Effects of Neostigmine Reversal of Nondepolarizing Neuromuscular Blocking Agents on Postoperative Respiratory Outcomes

A Prospective Study

Nobuo Sasaki, M.D., Matthew J. Meyer, M.D., Sanjana A. Malviya, B.S., Anne B. Stanislaus, M.S., Teresa MacDonald, R.N., Mary E. Doran, R.N., Arina Igumenshcheva, B.A., B.S., Alan H. Hoang, M.D., Matthias Eikermann, M.D., Ph.D.

ABSTRACT

Background: We tested the hypothesis that neostigmine reversal of neuromuscular blockade reduced the incidence of signs and symptoms of postoperative respiratory failure.

Methods: We enrolled 3,000 patients in this prospective, observer-blinded, observational study. We documented the intraoperative use of neuromuscular blocking agents and neostigmine. At postanesthesia care unit admission, we measured train-of-four ratio and documented the ratio of peripheral oxygen saturation to fraction of inspired oxygen (S/F). The primary outcome was oxygenation at postanesthesia care unit admission (S/F). Secondary outcomes included the incidence of postoperative atelectasis and postoperative hospital length of stay. *Post hoc*, we defined high-dose neostigmine as more than 60 μg/kg and unwarranted use of neostigmine as neostigmine administration in the absence of appropriate neuromuscular transmission monitoring.

Results: Neostigmine reversal did not improve S/F at postanesthesia care unit admission (164 [95% CI, 162 to 164] *vs.* 164 [161 to 164]) and was associated with an increased incidence of atelectasis (8.8% *vs.* 4.5%; odds ratio, 1.67 [1.07 to 2.59]). High-dose neostigmine was associated with longer time to postanesthesia care unit discharge readiness (176 min [165 to 188] *vs.* 157 min [153 to 160]) and longer postoperative hospital length of stay (2.9 days [2.7 to 3.2] *vs.* 2.8 days [2.8 to 2.9]). Unwarranted use of neostigmine (n = 492) was an independent predictor of pulmonary edema (odds ratio, 1.91 [1.21 to 3.00]) and reintubation (odds ratio, 3.68 [1.10 to 12.4]).

Conclusions: Neostigmine reversal did not affect oxygenation but was associated with increased atelectasis. High-dose neostigmine or unwarranted use of neostigmine may translate to increased postoperative respiratory morbidity. (ANESTHESIOLOGY 2014; 121:959-68)

NONDEPOLARIZING neuromuscular blocking agents (ND-NMBAs) are used during general anesthesia to facilitate tracheal intubation and to optimize surgical conditions. However, due to the variability of their duration of action, residual effects of ND-NMBA can last longer than clinically necessary. There is a growing body of evidence that postoperative residual neuromuscular blockade, defined as a train-of-four ratio (T4/T1) less than 0.9, places patients at higher perioperative risk for respiratory complications[1–3] and may increase hospital costs.[4]

In order to reduce or avoid postoperative residual paralysis, anesthesiologists typically monitor intraoperative neuromuscular transmission blockade and reverse residual neuromuscular blockade with acetylcholinesterase inhibitors. Our

---

What We Already Know about This Topic

- Clinicians assume that neostigmine administration reduces the risk of postoperative respiratory failure

What This Article Tells Us That Is New

- Neostigmine reversal did not reduce signs and symptoms of postoperative respiratory failure, and was associated with an increased incidence of atelectasis
- When given in high doses or unguided by neuromuscular transmission monitoring, neostigmine administration may be associated with an increased incidence of postoperative respiratory complications

---

group recently reported that the intraoperative use of ND-NMBA is associated with postoperative respiratory failure[5]

This article is featured in "This Month in Anesthesiology," page 1A.

primarily due to pulmonary edema, pneumonia, and atelectasis. In addition, we observed that neostigmine reversal did not decrease the incidence of postoperative respiratory failure but was associated with a higher incidence of postoperative oxygen desaturation.[6] However, in these patients who received neostigmine, qualitative neuromuscular transmission monitoring appeared to have a protective effect against hypoxia as the incidence of oxygen desaturation below 90% occurred less frequently when compared with those who received neostigmine without qualitative neuromuscular transmission monitoring.

We conducted this prospective observational trial to better understand the relationship between neostigmine reversal, neuromuscular transmission monitoring, and the postoperative respiratory outcomes of our patients. We hypothesized (null hypothesis) that neostigmine reversal, independent of measured residual neuromuscular blockade, has no effect on oxygenation (primary outcome). We further hypothesized that neostigmine reversal has no effect on postoperative hospital length of stay, the incidence of postoperative atelectasis, or utilization of hospital resources (secondary outcomes).

Post hoc, we hypothesized that high-dose neostigmine may be associated with increased respiratory morbidity and that the absence of appropriate neuromuscular monitoring before administration of neostigmine would explain part of the association between neostigmine reversal and postoperative respiratory complications. We also analyzed the relationship between time of neostigmine administration and extubation.

Materials and Methods

Following approval of Partners Institutional Review Board of the Massachusetts General Hospital, Boston, MA (2011P000454), we enrolled 3,000 patients in this prospective, observer-blinded, observational study at Massachusetts General Hospital (clinicaltrials.gov: NCT01718860). The requirement for written, informed consent was waived due to the observational study design and the understanding that only standard clinical methods were used to obtain measurements.

Standard anesthesia monitors (electrocardiogram, pulse oximetry, end-tidal carbon dioxide concentration, and oscillometric arterial blood pressure) were applied per conventional anesthesia care. Basic nerve stimulators capable of delivering train-of-four (TOF) stimuli and a 5-s tetanic stimulus were available in all Massachusetts General Hospital operating theaters and the anesthesia providers were familiar with their use. Quantitative neuromuscular monitoring devices were available upon request if not immediately in the theater. Upon extubation, patients were typically administered 6 l of oxygen through a simple facemask. In the postanesthesia care unit (PACU), oxygen is titrated by nursing clinical discretion. Standard recovery room monitoring was performed in the PACU.

Patients were enrolled in the study on admission to the PACU. Enrollment was dependent on the limited availability of study staff. Patients were included in the study if they received general anesthesia and were administered ND-NMBA (atracurium, cisatracurium, vecuronium, or rocuronium). General anesthesia was induced and maintained according to each patient's clinical need at the discretion of the clinical anesthetist.

Patients were excluded if they were less than 18 yr old or directly transferred to the intensive care unit. Patients were also excluded if they had procedures or conditions that did not allow for T4/T1 to be measured by ulnar nerve stimulation (*i.e.*, dual upper extremity bandages or external fixations).

The standard clinical method to diagnose residual neuromuscular blockade, acceleromyography of the adductor pollicis muscle using a quantitative TOF monitor (TOF-watch SX; Schering-Plough, Kenilworth, NJ), was applied within 10 min of PACU admission to measure the degree of neuromuscular blockade (T4/T1). The transducer was attached to the hand adapter with the flat side against the thumb, ensuring the orientation of the electrode was perpendicular with thumb trajectory on stimulation of adductor pollicis. Two surface electrodes were placed on cleaned skin over the ulnar nerve at the distal forearm; if well-adherent electrodes from the operating theater were still in place they were used.

Although supramaximal stimulation (50 mA) is recommended to obtain the maximum muscle response,[7] in accordance with our clinical practice, the stimulation current was set to 30 mA to achieve maximal measurement precision and minimize patient discomfort.[8] The TOF-watch SX was then calibrated to set the T1 response to 100% (Calibration 1 mode). The resulting TOF ratios (T4/T1) were obtained by dividing the magnitude of the response to the fourth stimulation (T4) by the magnitude of the response to the first stimulation (T1).

We applied two consecutive TOF stimuli to our patients representing the routine assessment for residual neuromuscular blockade taken at PACU admission. If the difference between T4/T1 values did not exceed 5%, the data were used for data analysis. If the difference in the TOF ratio between the two stimuli was greater than 5%, additional TOF stimuli were applied until two subsequent, consecutive TOF readings did not differ by more than 5%. We used the mean value of two consecutive T4/T1 values for the analysis.[4]

Patient information and clinical outcomes data were obtained from multiple sources including PACU nursing notes, the respiratory therapy ventilator database, electronic anesthesia records, and hospital billing data. A T4/T1 at PACU admission of less than 0.9 was considered indicative of residual neuromuscular blockade: these T4/T1 levels have been associated with respiratory morbidity in previous trials.[9,10] The study staff assessing the PACU T4/T1 and collecting the PACU clinical data were blinded to all intraoperative information except knowing the patient had received a ND-NMBA. The administrators who retrieved the postoperative clinical outcome data from hospital databases had no knowledge of the intraoperative course.

Oxygenation upon PACU admission was assessed by a ratio of oxygen saturation from pulse oximetry to fraction of inspired oxygen (S/F); this ratio has been correlated to the arterial oxygen partial pressure to fraction of inspired oxygen ratio.[11] We collected pulse oximetry oxygen saturation and administered oxygen flow rate from the PACU nursing clinical flowchart. Fractions of inspired oxygen were calculated based on oxygen flow rates.[12]

Clinical information collected on each patient included age, sex, and American Society of Anesthesiologists (ASA) physical status score. Surgery-specific data included procedure type, procedure start and finish, extubation time-stamp, anesthetic (volatile or IV), opioid (compounds and dose), ND-NMBA (compound and dose), neostigmine administration (dose and time-stamp), and terminal TOF counts (last documented TOF count before neostigmine administration or last documented TOF count before extubation for patients who did not receive neostigmine). For estimation of comparative effectiveness, we converted all doses of ND-NMBA to multiples of ED_{95} with the following conversion factors: 0.3 mg/kg rocuronium, 0.04 mg/kg vecuronium, 0.04 mg/kg cisatracurium, and 0.2 mg/kg atracurium.[13]

PACU times were determined and documented by PACU nurses not involved with the study. PACU length of stay until discharge readiness was defined as time from PACU admission to the time the patient no longer required postoperative monitoring in the PACU. Actual PACU length of stay was defined as time from PACU admission until actual departure from the PACU.

The occurrences of postoperative respiratory complications (i.e., atelectasis, pneumonia, and pulmonary edema) and mortality were retrieved from hospital billing data within 30 days after the index surgery. Reintubation was defined as the replacement of an endotracheal tube within 7 days of the index procedure following initial extubation in the operating room. Any patient who required replacement of an endotracheal tube for a second surgical procedure was excluded.

Unwarranted use of neostigmine was defined as neostigmine administration in the absence of neuromuscular transmission monitoring or if the last documented TOF before neostigmine administration was 0 of 4 twitches.

Study Outcomes

The primary outcome was oxygenation at PACU admission as measured by S/F ratio.

The secondary outcomes were postoperative hospital length of stay, incidence of postoperative atelectasis, and unplanned postoperative intensive care utilization including surgical intensive care unit, reintubation, and length of PACU admission until discharge and discharge readiness.

Exploratory outcomes were related to signs and symptoms of postoperative respiratory failure including pneumonia, pulmonary edema, reintubation, and mortality.

Statistical Analysis

Regression analysis was used to evaluate effects of neostigmine and other clinically meaningful predictors of respiratory failure on signs and symptoms of postoperative respiratory failure. Ordinal regression was used to analyze effects on S/F ratio and on length of stay. Logistic regression was used to evaluate the effects on dichotomous endpoints (diagnoses of atelectasis, pneumonia, pulmonary edema, reintubation, and mortality). S/F ratios were categorized into three groups (i.e., 101 to 200, 201 to 300, and >300). PACU lengths of stay were categorized into octiles. Postoperative length of stay was categorized into five groups (i.e., 1, 2, 3, 4, and 5 days or longer). The following variables were included in an a priori-defined multiple regression analysis models for confounder control throughout this study: age, body mass index, ASA score, duration of surgery, high-risk surgery based on our previously published data,[14] and T4/T1 at PACU admission.

Variables that were not normally distributed and variables that did not have an expected linear effect on outcome were categorized. The following confounders were categorized: ASA physical status score into two groups (1 or 2 vs. 3 through 5), age, body mass index and T4/T1 into quintiles, and duration of surgery into octiles. Abdominal surgery, thoracic surgery, neurosurgery, and cardiovascular surgery were categorized as high-risk surgery and included in the regression model as a dichotomous independent variable. Continuous data were reported as median (interquartile range). Categorical data were reported as percentage (frequency). All time intervals were presented as geometric means and associated 95% CIs. Post hoc, we defined "high-dose neostigmine" as greater than 60 µg/kg: the dose identified by receiver-operating characteristic curve analysis to best predict postoperative atelectasis.

The sample size estimation was calculated for our main endpoint: S/F ratio. Based on our preliminary data,[5] we expected clinicians to use neostigmine reversal in 63% of cases. We further expected an S/F difference of 10 (SD ±80) between patients with and without neostigmine reversal. An S/F difference of 10 approximates an oxygen saturation difference of 2% on room air. To be appropriately powered at 0.8, we calculated that a sample size of 3,000 patients would be sufficient to detect a difference in S/F ratio of 10 at an alpha-error of 0.05 between patients who received neostigmine and those who did not.

Data were analyzed using SPSS software (V 22.0, SPSS, Chicago, IL). Chi-square and Mann–Whitney U tests were used for comparisons between groups as appropriate. All statistical tests were two sided, and P value less than 0.05 was considered to be statistically significant.

Results

We enrolled 3,000 patients in this study; 2,893 patients (96.4%) were used in the final analysis due to missing core data points.

Table 1. Clinical Characteristics of the Subjects Who Received Neostigmine Reversal Compared with Those Who Did Not

Neostigmine	Not Received, 22.3% (644)	Received, 77.7% (2,249)
Clinical characteristics		
Age, yr	56 [44–68]	57 [45–67]
Sex (male: female)	46.1%: 53.9%	44.4%: 55.6%
Body weight, kg	79.5 [66.4–93.4]	80.3 [67.1–94.8]
Body mass index	27.4 [24.3–31.9]	27.9 [24.3–32.6]
ASA physical status score	2 [2–3]	2 [2–3]
Terminal TOF count	4 [4–4]	4 [3–4]
Neostigmine dose, μg/kg	NA	40.4 [29.7–52.6]
Time from reversal to extubation, min	NA	15.6 [15.2–16.1]
PACU clinical data		
T4/T1 at PACU admission	100 [92.5–106.5]	98.5 [91.5–105]
Postoperative residual paralysis (T4/T1 < 0.9)	18.4% (118)	20.8% (467)
Temperature at PACU	97.6 [97.0–98.1]	97.5 [97.0–98.0]
S/F ratio	164 [161–164]	164 [162–164]
Duration of surgery, min	125 [120–132]	111 [108–114]
Surgical specialty		
Abdominal surgery	8.7% (56)	25.1% (564)
Orthopedics and Trauma surgery	40.7% (261)	22.1% (496)
Neurosurgery	4.8% (31)	2.6% (58)
Gynecology and Breast surgery	11.4% (73)	14.2% (319)
Urology and Genitourinary surgery	8.3% (53)	12.8% (288)
Oromaxillofacial surgery	5.3% (34)	2.3% (51)
Thoracic surgery	2.2% (14)	6.8% (153)
Cardiovascular surgery	6.1% (39)	3.9% (87)
Others	12.6% (81)	10.1% (227)
Nondepolarizing NMBA		
Vecuronium	21.2% (138)	28.4% (635)
Cisatracurium	36.3% (236)	25.3% (565)
Rocuronium	37.0% (241)	44.0% (983)
Atracurium	5.2% (34)	3.4% (76)
Nondepolarizing NMBA (multiples of ED_{95}/h)	1.53 [0.96–2.09]	1.84 [1.32–2.74]
Opioid administration		
Hydromorphone, μg kg⁻¹ h⁻¹	5.8 [3.3–9.8]	6.0 [3.6–9.8]
Fentanyl, μg kg⁻¹ h⁻¹	1.09 [0.68–1.71]	1.17 [0.69–1.92]
Morphine, μg kg⁻¹ h⁻¹	40 [21–56]	30 [18–50]
Remifentanil, μg kg⁻¹ h⁻¹	0.074 [0.030–0.120]	0.095 [0.042–0.140]
Other anesthetics		
No inhalational anesthesia	7.6% (49)	7.2% (162)
Sevoflurane	61.8% (397)	61.6% (1381)
Isoflurane	26.2% (168)	24.4% (547)
Desflurane	1.6% (10)	2.5% (57)
Propofol, mg kg⁻¹ h⁻¹	1.22 [0.79–1.97]	1.26 [0.79–2.17]

Values are median [interquartile range] or percentages (frequencies). Time values are geometric means [95% CI].
ASA = American Society of Anesthesiologists; ED = effective dose; NA = not applicable; NMBA = neuromuscular blocking agent; PACU = postanesthesia care unit; S/F = oxygen saturation by pulse oximetry/fraction of inspired oxygen; T4/T1 = train-of-four ratio; TOF = train-of-four.

Characteristics of Patients Who Received and Did Not Receive Neostigmine Reversal

The clinical characteristics of the two groups, those who received neostigmine and those who did not, are shown in table 1. Out of 2,893 patients, approximately 20% presented with postoperative residual neuromuscular blockade at PACU admission. There was no significant difference in the incidence of postoperative residual neuromuscular blockade between patients who received neostigmine reversal and those who did not (20.9% *vs.* 18.5%; P = 0.10). Neostigmine was significantly more frequently administered as a ND-NMBA reversal agent in patients with the

following characteristics: high ND-NMBA dose, low terminal TOF-count, high ASA physical status score, short duration of procedure, and abdominal, thoracic, or genitourological procedures. ND-NMBA dose, terminal TOF-count before reversal, and three categories of surgical procedures (abdominal, thoracic, or genitourological) were identified in the logistic regression model as independent predictors of neostigmine administration.

Primary Outcome

Oxygenation at PACU admission did not differ between patients who received and did not receive neostigmine

reversal (S/F ratio 164 [95% CI, 162 to 164] *vs.* 164 [95% CI, 161 to 164]; *P* = 0.42).

Secondary Outcomes

Neostigmine reversal significantly increased the incidence of postoperative atelectasis after control for confounders in the regression model (8.8% *vs.* 4.5%; odds ratio [OR], 1.67 [95% CI, 1.07 to 2.59]; *P* = 0.024; fig. 1).

Neostigmine reversal affected neither time to PACU discharge readiness (161 min [95% CI, 157 to 165] *vs.* 153 min [95% CI, 147 to 160]; *P* = 0.16) nor actual PACU length of stay (222 min [95% CI, 216 to 228] *vs.* 226 min [95% CI, 215 to 238]; *P* = 0.66). Postoperative hospital length of stay did not differ between patients with neostigmine reversal and without (2.9 days [95% CI, 2.8 to 2.9] *vs.* 2.9 days [95% CI, 2.8 to 3.1]; *P* = 0.99).

Exploratory Outcomes

Neostigmine reversal had no significant effect upon the incidence of postoperative pneumonia (2.1% *vs.* 1.4%; *P* = 0.48), pulmonary edema (5.0% *vs.* 3.7%; *P* = 0.40), reintubation (0.5% *vs.* 0.5%; *P* = 0.67), and mortality (0.3% *vs.* 0%; *P* = 0.99).

Effects of High-dose Neostigmine on Clinical Outcomes

High-dose neostigmine had no effect on S/F ratio in the ordinal regression analysis (*P* = 0.11). The incidence of postoperative atelectasis was even higher in patients who received high-dose neostigmine (15.9% *vs.* 6.7%), and high-dose neostigmine, corrected for confounders, was associated with a nearly three-fold increase in the odds of postoperative atelectasis (OR, 2.75 [95% CI, 1.85 to 4.08]; *P* < 0.001). Other independent predictors of atelectasis included age, body mass index, T4/T1 at PACU admission, and high-risk surgery.

High-dose neostigmine was a significant predictor of longer postoperative hospital length of stay after correction for confounders in the ordinal regression analysis (2.9 days [95% CI, 2.7 to 3.2] *vs.* 2.8 days [95% CI, 2.8 to 2.9]; OR, 1.30 [95% CI, 1.02 to 1.64]; *P* = 0.032; fig. 2A). Other independent predictors of longer hospital length of stay in the ordinal regression analysis included age, ASA physical status score, duration of surgery, and high-risk surgery.

High-dose neostigmine was significantly associated with longer times to PACU discharge readiness (176 min [95% CI, 165 to 188]) than all others (157 min [95% CI, 153 to 160]) (fig. 2B). This association was significant after correction for confounders in the ordinal regression analysis (OR, 1.33 [95% CI, 1.02 to 1.64]; *P* = 0.011). Other predictors of longer time to PACU discharge readiness included age and duration of surgery.

Effects of Unwarranted Use of Neostigmine on Respiratory Outcomes

We evaluated the association between neuromuscular transmission monitoring status and the incidence of postoperative
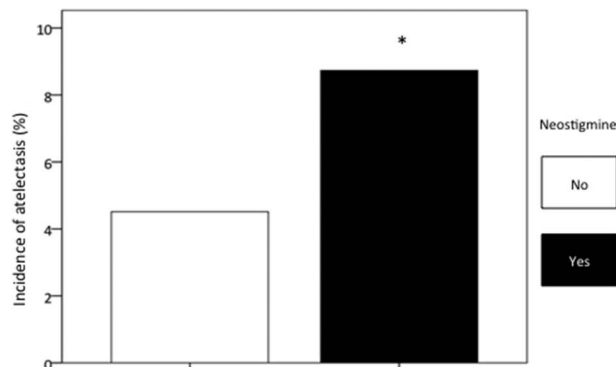
Fig. 1. Association between neostigmine reversal and increased incidence of atelectasis. The incidence of postoperative atelectasis was significantly greater in patients who received neostigmine. *P = 0.024 by logistic regression analysis.

respiratory complications and mortality in the subgroup of patients who received neostigmine reversal (n = 2,249). In this subgroup, 492 patients received neostigmine without appropriate guidance from neuromuscular transmission monitoring and were subsequently categorized as being exposed to the "unwarranted use of neostigmine." Patients with all other values of terminal TOF counts (1–4; n = 1,757) were considered to have received appropriate neuromuscular transmission monitoring before neostigmine reversal.

Unwarranted use of neostigmine was associated with increased incidences of pulmonary edema (OR, 1.91 [95% CI, 1.21 to 3.00]; *P* = 0.005) and reintubation (OR, 3.68 [95% CI, 1.10 to 12.4]; *P* = 0.035) after correction for confounding variables in the logistic regression model (fig. 3). Unwarranted use of neostigmine was also associated with a significantly shorter period of time from neostigmine administration to extubation (14.5 min [95% CI, 13.1 to 15.9] *vs.* 15.7 min [95% CI, 15.3 to 16.2]; *P* = 0.020). Summary of the study outcomes are provided in table 2.

Discussion

Neostigmine reversal did not affect oxygenation but was associated with increased atelectasis. Exploratory analysis revealed that high-dose neostigmine was associated with longer postoperative length of stay. Unwarranted use of neostigmine, neostigmine administration without appropriate guidance from neuromuscular transmission monitoring, was associated with increased respiratory morbidity.

Neostigmine is effective in reversing shallow and moderate nondepolarizing neuromuscular blockade[15] by inhibiting acetylcholinesterase[16] and increasing the amount of acetylcholine in the neuromuscular junction.[17] Neostigmine does not reverse deep neuromuscular blockade,[18–20] and neostigmine should not be given to patients who present with deep neuromuscular blockade[21,22] because it can result in incomplete reversal of neuromuscular blockade.

In a randomized controlled trial, Donati *et al.*[23] studied dose–response relationships for moderate and deep
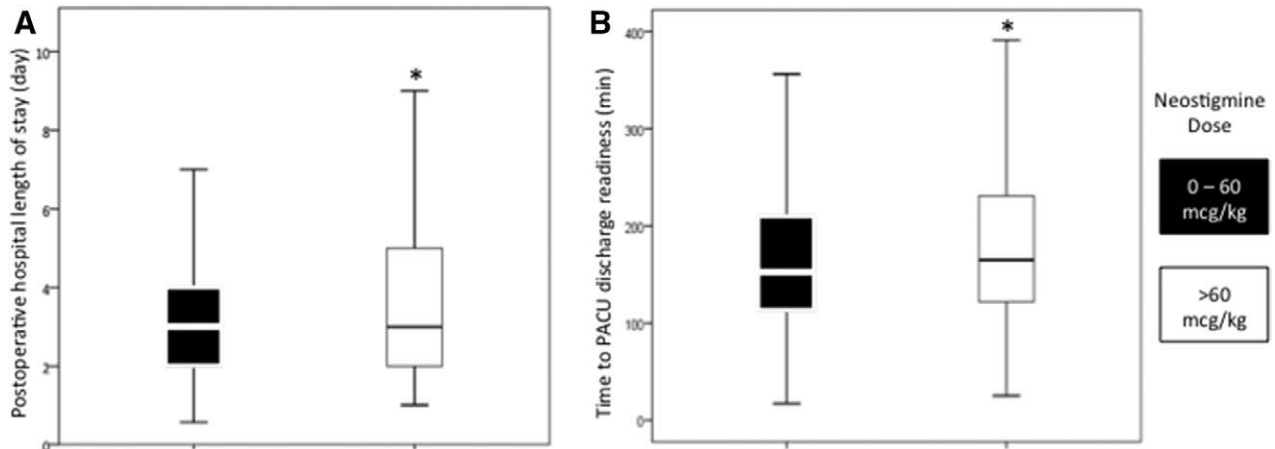
Fig. 2. (*A*) Dose-dependent effect of neostigmine on postoperative hospital length of stay. Postoperative hospital length of stay was significantly longer in patients who received high-dose neostigmine (2.9 days [95% CI, 2.7–3.2] *vs.* 2.8 days [95% CI, 2.8–2.9], *P* = 0.032, ordinal regression analysis). (*B*) Dose-dependent effect of neostigmine on time to postanesthesia care unit (PACU) discharge readiness. Time until PACU discharge readiness was significantly longer in patients who received high-dose neostigmine (176 min [95% CI, 165–188] *vs.* 157 min [95% CI, 153–160], *P* = 0.011, ordinal regression analysis). *Significant findings.
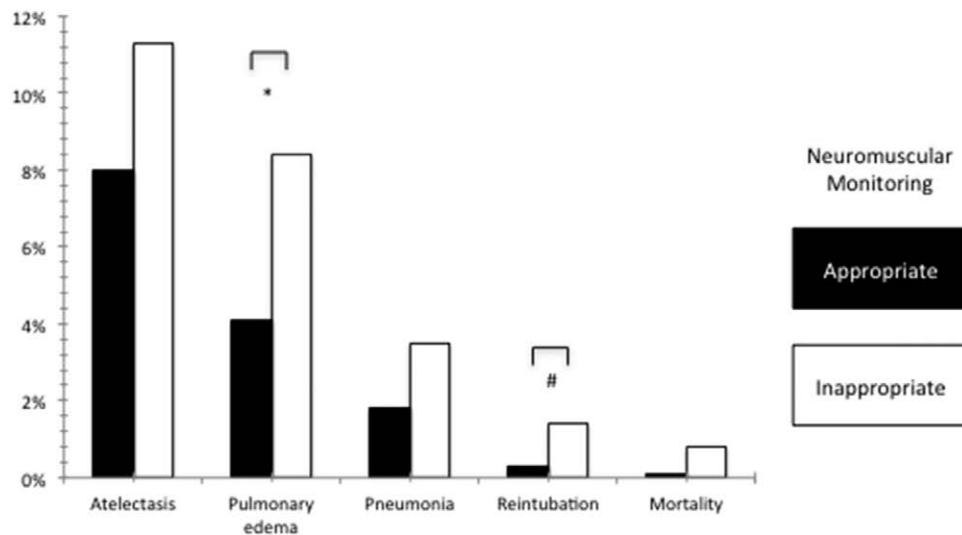
Fig. 3. Incidence of postoperative respiratory complications and mortality in patients who received neostigmine reversal. After correction for confounding variables, patients who received unwarranted neostigmine to reverse nondepolarizing neuromuscular blocking agents were significantly more likely to develop pulmonary edema (*P* = 0.005) and to be reintubated (#P = 0.035).

atracurium blockade in 85 patients. At height of first twitch recovery to either 1% or 10%, patients were administered neostigmine at 5, 10, 20, or 50 μg/kg, and first twitch height was measured each minute for either 15 (1% height of first twitch recovery at time of neostigmine administration) or 10 (10%) min. Neostigmine dose-dependently reversed neuromuscular transmission blockade, but neuromuscular recovery was incomplete when neostigmine was administered at 1%.[23]

The efficacy of ND-NMBA reversal with neostigmine is dependent on both ND-NMBA type and depth of neuromuscular blockade. The use of acetylcholinesterase inhibitors to reverse neuromuscular block is efficacious only if partial recovery is established and relative depth of blockade is known. Initial research recommended that at least

the second twitch of the TOF response should be detectable before administering neostigmine.[24]

Engbaek *et al.*[25] evaluated the effect of increasingly profound atracurium-induced neuromuscular blockade on time to recovery of neuromuscular function following neostigmine antagonism and reinforced the hazards of deep neuromuscular blockade. This study found that increasing intensity of neuromuscular blockade not only prolonged reversal time to T4/T1 greater than 0.7 but also increased the variation in reversal time.[25] Notably, the duration from neostigmine administration until T4/T1 recovery is also affected by type of anesthesia. T4/T1 recovery following long-term inhalation of volatile anesthetics may take up to 57 min when neostigmine is administered at a TOF count of two.[26]

Table 2. Results Categorized by Statistical Endpoint

Neostigmine	Not Received	Received	OR [CI]	P Value
Primary endpoint				
S/F ratio	164 [161–164]	164 [162–164]		0.42
Secondary endpoints				
Atelectasis	4.5% (29)	8.8% (196)	1.67 [1.07–2.59]	0.024*
Time to PACU DR, min	153 [147–160]	161 [157–165]		0.16
Actual PACU LOS, min	226 [215–238]	222 [216–228]		0.66
Postoperative LOS, d	2.9 [2.8–2.9]	2.9 [2.8–3.1]		0.99
Exploratory endpoints				
Pneumonia	1.4% (9)	2.1% (48)		0.48
Pulmonary edema	3.7% (23)	5.0% (113)		0.4
Reintubation	0.5% (3)	0.5% (12)		0.67
Mortality	0.0% (0)	0.3% (6)		0.99
Post hoc analyses				
High-dose neostigmine				
Atelectasis	6.7% (169)	15.9% (52)	2.75 [1.85–4.08]	< 0.001*
Time to PACU DR, min	157 [153–160]	176 [165–188]	1.33 [1.02–1.64]	0.011*
Postoperative LOS, min	2.8 [2.8–2.9]	2.9 [2.7–3.2]	1.30 [1.02–1.64]	0.032*
Unwarranted neostigmine				
Pulmonary edema	4.1% (72)	8.4% (41)	1.91 [1.21–3.00]	0.005*
Reintubation	0.3% (5)	1.4% (7)	3.68 [1.10–12.4]	0.035*

Values are geometric means [95% CI] and incidences (frequencies).

*Significant findings.

DR = discharge readiness; LOS = length of stay; OR = odds ratio; PACU = postanesthesia care unit; S/F = oxygen saturation by pulse oximetry/fraction of inspired oxygen.

In our study, the average time from neostigmine administration to extubation was 15.6 min (95% CI, 15.2 to 16.1). For patients exposed to the unwarranted use of neostigmine, the time from neostigmine administration to extubation was significantly shorter. This finding may demonstrate that clinicians who used neostigmine in the absence of guidance from neuromuscular transmission monitoring were not fully appreciating neostigmine's pharmacokinetics and pharmacodynamics.

There are data suggesting that neostigmine reversal improves postoperative outcomes. In the case–control study on data from 1995 to 1997, Arbous *et al.*[27] examined nearly 900,000 patients for the occurrence of severe morbidity and mortality within 24 h of anesthesia. Reversal of neuromuscular blockade was associated with a decreased risk of severe morbidity and mortality (OR, 0.10; 95% CI, 0.03 to 0.31),[27] likely resulting from a reduction in the incidence of postoperative residual paralysis.[1,3] Based on the observations of Arbous *et al.*,[27] we expected neostigmine reversal to improve clinical respiratory outcomes.

In our sample, neostigmine reversal was neither associated with improved oxygenation at PACU admission nor with shorter hospital stays but was associated with an increased incidence of postoperative atelectasis. High-dose neostigmine (>60 μg/kg) was also a strong predictor of postoperative atelectasis. High-dose neostigmine was also associated with longer time until PACU discharge readiness and longer postoperative hospital length of stay, independent of postoperative residual neuromuscular blockade upon PACU admission.

In the subgroup of patients who received neostigmine reversal, unwarranted use of neostigmine was associated with an increased incidence of pulmonary edema and reintubation.

Our results are consistent with findings from our previous epidemiological study which revealed an absence of beneficial effects of neostigmine on postoperative oxygenation and reintubation.[5,6] In a subgroup analysis of that sample, we observed a decreased incidence of desaturation in patients who received neostigmine with neuromuscular transmission monitoring.

The results we report here from our large, prospective, observational trial confirm our previous finding that neostigmine alone does not improve respiratory safety. Additionally, our results add to our previous studies[5,6] the important observation that the use of neostigmine may be harmful when given in high doses and when given without the proper guidance of neuromuscular transmission monitoring. Appropriate neuromuscular monitoring assists in the avoidance of incomplete neuromuscular blockade reversal, and neostigmine induced neuromuscular transmission failure.[28,29]

Our findings that high-dose neostigmine was associated with longer lengths of time until PACU discharge readiness and postoperative hospital discharge are consistent with our previous finding of an association between postoperative residual neuromuscular blockade and longer PACU length of stay.[4] High-dose neostigmine may result in postoperative neuromuscular weakness through mechanisms that would not be identified by our T4/T1 on PACU admission: (1) administering neostigmine to a patient who

has spontaneously recovered from ND-NMBA may cause a depolarizing neuromuscular blockade with no TOF-fade,[30] and (2) incomplete reversal of a deep neuromuscular blockade may expose the patient to an unidentified duration of respiratory muscle weakness before PACU arrival.

To our knowledge, there is limited research into the relationship between postoperative neuromuscular weakness caused by agents administered during general anesthesia and PACU and postoperative hospital length of stay. We have found the administration of high-dose neostigmine to be associated with greater utilization of hospital resources, and we believe that this association is due to the increased incidence of signs and symptoms of postoperative respiratory failure.[31,32]

We speculate that some of our anesthesia providers attempted to reverse deep neuromuscular blockade with a "full-reversal" dose of neostigmine (heuristically 5 mg at our institution for a patient of average weight) and then transferred extubated and weak patients to the PACU. Notably, our technique for assessing T4/T1 in the PACU[4] does not normalize the ratio to a preoperative value, and it is possible that the actual incidence of residual neuromuscular blockade would have been higher if electromyography, rather than acceleromyography, had been applied.

Even well-practiced, qualitative neuromuscular monitoring can leave patients at risk of postoperative respiratory complications. In the landmark study from 2005, Kopman *et al.*[33] administered 50 µg/kg of neostigmine at a TOF count of one. Ten minutes later, a T4/T1 was measured, and 0% had a T4/T1 greater than 0.9 while 85% of patients had a T4/T1 greater than 0.4.[33] These patients with a T4/T1 between 0.4 and 0.9 are in the risky position of having a level of residual neuromuscular blockade that permits normal breathing through an endotracheal tube and has no discernable fade by qualitative TOF monitoring, but is associated with increased upper airway muscle weakness, thus putting them at risk of pulmonary aspiration[34] and postoperative respiratory failure.[35]

Furthermore, it is not safe to administer neostigmine to a patient who has spontaneously recovered from neuromuscular blockade[36] because neostigmine dose-dependently affects respiratory muscle function[28] and increases upper airway collapsibility.[29] This acetylcholinesterase inhibitor–induced neuromuscular blockade is likely multifactorial in causation, including a depolarization block of neuromuscular transmission,[30] desensitization of acetylcholine receptors,[37] and an open channel block of acetylcholine receptors resulting in rapid closure.[38]

Both residual neuromuscular blockade and neostigmine-induced neuromuscular block cause upper airway dilator muscle dysfunction leading to upper airway obstruction. Postoperative upper airway obstruction has been associated with negative pressure pulmonary edema,[39] which may contribute to the association between unwarranted use of neostigmine reversal and the increased incidence of postoperative respiratory complications.

Clinical Implications

Neostigmine is pharmacologically efficacious to reverse partial neuromuscular blockade, but clinically ineffective in its current application at our institution. Our study identified high-dose neostigmine and the unwarranted use of neostigmine as possible explanations for the association between neostigmine reversal and adverse respiratory outcomes.[5,6]

A proportion of anesthetists seem to routinely not use conventional, qualitative peripheral nerve stimulators. In our study, from an institution in which both qualitative and quantitative neuromuscular transmission monitors are available, approximately one out of five patients who received a ND-NMBA did not have a single TOF count recorded. This behavior observed in our trial is not following expert recommendations[19]; it is also likely not unique to our institution, and this has been reflected in the observations of others.[40]

Many clinicians decide to antagonize ND-NMBA by "pharmacological forecast" and qualitative judgment based on the breathing pattern and various other subjective assessments of muscle strength.[40] Awareness of these systematic errors related to overreliance and overconfidence in clinical intuition may facilitate the adoption of well-studied expert recommendations into standard clinical practice.[19]

The results of our study have to be considered within the context of its design. Our data came from a single, tertiary referral, academic medical center. The administration of neostigmine was a clinical decision, and the subset of patients who were administered neostigmine may have been clinically higher risk patients than those who were not. We made all efforts to control for confounding related to the fact that the collectives of patients who were given neostigmine were potentially at higher risk. We applied a uniform, comprehensive multivariable regression model to all parts of the data analysis. The covariate selection for confounder control included ASA risk classification, high-risk surgical service, duration of surgery, age, body mass index, and T4/T1 at PACU admission. Our study identified associations between neostigmine reversal and clinical outcomes but can only generate hypotheses as to the mechanisms relating them.

Conclusions

Neostigmine reversal did not affect oxygenation but was associated with increased atelectasis. Exploratory analysis revealed that high-dose neostigmine was a strong predictor of atelectasis and was associated with longer postoperative hospital length of stay. Unwarranted use of neostigmine, neostigmine administration without appropriate guidance from neuromuscular monitoring, was associated with increased respiratory morbidity.

Acknowledgments

Competing Interests

Correspondence

Address correspondence to Dr. Meyer: Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02115. mjmeyer@mgh.harvard.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. 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; 107:130–7

2. Herbstreit F, Peters J, Eikermann M: Impaired upper airway integrity by residual neuromuscular blockade: Increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. ANESTHESIOLOGY 2009; 110:1253–60

3. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. ANESTHESIOLOGY 2008; 109:389–98

4. Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U: Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anaesth 2010; 105:304–9

5. Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT, Ehrenfeld JM, Martinez EA, Kurth T, Eikermann M: Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: Prospective propensity score matched cohort study. BMJ 2012; 345:e6329

6. Meyer MJ, Bateman BT, Kurth T, Eikermann M: Neostigmine reversal doesn't improve postoperative respiratory safety. BMJ 2013; 346:f1460

7. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J; 8th International Neuromuscular Meeting: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. Acta Anaesthesiol Scand 2007; 51:789–808

8. Brull SJ, Ehrenwerth J, Silverman DG: Stimulation with submaximal current for train-of-four monitoring. ANESTHESIOLOGY 1990; 72:629–32

9. Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. ANESTHESIOLOGY 1997; 86:765–71

10. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, Kuylenstierna R: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: Simultaneous videomanometry and mechanomyography of awake human volunteers. ANESTHESIOLOGY 1997; 87:1035–43

11. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network: Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007; 132:410–7

12. Catterall R, Kazantzis G, Hodges M: The performance of nasal catheters and a face mask in oxygen therapy. Lancet 1967; 1:415–7

13. Naguib M, Lien CA: Pharmacology of muscle relaxants and their antagonists, Miller's Anesthesia, 6th edition, Miller RD, Fleisher LA, Johns RA, Savarese JJ, Wiener-Kronish JP, Young WL (eds.). Philadelphia, Churchill Livingstone/Elsevier, 2005, pp 481–572

14. Brueckmann B, Villa-Uribe JL, Bateman BT, Grosse-Sundrup M, Hess DR, Schlett CL, Eikermann M: Development and validation of a score for prediction of postoperative respiratory complications. ANESTHESIOLOGY 2013; 118:1276–85

15. Bevan DR, Donati F, Kopman AF: Reversal of neuromuscular blockade. ANESTHESIOLOGY 1992; 77:785–805

16. Barrow ME, Johnson JK: A study of the anticholinesterase and anticurare effects of some cholinesterase inhibitors. Br J Anaesth 1966; 38:420–31

17. Fiekers JF: Interactions of edrophonium, physostigmine and methanesulfonyl fluoride with the snake end-plate acetylcholine receptor-channel complex. J Pharmacol Exp Ther 1985; 234:539–49

18. Jones RK, Caldwell JE, Brull SJ, Soto RG: Reversal of profound rocuronium-induced blockade with sugammadex: A randomized comparison with neostigmine. ANESTHESIOLOGY 2008; 109:816–24

19. Brull SJ, Murphy GS: Residual neuromuscular block: Lessons unlearned. Part II: Methods to reduce the risk of residual weakness. Anesth Analg 2010; 111:129–40

20. Kopman AF, Eikermann M: Antagonism of non-depolarising neuromuscular block: Current practice. Anaesthesia 2009; 64(suppl 1):22–30

21. Arndt GA, Gerry T, White P: Postoperative reparalysis after rocuronium following nebulized epinephrine. Can J Anaesth 1997; 44:321–4

22. Coveler LA, Gallacher BP: Postoperative rocuronium reparalysis. Can J Anaesth 1997; 44:1127

23. Donati F, Smith CE, Bevan DR: Dose-response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 1989; 68:13–9

24. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block. II. Br J Anaesth 1971; 43:478–85

25. Engbaek J, Ostergaard D, Skovgaard LT, Viby-Mogensen J: Reversal of intense neuromuscular blockade following infusion of atracurium. ANESTHESIOLOGY 1990; 72:803–6

26. Kim KS, Cheong MA, Lee HJ, Lee JM: Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Anesth Analg 2004; 99:1080–5

27. Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. ANESTHESIOLOGY 2005; 102:257–68; quiz 491–2

28. Eikermann M, Fassbender P, Malhotra A, Takahashi M, Kubo S, Jordan AS, Gautam S, White DP, Chamberlin NL: Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. ANESTHESIOLOGY 2007; 107:621–9

29. Herbstreit F, Zigrahn D, Ochterbeck C, Peters J, Eikermann M: Neostigmine/glycopyrrolate administered after recovery from neuromuscular block increases upper airway collapsibility by decreasing genioglossus muscle activity in response to negative pharyngeal pressure. ANESTHESIOLOGY 2010; 113:1280–8

30. Payne JP, Hughes R, Al Azawi S: Neuromuscular blockade by neostigmine in anaesthetized man. Br J Anaesth 1980; 52:69–76

31. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ; Participants in the VA National Surgical Quality Improvement Program: Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005; 242:326–41; discussion 341–3

32. Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr: Hospital costs associated with surgical complications: A report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004; 199:531–7

33. Kopman AF, Kopman DJ, Ng J, Zank LM: Antagonism of profound cisatracurium and rocuronium block: The role of objective assessment of neuromuscular function. J Clin Anesth 2005; 17:30–5

34. Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI: The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: Pharyngeal videoradiography and simultaneous manometry after atracurium. ANESTHESIOLOGY 2000; 92:977–84

35. Capron F, Fortier LP, Racine S, Donati F: Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. Anesth Analg 2006; 102:1578–84

36. Caldwell JE: Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. Anesth Analg 1995; 80:1168–74

37. Yost CS, Maestrone E: Clinical concentrations of edrophonium enhance desensitization of the nicotinic acetylcholine receptor. Anesth Analg 1994; 78:520–6

38. Legendre P, Ali DW, Drapeau P: Recovery from open channel block by acetylcholine during neuromuscular transmission in zebrafish. J Neurosci 2000; 20:140–8

39. Krodel DJ, Bittner EA, Abdulnour R, Brown R, Eikermann M: Case scenario: Acute postoperative negative pressure pulmonary edema. ANESTHESIOLOGY 2010; 113:200–7

40. Videira RL, Vieira JE: What rules of thumb do clinicians use to decide whether to antagonize nondepolarizing neuromuscular blocking drugs? Anesth Analg 2011; 113:1192–6