qkq.

Declaration of Competing Interest

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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References

1. Tung A, Fergusson NA, Ng N, Hu V, Dormuth C, Griesdale DEG. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. Br J Anaesth. 2020. https://doi.org/10.1016/j.bja.2019.12.041. Online ahead of print.
2. Mendonça FT, Barreto Filho JH, Hungria MBCS, Magalhães TC. Efficacy of a single dose of esmolol to prevent extubation-related complications during emergence from anesthesia: a randomized, double-blind, placebo-controlled trial. Braz J Anesthesiol. 2023;73:426–33.
3. Hu S, Li Y, Wang S, Xu S, Ju X, Ma L. Effects of intravenous infusion of lidocaine and dexmedetomidine on inhibiting cough during the tracheal extubation period after thyroid surgery. BMC Anesthesiol. 2019;19:66.
4. Yang SS, Wang NN, Postonogova T, et al. Intravenous lidocaine to prevent postoperative airway complications in adults: a systematic review and meta-analysis. Br J Anaesth. 2020;124:314–23.
5. Asai T, Koga K, Vaughan RS. Respiratory complications associated with tracheal intubation and extubation. Br J Anaesth. 1998;80:767–75.
6. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth. 2018;120:323–52.
7. Bostan H, Eroglu A. Comparison of the clinical efficacies of fentanyl, esmolol and lidocaine in preventing the hemodynamic responses to endotracheal intubation and extubation. J Curr Surg. 2012;2:24–8.
8. Prajwal Patel HS, Shashank MR, Shivaramu BT. Attenuation of hemodynamic response to tracheal extubation: a comparative study between esmolol and labetalol. Anesth Essays Res. 2018;12:180–5.
9. Yörükoglu D, Göktug A, Alanoglu Z, Tulunay M. Comparison of intravenous metoprolol, verapamil and diltiazem on the attenuation of haemodynamic changes associated with tracheal extubation. Eur J Anaesthesiol. 1999;16:462–7.
10. Azhar R, Gauhar A. Haemodynamic response to tracheal extubation: verapamil versus metoprolol. Gen Med Open Access. 2015:1–4.

11. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
12. Minogue SC, Ralph J, Lampa MJ. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. Anesth Analg. 2004;99:1253–7.
13. Ratnani E, Sanjeev OP, Singh A, Tripathi M, Chourasia HK. A comparative study of intravenous esmolol, labetalol and lignocaine in low doses for attenuation of sympathomimetic responses to laryngoscopy and endotracheal intubation. Anesth Essays Res. 2017;11:745–50.
14. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM. Esmolol attenuates cardiovascular responses to extubation. Anesth Analg. 1990;71:675–8.
15. Tektook NH, Ali S, Fadhil H. Comparative study between lidocaine and Metoprolol on hemodynamic attenuation during laryngoscope and endotracheal intubation. Gulf J Scientific Res. 2018;6:330–4.