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Identifying high dose neostigmine as a risk factor for post-operative respiratory complications: a case-control study

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ABSTRACT

Background: Neostigmine, an acetylcholinesterase inhibitor, is used to reverse the effects of non-depolarizing neuromuscular blocking agents. Inappropriate dosing of neostigmine can lead to post-operative respiratory complications. Post-operative respiratory complications are associated with major morbidity and mortality. The purpose of this case-control study was to determine neuromuscular blockade-related risk factors associated with post-operative respiratory complications (specifically, reintubation, respiratory insufficiency, hypoxia, and/or aspiration).

Methods: We performed an Institutional Review Board-approved case-control study of all patients who underwent a general anesthetic requiring neuromuscular blockade at Tufts Medical Center between March 22, 2013 and June 1, 2019. Cases were patients who experienced post-operative complications. We identified 58 controls and 116 cases from a database of 130,178 patients during the 74-month study period.

Results: After adjusting for covariates, the administration of high dose neostigmine (> 60 mg per kg ideal body weight) was associated with increased odds of post-operative respiratory complications (odds ratio = 8.2; 95% CI: 2.5–26.6, $P < 0.001$). Rocuronium dose and the use of train-of-four peripheral nerve stimulator were not associated with post-operative respiratory complications.

Conclusions: High dose neostigmine was identified as an independent risk factor for post-operative respiratory complications. Our study suggests that inappropriate dosing of neostigmine continues to be a problem despite growing evidence of an association with respiratory complications.

Key words: respiratory complications, neostigmine, reintubation.

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A variety of post-operative respiratory complications may occur in 1.3–6.9% of anesthetics and may be associated with major morbidity and mortality [1, 2]. Because of the risk of anoxic brain injury, quickly responding to a patient with respiratory distress is important to minimize the risk of injury [3]. Nevertheless, post-operative respiratory complications are the largest class of preventable injury in multiple closed claims databases, representing up to 34% of cases [4, 5]. Furthermore, post-operative respiratory complications are associated with several complications [6]. Therefore, understanding risk factors for post-operative respiratory complications is important to decrease post-operative morbidity and mortality as well as medical liability.

Unplanned post-operative reintubation is associated with a 9-fold increase in 30-day all-cause mortality [7]. Muscle weakness following reversal of neuromuscular blockade may increase the risk of unplanned reintubation [8]. Although the existing literature predominantly focuses on the complications of inadequate reversal of neuromuscular blockade, excess anticholinergic administration might induce respiratory muscle weakness and also lead to reintubation. The purpose of this study was to determine risk factors associated with post-operative respiratory complications (specifically, reintubation, respiratory insufficiency, hypoxia, and/or aspiration).

METHODS

This study was approved by the Tufts Health Sciences Campus Institutional Review Board on June 26, 2018 and the requirement for written informed consent was waived. This manuscript adheres to the STROBE guidelines for case-control studies.

We conducted a single-center, retrospective, case-control study of all patients aged 18 or older

TABLE 1. Demographic characteristics

Factor	Cases ($n = 58$)	Controls ($n = 116$)
ASA PS*, *n* (%)		
1	4 (7)	2 (2)
2	12 (21)	30 (26)
3	31 (53)	60 (51)
4	11 (19)	23 (20)
5	0 (0)	1 (1)
Age (years)**	57 (17)	61 (13)
Sex*, *n* (%)		
Female	41 (71)	35 (30)
Male	17 (29)	81 (70)
Height (cm)**	163 (12)	173 (10)
Body mass (kg)**	88 (27)	90 (21)
Body mass index (kg m^{-2})**	33 (10)	30 (6)
Procedure length (min)**	124 (93)	141 (67)
Rocuronium (mg)**	61 (22)	64 (24)
Train-of-four monitoring*, *n* (%)	38 (66)	59 (51)
High dose neostigmine*, *n* (%)		
Yes	18 (31)	6 (5)
No	17 (29)	42 (36)
Dose not documented	23 (40)	68 (59)

ASA PS – American Society of Anesthesiologists Physical Status. Values reported as number (%)* or mean (standard deviation)**.

TABLE 2. Post-operative respiratory complications

Factor	Total
Reintubation	34 (59%)
Aspiration	10 (17%)
Respiratory insufficiency	9 (16%)
Hypoxia/hypoxemia	7 (12%)
Total	60[a]

Values reported as number (%). [a]Total is greater than 58 because one patient had unplanned reintubation and respiratory insufficiency and one patient had unplanned reintubation and aspiration.

who underwent anesthesia with endotracheal intubation at Tufts Medical Center between March 22, 2013 and June 1, 2019. We identified patients who had post-operative respiratory complications by examining the Department of Anesthesiology and Perioperative Medicine Quality Assurance Database.

The primary outcome was the development of a post-operative respiratory complication, defined as reintubation, respiratory insufficiency, hypoxia, and/or aspiration, consistent with the definitions of the National Anesthesia Clinical Outcomes Registry Data Dictionary [9]. We adjusted for the following covariates: intraoperative administration of high dose neostigmine (> 60 mg per kg ideal body weight), dose of rocuronium, and documented use of train-of-four peripheral nerve stimulator [10]. After identifying all post-operative complications in the Quality Assurance Database, post-operative respiratory complications were verified by manual chart review.

Each case of post-operative respiratory complication was matched to 2 controls by age (> 80 or ≤ 80 years), American Society of Anesthesiologists Physical Status (≥ 3 or < 3), year of surgery (± 1 year), duration of surgery (≥ 3 or < 3 hours), and type of procedure (high-risk vs. low-risk for respiratory complications; high-risk was defined as cardiac, thoracic, or otolaryngological surgery as well as interventional pulmonary or cardiac procedures) [11].

Statistical analysis

SPSS (IBM v25.0, Armonk, NY, USA) with the specialized extension R Project for Statistical Computing (R v3.3.1, Vienna, Austria) was used to match the cases with controls. Stata v15 (StataCorp, Colle Station, TX, USA) was used to perform univariable and multiple variable logistic regression analyses. Results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *P*-values. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Between March 22, 2013 and June 1, 2019, we identified 58 cases and 116 controls out of a total cohort of 130,178 patients. Demographic data are presented in Table 1 and the types of post-operative respiratory complications observed are presented in Table 2. Results from the univariable and multiple variable regression analyses are presented in Table 3. After adjusting for co-variates, the administration of high dose neostigmine was associated with post-operative respiratory complications (OR = 8.2; 95% CI: 2.5–26.6, *P* < 0.001). Rocuronium dose and the use of train-of-four peripheral nerve stimulator were not associated with post-operative respiratory complications.

TABLE 3. Regression analysis of risk factors for post-operative respiratory complications

Factor	Univariable analysis			Multiple variable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
High dose neostigmine	7.4	2.50–21.90	< 0.001	8.2	2.50–26.60	< 0.001
Rocuronium dose	1.0	0.99–1.02	0.414	1.0	0.97–1.02	0.886
Train-of-four monitoring	1.8	0.96–3.50	0.068	0.9	0.30–2.70	0.841

DISCUSSION

Our results suggest that high dose neostigmine is associated with 8-fold increased odds of post-operative respiratory complications. Although our study is limited by a relatively low incidence over the study period, we were able to match patients on several important confounders. While these results are compelling, further validation is needed.

Unplanned post-operative reintubation and other respiratory injuries represent over 30% of medicolegal claims for injuries occurring in the post-anesthesia care unit [5]. High dose neostigmine administration may increase the risk for post-operative respiratory complications by causing an excess of acetylcholine at the neuromuscular junction, leading to depolarization block and resultant muscle weakness [12]. Although peripheral nerve stimulation can be used to guide neostigmine dosing, many patients do not receive such monitoring intraoperatively and therefore may receive doses of neostigmine that predispose them to respiratory complications.

The finding that high dose neostigmine is associated with post-operative respiratory complications is not surprising. In an operative setting, repeated administration of neuromuscular blocking agents can lead to a prolonged duration of action, exacerbating residual paralysis. When high doses of neostigmine (particularly those > 60 mg kg^{-1}) are given to reverse the effects of the neuromuscular blockade, partial neuromuscular transmission blockade can occur, causing post-operative respiratory complications [10]. It has been previously shown that unwarranted use of neostigmine was associated with increased pulmonary edema, reintubation, and a shorter period of time from neostigmine administration to extubation [13]. One factor that might lead to the administration of high dose neostigmine may be the use of total body weight to calculate the dose; generally, ideal body weight is used in studies examining the effects of neostigmine dosing, as total body weight dosing will result in higher doses (especially with the rising rates of obesity) and therefore increased risk of overdose [10].

When reversing neuromuscular blockade, it is important to assess the degree of muscle paralysis, which can be done by train-of-four (TOF) monitoring. A TOF ratio of less than 0.9 has been associated with significant pharyngeal muscle dysfunction [14]. Neostigmine should ideally not be administered until at least two twitches are present [8], as neostigmine is only effective to reverse milder levels of neuromuscular block and has not been shown to be effective in deep neuromuscular blockade [8, 15]. However, qualitative monitoring is insufficient to determine acceptable neuromuscular recovery, and acceleromyographic devices can be used to quantify the TOF ratio to ensure proper recovery [16]. In our study, only 66% of cases and 51% of controls had any reported TOF monitoring, and whether the T4/T1 ratio was greater than 0.9 before administering neostigmine was not reported because our institution only has qualitative peripheral nerve stimulators.

As in all studies, our study has limitations that need to be considered. First, we assessed neostigmine overdose as a binary outcome. It remains unclear whether specific doses are associated with increased post-operative respiratory complication rates, and such possibilities should be examined in future studies that include dosage. Second, we had a relatively small sample size of 58 cases. A larger sample size would have increased the statistical power of the study. Third, there is a risk for selection and observation bias given the nature of the data. To decrease the risk of bias, all patients who received general anesthesia with an endotracheal tube during the study timeframe were extracted from the Quality Assurance Database and considered as potential controls, while all patients who experienced post-operative respiratory complications under general anesthesia with an endotracheal tube were selected as cases. Patients who experienced non-respiratory complications were excluded as potential controls. All remaining patients were included in the case-control matching. Additionally, there is always a possibility of reporting errors in terms of inputting data into the electronic medical record. Fourth, while we did not find an association between use of peripheral nerve stimulator and respiratory complications, our data were limited because we did not have the exact train-of-four count or ratio. Future studies should be performed that include the train-of-four count or ratio immediately prior to the administration of neostigmine. Finally, since our institution is a tertiary referral center, the results of this study may not be applicable to those receiving care in primary or secondary institutions. Nevertheless, the majority of procedures requiring anesthesia occur in higher-level care facilities, so our results should be applicable in most instances.

Decreasing respiratory complications associated with neostigmine presents inherent challenges since it involves practice changes among clinicians. Most quality improvement interventions find that short-term effects are rarely sustained. However, several recent studies suggest that cognitive aids (e.g., a card that can be used at the point of care to remind clinicians about dosing strategies) may result in more long-term effects [8, 17]. Prospective studies are needed to determine whether interventions, such as cognitive aids to guide clinicians on

evidence-based approaches to reversal of neuromuscular blockade, may help to decrease the incidence of post-operative respiratory complications and their subsequent effects on patient outcomes.

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