Neostigmine Administration after Spontaneous Recovery to a Train-of-Four Ratio of 0.9 to 1.0

A Randomized Controlled Trial of the Effect on Neuromuscular and Clinical Recovery

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ABSTRACT

Background: When a muscle relaxant is administered to facilitate intubation, the benefits of anticholinesterase reversal must be balanced with potential risks. The aim of this double-blinded, randomized noninferiority trial was to evaluate the effect of neostigmine administration on neuromuscular function when given to patients after spontaneous recovery to a train-of-four ratio of 0.9 or greater.

Methods: A total of 120 patients presenting for surgery requiring intubation were given a small dose of rocuronium. At the conclusion of surgery, 90 patients achieving a train-of-four ratio of 0.9 or greater were randomized to receive either neostigmine 40 μg/kg or saline (control). Train-of-four ratios were measured from the time of reversal until postanesthesia care unit admission. Patients were monitored for postextubation adverse respiratory events and assessed for muscle strength.

Results: Ninety patients achieved a train-of-four ratio of 0.9 or greater at the time of reversal. Mean train-of-four ratios in the control and neostigmine groups before reversal (1.02 *vs.* 1.03), 5 min postreversal (1.05 *vs.* 1.07), and at postanesthesia care unit admission (1.06 *vs.* 1.08) did not differ. The mean difference and corresponding 95% CI of the latter were −0.018 and −0.046 to 0.010. The incidences of postoperative hypoxemic events and episodes of airway obstruction were similar for the groups. The number of patients with postoperative signs and symptoms of muscle weakness did not differ between groups (except for double vision: 13 in the control group and 2 in the neostigmine group; $P = 0.001$).

Conclusions: Administration of neostigmine at neuromuscular recovery was not associated with clinical evidence of anticholinesterase-induced muscle weakness.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B633. **(ANESTHESIOLOGY 2018; 128:27-37)**

THE use of reversal agents to antagonize neuromuscular blockade varies widely with country of practice, type of anesthetic practice, and individual clinician preference.[1–5] Most anesthesiologists routinely reverse neuromuscular blocking agents (NMBAs) if obvious muscle weakness is present at the time of tracheal extubation. However, if a single small dose (one to two times ED_{95}; the dose required to reduce single twitch height by 95%) of a nondepolarizing NMBA has been given and more than 2 h have elapsed since the time of administration, the decision process is more complex; the benefits of reversal with an anticholinesterase agent (or sugammedex) must be balanced with the potential risks. The primary advantage of routine use of neostigmine at the conclusion of surgery is a reduction in the risk of postoperative residual neuromuscular blockade (defined as a train-of-four [TOF] ratio less than 0.9). A high incidence of residual blockade (37 to 82%) has been reported when reversal agents are not administered.[4,6–8] Furthermore, failure to reverse the

What We Already Know about This Topic

- There is a high incidence of residual neuromuscular blockade when reversal drugs are not administered, and this is associated with postoperative adverse outcomes
- When there is substantial spontaneous recovery from neuromuscular blockade, it is unclear whether an anticholinesterase improves or impairs outcome

What This Article Tells Us That Is New

- In this randomized trial of patients achieving a train-of-four ratio of 0.9 or greater, half received either neostigmine 40 μg/kg or saline (control)
- There was no difference between groups in train-of-four ratios minutes after reversal or on recovery room admission and no difference in the incidence of postoperative muscle weakness, hypoxemia, or airway obstruction
- Anticholinesterases should be routinely administered after neuromuscular blockade, without fear of causing muscle weakness, unless full neuromuscular recovery has been documented with quantitative monitoring

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effects of NMBAs has been associated with an increased risk of postoperative pneumonia, coma, and mortality.[9,10] On the basis of these data, several editorials and reviews have recommended that, unless full neuromuscular recovery has been documented with quantitative monitoring, antagonism of NMBAs should be a routine practice.[5,11–13]

In contrast, other authors have cautioned against the routine administration of anticholinesterases to surgical patients.[14–16] Neostigmine has neuromuscular blocking properties when given in the absence of neuromuscular blockade,[14,15,17] which can induce a paradoxical reduction in the TOF ratio[15,17,18] and impair upper airway and breathing function.[19–21] Furthermore, database studies have also suggested that anticholinesterase reversal is associated with an increased risk of adverse postoperative respiratory events.[16,22,23]

Administration of an anticholinesterase to a patient in whom neuromuscular function has almost recovered could either increase the block and produce negative respiratory consequences[14–16,19–24] or have no adverse effect on neuromuscular recovery and result in no clinically important muscle weakness.[25–28] The aim of this randomized, double-blinded, placebo-controlled noninferiority study was to assess the effect of neostigmine (40 μg/kg) on neuromuscular function when given to patients after spontaneous recovery to a TOF ratio of 0.9 or greater. The dose of 40 μg/kg was selected because this represents an approximately average dose given by anesthesiologists,[3] yet is higher than the low-dose regimen (10 to 30 μg/kg) used to study reversal of shallow neuromuscular blockade by Fuchs-Buder *et al.*[27] TOF ratios were measured from the time of neostigmine administration until postanesthesia care unit (PACU) admission. In addition, patients were assessed for any adverse respiratory events (hypoxemia or airway obstruction) and signs and symptoms of muscle weakness during the early anesthesia recovery period. We tested the hypothesis that TOF ratios at the time of PACU admission would not be less in patients randomly assigned to receive neostigmine at TOFs of 0.9 to 1.0 compared with patients randomly assigned to receive saline (placebo) at that time (primary endpoint). We also tested the secondary hypotheses that the incidence of postextubation adverse respiratory events and signs or symptoms of muscle weakness would not be increased in patients randomly assigned to receive neostigmine.

Materials and Methods

Study Population and Perioperative Management

The NorthShore University HealthSystem Institutional Review Board (Evanston, Illinois) reviewed and approved this clinical investigation, which was registered at clinicaltrials.gov (NCT02433808, principal investigator Glenn Murphy, registration date April 2015, patient enrollment April 2015 to December 2016, full protocol can be obtained by request). The study was conducted at a single tertiary medical center (NorthShore University HealthSystem), and written informed consent was obtained from all of the subjects.

A total of 120 patients presenting for elective surgical procedures with an expected duration of at least 90 min were enrolled in this randomized, double-blinded, placebo-controlled noninferiority trial. Procedures were selected that required neuromuscular blockade for tracheal intubation but none thereafter. Exclusion criteria included American Society of Anesthesiologists physical status IV and V patients, ages less than 18 or more than 80 yr, need for succinylcholine for rapid sequence intubation, presence of renal insufficiency (defined as a serum creatinine concentration greater than 2.0 mg/dl) or renal failure (serum creatinine greater than three times the baseline), significant liver disease (cirrhosis or hepatic failure), presence of neuromuscular disease, or patients assessed as potentially unable to complete an examination of muscle strength in the PACU due to preoperative disease states or the nature of the surgical procedure. In addition, patients not achieving a TOF ratio of 0.9 or greater at the end of surgery were excluded from further participation in the investigation. The research assistants evaluated eligibility, obtained informed consent, and enrolled the participants.

Patients were assigned to one of two groups using a computer-generated randomization table (simple randomization without restrictions, pharmacy administered). The allocation sequence was generated by one of the study investigators. The randomization assignments were provided by the study investigator to the operating room pharmacy, which prepared the study drugs. Anesthesia care teams were provided with one of two syringes: a 10-ml syringe containing 40 μg/kg neostigmine with 8 μg/kg glycopyrrolate or a 10-ml syringe containing an equal volume of saline. Both syringes contained clear fluid, appeared identical, and were labeled *study drug*. At the end of the surgical procedure, patients in the neostigmine group were administered neostigmine and glycopyrrolate, and those in the control group were given saline. Throughout the perioperative period, care providers, patients, and research team members were blinded to group assignment. The administration of all other anesthetic agents was standardized to reflect the usual clinical practices.

Patients were premedicated with 2 mg of midazolam before transport to the operating room. Standard monitoring was applied to all of the patients, which included electrocardiography, pulse oximetry, noninvasive blood pressure measurements, capnography, central temperature assessment (nasopharyngeal or esophageal), and Bispectral Index monitoring (BIS system, Covidien/Medtronic, USA). Anesthesia was induced with propofol 1 to 2 mg/kg, lidocaine 50 mg, and fentanyl 100 μg. Clinicians were instructed to administer a small dose of rocuronium (one to less than two times ED_{95}) that would facilitate tracheal intubation and to give no additional NMBA for the remainder of the procedure.

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Anesthesia was maintained with sevoflurane 1.0 to 3.0%, with the concentration adjusted to maintain Bispectral Index values of 40 to 60 and systemic blood pressure within 20% of baseline measures. Hypotension was treated with phenylephrine 80 μg, ephedrine 5 to 10 mg, or a fluid bolus, as clinically indicated. The lungs were ventilated with 50% oxygen and air and ventilation adjusted to achieve an end-tidal carbon dioxide of 30 to 34 mmHg. Additional doses of fentanyl, up to 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$, were administered at the discretion of the anesthesia care team. In procedures associated with moderate-to-severe pain, intravenous hydromorphone 1 to 2 mg was given at the conclusion of the surgical procedure. Antiemetic prophylaxis included intravenous dexamethasone 8 mg at induction of anesthesia and ondansetron 4 mg within 30 min of tracheal extubation. A forced-air warming system was used to maintain core temperatures greater than 35°C and upper extremity temperatures greater than 32°C.

Neuromuscular monitoring was conducted in accordance with good clinical research practice guidelines in pharmacodynamic studies of NMBAs.[29] After cleansing the skin, two surface electrodes, separated by 3 cm, were placed over the ulnar nerve. The acceleration transducer of the TOF-Watch SX (Bluestar Enterprises, USA) was attached to the distal phalanx of the thumb *via* a hand adapter. The hand adapter (TOF-Watch Hand Adapter, Bluestar Enterprises) applied a constant preload and also allowed a reproducible baseline thumb position. A 5-s, 50-Hz tetanic stimulation was applied to reduce the time required to achieve baseline signal stabilization. The TOF-Watch SX was then calibrated (CAL 2 mode) and, after signal stability was achieved, baseline TOF values were recorded. Rocuronium was then administered as described above. The TOF-Watch SX was positioned so that members of the anesthesia care team were blinded to TOF ratio data. Intraoperative use of a peripheral nerve stimulator to assess depth of neuromuscular blockade subjectively was permitted by the protocol.

At the conclusion of the surgical procedure, a member of the research team measured TOF ratios with the TOF-Watch SX. Subjects not achieving a TOF value of 0.9 or greater were excluded from further study participation. Clinicians were instructed to administer these patients neostigmine (50 μg/kg) and to perform tracheal extubation when standard clinical criteria were met (see below). Neuromuscular and clinical recovery data were collected in the remaining subjects who had spontaneously recovered to a TOF ratio of 0.9 or greater. Patients randomly assigned to the neostigmine group were administered 40 μg/kg neostigmine and glycopyrrolate, and those assigned to the control group were given saline. Tracheal extubation was performed when the following clinical criteria were achieved: following commands, 5-s head lift, adequate spontaneous ventilation, and absence of fade with subjective TOF assessment. Patients were then transferred to the PACU; use of nasal cannula oxygen during transport was at the discretion of the anesthesia care team. On arrival to the PACU, all of the patients received 2 l/min oxygen *via* a nasal cannula. Management of patient care in the PACU was per standard protocols.

Data Collection

TOF ratio measurements were manually recorded by a research assistant on a data collection sheet immediately before administration of neostigmine or saline and then every 12 s thereafter until tracheal extubation was performed. The research team attempted to collect at least 5 min of TOF data (the peak clinical effect of neostigmine occurring approximately 5 min after administration).[15] For analysis, TOF ratios at each 1-min interval were determined by averaging the TOF measurement at that time with the TOF ratio measured immediately before and after that value. The time from administration of the contents of the study syringes until tracheal extubation was recorded. After removal of the endotracheal tube, a portable pulse oximeter (Rad-5, Masimo, USA) was attached to the patient's finger and peripheral oxygen saturation measured by pulse oximetry (Spo_2) monitored continuously by a research assistant from the time of extubation until admission to the PACU. Spo_2 measurements were manually recorded every 30 s and lowest Spo_2 determined. In addition, patients were carefully monitored by the research team for any evidence of upper airway impairment during transport to the PACU. Episodes of airway obstruction were recorded, as was the need for interventions to treat upper airway events.

On arrival to the PACU, TOF ratios were again assessed. Two consecutive TOF measurements were obtained and the average of the two values recorded. If measurements differed by more than 10%, additional TOF measurements were obtained (up to four TOF values), and the closest two ratios were averaged. The time from neostigmine administration until TOF measurements in the PACU was determined. Pulse oximetry was monitored continuously in the PACU, and Spo_2 data were recorded by PACU nursing staff on a data collection sheet. Episodes of moderate (Spo_2 of 93 to 90%) and severe (Spo_2 of less than 90%) hypoxemia were documented, as was the lowest Spo_2 observed during the PACU admission. The need for additional oxygen therapy or manual stimulation to maintain Spo_2 values greater than 93% was also noted. In addition, PACU nursing staff assessed patients during the admission for episodes of upper airway obstruction and subsequent interventions used to treat these episodes. The presence of nausea and emesis was noted.

Fifteen minutes after PACU admission, patients were assessed for 11 signs and 16 symptoms of muscle weakness. The research assistant performed testing in a standardized manner. Patients were initially requested to perform 11 tests of muscle strength (objective signs of muscle weakness). Patients either passed (negative response) or failed (positive response) each of the tests. After each of the tests was performed, patients were asked whether the test was difficult to complete or uncomfortable to perform (subjective symptom of muscle weakness). The presence of a symptom was recorded as a positive response and the absence of a

symptom was recorded as a negative response. Patients were then questioned about five additional symptoms of residual muscle paresis unrelated to the 11 tests of muscle strength. After the assessment was completed, patients were asked to quantify the degree of overall weakness experienced at the time of the examination on an 11-point verbal rating scale (0 = no muscle weakness, 10 = most severe muscle weakness experienced).

Patient demographic data and type of surgical procedure were recorded from electronic preoperative medical forms. The electronic anesthesia record was used to determine the duration of the surgical procedure; volume of crystalloid; blood loss; total intraoperative doses of rocuronium, fentanyl, and hydromorphone; and temperature at the end of the procedure. Baseline TOF ratios (before administration of NMBA) often exceed 1.00 when quantified with the TOF-Watch SX. For example, if the baseline TOF was 1.15, a TOF of 0.90 measured at the end of surgery represented a corrected or normalized TOF ratio of 0.78. Therefore, TOF values recorded immediately before administration of the contents of the study syringes were also corrected for baseline measures.

Statistical Analysis

The primary outcome measure was the TOF ratio at the time of PACU admission. Sample sizes were calculated based on the hypothesis that TOF ratios at the time of PACU admission would not be less in patients randomly assigned to receive neostigmine at TOFs of 0.9 to 1.0 compared with patients randomly assigned to receive saline (placebo) at that time (PASS 2005, Number Cruncher Statistical Systems, USA). Group sample sizes of 41 and 41 achieved 80% power to detect noninferiority using a one-sided, two-sample *t* test. The margin of equivalence was −0.05. The true difference between the means was assumed to be 0.00. The significance level (α) of the test was 0.05. The data were drawn from populations with SDs of 0.09 and 0.09. We studied 60 patients per group to account for the patients who would potentially not achieve recovery of neuromuscular function at the time of reversal (*i.e.*, they would have a TOF ratio of 0.9 or less).

Data for the primary outcome variable, TOF ratio at PACU admission are reported as the mean ± SD for both the control group and the neostigmine group. These primary outcome data were compared between groups using a one-sided, two-sample *t* test (NCSS 2004, Number Cruncher Statistical Systems). The mean difference and its 95% CI were calculated. The criterion for rejection of the null hypothesis was $P < 0.05$.

Secondary variables that were characterized by nominal data (*e.g.*, the presence of signs and symptoms of muscle weakness) are summarized as the number of patients in each category and the percentage of all patients in that group that they represent. These variables were compared between the randomized groups using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected number less than five, the Fisher exact probability test (NCSS). The Miettinen and Nurminen score was used to calculate 99% CIs for differences in percentages where they are reported. Variables that were characterized by ordinal data and nonnormally distributed continuous data (*e.g.*, time from neostigmine administration to PACU TOF measurement or general weakness) are summarized as median and interquartile range. These variables were compared between the randomized groups using the Mann–Whitney U test (StatsDirect version 3.0.198, StatsDirect, United Kingdom). Median differences and their 99% CIs were calculated where they are reported. Variables that were characterized by normally distributed continuous data (*e.g.*, rocuronium doses or TOF ratios before reversal) are summarized as mean and SD. These variables were compared between the randomized groups using the unpaired *t* test (NCSS). Mean differences and their 99% CIs were determined. Because of the large number of comparisons that were made, the criterion for rejection of the null hypothesis was a two-tailed $P < 0.01$ for all between-group comparisons. Continuous data measured repeatedly over time (*e.g.*, TOF ratios and arterial oxygen saturations in the first 5 min after placebo or neostigmine administration) were compared between and within groups over time using a two-factor ANOVA with repeated measures on one factor (time) with $P < 0.01$ the criterion for rejection of the null hypothesis; *post hoc* analysis using the Holm–Sidak method for pairwise multiple comparisons was planned to be used where indicated (SigmaPlot 11.0, Systat Software, Inc., USA).

Results

A total of 120 patients were enrolled in the clinical trial. Five patients were excluded from additional analysis when the anesthesia care team used succinylcholine instead of rocuronium for tracheal intubation. One patient was excluded when the pharmacy was unable to prepare the study syringes. At the conclusion of the surgery, 24 patients (21.1%) did not achieve a TOF ratio threshold of 0.9 and were excluded from additional data analysis. Quantitative neuromuscular and clinical recovery data were collected on the remaining 90 patients (47 in the neostigmine group and 43 in the control group; fig. 1).

Patient characteristics are presented in table 1. The study groups did not differ in sex, weight, height, American Society of Anesthesiologists physical status, types of surgical procedures, or preexisting medical conditions. No differences were observed between the two groups in anesthesia time, administration of crystalloids, blood loss, doses of intraoperative opioids (fentanyl and hydromorphone), or core temperature at the end of the procedure (table 2). The doses of rocuronium used at induction of anesthesia in the control group (26 ± 7 mg) and the neostigmine group (25 ± 8 mg; $P = 0.639$) were also similar (table 2).

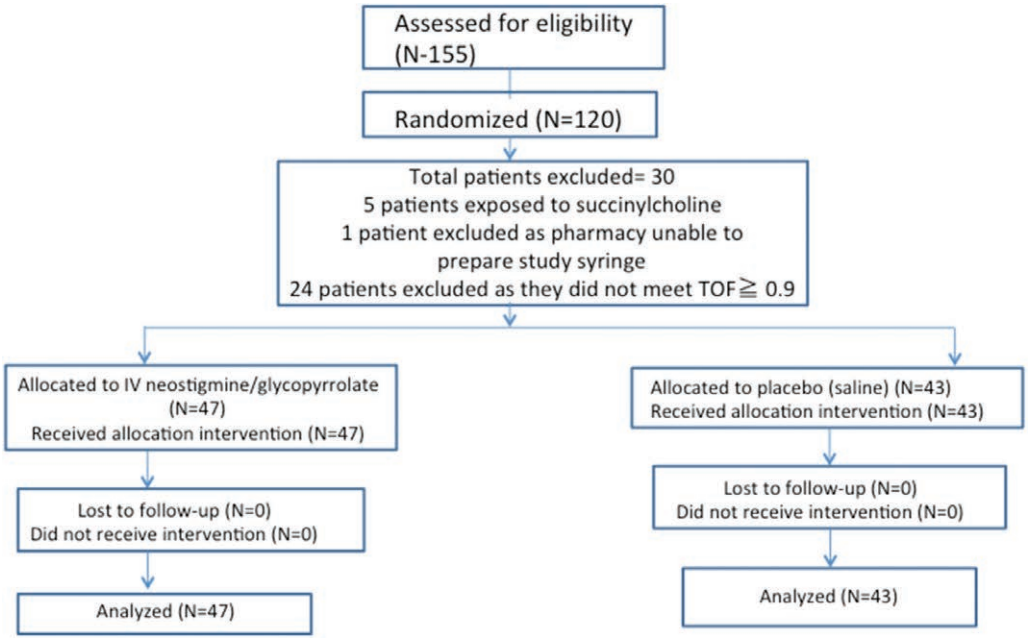

Fig. 1. Study flowchart. TOF = train-of-four.

Table 1. Patient Characteristics

	Control Group	Neostigmine Group
Sample size	43	47
Sex, men	15 (34.9%)	15 (31.9%)
Age, yr	50.4 ± 16.3	55.6 ± 14.6
Weight, kg	76.9 ± 18.3	74.5 ± 15.4
Height, cm	168.5 ± 10.9	168.5 ± 10.0
ASA physical status	2 (2–2)	2 (2–2)
Smoking history	0 (0%)	5 (10.6%)
Drinking history	1 (2.3%)	0 (0%)
Hypertension	10 (23.3%)	11 (23.4%)
History of coronary artery disease	2 (4.7%)	3 (6.4%)
Congestive heart failure	0 (0%)	1 (2.1%)
Arrhythmia	1 (2.3%)	1 (2.1%)
Asthma	6 (14.0%)	5 (10.6%)
Sleep apnea	4 (9.3%)	3 (6.4%)
Diabetes mellitus	4 (9.3%)	3 (6.4%)
Thyroid disease	6 (14.0%)	11 (23.4%)
Procedure		
Orthopedic	5 (11.6%)	6 (12.8%)
Ears, nose, and throat	15 (34.9%)	13 (27.7%)
Gynecologic	14 (32.6%)	18 (38.3%)
Endocrine	9 (20.9%)	10 (21.3%)

Data are mean ± SD, median (interquartile range), or number of patients (%).

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; drinking history = alcohol consumption more than 2 drinks per day.

TOF ratios in the control and neostigmine groups at PACU admission, the primary outcome, did not differ between groups (1.059 ± 0.070 and 1.076 ± 0.060, respectively; difference [95% CI], −0.018 [−0.046 to 0.010]). Additional quantitative neuromuscular monitoring data are presented in table 2 and figure 2. Mean TOF ratios measured before reversal (1.02 *vs.* 1.03), as well as normalized values (0.95 *vs.* 0.97) at that time, did not differ between the control and study groups, respectively. Similarly, TOF measurements between 1 min postreversal and 5 min postreversal were not different between groups. At PACU admission, TOF ratios had increased in both groups from prereversal values (from 1.02 to 1.06 in the control group and from 1.03 to 1.08 in the neostigmine group; $P < 0.001$ for both increases). Reductions in TOF values were not observed in any subject in either study group.

Data relating to postoperative oxygenation and adverse airway events after tracheal extubation are presented in table 2 and figure 3. During the time between tracheal extubation and admission to the PACU, the lowest observed peripheral oxygenation measures (Spo_2) did not differ between groups (94% control group *vs.* 95% neostigmine group). Only one episode of airway obstruction (neostigmine group) was noted during this time. During the PACU admission, the percentages of patients with moderate hypoxemic events (39.5% *vs.* 19.2%), severe hypoxemic events (18.6% *vs.* 8.5%), and requiring additional oxygen therapy (34.9% *vs.* 14.9%) were larger in the control group than in the neostigmine group, although this difference was not statistically significant given our conservative criterion for rejection of the null hypothesis ($P = 0.033$, 0.159, and 0.028, respectively). Only three episodes of airway obstruction were observed in the PACU (two in the control group and one in the neostigmine group).

Signs and symptoms of muscle weakness in the PACU are presented in table 3. No differences were observed between

Table 2. Perioperative Data

	Control Group	Neostigmine Group	Difference (99% CI)	*P* Value
Intraoperative data				
Anesthesia duration, min	155 (119–201)	171 (136–212)	−13 (−44 to 16)	0.209
Blood loss, ml	25 (15–75)	50 (10–100)	−5 (−50 to 15)	0.367
Crystalloid volume, ml	1393 ± 491	1302 ± 546	91 (−198 to 380)	0.411
Temperature at end of procedure, °C	36.1 ± 0.6	36.1 ± 0.6	0.0 (−0.4 to 0.3)	0.935
Total rocuronium dose, mg	25.6 ± 6.7	24.9 ± 8.0	0.7 (−3.4 to 4.8)	0.639
Total fentanyl dose, μg	150 (100–200)	150 (100–250)	0 (−50 to 0)	0.208
Total dilaudid dose, mg	0 (0–0.2)	0 (0–0.2)	0 (0–0)	0.908
Train-of-four ratio before reversal	1.02 ± 0.08	1.03 ± 0.07	−0.01 (−0.05 to 0.03)	0.506
Corrected train-of-four ratio before reversal	0.95 ± 0.06	0.97 ± 0.06	−0.02 (−0.06 to 0.01)	0.108
Transport data				
Lowest Spo_2, %	94.1 ± 3.6*	94.6 ± 3.2‡	−0.5 (−2.4 to 1.4)	0.508
Airway obstruction	0 (0%)	1 (2.1%)	−2.1% (−16.0 to 11.5%)	> 0.999
Treatment of obstruction	0 (0%)	0 (0%)	0% (−12.4 to 13.4%)	–
Spo_2 on PACU arrival, %	95.9 ± 3.0	96.6 ± 2.7	−0.75 (−2.3 to 0.9)	0.236
Oxygen during transport	30 (69.8%)	32 (68.1%)	1.7% (−23.5 to 26.3%)	0.863
PACU data				
Train-of-four ratio in PACU	1.06 ± 0.07†	1.08 ± 0.06‡	−0.02 (−0.06 to 0.02)	0.216
Time neostigmine to PACU train-of-four measurement, min	14.0 (11.0–18.5)†	14 (11–17)‡	1 (−2 to 4)	0.571
Patients with episodes Spo_2 90–93%	17 (39.5%)	9 (19.2%)	20.4% (−4.4 to 43.6%)	0.033
No. of episodes Spo_2 90–93%	0 (0–1)	0 (0–0)	0 (0–0)	0.046
Patients with episodes Spo_2 < 90%	8 (18.6%)	4 (8.5%)	10.1% (−9.5 to 30.8%)	0.159
No. of episodes Spo_2 < 90%	0 (0–0)	0 (0–0)	0 (0–0)	0.149
Needed additional oxygen therapy	15 (34.9%)	7 (14.9%)	20.0% (−3.6 to 42.6%)	0.028
Needed stimulation	12 (27.9%)	6 (12.8%)	15.1% (−7.1 to 37.3%)	0.073
Lowest Spo_2 observed, %	94 (90–97)	95 (94–96)	−1 (−3 to 1)	0.261
Airway obstruction	2 (4.7%)	1 (2.1%)	2.5% (−11.9 to 18.8%)	0.604
Treatment of airway obstruction	1 (2.3%)	1 (2.1%)	0.2% (−13.9 to 15.4%)	> 0.999
Nausea events	10 (23.3%)	9 (19.2%)	4.1% (−18.5 to 27.1%)	0.633
Emetic episodes	3 (7.0%)	4 (8.5%)	−1.5% (−19.1 to 16.6%)	> 0.999

Data are mean ± SD, median (interquartile range), or number of patients (%). Data reported as mean ± SD were compared using the unpaired *t* test, data reported as median (interquartile range) were compared using the Mann–Whitney U test, and data reported as number of patients (%) were compared using Pearson chi-square test, or when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. No *P* value met the criterion for rejection of the null hypothesis ($P < 0.01$). n = 43 in the control group and n = 47 in the neostigmine group, except where indicated. Need stimulation included patients requiring manual stimulation to increase oxygenation.

*N = 42. †N = 40. ‡N = 44.

PACU = postanesthesia care unit; Spo_2 = arterial oxygen saturation measured by pulse oximetry.

the groups in the number of patients with either signs or symptoms of residual paresis with the exception of double vision (13 control group *vs.* 2 neostigmine group, $P = 0.001$). The most commonly failed test of muscle strength was the 5-s head lift (14.0% control group and 6.5% neostigmine group). The most common symptoms of muscle weakness in the control and neostigmine groups were generalized weakness (48.8% *vs.* 26.7%), blurry vision (44.2% *vs.* 28.9%), and double vision (30.2% *vs.* 4.4%).

Discussion

In 1995, Caldwell[17] raised the question, "If a clinician administers a single dose of an NMBA to facilitate endotracheal intubation and gives none thereafter, should an anticholinesterase be administered, even if several hours have passed?" In that circumstance, the benefits of neostigmine reversal (reduced incidence of postoperative residual neuromuscular blockade) must be balanced against potential risks (cholinergic side effects and neostigmine-induced muscle weakness). In the present investigation, patients were given a small dose of rocuronium (approximately the ED_{95}) at induction of anesthesia and no additional NMBA for intraoperative relaxation. Despite an average duration of anesthesia of 163 min, 21% of patients had not spontaneously recovered to a TOF ratio of 0.9 or greater at the end of the procedure. In the remaining subjects with objective evidence of acceptable neuromuscular recovery, administration of 40 μg/kg neostigmine resulted in a small increase in TOF values in all patients, with no difference in TOF values between placebo and neostigmine groups at any time, including the time of PACU admission. In addition, patients randomly assigned to receive neostigmine at TOF ratios of 0.9 or greater did not have a higher incidence of hypoxemic events or airway obstruction during transport to the PACU

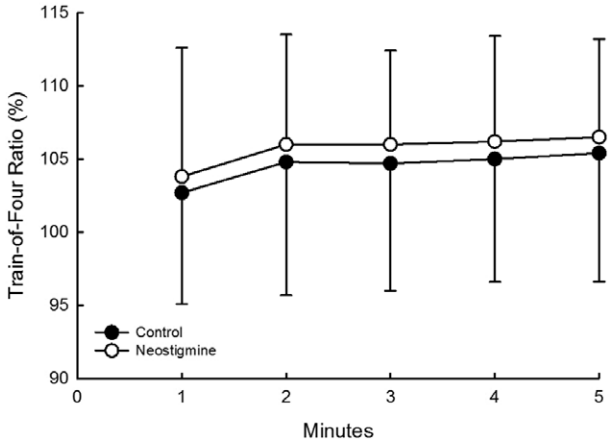

Fig. 2. Train-of-four ratios 1 to 5 min after administration of neostigmine or saline (control group).

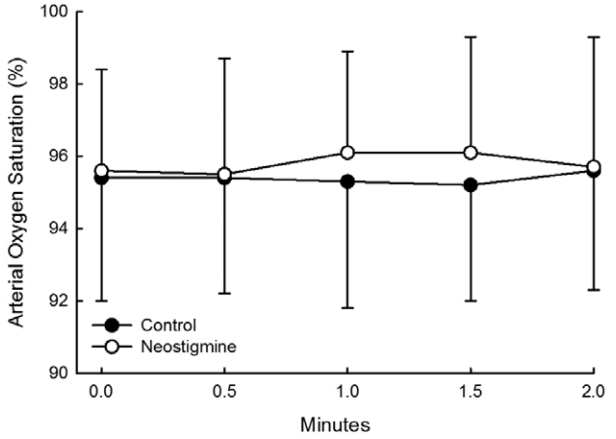

Fig. 3. Peripheral arterial oxygen saturation (Spo_2) values measured during the time from tracheal extubation to admission to the postanesthesia care unit.

or PACU admission when compared with those administered saline. A careful assessment of muscle strength also revealed that patients administered neostigmine after spontaneous recovery from NMBAs had occurred did not have more signs or symptoms of muscular weakness in the PACU.

There are several reasons clinicians may elect not to administer a reversal agent at the end of surgery. Most anesthesiologists believe antagonism of neuromuscular blockade is not required if there is absence of fade using a peripheral nerve stimulator or no evidence of muscle weakness on clinical examination[3,30,31]; however, both assessment methods are insensitive in detecting clinically significant levels of residual neuromuscular blockade (TOF ratios between 0.4 and 0.9).[13] The most frequently cited rationale for omitting reversal agents is the time interval since the last dose of NMBA.[3,30,31] Antagonism was considered unnecessary by anesthesiologists when more than 60 min had elapsed since a single dose of an intermediate-acting NMBA was given.[31–33] Clinical trials do not support this belief. Two or more hours after a two times ED_{95} dose of vecuronium, rocuronium, or atracurium, approximately 40% of patients had TOF ratios less than 0.9.[4] The only method available to reliably detect the presence or absence of incomplete neuromuscular recovery is quantitative neuromuscular monitoring; omission of neostigmine can be considered if TOF ratios of 0.9 or greater are observed. However, these monitors are infrequently used by anesthesiologists in the perioperative period.[3] The present study was specifically designed to minimize the risk of residual neuromuscular blockade at the conclusion of surgery. Patients undergoing procedures with an expected duration of at least 90 min and not requiring maintenance of neuromuscular blockade were enrolled. Furthermore, a small dose of rocuronium (approximately the ED_{95}) was used to facilitate tracheal intubation. Despite application of neuromuscular management strategies that have been documented to decrease the risk of incomplete neuromuscular recovery and a relatively long duration of anesthesia (160 min), residual paresis was still present in 24 (21%) of the 114 patients at the end of surgery.

Another important reason that clinicians may decide to omit anticholinesterases is related to concerns that neostigmine can induce neuromuscular transmission failure. In 1980, Payne *et al.*[14] reported that, whereas a 2.5-mg dose neostigmine antagonized neuromuscular blockade, a second 2.5-mg dose of the drug depressed the peak tetanic contraction and reestablished tetanic fade. Similar findings were reported by Goldhill *et al.*[15] and Astley *et al.*,[24] although the effects persisted for only about 10 to 20 min. Caldwell[17] observed decreases in the TOF ratio in 8 of 40 patients given neostigmine (40 μg/kg) 2 to 4 h after a single intubating dose of vecuronium; in all 8 patients, the TOF ratio had recovered to 0.9 or greater at the time of reversal. In contrast to these findings, we observed that TOF ratios did not decrease in any patient after 40 μg/kg neostigmine, even in those with objective evidence of full neuromuscular recovery (normalized TOF of 1.0). Furthermore, small increases in the TOF ratio were observed in subjects with TOF values between 0.9 and 1.0 after anticholinesterase administration. Previous investigators have reported that moderate doses of neostigmine (2.5 mg) increased TOF values when given at a TOF ratio of 0.9, with the peak effect occurring at 5 min.[15] The reasons that our findings differed from those of Caldwell,[17] despite having a similar study design, are uncertain but may be related to differences in the type of NMBA used (vecuronium *vs.* rocuronium), monitoring technology (mechanomyography *vs.* acceleromyography), or timing of neostigmine administration (during the procedure under isoflurane anesthesia *vs.* the end of surgery in the absence of inhalational agents). In contrast to the conclusions of other small, unblinded investigations,[14,17,24] the results of the present clinical trial demonstrate that moderate doses of neostigmine do not produce any objective evidence of muscle weakness, as measured by fade in the TOF ratio.

Data from Massachusetts General Hospital (Boston, Massachusetts) have suggested that neostigmine can induce

Table 3. Muscle Strength Assessment at 15 min after Postanesthesia Care Unit Admission

	Control Group	Neostigmine Group	Difference (99% CI)	*P* Value
Head lift, 5-s				
Sign	6 (14.0%)	3 (6.5%)*	7.4% (–10.8 to 27.1%)	0.305
Symptom	9 (20.9%)	4 (8.7%)*	12.2% (–8.0 to 33.3%)	0.102
Hand grip, 5-s				
Sign	2 (4.7%)	0 (0%)*	4.7% (–8.4 to 20.6%)	0.231
Symptom	2 (4.7%)	2 (4.4%)*	0.3% (–15.5 to 16.9%)	0.945
Eye opening, 5-s				
Sign	4 (9.3%)	1 (2.2%)	7.1% (–8.5 to 25.0%)	0.198
Symptom	5 (11.6%)	3 (6.7%)	5.0% (–13.2 to 24.2%)	0.479
Protrude tongue, 5-s				
Sign	2 (4.7%)	1 (2.2%)	2.4% (–12.5 to 18.7%)	0.612
Symptom	2 (4.7%)	3 (6.7%)	–2.0% (–19.0 to 15.0%)	0.999
Ability to smile				
Sign	3 (7.0%)	3 (6.7%)	0.3% (–17.1 to 18.2%)	0.999
Symptom	4 (9.3%)	4 (8.9%)	0.4% (–18.1 to 19.4%)	0.999
Ability to swallow				
Sign	2 (4.7%)	1 (2.2%)	2.4% (–12.5 to 18.7%)	0.612
Symptom	2 (4.7%)	2 (4.4%)	0.2% (–15.9 to 16.8%)	0.999
Ability to speak				
Sign	2 (4.7%)	1 (2.2%)	2.4% (–12.5 to 18.7%)	0.612
Symptom	2 (4.7%)	3 (6.7%)	–2.0% (–19.0 to 15.0%)	0.999
Ability to cough				
Sign	3 (7.0%)	1 (2.2%)	4.8% (–10.5 to 21.9%)	0.355
Symptom	3 (7.0%)	1 (2.2%)	4.8% (–10.5 to 21.9%)	0.355
Track object with eyes				
Sign	3 (7.0%)	2 (4.4%)	2.5% (–13.9 to 20.1%)	0.673
Symptom	3 (7.0%)	2 (4.4%)	2.5% (–13.9 to 20.1%)	0.673
Ability to breathe deeply				
Sign	1 (2.3%)	1 (2.2%)	0.1% (–14.6 to 15.3%)	0.999
Symptom	2 (4.7%)	2 (4.4%)	0.2% (–15.9 to 16.8%)	0.999
Tongue depressor test				
Sign	2 (4.7%)	1 (2.2%)	2.4% (–12.5 to 18.7%)	0.612
Symptom	2 (4.7%)	3 (6.7%)	–2.0% (–19.0 to 15.0%)	0.999
Blurry vision	19 (44.2%)	13 (28.9%)	15.3% (–11.2 to 40.0%)	0.136
Double vision	13 (30.2%)	2 (4.4%)	25.8% (5.8 to 46.5%)	0.001
Facial weakness	3 (7.0%)	3 (6.7%)	0.3% (–17.1 to 18.2%)	0.999
Facial numbness	4 (9.3%)	4 (8.9%)	0.4% (–18.1 to 19.4%)	0.999
General weakness	21 (48.8%)	12 (26.7%)	22.2% (– 4.6 to 46.2%)	0.032
Overall weakness	0 (0–2)	0 (0–1)	0 (0–1)	0.037

Data are median (range) or number of patients (%). Overall weakness was evaluated on an 11-point verbal rating scale (0 = no muscle weakness, 10 = most severe muscle weakness experienced). Tongue depressor test included the ability to resist the removal of a tongue depressor held between the incisors teeth. Data as median (interquartile range) were compared using the Mann–Whitney U test, and data reported as number of patients (%) were compared using the Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. Only double vision met the criterion for rejection of the null hypothesis ($P < 0.01$). N = 43 in the control group and 45 in the neostigmine group, except where indicated.
*N = 46.

muscle weakness and adversely affect respiratory outcomes. In animal models and human volunteers, neostigmine treatment after full recovery from neuromuscular blockade can impair upper airway dilator volume or critical closing pressure, genioglossus muscle function, diaphragmatic function, and breathing.[19–21] In addition, large observational and database studies from the same institution have described an association between neostigmine administration or unwarranted neostigmine use and an increased incidence of atelectasis, pulmonary edema, desaturations, postoperative pulmonary complication, and longer PACU and hospital stays.[22,23] The investigators hypothesized that "It is not safe to administer neostigmine to a patient who has spontaneously recovered from neuromuscular blockade because neostigmine dose-dependently affects respiratory muscle function and increases upper airway collapsibility."[22] In contrast to these findings, other investigators have reported no clinical evidence of respiratory muscle weakness in postoperative patients given neostigmine at near or full neuromuscular recovery.[15,25,26,28] Furthermore, a secondary analysis of the database findings from the Massachusetts General Hospital revealed that appropriate administration of neostigmine (monitoring and

dosing) resulted in a decreased risk of postoperative hypoxemic events and pulmonary complications.[16,23]

In the present investigation, reversal of neuromuscular blockade with neostigmine at TOF ratios of 0.9 or greater did not adversely affect upper airway function in postoperative surgical patients. Research assistants and PACU nurses carefully monitored patients for evidence of impairment of upper airway musculature during a high-risk period for postoperative respiratory events. Episodes of airway obstruction during transport from the operating room to the PACU and during PACU admission were infrequent and did not differ between study groups. Our findings are consistent with previous studies that have noted that postextubation airway obstruction is uncommon after neostigmine antagonism at recovery at a TOF ratio of 0.9 or greater.[34–36] In addition, neostigmine reversal was not associated with an increased risk of postoperative hypoxemic events. No differences between the neostigmine and control groups were noted in Spo_2 values during transport to the PACU. During PACU admission, fewer patients (approximately one half) in the neostigmine group had episodes of moderate or severe hypoxemia, required stimulation to maintain oxygenation, or needed additional oxygen therapy compared with the control group; however, these differences were not statistically significant, possibly because the study was not powered to examine these secondary outcomes.

Symptoms of muscle weakness (difficulty swallowing and diplopia) have been described in awake volunteers administered neostigmine (30 μg/kg) after spontaneous neuromuscular recovery to a TOF ratio of 1.0.[21] To further assess patients for possible neostigmine-induced muscle weakness, all of the subjects in our investigation were examined for 16 symptoms and 11 signs of impaired muscle function in the PACU. As noted previously,[37] more than 90% of patients admitted to the PACU with TOF ratios of 0.9 or greater were able to perform tests (signs) of muscle strength (with the exception of 5-s head lift, failed by 14.0% of control group and 6.5% of the neostigmine group), with no differences observed between study groups. The most common symptoms of muscle weakness described by patients in the PACU were blurry vision, double vision, and general weakness, with fewer symptoms noted in the neostigmine groups (4 to 29%) than in the control group (30 to 49%; $P = 0.001$ for double vision). These findings are not unexpected. Studies in both awake volunteers and postoperative surgical patients have reported that the most frequently described symptoms of residual paresis after recovery to a TOF ratio of 0.9 or greater are visual problems (34 to 70% of subjects) and general weakness or fatigue (44 to 45% of subjects).[37–39] Our findings suggest that use of reversal agents may decrease the risk of patients experiencing unpleasant symptoms of muscle weakness after surgery.

There are several limitations to this clinical trial. Although the incidence of observable upper airway events was not increased in patients administered an anticholinesterase, neostigmine might produce more subtle effects on the respiratory system that were not detectable on clinical examination (*e.g.*, upper airway critical closing pressure).[21] Second, only one dose of neostigmine (40 μg/kg) was examined in the investigation; it is possible that larger doses could induce muscle weakness. Surveys have indicated that the most common dose of neostigmine administered by anesthesiologists in the United States is 50 μg/kg, with many respondents indicating that they used even larger doses.[3] Third, study solutions were administered when the TOF-Watch SX displayed a TOF ratio of 0.9 (to represent standard clinical practices). When normalized for higher baseline TOF measures, a TOF of 0.9 on the TOF-Watch SX may represent a lower actual TOF ratio. However, only 7 of the 90 patients in the study group had not achieved a normalized TOF of 0.9 at the time of reversal. Finally, neuromuscular monitoring was conducted for at least 5 min after neostigmine administration; some investigators have determined that the peak effect of neostigmine occurs 6 to 10 min after it is given.[40]

In conclusion, administration 40 μg/kg neostigmine to patients with objective evidence of neuromuscular recovery (TOF ratios 0.9 to 1.0) did not adversely affect TOF values, respiratory function, or signs and symptoms of muscle strength. Furthermore, a high incidence of incomplete neuromuscular recovery (21%) was observed despite the use of a small dose of rocuronium and a relatively long duration of anesthesia (163 min). Clinicians should not avoid the use of neostigmine due to concerns related to anticholinesterase-induced muscle weakness. In light of the high risk of residual neuromuscular blockade in postoperative surgical patients, neostigmine should be routinely administered unless full neuromuscular recovery has been documented with quantitative neuromuscular monitoring.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: dgmurphy2@yahoo.com. Raw data available at: dgmurphy2@yahoo.com.

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America Helps Germany in "the Battle for Borocaine"

Manufactured by Sharp & Dohme of Baltimore, each corked vial (*above*) contained 20 soluble hypodermic tablets of Borocaine "under license from the British Drug Houses, Ltd., London." Because each tablet contained 0.1 g of procaine borate, dissolving a tablet in 5 ml of sterile water yielded a 2% solution of this ester local anesthetic. Unfortunately for Borocaine's British licensing firm, the American Medical Association's Chemical Laboratory determined that the "formula $2(C_{13}H_{20}O_2N_2)$, $4H_2O$, $5B_2O_3$, as given by the manufacturer…is incorrect; on the other hand, it appears that borocaine has the formula $C_{13}H_{20}O_2N_2.5HBO_2$" and is "identical to the one first prepared by Einhorn and Uhlfelder some years ago" in Germany. And this is how America helped Germany in "the Battle for Borocaine." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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