PCRC Proposal Cover Sheet

Title of Study or Project:	Variation in management of neuromuscular blocking agents, monitoring, reversal and the risk of pulmonary complications after major surgery
Primary Institution:	University of Michigan
Principal Investigator:	Tim Dubovoy, MD
Co-Investigators:	Nirav Shah, MD, Shelley Housey, MPH, Amy Shanks, PhD, Sachin Kheterpal MD, MBA
Type of Study:	☐ Retrospective Observational ☐ Exploratory
IRB Number/Status:	Pending
Hypothesis:	The goal of the proposed study is to use a broadly representative observational dataset to identify the optimal neostigmine administration pattern of care. Three specific aspects of NMB management and reversal will be evaluated: duration since last NMB administration, dose of neostigmine, and most recent TOF documented prior to reversal. Using administrative and clinical registry data, the impact on pulmonary complications will be evaluated using a multicenter, national dataset integration detailed intraoperative management and outcome data.
Number of Patients/Participants:	
Power Analysis:	
Proposed statistical test/analysis:	
Resources (Brief summary of resources for data collection, personnel, financial):	

Variation in management of neuromuscular blocking agents, monitoring, reversal and the risk of pulmonary complications after major surgery

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Background

Despite advances in the areas of technology, pharmacology, and quality assurance, residual neuromuscular blockade (RNMB) remains a persistent problem. During the 1980s the incidence of RNMB, defined as train-of-four (TOF) ratios <0.7 in the PACU, was reported to be between 21% and 36% of patients receiving neuromuscular blocking agents.[2-4] In contemporary anesthesia practice, RNMB in the PACU, defined as TOF ratios <0.9, can be detected in up to 60% of patients, even after the majority of blocks had already been reversed with anticholinesterases.[1,5] Ref## (RECITE). Residual NMB impact patient comfort, immediate postoperative events in the recovery room, and is associated with complications such as atelectasis, pneumonia, pulmonary failure, and reintubation.

Despite drug shortages and the advent of suggamadex, neostigmine remains the mainstay of modern clinical practice to reverse the effects of non-depolarizing neuromuscular blockade. Some data demonstrates that the unnecessary use of neostigmine may exacerbate the problem of RNMB. However, the appropriate use of neostigmine may ameliorate the risks of RNMB. The widespread observation of RNMB and pulmonary complications persists due to absence of published monitoring standards or consensus regarding need, timing, and dosing of neostigmine.

The goal of the proposed study is to use a broadly representative observational dataset to identify the optimal neostigmine administration pattern of care. Three specific aspects of NMB management and reversal will be evaluated: duration since last NMB administration, dose of neostigmine, and most recent TOF documented prior to reversal. Using administrative and clinical registry data, the impact on pulmonary complications will be evaluated using a multicenter, national dataset integration detailed intraoperative management and outcome data.

Materials and Methods

Data sources

Institutional review board approval was obtained from each organization to contribute a limited dataset to the Multicenter Perioperative Outcomes Group (MPOG) central repository and a separate approval was obtained for the conduct of research using this limited dataset (HUMXXXX, University of Michigan, Ann Arbor, Michigan USA). Patient informed consent is waived for this study since there is no care intervention and no protected health information is being used for analysis.

This is a retrospective observational study using the MPOG central repository limited dataset. The MPOG data contribution methodology has been described previously, but is briefly summarized here. Each contributing center uses a modern intraoperative electronic health record (EHR) to record all medicolegal aspects of intraoperative care. All medications, procedures, events, observations, and physiologic data is stored in the EHR. Automated physiologic interfaces are used to capture monitoring data. In addition, some MPOG centers record and contribute a structured preoperative history and physical and laboratory values. All preoperative and intraoperative data were collected at the point of care via routine clinical documentation by the anesthesiology resident, fellow, attending anesthesiologist, or certified registered nurse anesthetists. Several distinct EHRs are integrated into a consistent MPOG data model and data dictionary across all MPOG sites. The transformation of data structures and synchronization of clinical terminology into a common MPOG standard allows integration and comparison of data across centers despite different EHRs and underlying clinical terminology. A rigorous data diagnostics and validation process is used to maximize accuracy of the data contribution. Nearly 100 automated data diagnostics are performed on a monthly basis at each site and presented to a physician or nurse anesthesiology clinical quality reviewer (ACQR). Any diagnostics not passing MPOG standards are manually reviewed, addressed, and documented by the ACQR. In addition, between 5 and 20 cases are individually reviewed by the ACQR to ensure the MPOG extract represents the EHR data accurately and completely. More than 30 individual tests are performed on each case to ensure data accuracy and completeness.

Patient population

All adult patients (≥ 18 years of age) undergoing surgery under general anesthesia with endotracheal intubation receiving an intermediate duration non-depolarizing neuromuscular blockade agent (NMB) by bolus or infusion were included (atracurium, cisatracurium, vecuronium, rocuronium) between January 1, 2004 to September 1, 2015 were evaluated for inclusion in the primary analysis. We excluded outpatient procedures, ASA physical status 5 or 6 patients, patients who were intubated prior to OR arrival, patients remaining intubated at the conclusion of anesthesia period, cardiac surgery, lung or liver transplantation, cases where neostigmine was administered to facilitate intraoperative neurologic monitoring with subsequent re-dosing of NMB agents, patients receiving median PEEP > 10 cm H20, patients with myasthenia gravis or those receiving pyridostigmine therapy, patients with documented BMI >= 60 kg/m2. For any patient undergoing multiple included procedures during a 30 day period or a given inpatient stay, only first procedure was included in the analysis.

The following MPOG centers are contributing data consistent with inclusion in the current proposal: University of Michigan, Oregon Health & Science University, University of Colorado, University of Vermont, University of Virginia, Yale University, Cleveland Clinic, Beaumont Health System, and St. Joseph Mercy Health System.

Outcomes

The primary outcome was any major postoperative pulmonary complications including re-intubation, respiratory failure, pneumonia, or pulmonary edema that is not observed to be present-on-admission. These outcomes are defined using discharge ICD9 billing codes collected as part of the standard administrative processes at these hospitals (518.5, 518.51, 518.52, 518.81 518.82, 518.84, 514, 518.4, 276.6, 276.69, 481, 482.0, 482.1 482.30, 482.40, 482.41, 482.42, 482.82, 482.83, 482.89, 496, 483.8, 484.6, 485, 507.0).

Exposure variables

Three exposure variables of interest will assessed to establish the relationship between each variable and the adjusted risk of pulmonary complications:

1) total neostigmine dose
2) time from last non-depolarizing NMB to extubation
3) last subjective train of four documented prior to neostigmine administration (or extubation if neostigmine is not administered).

First, the total dose of neostigmine in mcg/kg prior to extubation will be calculated based upon total body weight. Five categorical definitions will be used as exposure variables 0, 1 – 20, 21-40 (reference), 41-60, 61-80, and 80 or more mcg/kg. Second, the time from the last bolus NMB administration (or termination of NBM infusion) to extubation will be categorized into an ordinal variable: 0 – 60 minutes (reference), 61-120 minutes, 121 – 180 minutes, 181 – 240 minutes, 241 – 300 minutes, and 301 or more minutes. Finally, the last subjective train of four documentation prior to neostigmine administration, but after last NMB bolus administration will be analyzed using 5 categorical variables: not documented, 0 or 1 / 4 twitches, 2 twitches, 3 or 4 twitches (reference), and sustained tetany.

Confounder variables

A variety of patient, procedural, and physiologic parameters may affect the risk of pulmonary complication and must be accounted for in an assessment of neuromuscular blockade management: Patient and procedural variables included age, sex, body mass index, ASA 3 or 4 physical status, emergent procedure, preoperative SpO2 <= 94%, Elixhauser comorbidity score using discharge ICD9 and preoperative history ICD9 (each component of the score will be included as a distinct variable), surgical procedure body region as determined by primary anesthesia CPT, surgical duration in minutes, and anesthesia base CPT code base units as a proxy for procedural complexity. Intraoperative variables used for risk adjustment included total non-depolarizing NMB administration in ED95/kg/hour (time from first administration to extubation), a categorical variable representing the specific NMB agent used (or multiple agents), median tidal volume in ml/kg ideal body weight, median PEEP between 5 and 10 cmH20, # of units of packed red blood cells administered, fluid administration in ml/kg, median depth of anesthesia in age-adjusted quintiles, magnesium administration, and morphine equivalents in mcg/kg/hour. Conversion of NMB doses to ED95 was based upon the following medication specific ratios: vecuronium 0.05 mg/kg, rocuronium 0.3 mg/kg, atracurium 0.26 mg/kg, cisatracurium 0.05 mg/kg using ideal body weight. In the case of multiple NMB use, each agent was converted to an ED95 equivalent and then summed. The impact of preexisting pulmonary disease as a confounder will be addressed by the inclusion of the Elixhauser elements for COPD and other diseases.

Statistical Analysis

To evaluate each of the three exposure variables of interest, a primary analysis will consist of a multivariate logistic regression with pulmonary complication as the dependent dichotomous outcome.

Independent variables included for each model will be the exposure variable of interests and the confounder variables. Center effects will be addressed through the use of a categorical variable representing each organization. In addition, specific preplanned subgroup analyses to isolate the effect of the exposure variables will be performed:

1) Patients receiving 0 mcg/kg neostigmine
2) Patients receiving neostigmine despite most recent TOF of 0 or 1 twitches
3) Patients with documentation of TOF within 30 minutes of neostigmine administration (or extubation if no neostigmine administered)
4) Patients without TOF documentation

Three subgroup analyses to identify any NMB agent-specific patterns of care will be performed: Patients receiving rocuronium, vecuronium, or cisatracurium alone versus other NMB agents. A subgroup analysis of patients with BMI >= 30 kg/m2 will also be performed.

For each analysis, collinearity diagnostics and Pearson correlations will be conducted on all pairs of variables to assess for independence. Condition indices more than 30 will be used to identify covariates that are highly correlated with one another before building the logistic regression model. All remaining variables will then be entered in a non-parsimonious logistic regression model. The Omnibus test is used to evaluate the goodness of fit by the presence of statistically significant differences between the explained and unexplained variance within the model. The resultant chi-square statistic value is a measure of the relationship between observed and expected frequencies. A P value of <0.05 in this test denotes that the null hypothesis is rejected. The predictive value of the resulting regression model is then evaluated using a receiver operating characteristic area under the curve. The area under the curve represents the fractions of outcomes, both positive and negative, that are accurately predicted by the model. All variables deemed to be significant in the logistic regression model ($P < 0.05$) will be established as independent predictors of the study.

Limitations

In addition to residual neuromuscular blockade, other clinical factors may contribute to pulmonary complications in the postoperative period. The absence of postoperative fluid administration, opioid management, and other pertinent data limits the definitiveness of the current analysis. In addition, because the data are collected as part of routine clinical or administrative processes, they are subject to recording errors.

Questions for group:

1) Should we include a sub-analysis for sites with NSQIP/MSQC data
    a. Much more limited sample size and procedural variety
    b. Much more definitive outcome definition and risk adjustment
2) Are we focusing on the right outcomes?
3) Are there are other questions regarding NMB monitoring or reversal that can be addressed in this paper without confusing it too much?
    a. Patients receiving succinylcholine alone
4) Analysis: is there a better way to manage the interaction between all these exposures of interest
    a. TOF monitoring
    b. Neostigmine dose
    c. Time from last NMB dose
5) Should we exclude patients that may have 'edge-case' impact, or let the risk adjustment handle it?
    a. Renal disease
    b. Liver disease
6) Exposure variables
    a. Should we divide up twitches into different categories?

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13. http://www.ncbi.nlm.nih.gov/pubmed/25902322 (RECITE study)
14. http://www.ncbi.nlm.nih.gov/pubmed/23337416 (symptoms of RNMB)
15. http://www.ncbi.nlm.nih.gov/pubmed/24162461 (RNMB causes)