ORIGINAL CLINICAL RESEARCH REPORT

Effects of Anticholinesterase Reversal Under General Anesthesia on Postoperative Cardiovascular Complications: A Retrospective Cohort Study

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BACKGROUND: The anticholinesterase neostigmine and the muscarinic inhibitor glycopyrrolate are frequently coadministered for the reversal of neuromuscular blockade. This practice can precipitate severe bradycardia or tachycardia, but whether it affects the incidence of cardiovascular complications remains unclear. We hypothesized that anticholinesterase reversal with neostigmine and glycopyrrolate versus no anticholinesterase reversal increases the risk of postoperative cardiovascular complications among adult patients undergoing noncardiac surgery with general anesthesia.

METHODS: We conducted a prespecified retrospective analysis of hospital registry data from a major health care network for patients undergoing surgery with general anesthesia from January 2007 to December 2015. The primary outcome was a composite of cardiac dysrhythmia, acute heart failure, transient ischemic attack, ischemic stroke, and acute myocardial infarction within 30 days after surgery. We performed sensitivity analyses in subgroups and propensity score adjustment and explored the association between exposure and outcome in subgroups of patients with high risk of cardiovascular complications.

RESULTS: Of the 98,147 cases receiving neuromuscular blockade, 73,181 (74.6%) received neostigmine and glycopyrrolate, while 24,966 (25.4%) did not. A total of 5612 patients (7.7%) in the anticholinesterase reversal group and 1651 (6.6%) in the control group ($P < .001$) experienced the primary outcome. After adjustment for clinical covariates, neostigmine and glycopyrrolate exposure was significantly associated in a dose-dependent fashion (P for trend <.001, respectively) with tachycardia (adjusted odds ratio = 2.1 [95% CI, 1.97–2.23]; $P < .001$) and bradycardia (adjusted odds ratio = 2.84 [95% CI, 2.49–3.24]; $P < .001$) but not with postoperative cardiovascular complications (adjusted odds ratio = 1.03 [95% CI, 0.97–1.1]; $P = .33$). We identified a significant effect modification of anticholinesterase reversal by high age, high-risk surgery, and history of atrial fibrillation (P for interaction = .002, .001, and .02, respectively). By using linear combinations of main effect and exposure–risk interaction terms, we detected significant associations between anticholinesterase reversal and cardiovascular complications toward a higher vulnerability in these patient subgroups.

CONCLUSIONS: Neuromuscular blockade reversal with neostigmine and glycopyrrolate was associated with an increased incidence of intraoperative tachycardia and bradycardia but not with 30-day postoperative cardiovascular complications. Exploratory analyses suggest that a high postoperative cardiovascular complication risk profile may modify the effects of anticholinesterase reversal toward clinical relevance. (Anesth Analg 2020;130:685–95)

KEY POINTS

- **Question:** Is intraoperative reversal of neuromuscular blockade with neostigmine and glycopyrrolate associated with postoperative cardiovascular complications after noncardiac surgery?
- **Findings:** Neuromuscular blockade reversal with neostigmine and glycopyrrolate was associated with arrhythmias but not with postoperative cardiovascular complications during the first 30 days after surgery.
- **Meaning:** Heart rate changes observed following neuromuscular blockade reversal with neostigmine and glycopyrrolate are not associated with postoperative cardiovascular complications except possibly in patients at high risk of these outcomes.

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Accepted for publication January 24, 2019.

Funding: Supported by an investigator-initiated grant from MERCK (MISP: 57669; to M.E.).

DOI: 10.1213/ANE.0000000000004099

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

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More than 230 million major surgical procedures occur annually around the world.[1] Nondepolarizing neuromuscular blocking drugs are frequently administered during general anesthesia to facilitate surgery, tracheal intubation, and controlled ventilation.[2] In both Europe and the United States, most patients receiving neuromuscular blocking drugs also receive an acetylcholinesterase inhibitor, most commonly neostigmine, to accelerate the reversal of neuromuscular blockade.[3]

Acetylcholinesterase inhibitors inhibit the catalyzed hydrolysis of acetylcholine, which surmounts competitive blockade by neuromuscular blocking drugs. Acetylcholinesterase inhibitors also increase cholinergic activation of muscarinic receptors, producing parasympathetic effects such as bradycardia, increased gastrointestinal motility, and bronchial secretions. To prevent these effects,[4] antimuscarinic drugs are coadministered with neostigmine.[5,6]

Cardiac rate and rhythm can be profoundly affected by the combined procholinergic and antimuscarinic effects of neostigmine and glycopyrrolate. Case reports have documented severe bradycardia and asystole following coadministration of these drugs.[7,8] However, small cohort studies have shown that this drug combination significantly increases average heart rate (HR)[9,10] and can precipitate tachyarrhythmias.[11] Neostigmine and glycopyrrolate coadministration can also produce a period of tachycardia followed by bradycardia.

Cardiac arrhythmias and tachycardia in the perioperative period are associated with adverse cardiac events.[12,13] However, no large-scale studies have addressed whether HR and rhythm changes associated with neostigmine and glycopyrrolate coadministration affect the risk of postoperative cardiovascular complications, an important outcome to be considered in future perioperative quality initiatives.[14,15] In this study, we conducted a retrospective cohort analysis to test the primary hypothesis that neuromuscular blocking drug reversal with neostigmine and glycopyrrolate versus no neuromuscular blocking drug reversal is associated with increased rates of cardiovascular complications within 30 postoperative days among adult patients undergoing noncardiac surgery with general anesthesia.

METHODS

Study Design and Setting

We conducted a prespecified analysis of hospital registry data for patients undergoing surgery with general anesthesia at Massachusetts General Hospital and 2 affiliated community hospitals between January 2007 and December 2015. The Partners Institutional Review Board at Massachusetts General Hospital approved this study and waived the requirement for written informed consent before data retrieval (Protocol: 2014P000708). The study was performed according to an a priori defined statistical analysis plan. A strengthening the reporting of observational studies in epidemiology[16] statement is provided (see "Strengthening the Reporting of Observational Studies in Epidemiology Checklist").

Data Sources

Data were retrieved from different sources at Partners HealthCare, including the Massachusetts General Hospital Research Patient Data Registry, Enterprise Performance Systems Inc, and Anesthesia Information Management System. Research Patient Data Registry is a centralized clinical data registry that compiles data from hospital electronic health records, such as demographic data and billing codes, for research purposes. Enterprise Performance Systems Inc is a financial tracking database used for value-based quality metrics and internal cost tracking and contains encounter-level data on resource utilization, length of stay, and actual hospital costs. The Anesthesia Information Management System data warehouse contains data transmitted directly from the perioperative record, anesthesia equipment, and patient monitors. All covariates were defined a priori based on literature review and physiological plausibility.

Subject Selection

The study cohort consisted of all adult patients undergoing surgical procedures under general endotracheal anesthesia who were extubated at the end of the case. Cardiac surgery cases and patients with an American Society of Anesthesiologists (ASA) physical status >IV were not eligible. We also excluded patients who underwent any other surgical procedures within 4 weeks before the index case or for whom the data on the exposure variable (neuromuscular blocking drug reversal) or the outcome variable (postoperative cardiovascular complications) were missing in our data set. Moreover, we excluded cases where neostigmine and glycopyrrolate were administered >3 minutes apart or where neuromuscular blocking drug reversal was conducted <5 minutes before extubation.

Exposure Variable

The binary independent variable was the administration of neostigmine and glycopyrrolate during surgery ("neuromuscular blocking drug reversal") given simultaneously or within a 3-minute time period.

Primary Outcome

The primary outcome was an a priori defined dichotomized composite measure of postoperative cardiovascular complications within 30 postoperative days: cardiac dysrhythmia, acute heart failure, transient ischemic attack, ischemic stroke, and acute

myocardial infarction. The components of this composite outcome were identified by using diagnostic codes from the International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revision (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C753). Two coauthors (F.T.S. and A.-L.L.) manually translated International Classification of Diseases, Ninth Revision, codes into the most relevant International Classification of Diseases, Tenth Revision, codes using the following websites: "www.icd9data.com" and "www.icd-10data.com."

Heart Rate Data

Electrocardiography was used to quantify HR. We extracted HR data from the Anesthesia Information Management System as the mean of 1-minute periods. For validation, we used medical chart review in 100 randomly assigned cases. In addition, we conducted a review of patients' charts when extreme and possibly implausible HR values were observed. We analyzed HR during the interval of 5 minutes before to 15 minutes after coadministration of neostigmine and glycopyrrolate. To obtain HR data for the cohort that did not receive neostigmine/glycopyrrolate reversal, we used the mean time between neostigmine/glycopyrrolate coadministration and extubation in the exposed cohort as the reference time point for the control group. This reference time point was 19 minutes before extubation.

Secondary Outcomes

The secondary outcomes were intraoperative HR maximum and minimum values recorded within 15 minutes after neostigmine administration. Tachycardia was defined as HR >100 beats/min and a 20% increase from the baseline, and bradycardia was defined as HR <50 beats/min and a 20% decrease from the baseline during the 15-minute postneostigmine administration epoch (coefficient $\rho = .2$). HR extremes were tachycardia, bradycardia, or both. HR baseline was the median of the recorded HRs within 5 minutes before neostigmine administration.

Covariate Data

All multivariable analyses were controlled for predefined confounding variables that were identified by either literature research or based on physiological plausibility. Covariates included age, sex, body mass index, Charlson comorbidity index, ASA physical status, emergent versus nonemergent status of surgery, admission type (inpatient/ambulatory), year of surgery, surgery type, prescriptions for β-blockers and antiplatelet drugs within 4 weeks before surgery, and adverse admission (defined as admission from a facility that carries a high percentage of frail patients: long-term care, an intermediate-care facility, a skilled nursing facility, and a swing bed provider). Intraoperative data were controlled for duration of surgery, neuromuscular blocking drug dose expressed as multiples of the effective dose needed to reduce twitch height by 95%, intraoperative fluid volume given, total intraoperative vasopressor dose expressed as norepinephrine equivalents, and packed red blood cell units transfused. Taking into consideration procedural complexity, we included work relative value units in our model.

Statistical Analysis

Baseline characteristics that were continuous variables were expressed as mean (±SD) or median (25th and 75th percentiles) and compared using a 2-tailed *t* test or Wilcoxon rank sum test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared using a χ^2 test. The linearity assumption was tested for all continuous variables in the primary regression model. In case of nonlinearity, variables were divided into quintiles (alternatively, we performed an additional sensitivity analysis based on fractional polynomials, see Supplemental Digital Content, Additional Sensitivity Analysis: Fractional Polynomials Analysis, http://links.lww.com/AA/C753). The analyses of both primary and secondary outcomes were performed using multivariable logistic regression with a priori identified covariates, as described earlier.

Sensitivity Analyses. To examine the possible effect modifications on the association between neuromuscular blocking drug reversal with neostigmine/glycopyrrolate and the primary outcome, we conducted interaction term analyses between the exposure and the following variables, respectively: age, body mass index, ASA physical status, and duration of surgery. We included these interaction terms separately into the primary regression model. In case of significant interaction, we used linear combinations of the respective main effect and interaction term to assess the association between the exposure and the outcome across different patient subgroups.

The primary analysis was performed using the complete case method. To control for selection bias due to missing data, we utilized the multiple imputation by chained equations method.[17] In addition, we assessed if our primary results remained stable under varying definitions of neuromuscular blocking drug reversal. While in the primary analysis, we used neuromuscular blocking drug reversal with neostigmine/glycopyrrolate as a binary (yes/no) exposure variable, in the sensitivity analyses, we used total neostigmine dose as a continuous and as a binary

exposure variable (high [>60 μg/kg] versus low dose [0–60 μg/kg]).[18] To account for the risk of pulmonary complications that might be associated with cardiovascular complications, we reran the primary analysis, including the Score for Prediction of Postoperative Respiratory Complications[19] in the confounder model. Furthermore, we accounted for history of cardiovascular diseases by including a composite variable of history of atrial fibrillation, heart failure, aortic and/or mitral valve stenosis, and coronary artery disease in the confounder model. To evaluate the influence of model choice on the findings, we performed mixed-effects modeling with anesthesia provider as a random effect and included the same covariates from the primary analysis.

We calculated a propensity score for the probability of receiving neuromuscular blocking drug reversal to account for the imbalanced likelihood of receiving this treatment. The treatment model contained the covariates of the primary model.[20] The effectiveness of the propensity score adjustment was evaluated through the absolute standardized differences of covariates before and the weighted conditional standardized differences of covariates after propensity score adjustment.[21] We used a standardized difference of ≥0.1 as an indicator for a nonnegligible imbalance between exposure and control group, as has been reported previously.[22] Subsequently, we ran the primary model adjusted for the newly generated propensity score. To further adjust for potential covariates that were (still) imbalanced after propensity score adjustment, we ran the propensity score–adjusted primary model including those covariates.

Considering bias arising from unobserved readmission to out-of-network hospitals, we conducted 2 further sensitivity analyses (Supplemental Digital Content, Additional Sensitivity Analysis: Postoperative 30-Day Period, http://links.lww.com/AA/C753).

To examine the goodness of fit of the predefined primary confounder model, we performed the Hosmer–Lemeshow test. To assess the discrimination and accuracy of the confounder model, we estimated the risk of cardiovascular complications independent of neuromuscular blocking drug reversal through the concordance c-statistic (area under the receiver operating characteristic curve) and calculated the Brier score.

For the secondary outcome, we calculated the average HR increase within 2 minutes after neostigmine administration and additionally conducted a 2-sample *t* test to compare the HRs in the exposure and the control groups at 2 minutes and 15 minutes after neostigmine administration or the reference time point.

Exploratory Analyses. For exploratory analysis, we tested in separate analyses whether the association between the neuromuscular blocking drug reversal with neostigmine/glycopyrrolate and postoperative cardiovascular complications was modified by history of heart failure, coronary artery disease, aortic and/or mitral valve stenosis, or atrial fibrillation by building interaction terms: *history of cardiac disease (binary)*neuromuscular blocking drug reversal with neostigmine and glycopyrrolate (binary)*.

Furthermore, we analyzed a possible modification of the association between the exposure and the outcome through vascular or neurosurgery and high age (defined as ≥70 years), respectively. Therefore, we also built the interaction terms *neurosurgery/vascular surgery versus nonneurosurgery/nonvascular surgery*neuromuscular blocking drug reversal with neostigmine and glycopyrrolate (binary)* and *age (high versus low)*neuromuscular blocking drug reversal with neostigmine and glycopyrrolate (binary)*. We included these interaction terms separately into the primary regression model. In case of significant interaction, we proceeded as described above. In addition, we calculated the adjusted absolute risk difference for the outcome across the respective subgroups (Supplemental Digital Content, Figures 1–3, http://links.lww.com/AA/C753).

Finally, by using multivariable logistic regression with the covariates of the primary model, we analyzed the association of neostigmine/glycopyrrolate dose ratio and glycopyrrolate dose with intraoperative tachycardia/bradycardia (and furthermore with hypertension/hypotension, see Supplemental Digital Content, Exploratory Analysis: Hypertension and Hypotension as Outcomes and Table 2, http://links.lww.com/AA/C753).

Statistical analyses were conducted using Stata version 13.1 (StataCorp LP, College Station, TX), R statistical software V3.3.3, and RStudio V1.0 (RStudio Inc, Boston, MA). We considered a 2-tailed $P < .05$ statistically significant.

A Priori Power Analysis. We conducted an a priori power analysis based on previously observed neostigmine-related postoperative complications with an odds ratio of 1.19 for postoperative respiratory complications.[23] Using the cardiovascular complication rate of 7.4% observed in our cohort in which about 3/4 and 1/4 of the patients did and did not receive neostigmine/glycopyrrolate reversal, respectively, we estimated an event rate of 7.7% in the neostigmine/glycopyrrolate reversal group and 6.5% in the control group. By using a 2-tailed independent sample *z* test, we calculated that our total sample size of 98,147 cases would provide a power of >99% to identify the assumed effect size (α error = .05).

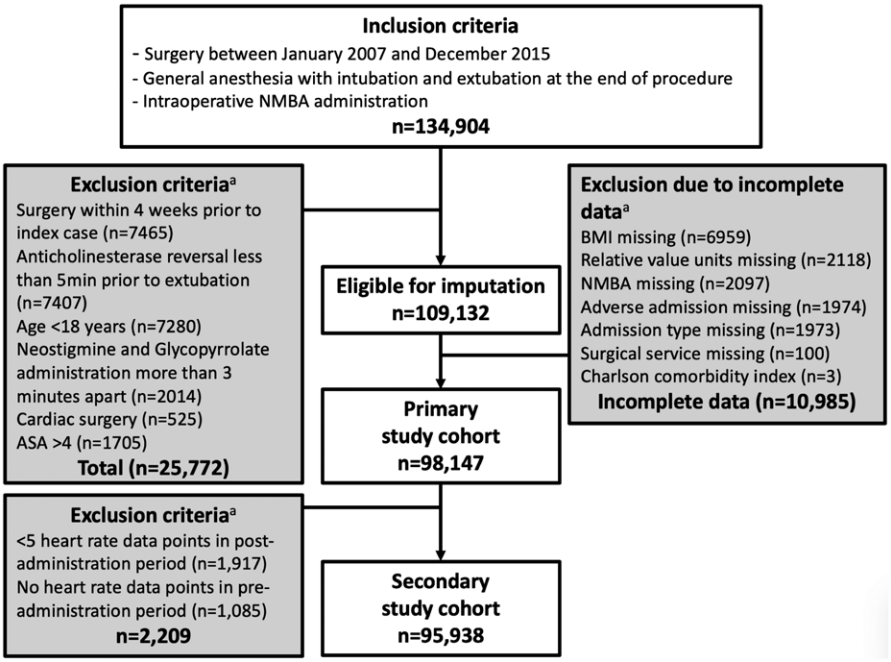

Figure 1. Study flow of patients. ASA indicates American Society of Anesthesiologists; NMBD, neuromuscular blocking drug. [a]Multiple exclusions may apply to the same case.

RESULTS

A total of 134,904 cases from January 2007 to December 2015 undergoing surgery with general anesthesia and intraoperative muscle relaxation with neuromuscular blocking drugs were considered for inclusion. A total of 25,772 cases (19.1%) were excluded after applying the exclusion criteria. Of the remaining 109,132 cases, 10,985 (10.1%) were excluded due to missing data in any of the variables of the regression model (see Figure 1). In the remaining primary cohort of 98,147 cases, there were 73,181 (74.6%) that received neostigmine and glycopyrrolate for neuromuscular blocking drug reversal compared to 24,966 (25.4%) that did not. Baseline characteristics of the study population by exposure cohort are compared in Table 1.

Primary Outcome

A total of 7263 patients (7.4%) experienced cardiovascular complications within 30 days after surgery (5612 [7.7%] in the neuromuscular blocking drug reversal group and 1651 [6.6%] in the control group). The odds ratio for the association of neuromuscular blocking drug reversal with neostigmine/glycopyrrolate and postoperative cardiovascular complications was 1.17 in crude analysis ([95% CI, 1.11–1.24]; $P < .001$), and 1.03 ([95% CI, 0.97–1.10]; $P = .33$) after adjusting for multiple predefined confounders (see Table 2).

Sensitivity Analysis

There was no significant interaction among the exposure and body mass index, ASA physical status, duration of surgery, and neuromuscular blocking drug (P for interaction = .811, .406, .708, and .623, respectively). Age showed a significant effect modification (P for interaction = .03). Therefore, we have estimated the associations between neuromuscular blocking drug reversal with neostigmine/glycopyrrolate and postoperative cardiovascular complications at the ages of 20, 30, 40, 50, 60, 70, 80, 90, and 100 years (Supplemental Digital Content, Table 3, http://links.lww.com/AA/C753).

Sensitivity analyses, performed by rerunning our primary regression model using neostigmine as a continuous variable (adjusted odds ratio = 1.003 [95% CI, 0.99–1.02]; $P = .70$) and as high dose of neostigmine of >60 µg/kg (adjusted odds ratio = 0.97 [95% CI, 0.89–1.04]; $P = .38$), as well as including history of cardiovascular disease in the confounder model (adjusted odds ratio = 1.05 [95% CI, 0.98–1.12], $P = .17$), confirmed the robustness of our primary results. Adjustment for the risk of pulmonary complications by including the Score for Prediction of Postoperative Respiratory Complications in the primary model did not affect the primary findings (adjusted odds ratio = 1.04 [95% CI, 0.97–1.11]; $P = .28$).

A total of 98,147 cases of the primary study cohort were performed by 738 individual anesthesia providers (certified registered nurse anesthetists, residents, and attendings). The mixed-effects model analysis with anesthesia provider as a random effect yielded results similar to the primary analysis (adjusted odds ratio = 1.03 [95% CI, 0.97–1.10]; $P = .30$; see Table 2).

After propensity score adjustment, the following covariates were (still) imbalanced: work relative value units and surgery type (Supplemental Digital Content, Table 4, http://links.lww.com/AA/C753). To further

Table 1. Characteristics of Study Population by Exposure Variable Neostigmine/Glycopyrrolate Reversal

	All Patients (n = 98,147)	No Neostigmine/ Glycopyrrolate Reversal (n = 24,966)	Neostigmine/ Glycopyrrolate Reversal (n = 73,181)
Age (y), mean ± SD	54.50 ± 16.48	53.19 ± 17.07	54.95 ± 16.26
Sex (female), n (%)	54,083 (55.1)	13,562 (54.3)	40,521 (55.4)
Body mass index (kg/m^2) quintiles, n (%)			
First: <23.0	19,630 (20.0)	5078 (20.3)	14,552 (19.9)
Second: 23.0–25.8	19,631 (20.0)	5149 (20.6)	14,482 (19.8)
Third: 25.8–28.8	19,646 (20.0)	5106 (20.5)	14,540 (19.9)
Fourth: 28.8–33.1	19,628 (20.0)	5033 (20.2)	14,595 (19.9)
Fifth: >33.1	19,612 (20.0)	4600 (18.4)	15,012 (20.5)
Charlson comorbidity index, median (interquartile range)	2 (0–3)	1 (0–3)	2 (0–4)
ASA physical status, n (%)			
I	9674 (9.9)	3055 (12.2)	6619 (9)
II	59,326 (60.4)	15,165 (60.7)	44,161 (60.3)
III	27,773 (28.3)	6374 (25.5)	21,399 (29.2)
IV	1374 (1.4)	372 (1.5)	1002 (1.4)
Year, n (%)			
2007	8202 (8.4)	3341 (13.4)	4861 (6.6)
2008	9379 (9.6)	3293 (13.2)	6086 (8.3)
2009	10,100 (10.3)	2742 (11.0)	7358 (10.1)
2010	10,410 (10.6)	2214 (8.9)	8196 (11.2)
2011	11,028 (11.2)	2760 (11.1)	8268 (11.3)
2012	12,061 (12.3)	2604 (10.4)	9457 (12.9)
2013	12,763 (13.0)	3001 (12.0)	9762 (13.3)
2014	12,204 (12.4)	2532 (10.1)	9672 (13.2)
2015	12,000 (12.2)	2479 (9.9)	9521 (13.0)
Adverse admission, n (%)	5525 (5.6)	1556 (6.2)	3969 (5.4)
Surgery type, n (%)			
Nonoperating room anesthesia	2749 (2.8)	1275 (5.1)	1474 (2.0)
Burn surgery	936 (1.0)	351 (1.4)	585 (0.8)
Trauma surgery	4401 (4.5)	581 (2.3)	3820 (5.2)
General surgery	18,039 (18.4)	2961 (11.9)	15,078 (20.6)
Gynecology	9080 (9.3)	1628 (6.5)	7452 (10.2)
Neurosurgery	9937 (10.1)	3288 (13.2)	6649 (9.1)
Oral/maxillofacial surgery	2106 (2.1)	1073 (4.3)	1033 (1.4)
Orthopedic surgery	17,770 (18.1)	6576 (26.3)	11,194 (15.3)
Others	612 (0.6)	170 (0.7)	442 (0.6)
Otolaryngology	779 (0.8)	271 (1.1)	508 (0.7)
Pediatric surgery	459 (0.5)	116 (0.5)	343 (0.5)
Plastic surgery	5173 (5.3)	1913 (7.7)	3260 (4.5)
Radiology	720 (0.7)	215 (0.9)	505 (0.7)
Surgical oncology	4771 (4.9)	1238 (5.0)	3533 (4.8)
Thoracic surgery	7228 (7.4)	681 (2.7)	6547 (8.9)
Transplant	1886 (1.9)	366 (1.5)	1520 (2.1)
Urology	7979 (8.1)	1333 (5.3)	6646 (9.1)
Vascular surgery	3522 (3.6)	930 (3.7)	2592 (3.5)
Emergency surgery	3847 (3.9)	853 (3.4)	2994 (4.1)
Ambulatory surgery	18,631 (19.0)	4861 (19.5)	13,770 (18.8)
Duration of surgery (min), median (interquartile range)	168.2 (111.41–246.85)	179.13 (126.70–259.96)	161.66 (107.04–242.48)
Work relative value units, median (interquartile range)	16.64 (10.49–23.50)	15.37 (10.49–21.79)	17.31 (10.49–24.21)
Neuromuscular blocking drug dose (multiples of the effective dose needed to reduce twitch height by 95%), median (interquartile range)	2.84 (2.00–4.17)	2.45 (1.80–3.48)	3.00 (2.10–4.38)
Packed red blood cell transfusion, n (%)			
0 U	94,537 (96.3)	23,937 (95.9)	70,600 (96.5)
1–2 U	2881 (2.9)	811 (3.2)	2070 (2.8)
3+ U	729 (0.7)	218 (0.9)	511 (0.7)
Total intraoperative fluid resuscitation (mL), median (interquartile range)	1500 (1000.00–2407.61)	1500 (1000.00–2250.00)	1500 (1000.00–2500.00)
Total vasopressor dose (mg of norepinephrine equivalents), median (interquartile range)	0.03 (0.00–0.24)	0.01 (0.00–0.20)	0.03 (0.00–0.25)
β-Blocker prescription 4 wk before surgery, n (%)	11,874 (12.1)	2842 (11.4)	9032 (12.3)
Antiplatelet prescription 4 wk before surgery, n (%)	10,814 (11.0)	2511 (10.1)	8303 (11.3)

Abbreviation: ASA, American Society of Anesthesiologists.

Table 2. Results of Primary, Secondary, and Sensitivity Analyses

Primary Outcome	Incidence: No Neostigmine/ Glycopyrrolate Reversal (n = 24,966)	Incidence: Neostigmine/ Glycopyrrolate Reversal (n = 73,181)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)	*P*
Postoperative cardiovascular complication, n (%)	1651 (6.6)	5612 (7.7)	1.17 (1.11–1.24)	1.03 (0.97–1.10)	.33
MI	94 (0.4)	342 (0.5)	1.24 (0.99–1.56)	1.19 (0.93–1.53)	.17
Ischemic stroke	231 (0.9)	693 (0.9)	1.02 (0.88–1.19)	1.07 (0.91–1.27)	.40
Transient ischemic attack	109 (0.4)	334 (0.5)	1.05 (0.84–1.30)	1.12 (0.89–1.43)	.34
Dysrhythmia	799 (3.2)	3166 (4.3)	1.37 (1.26–1.48)	1.07 (0.98–1.16)	.14
Acute heart failure	597 (2.4)	1857 (2.5)	1.06 (0.97–1.17)	0.98 (0.88–1.09)	.68
Secondary outcome, n (%)	n = 24,407	n = 71,531			
Heart rate extreme	1855 (7.6)	10,712 (15)		2.29 (2.17–2.42)	<.001
Bradycardia	288 (1.2)	2077 (2.9)		2.84 (2.49–3.24)	<.001
Tachycardia	1586 (6.5)	8700 (12.2)		2.10 (1.97–2.23)	<.001
Sensitivity analyses					
Neostigmine (continuous variable)				1.00 (0.99–1.02)	.70
Neostigmine >60 μg/kg (yes/no)				0.97 (0.89–1.05)	.45
Random effect of anesthesia provider				1.03 (0.97–1.10)	.31
Imputation analysis for missing data				1.04 (0.98–1.12)	.18

Abbreviation: MI, myocardial infarction.

[a]Adjusted for age, sex, body mass index, Charlson comorbidity index, American Society of Anesthesiologists physical status, emergency status of surgery (emergent/nonemergent), admission type (inpatient/ambulatory), adverse admission, year of surgery, surgery type, a prescription of β-blockers or antiplatelets within 4 wk before surgery, duration of surgery, neuromuscular blocking drug dose expressed as multiples of the dose needed to reduce twitch height by 95%, intraoperative fluid resuscitation, intraoperative vasopressor dose, packed red blood cell units, and work relative value units.

adjust for these imbalances, we ran the propensity score–adjusted primary model including these variables as confounders. The result of this analysis was consistent with the primary finding of a nonsignificant association between neostigmine/glycopyrrolate reversal and postoperative cardiovascular complications (adjusted odds ratio = 1.04 [95% CI, 0.98–1.11]; *P* = .21), which indicated that the statistical significance of the primary results was not altered through treatment selection bias.

The Hosmer–Lemeshow test (*P* = .17) indicated no evidence of poor fit of the model. The model discrimination of the confounder model used in the primary analysis was assessed through the concordance c-statistic (area under the curve = 0.79; Supplemental Digital Content, Figure 4, http://links.lww.com/AA/C753). We calculated a Brier score of 0.064, which reflected an acceptable degree of accuracy and can be interpreted as the mean squared difference between predictions and actual events. The predictions from the model were diverse and ranged from 0.02% to 63.30%, reflecting good variability in the predicted risk. In addition, the predictions were well calibrated and closely approximated the actual risk across a range of values (Brier reliability = 0.0002).

A total of 8 variables in the primary regression model contained the missing data. Multiple imputation was conducted, and the imputed cohort included all 10,985 cases (10.1%) that were dropped due to missing values in the primary regression model. Imputation of missing data did not affect the primary results (adjusted odds ratio = 1.04 [95% CI, 0.98–1.12]; *P* = .18).

Secondary Outcomes

After receiving neostigmine and glycopyrrolate, 12.2% of patients experienced >20% HR increases resulting in tachycardia, while 2.9% experienced >20% HR decreases resulting in bradycardia (see Table 2). During the equivalent time period before extubation, patients who did not receive neuromuscular blocking drug reversal experienced much lower incidences of both tachycardia (6.5%) and bradycardia (1.2%). After adjustment for the confounder model of the multivariable primary analysis, tachycardia (adjusted odds ratio = 2.1 [95% CI, 1.97–2.23]; *P* < .001), bradycardia (adjusted odds ratio = 2.84 [95% CI, 2.49–3.24]; *P* < .001), and either HR extreme (high or low; adjusted odds ratio = 2.29 [95% CI, 2.17–2.42]; *P* < .001) were independently associated with neostigmine/glycopyrrolate reversal (see Table 2). Within 2 minutes after neostigmine administration, the mean HR in the exposure group increased by 11% (from 71 to 79 beats/min) compared to 0.6% (from 70.6 to 71.0 beats/min) in the control group (*P* < .001; see Figure 2). However, 15 minutes later, the mean HRs in both exposed and control groups were almost identical (77.8 beats/min in the exposure versus 78.3 beats/min in the control group).

Exploratory Analyses

The interaction terms for history of high age, vascular or neurosurgery, and atrial fibrillation were significant

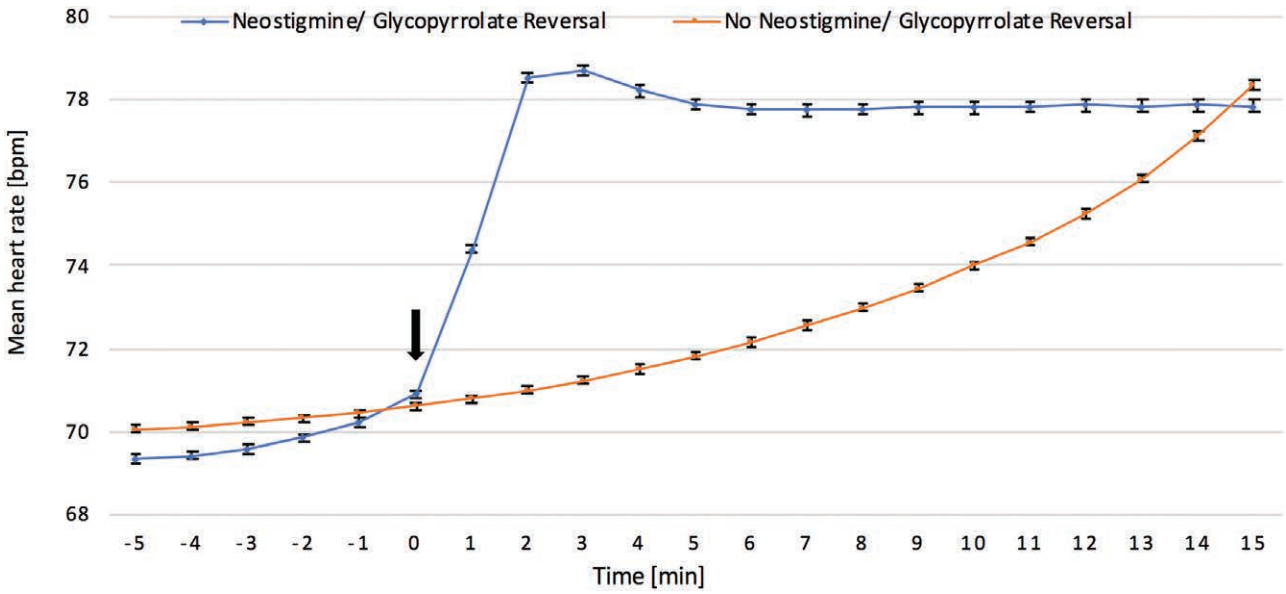

Figure 2. Mean heart rate of neostigmine/glycopyrrolate reversal group (blue) and control group (orange). The black arrow indicates the time point of neostigmine/glycopyrrolate reversal or reference time point defined as 19 minutes before extubation. Error bars are 95% CIs.

(*P* for interaction = .002, .001, and .02, respectively), whereas the interaction terms for heart failure, coronary artery disease, and aortic and/or mitral valve stenosis were not (*P* for interaction = .34, .25, and .71, respectively).

Linear combinations of the respective main effect and exposure–risk interaction term derived from the primary study cohort showed significant associations between neuromuscular blocking drug reversal with neostigmine/glycopyrrolate and postoperative cardiovascular complications for vascular surgery and neurosurgery patients (adjusted odds ratio = 1.16 [95% CI, 1.02–1.32]; *P* = .02), patients with history of atrial fibrillation (adjusted odds ratio = 1.21 [95% CI, 1.08–1.37]; *P* = .001), and patients of high age (adjusted odds ratio = 1.14 [95% CI, 1.03–1.26]; *P* = .01). For patients undergoing nonvascular and nonneurosurgery (adjusted odds ratio = 0.95 [95% CI, 0.89–1.02]; *P* = .19), patients with no history of atrial fibrillation (adjusted odds ratio = 0.98 [95% CI, 0.91–1.06]; *P* = .65), and patients of nonhigh age (adjusted odds ratio = 0.99 [95% CI, 0.91–1.07]; *P* = .71), the associations between exposure and outcome were nonsignificant.

Finally, a higher neostigmine/glycopyrrolate dose ratio was significantly associated with lower odds of tachycardia (adjusted odds ratio = 0.93 [95% CI, 0.91–0.94]; *P* < .001) and higher odds of bradycardia (adjusted odds ratio = 1.15 [95% CI, 1.13–1.17]; *P* < .001). Independent of the neostigmine/glycopyrrolate dose ratio, high glycopyrrolate dose was significantly associated with increased odds of tachycardia and decreased odds of bradycardia (*P* for trend < .001, respectively; Supplemental Digital Content, Table 5, http://links.lww.com/AA/C753).

DISCUSSION

In this retrospective cohort of 98,147 patients who received general anesthesia with endotracheal intubation at Massachusetts General Hospital and 2 affiliated community hospitals, coadministration of neostigmine and glycopyrrolate to reverse the effects of neuromuscular blocking drugs was significantly associated in a dose-dependent fashion with intraoperative tachycardia and/or bradycardia (a higher neostigmine/glycopyrrolate dose ratio was significantly associated with lower odds of tachycardia and higher odds of bradycardia) but not with increased or decreased odds of cardiovascular complications within 30 postoperative days after adjustment for confounding factors (adjusted odds ratio = 1.03 [95% CI, 0.97–1.10]; *P* = .33). This finding remained consistent following sensitivity analyses, propensity score adjustment, and adjustment for interclinician variability. However, in exploratory analyses, we identified a significant effect modification of anticholinesterase reversal by high age, high-risk surgery, and history of atrial fibrillation. By using linear combinations of main effect and exposure–risk interaction terms, we then identified significant associations between anticholinesterase reversal and cardiovascular complications toward a higher vulnerability in these patient subgroups.

Our finding that average HR rises soon after coadministration of neostigmine and glycopyrrolate is consistent with prior reports on small patient

cohorts.[10,24,25] We also found a nontrivial incidence of bradycardia (2.9%) and a higher incidence of tachycardia (12.2%) that are likely induced by neostigmine and glycopyrrolate administration, because these outcomes represent large changes from baseline HRs in exposed patients and are much less frequent in control patients. Data included in a recent meta-analysis by Hristovska et al[26] indicate that 19 (7.1%) of 266 study patients who received neostigmine with glycopyrrolate experienced bradycardia, while the incidence with sugammadex (4 of 621 = 0.6%) was significantly lower (P = .01). While HR increases are known to depend on the neostigmine/glycopyrrolate dose ratio (usually 5:1),[27] we found no other large cohort study reporting the incidence of tachycardia produced by these drugs. Hristovska et al[26] reported tachycardia in 4 (2.3%) of 173 patients who received neostigmine and in 1 (0.6%) of 165 patients receiving sugammadex. These rates were not significantly different (P = .32).

Furthermore, neostigmine can induce depolarizing neuromuscular block and muscle weakness when administered to patients with normal neuromuscular function. A bundle intervention designed to reduce inappropriate neostigmine use resulted in fewer postoperative complications.[28–30] Another recent large study by Belcher et al[31] compared postanesthesia care unit outcomes in noncardiac surgery patients exposed to neostigmine versus nonexposed patients, finding that neostigmine was associated with a significantly lower incidence of major complications, specifically including cardiac arrest, reintubations, and intensive care unit admissions, as well as a lower incidence of bradycardia. These results agree with our finding that neostigmine does not increase the risk of cardiovascular complications and suggest that respiratory compromise associated with inadequate neuromuscular blocking drug reversal may be a major mediator of some cardiovascular complications.[32–35] Our analysis did not support the superiority of neostigmine administration for outcomes during a longer, 30-day postoperative period.

The plausibility of our hypothesis is supported by recent studies linking intraoperative tachycardia with postoperative cardiac complications.[13,36,37] A recent retrospective cohort study by Helwani et al[38] suggests that most perioperative myocardial ischemia is due to demand, which is directly linked to HR. Considering the relative incidences of tachycardia in the cohort exposed to neostigmine/glycopyrrolate and the control group, it seems reasonable that these drugs could induce cardiac dysfunction that may persist beyond the operating room environment. However, the duration of tachycardia may be another important influence on cardiovascular outcomes in the postoperative period.[36] Indeed, the observed difference in HR between patients who received and did not receive reversal agents lasted for a few minutes only (see Figure 2). The increase in HR before extubation observed in the control group likely reflects the decreasing depth of anesthesia in patients at the end of surgery. Shortly before extubation, there was no difference in the HR between the 2 groups, which may explain why there was no significant difference in postoperative cardiovascular complications.

It is also possible that neostigmine has cardioprotective activity. In human subjects with preexisting heart failure, administration of the acetylcholinesterase inhibitor pyridostigmine reduced episodes of ventricular arrhythmias.[39] In a small randomized controlled crossover trial of patients with inducible myocardial ischemia during exercise stress tests, pyridostigmine increased the time to electrocardiographic ischemia and increased peak oxygen consumption.[40]

Our exploratory analyses suggest that patients presenting with a high risk of cardiovascular complications (high age, vascular surgery and neurosurgery, and history of atrial fibrillation) may be more vulnerable to anticholinesterase-induced cardiovascular complications. These findings are potentially clinically meaningful but need to be confirmed in future studies designed to test these hypotheses.

Our study has several strengths. We analyzed data up to 30 days after surgery, a period that captures the most consequential perioperative outcomes. Second, sensitivity analysis and propensity score adjustment suggest that our primary outcome analysis remains consistent. Third, we accounted for interclinician variability using a mixed-effects model and tested for effect modification across many covariates.

As with all retrospective studies using administrative databases, interpretation is subject to selection bias, such as misclassification due to incorrect data input. However, the potential for bias of this type is counterbalanced by the large number of patients included in our analysis. In addition, we did not control for intraoperative β-blocker use due to inaccessibility to those data. It is also possible that unknown meaningful confounders have been omitted from our propensity score adjustment model. Given the established risks of pulmonary complications in patients who do not receive reversal of neuromuscular blocking drugs, controlled trials to further evaluate the impact of neostigmine on cardiovascular outcomes would not be justified.

In summary, in this large population-based observational study on 98,147 cases, neuromuscular blocking drug reversal with neostigmine and glycopyrrolate was not significantly associated with increased 30-day postoperative cardiovascular complications. However, high-risk groups may exist,

which are vulnerable to the cardiovascular side effects of neostigmine/glycopyrrolate administration. ■

DISCLOSURES

Name: Denys Shaydenfish, Cand Med.
Contribution: This author helped write the first draft of the manuscript, review the literature, extract the data, code the data, analyze the data, write and submit the manuscript, and revise and approve the final version of the manuscript.
Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
Name: Xinling Xu, PhD.
Contribution: This author helped code the data, analyze the data, revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Timothy T. Houle, PhD.
Contribution: This author was the principal investigator and helped extract the data, code the data, design the study, analyze the data, write the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Matthias Eikermann, MD, PhD.
Contribution: This author was the guarantor of the study and responsible for the entire process of designing the study to publishing the manuscript. He helped conceive the study hypothesis, design the study, and write and edit the manuscript; approved the final version of the manuscript.
Conflicts of Interest: M. Eikermann received an unrestricted, philanthropic donation by Jeff and Judy Buzen.
Name: Stuart A. Forman, MD, PhD.
Contribution: This author was the inventor of the idea of the study, helped conceive the study hypothesis, design the study, and approved the final version of manuscript.
Conflicts of Interest: None.
This manuscript was handled by: Tong J. Gan, MD.

REFERENCES

1. Weiser TG, Haynes AB, Molina G, et al. Size and distribution of the global volume of surgery in 2012. *Bull World Health Organ*. 2016;94:201–209F.
2. Blobner M, Frick CG, Stäuble RB, et al. Neuromuscular blockade improves surgical conditions (NISCO). *Surg Endosc*. 2015;29:627–636.
3. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. *Anesth Analg*. 2010;111:110–119.
4. Backman SB, Bachoo M, Polosa C. Mechanism of the bradycardia produced in the cat by the anticholinesterase neostigmine. *J Pharmacol Exp Ther*. 1993;265:194–200.
5. Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia*. 2009;64(suppl 1):22–30.
6. Hammond J, Wright D, Sale J. Pattern of change of bronchomotor tone following reversal of neuromuscular blockade. Comparison between atropine and glycopyrrolate. *Br J Anaesth*. 1983;55:955–959.
7. Shields JA. Heart block and prolonged Q-Tc interval following muscle relaxant reversal: a case report. *AANA J*. 2008;76:41–45.
8. Cachemaille M, Olofsson M, Livio F, Pascale P, Zingg T, Boegli Y. Recurrent asystole after neostigmine in a heart transplant recipient with end-stage renal disease. *J Cardiothorac Vasc Anesth*. 2017;31:653–656.
9. Cozanitis DA, Dundee JW, Merrett JD, Jones CJ, Mirakhur RK. Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation. *Br J Anaesth*. 1980;52:85–89.
10. Heinonen J, Salmenperä M, Takkunen O. Advantages of glycopyrrolate over atropine during reversal of pancuronium block. *Acta Anaesthesiol Scand*. 1982;26:147–150.
11. Kadoya T, Seto A, Aoyama K, Takenaka I. Development of rapid atrial fibrillation with a wide QRS complex after neostigmine in a patient with intermittent Wolff-Parkinson-White syndrome. *Br J Anaesth*. 1999;83:815–818.
12. Gawande AA, Kwaan MR, Regenbogen SE, Lipsitz SA, Zinner MJ. An Apgar score for surgery. *J Am Coll Surg*. 2007;204:201–208.
13. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. *J Am Geriatr Soc*. 2001;49:1080–1085.
14. Feldheiser A, Aziz O, Baldini G, et al. Enhanced recovery after surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016;60:289–334.
15. Hedrick TL, McEvoy MD, Mythen MMG, et al; Perioperative Quality Initiative (POQI) 2 Workgroup. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on postoperative gastrointestinal dysfunction within an enhanced recovery pathway for elective colorectal surgery. *Anesth Analg*. 2018;126:1896–1907.
16. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4:e297.
17. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16:219–242.
18. Sasaki N, Meyer MJ, Malviya SA, et al. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. *Anesthesiology*. 2014;121:959–968.
19. Brueckmann B, Villa-Uribe JL, Bateman BT, et al. Development and validation of a score for prediction of

postoperative respiratory complications. *Anesthesiology*. 2013;118:1276–1285.
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
21. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. *Pharmacoepidemiol Drug Saf*. 2008;17:1202–1217.
22. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol*. 2001;54:387–398.
23. McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *Anesthesiology*. 2015;122:1201–1213.
24. Ostheimer GW. A comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with neostigmine. *Anesth Analg*. 1977;56:182–186.
25. Mirakhur RK, Dundee JW, Clarke RS. Glycopyrrolate-neostigmine mixture for antagonism of neuromuscular block: comparison with atropine-neostigmine mixture. *Br J Anaesth*. 1977;49:825–829.
26. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database Syst Rev*. 2017;8:CD012763.
27. Mirakhur RK, Dundee JW, Jones CJ, Coppel DL, Clarke RS. Reversal of neuromuscular blockade: dose determination studies with atropine and glycopyrrolate given before or in a mixture with neostigmine. *Anesth Analg*. 1981;60:557–562.
28. Kent NB, Liang SS, Phillips S, et al. Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers: a double-blind, placebo-controlled, randomised volunteer study. *Anaesthesia*. 2018;73:1079–1089.
29. Rudolph MI, Chitilian HV, Ng PY, et al. Implementation of a new strategy to improve the peri-operative management of neuromuscular blockade and its effects on postoperative pulmonary complications. *Anaesthesia*. 2018;73:1067–1078.
30. Rudolph MI, Ng PY, Deng H, et al. Comparison of a novel clinical score to estimate the risk of residual neuromuscular block prediction score and the last train-of-four count documented in the electronic anaesthesia record: a retrospective cohort study of electronic data on file. *Eur J Anaesthesiol*. 2018;35:883–892.
31. Belcher AW, Leung S, Cohen B, et al. Incidence of complications in the post-anesthesia care unit and associated healthcare utilization in patients undergoing non-cardiac surgery requiring neuromuscular blockade 2005-2013: a single center study. *J Clin Anesth*. 2017;43:33–38.
32. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg*. 2008;107:130–137.
33. Cammu GV, Smet V, De Jongh K, Vandeput D. A prospective, observational study comparing postoperative residual curarisation and early adverse respiratory events in patients reversed with neostigmine or sugammadex or after apparent spontaneous recovery. *Anaesth Intensive Care*. 2012;40:999–1006.
34. Martinez-Ubieto J, Ortega-Lucea S, Pascual-Bellosta A, et al. Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine versus sugammadex. *Minerva Anestesiol*. 2016;82:735–742.
35. Norton M, Xará D, Parente D, Barbosa M, Abelha FJ. Residual neuromuscular block as a risk factor for critical respiratory events in the post anesthesia care unit. *Rev Esp Anestesiol Reanim*. 2013;60:190–196.
36. House LM, Marolen KN, St Jacques PJ, McEvoy MD, Ehrenfeld JM. Surgical Apgar score is associated with myocardial injury after noncardiac surgery. *J Clin Anesth*. 2016;34:395–402.
37. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M. Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. *Anesth Analg*. 2002;95:273–277.
38. Helwani MA, Amin A, Lavigne P, et al. Etiology of acute coronary syndrome after noncardiac surgery. *Anesthesiology*. 2018;128:1084–1091.
39. Behling A, Moraes RS, Rohde LE, Ferlin EL, Nóbrega AC, Ribeiro JP. Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure. *Am Heart J*. 2003;146:494–500.
40. Castro RR, Porphirio G, Serra SM, Nóbrega AC. Cholinergic stimulation with pyridostigmine protects against exercise induced myocardial ischaemia. *Heart*. 2004;90:1119–1123.