DEVELOPMENT OF AN INTRAOPERATIVE COGNITIVE AID TO GUIDE NEOSTIGMINE USE FOR PHARMACOLOGIC REVERSAL OF NEUROMUSCULAR BLOCKADE

by

Laura Cornette

A doctoral scholarly project submitted to the faculty of
The University of North Carolina at Charlotte
in partial fulfillment of the requirements
for the degree of Doctor of Nursing Practice

Charlotte

2023

Approved by:

Dr. Stephanie Woods

Dr. Lorraine Schoen

Dr. Emily Bludov

Dr. Katie Shue-McGuffin

Dr. Tricia Turner

Author Note

There are no conflicts of interest to disclose. Correspondence concerning this article should be addressed to Laura Cornette. Email: Laura.Cornette@atirumhealth.org

ABSTRACT

LAURA CORNETTE. Development Of An Intraoperative Cognitive Aid To Guide Neostigmine Use For Pharmacologic Reversal Of Neuromuscular Blockade.
(Under the direction of DR. STEPHANIE WOODS)

Insufficient recovery from non-depolarizing neuromuscular blocking agents results in impaired pulmonary and upper airway mechanics and increases patients' risk of experiencing adverse respiratory events postoperatively (Kheterpal et al., 2020; Rudolph et al., 2018a; Leslie et al., 2021; Saager et al., 2019). Postoperative pulmonary complications (PPCs) are associated with an increase in hospital length of stay, rate of readmission, and overall morbidity and mortality (Kheterpal et al., 2020). The incidence of residual neuromuscular blockade following general anesthesia remains as high as 60% despite the standard use of anticholinesterase reversal agents (Saager et al., 2019). A quality improvement project (QI) was conducted to determine if anesthesia providers' practices using neostigmine to antagonize neuromuscular blockade were consistent with current evidence-based clinical recommendations. A survey was distributed to all anesthesia providers at a level-1 trauma center, and data was collected anonymously over one month. While 96.1% of respondents correctly identified the mechanism of action of neostigmine, about half of these respondents failed to recognize the correct peak effect of neostigmine. The survey results also revealed significant provider variability in dosing neostigmine according to the number of twitches elicited using a peripheral nerve stimulator in the train-of-four mode. The survey results were compared to the practice guidelines identified in the literature review and analysis to describe educational opportunities surrounding neostigmine use at this facility. The survey findings and literature synthesis informed the creation of an intraoperative cognitive aid to guide the reversal of muscle paralysis using neostigmine. This QI project recommends

ongoing evaluation and analysis of practice trends to promote best practices consistent with contemporary literature.

ACKNOWLEDGEMENTS

I want to acknowledge and extend my sincere gratitude to my committee chair, Dr. Stephanie Woods, who made this work possible. Her guidance was instrumental in conducting a meaningful quality improvement project. I would like to thank my committee members for their patience, dedication, and feedback throughout this process. I would also like to thank Associate Professor at The School of Nursing, Dr. Job Chen, for the time he selflessly devoted to assisting me with statistical analysis.

I would like to give a special thanks to my colleagues and co-investigators of this quality improvement project— Michael Pleva and Kevin Stovall. Your tireless commitment and seamless communication throughout this process were essential to the success of this quality improvement project. It was a privilege to work alongside each of you.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Ach	Acetylcholine
CRNA	Certified Registered Nurse Anesthetist
NMB	Neuromuscular Blockade
nNMBA	Non-depolarizing Neuromuscular Blocking Agent
NMJ	Neuromuscular Junction
OR	Operating Room
PACU	Post Anesthesia Care Unit
PDSA	Plan Do Study Act
PNS	Peripheral Nerve Stimulator
PONV	Post-Operative Nausea and Vomiting
PPC	Post-Operative Pulmonary Complication
QI	Quality Improvement
SRNA	Student Registered Nurse Anesthetist
TOF	Train-of-Four
TOFC	Train-of-Four Count
TOFR	Train-of-Four Ratio

CHAPTER 1: INTRODUCTION

The introduction of non-depolarizing neuromuscular blocking agents (nNMBAs) into clinical practice revolutionized surgery and substantially decreased the mortality rate of general anesthesia (Barash, Bieterman, & Hersey, 2015). In current practice, anesthesia providers routinely administer nNMBAs intraoperatively to optimize surgical exposure, facilitate tracheal intubation, and control patients' ventilation. Although the introduction of nNMBAs provided countless tangible benefits, nNMBAs also presented new challenges that modern clinicians are still tackling. At the forefront of these challenges is the incomplete recovery from nNMBAs causing residual muscle weakness.

The potential for residual neuromuscular blockade (NMB) to cause clinically relevant problems has been established for decades (Brull & Kopman, 2017). However, in more recent years, the subject garnered more attention as several studies concluded that residual NMB, defined as a Train-of-Four ratio (TOFR) less than 0.9, was an independent risk factor for the development of critical postoperative pulmonary complications (PPCs) (Kheterpal et al., 2020; Rudolph et al., 2018a; Leslie et al., 2021; Saager et al., 2019; Aytac et al., 2018; Fortier et al., 2015). Despite technological advancements in NMB monitoring modalities and the introduction of a novel reversal agent—sugammadex, residual NMB in the post anesthesia care unit (PACU) remains a prevalent problem (Saager et al., 2019). Proper monitoring of neuromuscular depth and effectively dosing pharmacologic reversal agents according to evidence-based techniques may reduce the burden of residual NMB, attenuate preventable adverse respiratory events, and enhance patient safety.

A quality improvement (QI) project focusing on the evidence-based reversal of neuromuscular blockade using neostigmine/glycopyrrolate was conducted as a part of a larger QI project on the overarching topic of evidence-based neuromuscular blockade management. The QI project also investigated qualitative monitoring of the neuromuscular junction (NMJ) using the peripheral nerve stimulator (PNS) and reversal using sugammadex. Each arm of the QI project was used to inform the creation of a comprehensive intraoperative cognitive aid to provide evidence-based guidelines for monitoring techniques and pharmacologic reversal strategies to reduce residual neuromuscular paralysis. A brief description of monitoring the NMJ using the PNS is provided for context, as its use directly guides the dose selection of neostigmine to reverse muscle paralysis.

Background

Anticholinesterase medications have been the mainstay for pharmacologic reversal of nNMBAs for decades of clinical practice (Tajaate et al., 2018). Various clinical studies have demonstrated that routine reversal with the anticholinesterase neostigmine is essential to antagonize residual NMB (Tramèr & Fuchs-Buder, 1999). However, there is also ample evidence confirming the presence of persistent residual neuromuscular (NM) dysfunction even following the administration of neostigmine (Kim et al., 2019; Aytac et al., 2018; Fortier et al., 2015). In a 2017 article published in *Anesthesiology,* Brull & Kopman reported that 20-40% of patients demonstrated objective signs of residual paralysis in the PACU after the administration of anticholinesterase reversal.

Neostigmine is the most widely used anticholinesterase reversal agent (Hristovska, 2017). Neostigmine antagonizes nNMBAs by indirectly increasing acetylcholine (Ach) concentrations. Specifically, neostigmine inhibits the acetylcholinesterase enzyme that is responsible for the

degradation of Ach, increasing the amount of Ach available to bind to NMJ receptors and depolarize the muscle fiber (Hristovska, 2017). Glycopyrrolate, an anticholinergic agent, is given to counteract the unwanted cholinergic side effects of neostigmine, including bradycardia, increased salivation, and bronchoconstriction. One of the most significant advantages of neostigmine is the drug's ability to reverse aminosteroidal and curariform types nNMBAs. Other benefits of neostigmine include low costs and robust data related to clinical practice (Luo et al., 2018).

The dose and timing of neostigmine administration can substantially influence the drug's efficacy. The selection of an appropriate dose of neostigmine is a complex subject. Underdosing neostigmine may exacerbate the potential respiratory impairment associated with residual NMB, while overdosing neostigmine could result in a paradoxical depolarizing block (Kent et al., 2018). Anesthesia providers must use caution in relying on subjective clinical indicators of recovery to guide their pharmacologic reversal strategy using neostigmine, as current literature reveals that clinical signs such as grip strength, tongue protrusion, and a 5-second head lift that indicate a progressive recovery from neuromuscular blockade may not accurately reflect a patient's ability to maintain satisfactory airway patency (Nagelhout, 2018). Additionally, reliance on clinical indicators of recovery can underestimate the depth of NMB, leading providers to select an insufficient dose of neostigmine/glycopyrrolate. There is considerable variation in practice techniques for dosing neostigmine. While clinicians' practice environments may influence the dose selection, many providers are concerned that adverse effects such as cardiac arrhythmias and postoperative nausea and vomiting have the greatest impact on their neostigmine dose selection (Lien, 2010).

Consideration of the pharmacokinetic profile of neostigmine strongly influences the timing of administration. Dubovoy et al. (2016) found that tracheal extubation often occurs before neostigmine's peak effect at 10 minutes. Tracheal extubation prior to the return of upper airway protective reflexes may result in obstruction, aspiration, or the need for reintubation (Kirmeier et al., 2019). There is a growing body of literature supporting that neostigmine can produce more efficient and reliable recovery from nNMBAs when administered at a higher TOF count (Brull & Murphy, 2010).

A PNS is often used to gauge the depth of remaining paralysis at the NMJ. The reversal dose of neostigmine should be selected according to the subjectively assessed depth of NMB (Murphy, 2018). Electrical stimulus using the PNS is conducted through gel electrodes placed on the skin along the desired nerve tract. The Train-of-Four (TOF) mode, which provides four electrical stimuli 0.5 seconds apart at a supramaximal muscle contraction current, is the most commonly used PNS modality (Murphy, 2018; Naguib et al., 2018). The number of responses elicited to the four stimuli is termed the train-of-four count (TOFC). Moreover, the Train-of-Four Ratio (TOFR), comparing the amplitude of the fourth twitch to the amplitude of the first twitch to produce a numerical value, correlates with recovery at the NMJ (Thilen & Bhananker, 2016). It is imperative to recognize the limitations of using tactile and visual assessments of muscle response to detect residual weakness (Brull & Silverman, 1993). Lien (2010) notes that when four twitches of equal strength are present, clinicians are unable to distinguish between a TOFR of 0.6-0.9.

Problem Statement

Residual paralysis following general surgery is a significant risk factor implicated in the development of major pulmonary complications. Kirmeier et al. (2019) found that patients

demonstrating a TOFR of less than 0.9 exhibited impaired respiratory control during hypoxia, increased propensity for airway obstruction, and higher aspiration rates. PPCs, including respiratory failure, the need for reintubation within 24 hours, and pneumonia, are associated with pathophysiologic, financial, and emotional burdens. According to a multicenter, prospective study conducted by Kirmeier et al. (2019), approximately 5% of adult patients undergoing non-cardiac surgery will experience a major PPC, resulting in increased mortality and $100,000 in additional costs per occurrence. As the number of surgical procedures performed annually continues to rise exponentially, accurate monitoring and prudent reversal of NMB are essential components of safe anesthesia practice. Several studies implicate considerable variation in provider reversal management and inter-individual pharmacologic variability as important influencers for residual NMB (Ji et al., 2021; Murphy, 2018; Saager et al., 2019). Although reversal of neuromuscular paralysis using neostigmine/glycopyrrolate is performed daily during the delivery of anesthetics, there is not a standardized approach to dose selection or timing of administration. Current literature supports that using an algorithm-based approach to select the optimal dose of neostigmine can reduce the incidence of residual NMB (Brull & Murphy, 2010). Reducing the incidence of residual NMB is a key, modifiable risk factor to improve postoperative outcomes for patients and healthcare systems.

Clinical Question

In adult surgical patients requiring neuromuscular paralysis, how does best-practice evidence in the literature, compared to current knowledge and practice, inform the development of a clinical cognitive aid focused on the reversal of neuromuscular blockade using neostigmine/glycopyrrolate?

Purpose

The broad aim of this quality improvement project was to identify current practice habits surrounding the monitoring and management of neuromuscular blocking agents among anesthesia providers at a single facility. The QI project elicited feedback on foundational knowledge and practice techniques for using neostigmine/glycopyrrolate as a reversal agent through surveying methods. A comprehensive review and synthesis of the current literature were necessary to evaluate the safety and efficacy of neostigmine/glycopyrrolate as a longstanding reversal agent and summarize the updated recommendations for its use. Current practice trends for NMB reversal using neostigmine/glycopyrrolate were identified and analyzed in relation to best practices in current literature. Findings informed the guidelines for neostigmine/glycopyrrolate use that were included in the cognitive aid.

CHAPTER 2: LITERATURE REVIEW

A literature review was conducted using the search terms "neostigmine," "neuromuscular blockade," "residual paralysis," "neuromuscular monitoring," "sugammadex," "postoperative pulmonary complications," "reversal," "general anesthesia," and "delayed emergence." An extensive electronic search was completed using multiple databases, including PubMed, Science Direct, Cochrane Database of Systematic Reviews (CDSR), and CINAHL Complete. Relevant, peer-reviewed articles and research published from 1985 through 2021 with full-text availability in the English language were included. Studies that included non-human subjects, patients less than 18 years of age, and emergency and outpatient surgery were excluded

Neostigmine for Reversal of Neuromuscular Blocking Agents

Background

Neostigmine was first introduced to clinical practice in 1931 (Neely et al., 2021). As such, neostigmine's mechanism of action and safety profile have been extensively studied, and

there is robust supporting data to inform clinical practice. Following a comparative meta-analysis of 14 studies that included randomized controlled trials (RCTs) and retrospective trials, Ji et al. (2021) concluded that neostigmine substantially shortens the time to extubation and post-anesthesia care unit (PACU) length of stay. Notably, this study only compared the administration of neostigmine with spontaneous recovery from a non-depolarizing block in the control group — indicating that neostigmine was more effective than omitting the administration of a reversal agent (Ji et al., 2021). Similarly, in a propensity-matched study of over 2500 cases from the National Surgery Quality Improvement Program Database, researchers at the Vanderbilt Medical Center concluded that "cases who were not reversed were 2.26 times as likely to develop pneumonia after surgery compared to cases who received reversal with neostigmine" (Bulka et al., 2016).

Indications

Neostigmine is an acetylcholinesterase inhibitor widely used to accelerate the reversal of nNMBAs and recovery of the NMJ at the end of surgery (Hristovska et al., 2017). Neostigmine is FDA approved to reverse the effects of nNMBAs after surgery and prior to attempting tracheal extubation (Neely et al., 2021). Neostigmine acts by blocking the breakdown of acetylcholine at the NMJ to compete with the existing non-depolarizing blocking drug for receptor-binding sites. (Neely et al., 2021). The resultant increased concentration of acetylcholine present at the NMJ causes muscles to contract with full strength, allowing patients to initiate independent ventilation and protect their airways prior to tracheal extubation (Kim et al., 2019).

Pharmacology

Anesthesia providers must have a comprehensive understanding of the pharmacologic profile of neostigmine to optimize patients' respiratory function at the time of extubation. The

onset of action of neostigmine is typically within 1 min, with peak antagonistic effects occurring between 7 and 10 min and up to 15 minutes following neostigmine administration (Neely et al., 2021; Flood, Rathmell & Shafer, 2015). In an update published reevaluating the safety and efficacy of neostigmine for reversal of nNMBAs, Luo et al. (2018) noted the elimination half-life of neostigmine to be 77 minutes. Importantly, this half-life may be prolonged by increasing age, impaired renal function, concomitant anesthetics, decreasing body temperature, the type and dose of nNMBA used, and acid-base status (Miller et al., 2014).

Dosing Neostigmine Administration

Neostigmine should be dosed according to actual body weight (Ji et al., 2021). The recommended dose of neostigmine for the reversal of nNMBAs is 0.03-0.07 mg/kg. Traditional teaching states that the maximum dose of neostigmine is 5 mg (Neely et al., 2021). However, because neostigmine is dosed according to actual body weight, the maximum safe doses of 0.06-0.08 mg/kg may exceed 5 mg. The literature consistently supports that there is no added benefit beyond these doses due to the previously discussed plateau effect (OpenAnesthesia, 2022). The standard recommended doses of neostigmine according to TOFC described in the literature are 0.05-0.07 mg/kg when the TOFC=3 and 0.03-0.05 mg/kg when the TOFC=4 (Caldwell, 2009). However, efforts to pinpoint a dose-response curve for neostigmine have concluded largely variable results, making selecting the exact dose to achieve optimal recovery increasingly complex (Murphy, 2018). In a prospective, randomized controlled study, Kim et al. (2004) found that 15 minutes following neostigmine administration, only 95% of patients had achieved a TOFR>0.9. Kirkegaard et al. (2002) reported a range as wide as 7-143 minutes for patients to reach a TOFR of 0.9 when four tactile TOF responses were present at the time of reversal with neostigmine. Conversely, Schaller et al. (2010) reported that the administration of 0.034 mg/kg

of neostigmine achieved adequate recovery in five minutes for patients with a TOFR between 0.5-0.9. The literature consistently reports that the dose of neostigmine must be selected based on the extent of remaining neuromuscular paralysis. In addition to using a PNS to assess the depth of residual NMB, providers must consider the half-life of the nNMBAs used and the adjuvant anesthetics used to select the ideal dose of neostigmine (Luo et al., 2018).

Timing Neostigmine Administration

In a randomized control trial of 120 patients, Murphy (2018) emphasized the time of tracheal extubation as a critical point to assess the burden of residual NMB. There is a growing body of evidence that suggests lower doses of neostigmine are more efficacious for antagonizing shallow residual neuromuscular block (Brull & Murphy, 2010). Reduced doses of neostigmine as low as 0.02 mg/kg appear to be sufficient to antagonize shallow degrees of residual paralysis (Preault et al., 2016). Plaud et al. (2010) reported that successful reversal with neostigmine is highly dependent upon achieving a greater degree of spontaneous recovery before administration. Further systematic reviews by Kim et al. (2004) and Kirkegaard et al. (2002) substantiated these claims, concluding that completeness of reversal was maximized when there were four observable twitches present on the TOF assessment.

Deep Neuromuscular Blockade

One notable drawback of using neostigmine as a reversal agent is the inability to effectively antagonize deep levels of NMB. Multiple studies have repeatedly demonstrated that neostigmine cannot reverse profound NMB, evidenced by the presence of only post-tetanic twitches or a TOFC<2 (Brull & Kopman, 2017). Once neostigmine has inhibited almost all of the anticholinesterase enzyme, further administration cannot accelerate recovery (Luo et al., 2018). Therefore, neostigmine reversal should be attempted if a deep degree of NMB is present.

Neostigmine use for reversal is deemed clinically appropriate once a patient has recovered to a TOFC of two or greater (Sasaki et al., 2014). In an updated study of 48,449 patients aimed to investigate the association between the dose of neostigmine given and the incidence of respiratory complications, McLean et al. (2015) defined appropriate use of neostigmine as doses less than or equal to 0.06 mg/kg after the recovery of two or more TOFC. Researchers concluded that when neostigmine was used appropriately, the previously noted association between nNMBAs and a dose-dependent increase in respiratory complications was eliminated (McLean et al., 2015). In other words, when neostigmine was used according to the appropriate criteria, the total dose of nNMBAs could no longer be used to predict the risk of respiratory complications (McLean et al., 2015).

Paradoxical Block

There is debate in the literature concerning the potential for neostigmine to cause a paradoxical depolarizing block if administered after spontaneous recovery to a TOFR > 0.9. Kent et al. (2018) suggest that overdosing neostigmine could also lead to a depolarizing block from excessive acetylcholine, extending the amount of time for NMJ recovery and subsequent extubation. Conversely, Murphy et al. (2018) concluded that "administration of neostigmine at neuromuscular recovery was not associated with clinical evidence of anticholinesterase-induced muscle weakness" (p. 35). In an attempt to elucidate a specific dose-response relationship of neostigmine according to the TOFR, Fuchs-Buder et al. (2016) found that increasing the dose of neostigmine from 10 mcg/kg to 30 mcg/kg decreased recovery from a TOFR of 0.4 to 0.9 or 1. The findings from Fuchs-Buder et al. (2016) agree with the suggestion that overestimating the dose of neostigmine can result in delayed recovery. Interestingly, however, this same study did not note a similar pattern when an 'overestimated' dose was given at a TOFR of 0.6.

Limitations of Use

Anesthesia providers must be aware of the limitations and clinical precautions associated with using neostigmine. The inherent pitfalls of an indirect-acting reversal agent, such as limited and unpredictable efficacy, also must be taken into account in clinical practice (Hristovska et al., 2017). The limited efficacy associated with neostigmine is often explained by a 'ceiling effect' that occurs at a dose of 0.07 mg/kg. Neostigmine's effectiveness reaches a plateau even once 100% of the acetylcholinesterase enzyme is inhibited due to a neurotransmitter control mechanism restricting the further release of acetylcholine. (Fuchs-Buder, 2016).
Moreover, discrepancies exist in the literature about whether or not neostigmine can truly reduce the incidence of residual paralysis. Sasaki et al. reported a similar incidence of residual NMB regardless of whether or not patients received neostigmine. Fortier et al. confirmed these findings in a blinded, multicenter, prospective study. On the other hand, current studies identified that appropriate dosing of neostigmine to reverse residual paralysis can effectively eliminate any increased risk for respiratory complications (Bulka et al., 2016; McLean et al., 2015).

Another key consideration of neostigmine's use highlighted in the literature is the need for co-administration of an antimuscarinic agent such as glycopyrrolate or atropine (Tajaate et al., 2018). Several sources emphasized that the appropriate selection of an antimuscarinic agent based on an onset time that closely matches the onset time of neostigmine is crucial to reliably attenuate the undesirable effects of muscarinic stimulation (Evers et al., 2011). Multiple studies supported glycopyrrolate as a preferred choice due to its similar onset of action and a lesser degree of tachycardia (Evers et al., 2011; Li et al., 2021).

Adverse Effects

Of particular concern to the anesthesia provider are the potential negative cardiac and respiratory effects associated with the effects of neostigmine binding at muscarinic receptors. Neostigmine can produce potentially serious bronchoconstriction and bradyarrhythmias, such as junctional escape rhythms and even asystole. (Li et al., 2021). One study noted the incidence of cardiac adverse effects in geriatric patients that received neostigmine to be 14% (Luo et al., 2018). Notably, dysrhythmias only occurred in patients with preexisting cardiac disease (Luo et al., 2018). In a retrospective cohort study that reviewed 98,147 cases, researchers only found significant associations between anticholinesterase reversal and an increased risk of cardiovascular complications if patients were of advanced age, undergoing high-risk surgery, or had a history of atrial fibrillation (Shaydenfish et al., 2020).

Administering a ratio of 0.02 mg of glycopyrrolate per 1 mg of neostigmine is ubiquitous in clinical practice and has been for decades (Howard et al., 2017). A meta-analysis conducted by Howard et al. (2017) was one of the first studies to reevaluate glycopyrrolate as the conclusively superior antimuscarinic agent. Ultimately, the analysis demonstrated that glycopyrrolate was the most efficacious, with the lowest incidence of unwanted adverse effects (Howard et al., 2017). Glycopyrrolate is typically effective in avoiding unwanted decreases in heart rate and, subsequently, cardiac output and in counteracting the increased secretion production that results from neostigmine administration. However, it is imperative that providers be vigilant of the sympathetic nervous stimulation caused by glycopyrrolate, as research reflects the inability of patients with certain preexisting cardiac comorbidities to tolerate such stimulation (Shaydenfish et al., 2020).

Additional commonly experienced adverse side effects reported in the literature included increased secretions, nausea, miosis, and increased peristalsis (Li et al., 2021). There is a

common belief by some clinicians that neostigmine use leads to an increased incidence of postoperative nausea and vomiting (PONV). In a qualitative review of numerous prospective clinical studies, Gan (2006) suggests that the relationship between neostigmine use and PONV is dose-dependent, with only high doses (50 μg/kg) increasing the risk. Other reviews concluded no difference in the rates of PONV regardless of neostigmine use (Cheng et al., 2005).

Neostigmine vs. Sugammadex

The recent FDA approval of a direct-acting reversal agent with a unique mechanism of action fueled numerous comparative studies analyzing the chief differences between neostigmine and sugammadex and the respective clinical practice implications. Collectively, many studies agree on the benefits of a more rapid and effective reversal devoid of the unwanted muscarinic effects with sugammadex compared to neostigmine (US Food and Drug Administration, 2015). In a Cochrane systematic review that examined 41 studies, including 4206 participants, Hristovska et al. (2017) concluded that sugammadex is more efficient at reversing neuromuscular blockade than neostigmine. Sugammadex was 6.6 times faster than neostigmine in achieving a TOFR >0.9 when the TOFC accounted for two twitches and 16.6 times faster when the patient was under profound paralysis (Hristovska et al., 2017). Gelder et al. (2012) conducted a randomized control trial including 140 patients, revealing that sugammadex provided a superior reversal compared to neostigmine. In addition to sugammadex being 3.4 times faster than neostigmine, 94% of the patients who received sugammadex recovered within five minutes of administration, compared to 20% of the patients treated with neostigmine (Gelder et al., 2012). Hristovska et al. (2017) found that sugammadex caused 40% fewer adverse events, including PONV, bradycardia, and the need for supplemental oxygen, compared to neostigmine.

Although literature favoring sugammadex over neostigmine exists, several studies have also failed to identify a definitive link between a greater reduction in adverse pulmonary outcomes with sugammadex than neostigmine. In a prospective, double-blinded RCT published in the Journal of Clinical Anesthesia, Kim et al. (2019) found no significant differences in the Postoperative Quality Recovery Scale at 15 min and 40 min after surgery between patients receiving neostigmine compared to sugammadex. Likewise, the results of a prospective observational study of 22,803 patients conducted by Kirmeier et al. (2019), concluded no improvement in pulmonary outcomes when sugammadex was used compared to neostigmine or when patients were extubated at a TOFR of 0.9. Furthermore, Abola et al. (2020) conducted a randomized control trial and found no difference in the patient's inspiratory spirometry scores regardless of whether the patient received neostigmine or sugammadex. In this study, the hand strength, extubation time, and discharge readiness were all comparable across the neostigmine and sugammadex groups. Notably, a limitation of this study was the higher percentage of patients in the neostigmine group that were reversed with two to four twitches, inferring that the neostigmine group had a less profound neuromuscular block (Abola et al., 2020). Finally, in Japan, where sugammadex is used routinely used on most patients, researchers conducted a multicenter observational study. They found that, in the absence of neuromuscular monitoring and after reversal with sugammadex, 9.4% of patients still had a TOFR<0.9 after extubation (Kotake et al., 2013).

Summary of Findings in the Literature

Neostigmine competitively reverses muscle paralysis by increasing the amount of acetylcholine in the NMJ. Anesthesia providers must be well versed in neostigmine administration, understanding that both underdosing and overdosing can potentially lead to

prolonged muscle paralysis (Kent et al., 2018). If the use of neostigmine is deemed clinically inappropriate to reverse neuromuscular blockade, providers must critically consider the timing of administration. Timing tracheal extubation to align with the peak antagonistic effects of neostigmine is essential in ensuring optimal upper airway recovery (Neely et al., 2021).

Theoretical Framework

The Plan, Do, Study, Act (PDSA) model was used to guide the strategic planning of the quality improvement project investigating evidence-based reversal using neostigmine/glycopyrrolate and to evaluate outcomes. The PDSA model is used extensively by the Institute for Healthcare Quality Improvement (IHI) to implement change or to improve existing processes to enhance patient care outcomes (McBride et al., 2018). The cyclical nature of the PDSA components emphasizes the need for continual analysis and refinement of changes. Initial PDSA cycles are typically employed to examine change implementation on a small scale (Perla et al., 2013). As data from projects is compiled and compared to initial predictions, follow-up cycles can be used to adapt the change idea under more robust conditions (Perla et al., 2013).

The “plan” component was the completion of a thorough review of the literature and the creation of a validated survey to assess current knowledge and practice habits among anesthesia providers for managing neuromuscular blockade. The “do” was the distribution of a survey via SurveyMonkey to all anesthesia providers. The successful implementation of the plan required collaboration from all dissertation committee members to promote meaningful engagement in the survey.

The “study” element entailed the analysis of survey responses to identify key trends surrounding techniques for NMB reversal using neostigmine/glycopyrrolate among anesthesia

providers. The results were collected on SurveyMonkey and exported securely into Excel for review and detailed statistical analysis. Individual data points were aggregated according to subject content to evaluate areas of weakness and determine central themes for further education to promote adherence to a standardized reversal approach according to evidence-based practice. The evidence synthesis plus model guided the integration of survey findings and the current evidence identified in the literature synthesis to tailor the content of the practice guidelines presented on the cognitive aid. The final "act" component of the PDSA model was the creation of the intraoperative cognitive aid.

CHAPTER 3: METHODOLOGY

This project followed the evidence synthesis plus project model and was the first step in translating research into practice related to neuromuscular blockade reversal using neostigmine/glycopyrrolate in anesthesia (Bonnell & Smith, 2018). This project included a comprehensive review and synthesis of current literature and analysis of survey data of current clinical practice for monitoring neuromuscular blockade and administering pharmacologic reversal agents. After integrating knowledge gained from the literature review and survey findings, evidence-based guidelines were described on a cognitive aid to guide best practices for the administration of neostigmine/glycopyrrolate to reverse neuromuscular blockade.

Setting

The survey was distributed to the Certified Registered Nurse Anesthetists (CRNAs) and physician anesthesiologists on staff at an urban Level One trauma center. The trauma center serves a large population in the region, acting as one of the five Academic Medical Center Teaching Hospitals in the area. The facility provides extensive surgical services across an expansive care network and is distinguished as a certified transplant center for heart, kidney,

liver, and pancreas. The institution's innovative technology allows many of these procedures to be performed using minimally-invasive laparoscopic or robotic surgical approaches. While these less-invasive approaches offer numerous benefits, including decreased pain and a shorter hospital stay, surgeons must rely upon precision to achieve successful outcomes (Bruintjes et al., 2017; Barash et al., 2017). Such precision typically warrants the use of pharmacologic muscle relaxation to avoid inadvertent patient movement that could jeopardize damaging surrounding organs. Appropriate management of neuromuscular blockade is integral to achieving optimal patient outcomes, as paralytic use is standard daily practice for anesthesia providers.

Subjects

The QI project utilized a convenience sampling method to select survey participants. Anesthesia staff received a 25-item, anonymous survey related to current practices with neuromuscular blockade management. Seven questions specifically targeted neostigmine/glycopyrrolate use as a part of the larger 25-item survey. The survey excluded Student Registered Nurse Anesthetists (SRNAs) from participation. SRNAs practice under the licenses of their CRNA and physician anesthesiologist preceptors. SRNAs were excluded because their clinical decisions are largely dictated by their supervising anesthesia personnel. The population included 212 anesthesia providers—165 Certified Registered Nurse Anesthetists (CRNAs) and 47 Anesthesiologists.

Intervention

The survey findings were used to gain insight into NMB monitoring and reversal techniques used in current practice. Once current practice habits were identified, the trends in knowledge deficits were analyzed, and evidence-based guidelines from the synthesis of the literature were integrated to inform the creation of a cognitive aid. The intended use of the

cognitive aid was to serve as an intraoperative reference and an adjunct resource to promote evidence-driven clinical decision-making to select an appropriate reversal dose. The cognitive aid incorporated the three central components of NMB management that were previously referenced—qualitative monitoring using a PNS, pharmacological reversal using neostigmine, and pharmacological reversal using sugammadex. The cognitive aid provided written and pictorial instructions on electrode placement, a reversal dosing guide based on PNS output, and a decision tree for reversal selection according to key precautions and adverse effects associated with each respective reversal agent.

Data Collection

Data from the quantitative survey results were obtained through SurveyMonkey. The survey used several question types: multiple-choice, matching, true/false, and multiple correct. The survey questions were validated by the appointed clinical experts and approved by all Doctoral dissertation committee members prior to submission to the Institutional Review Board (IRB) at the affiliated hospital and graduate program institutions. Seven survey questions specifically aimed to evaluate anesthesia providers' knowledge of appropriate neostigmine administration and providers’ daily practice habits. The survey was designed to elicit clinicians' guiding principles for neuromuscular blockade management, assess the factors influencing their standard clinical practice, and extract commonly held misconceptions. Additionally, the validated survey questions provided feedback on baseline provider knowledge of core anesthesia monitoring and pharmacology concepts to identify areas necessitating further education. Only the questions that targeted knowledge of current evidence-based practice guidelines were scored as correct or incorrect and factored into the overall survey score. The final survey that was distributed is included in Appendix B for reference.

An email containing a brief description of the quality improvement project's purpose and how to access the survey was sent to CRNAs and anesthesiologists. The email contained a direct link to take the survey on SurveyMonkey and detailed instructions about where to access the QR codes for scanning and redirection to the survey. The laminated QR codes were affixed to the anesthesia machine in 23 operating rooms and accessible in the anesthesia break rooms. The survey's primary goal was to assess current practice habits surrounding the management of neuromuscular blockade among anesthesia providers. Subsequently, the data obtained were analyzed to identify facility-specific education needs to inform the development of the cognitive aid. Internal consistency— how closely related a set of items are as a group of the instrument was measured using Cronbach's alpha. Cronbach's alpha is used to create reliable and valid questionnaires to augment the accuracy of assessments and evaluations (Tavakol & Dennick, 2011).

Timeline for data collection

The doctoral project was introduced with a brief description of the background and significance of residual neuromuscular weakness at a monthly anesthesia grand rounds meeting. Next, data collection was initiated after successfully securing the required institutional IRB and DNP Council approval and after all of the committee members involved in the QI project approved the oral defense of the project proposal. The survey was distributed and available for completion for one month, from August 29th, 2023-September 29th, 2023. An email reminder to complete the open survey was sent to anesthesia providers on September 21st, 2023. A final email reminder was sent on September 28th, 2023. Three weeks were dedicated to compiling the data for statistical analysis. Information obtained from this data analysis and findings from the in-depth literature synthesis were used to inform the cognitive aid development. A draft of the

proposed cognitive aid was submitted for committee approval on November 30th, 2023. A two-week period was granted to allow committee members to review the cognitive aid and offer suggested revisions.

Data management strategies and confidentiality of data

The survey responses were de-identified to ensure the confidentiality of the respondents' answers. Participants' anonymity was upheld through the omission of inquiry regarding personally identifiable demographic information, including name, contact information, age, sex, gender, race, and political or religious affiliation. The demographic data obtained relating to the sample population only pertained to the professional title/academic degree held and the number of years since the completion of anesthesia training. Anesthesia providers received the following message prior to beginning the survey: *"Participation in this survey is entirely voluntary, and responses are anonymous. You will not be asked to provide any personal identifying information. This survey has been approved by the Institutional Review Board at the designated affiliate university and the healthcare system. The results from this survey will be used to complete a quality improvement project as part of the Doctorate Nurse Anesthesia Program curriculum. I consent to participate in this survey"*. As such, providers self-selected whether or not they chose to complete the survey. As a result of the method chosen, the project's findings do not extend to the general population of anesthesia providers– only to those who participate in the research (Stratton, 2021). Data sharing during the project was strictly limited to members of the project committee, and all files were exchanged using encrypted links.

Data Analysis Description

The survey included multiple choice, multiple correct, and true/false style questions. The primary outcome of the quality improvement project was performance. If greater than 80% of

respondents answered the survey item correctly, respondents' knowledge of the subject matter was deemed adequate. Questions that less than 80% of respondents answered correctly were delineated as areas of high training needs and were used as focal points of the cognitive aid. The data set was summarized using descriptive statistics, including frequency counts, central tendency and variation measures, and percentile ranks. The descriptive statistics were used to analyze the content areas where respondents' answers deviated from the recommendations identified in the current literature. The de-identified SurveyMonkey results were exported securely into Excel. After interpreting the survey data and synthesizing the relevant literature, an educational, cognitive aid detailing the best practices for the pharmacologic reversal of neuromuscular blockade using neostigmine/glycopyrrolate was developed. This method is consistent with the evidence synthesis plus project model.

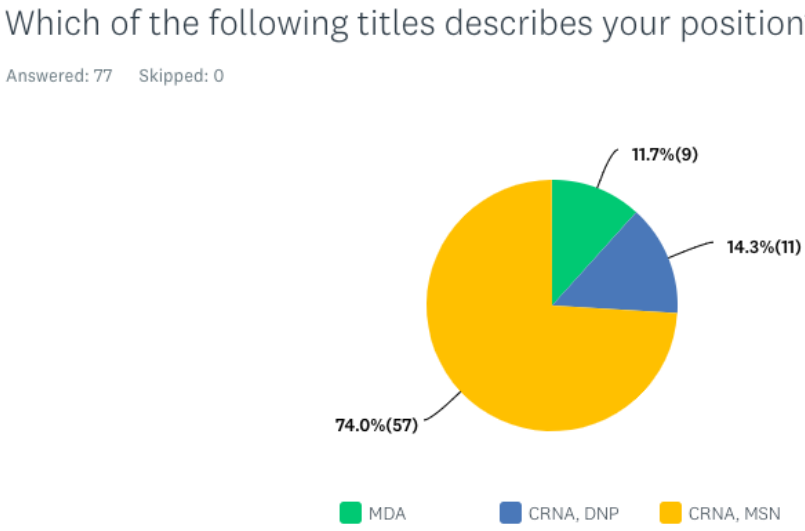
CHAPTER 4: RESULTS

Sample Characteristics

Demographic characteristics, including professional title and years of experience of the sample population, are depicted in Figures 1.1 and 1.2, respectively. The majority of anesthesia providers held a master's degree (n=57). The remaining respondents held a doctorate degree (n=11) or a medical doctor degree (n=9). Nearly half of the respondents had under 5 years of experience (n=37), while 14 individuals (18.2%) had 6-10 years of experience and 15 individuals (19.5%) had 11-20 years of experience. There were only 11 (14.3%) respondents that reported greater than 20 years of experience in anesthesia practice. Seventy-seven anesthesia providers completed the survey. In total, 41.2% of staff CRNAs and 19.1% of staff physician anesthesiologists participated in the survey, with a total return rate of 35.8% in this quality

improvement project. The survey did not inquire about other demographic information such as age, race, ethnicity, or gender.

Figure 1. Anesthesia Providers Stratified According To Position Title

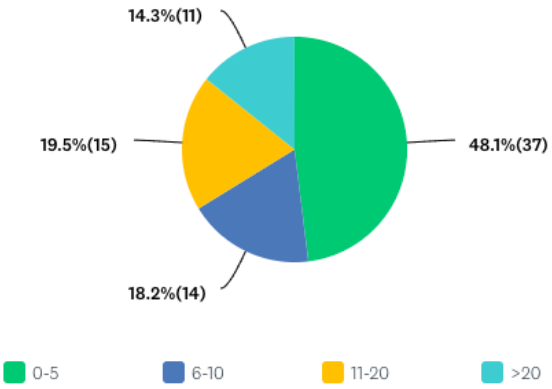


ANSWER CHOICES	RESPONSES	
MDA	11.7%	9
CRNA, DNP	14.3%	11
CRNA, MSN	74.0%	57
TOTAL		77

Figure 2. Anesthesia Providers Stratified According To Years Of Experience

Years of experience

Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
0-5 (1)	48.1%	37
6-10 (2)	18.2%	14
11-20 (3)	19.5%	15
>20 (4)	14.3%	11
TOTAL		77

Findings

The frequencies for each item on the survey are reported in Table 1 and 2. Table 1: "Findings on knowledge of evidence-based administration of neostigmine," depicts four survey items and details the percentage of respondents correctly answering the corresponding question. Seventy-four respondents (96%) correctly identified the pharmacologic class and mechanism of action at neostigmine. Only 50.65% (*n*=38) of anesthesia providers identified the time of 5-6 minutes for neostigmine to reach peak effect as incorrect. Respondents who answered the mechanism of action item correctly also recognized the potential for neostigmine to cause paradoxical weakness at doses in excess of 0.07 mg/kg. Only 27.63% (*n*=21) of respondents believed neostigmine could be safely administered according to weight-based dosing recommendations if the calculated dose exceeded 5 mg. This belief diverges from the evidence in the literature that supports that a maximum dose of 0.06-0.08 mg/kg of neostigmine based on

actual body weight may be safely administered to effectively reverse nNMBAs. Lastly, findings from Table 1 showed that most, 89.61% (*n*=69), respondents believed that sugammadex was not associated with significantly more bradycardia than neostigmine. This finding is consistent with systematic reviews that concluded that neostigmine and sugammadex were "comparably safe," and the rates of bradycardia—2.4% for sugammadex and 2.2% for neostigmine, were not statistically significant (Ruetzler et al., 2022).

Over half, 59.74% (*n*=46) of respondents, believed that neostigmine could adequately reverse neuromuscular paralysis in patients demonstrating a train-of-four count of one out of four on clinical exam. These findings indicate that inappropriate administration of neostigmine is occurring in daily practice, as only one TOFC is consistent with a deep level of NMB, and reversal using neostigmine should not be attempted until a greater degree of spontaneous recovery is achieved. Additionally, the data in Table 2: “Findings on current practice related to neostigmine," revealed that nearly half, 42.86% (*n*=33) of the respondents reported neglecting to re-assess the train-of-four count at least 10 minutes and up to 15 minutes after neostigmine administration before extubating patients. These findings are inconsistent with the recommendations by Murphy (2018) that stressed the need to re-assess the burden of residual NMB at the time of tracheal extubation to help prevent residual paralysis. Over half, 52.63% (*n*=30) of the respondents, stated that the side effect profile of neostigmine has no impact on the clinical decision to use the drug for neuromuscular blockade reversal. This finding reflects that these providers do not believe the side effect profile of neostigmine/glycopyrrolate is significant enough to alter their use of these medications. There may be a need to further explore providers’ knowledge of side effect incidence and severity.

Table 1. Findings on knowledge of evidence-based administration of neostigmine

Item	Descriptor		Frequencies	Percent with the correct answer
Neostigmine is a competitive, reversible acetylcholinesterase inhibitor. At doses greater than 0.07 mg/kg, further administration of neostigmine may result in NMJ dysfunction causing paradoxical weakness.	**True** False		*n* = 74 *n* = 3	96.10%
Tracheal extubation should occur following neostigmine's peak action at 5-6 minutes.	True **False**		*n* = 38 *n* = 39	50.65%
The maximum recommended dose of neostigmine is 0.07 mg/kg, regardless of if the calculated dose exceeds 5 mg.	True **False**		*n* = 21 *n* = 55	27.63%
Match the correct dose of neostigmine according to the clinically assessed train-of-four count.	TOFC	Answer Choice		
	1	Not recommended to use	*n* = 46	59.74%
	2		*n* = 61	80.26%
	3	0.05-0.07 mg/kg	*n* = 47	61.04%
	4	0.05 mg/kg	*n* = 46	59.74%
		0.03 mg/kg		
A greater degree of clinically significant bradycardia occurs with sugammadex administration compared to neostigmine.	True **False**		*n* = 8 *n* = 69	89.61%

Table 2. Findings on current practice related to neostigmine

Item	Descriptor	Number/Frequencies	Response percentage
I commonly administer less than the recommended 0.2 mg of glycopyrrolate per 1 mg of neostigmine during the pharmacologic reversal of neuromuscular blockade.	True False	*n*=42 *n*=35	54.55% 45.45%
Which of the following side effects, if any, influence your decision to use neostigmine for reversal of neuromuscular blocking agents (Select all that apply)?	None of the above Bradyarrhythmias Urinary retention Propensity for PONV Bronchoconstriction	*n*=40 *n*=25 *n*=12 *n*=23 *n* = 19	52.63% 32.89% 15.79% 30.26% 25.00%
I routinely re-assess the train-of-four count at least 10 minutes and up to 15 minutes after neostigmine administration and prior to extubating patients.	True False	*n*=44 *n*=33	57.14% 42.86%

Next, each of the demographic variables was independently examined to determine if any association existed between either years or experience or title and performance on the knowledge test. Logistic regression analysis used years of experience as the independent variable to test whether the odds of answering survey questions correctly were influenced by experience level. Results of the logistic regression indicated that there was a significant negative association

between increasing years of experience and the likelihood of respondents selecting the correct dose of neostigmine according to the elicited TOFC (odds ratio = 0.46, p = .002). Years of experience had no statistically significant effect on the other questions. Overall, increasing years of experience seemed to negatively impact performance on the knowledge questions.

CHAPTER 5: DISCUSSION

Implications for Practice

Survey results indicated that anesthesia providers administer widely variable doses of neostigmine to reverse muscle paralysis. This reflects a need to provide educational opportunities regarding current evidence-based dosing recommendations for neostigmine according to the TOF count. It is imperative that anesthesia providers are knowledgeable on the appropriate neostigmine dose that is needed to effectively counteract the existing depth of neuromuscular blockade and avoid adverse sequelae resulting from residual paralysis.

Anesthesia providers clearly understood neostigmine's mechanism of action and target receptors. One of the key inconsistencies between the literature and the survey results was the timing of neostigmine administration. About half of the providers indicated that they extubate patients 5-6 minutes after the administration of neostigmine. However, the peak effect of neostigmine does not occur for 10 minutes (Neely et al., 20121). The survey results indicated that many providers do not allow a sufficient amount of time for neostigmine to take effect prior to attempting tracheal extubation. The clinical decision to extubate a patient when upper airway integrity impairment is still present may predispose patients to aspiration, atelectasis, and pneumonia. Extubation before the complete recovery of protective airway reflexes could also result in inadequate tidal volumes and subsequent physiologic derangements such as respiratory acidosis.

The survey results demonstrated a need to review the side effect profile associated with neostigmine administration. Considering individual patients' comorbidities is necessary to perform an adequate risk analysis when selecting a reversal agent. Failing to do so could result in untoward complications for the patient by exacerbating underlying pathologies. For example, neostigmine may not be the safest first-line agent in an elderly asthmatic patient with severe prostatic hypertrophy and urinary retention. Results according to stratified demographics suggested that there may be a need to specifically target educational information to the audience with greater years of experience.

Importantly, the survey results served as the foundation to guide the framework for developing a tailored cognitive aid. Topics with poor performance were translated into areas of focus for the cognitive aid. For example, an infographic of the correct electrode placement for qualitative TOF monitoring and a table of a neostigmine/glycopyrrolate dosing guide according to twitches were included. Adverse effects of neostigmine and a list of patient comorbidities warrant cautious use of neostigmine were included to augment evidence-based clinical decision-making. Adverse effects were highlighted because around half of the anesthesia providers surveyed indicated that they routinely administer less than 0.2 mg of glycopyrrolate per 1 mg of neostigmine. Underdosing glycopyrrolate can result in more profound, clinically relevant cholinergic side effects. An algorithm for extubation readiness was included because the overarching survey results indicated that most anesthesia providers underestimated the depth of neuromuscular blockade that correlated with specific TOF values.

Strengths

One notable strength of this quality improvement project was the thorough review of the literature. Multiple databases were searched between the years 1985 and 2021. The review and

analysis highlighted existing inconsistencies in study results to explore recommendations grounded in strong evidence from large-scale randomized controlled trials. Identifying conflicting findings also helped to avoid reporting bias. The thorough review and literature synthesis provided evidence to validate the constructed survey questions. All committee members and several objective clinical experts reviewed and validated the questions.

A descriptive research method, specifically surveying, used in this quality improvement project provided detailed, valuable data. A survey was a cost-effective way to gather a high volume of data. The clinical question was able to be addressed in a relatively short period. The prompt turnaround time from data collection to the development of the cognitive aid was beneficial to keep the topic of evidence-based reversal using neostigmine/glycopyrrolate relevant in the clinical setting. There was only one missing data point from a single skipped survey question, and all other respondents answered the survey in its entirety.

There are several strengths to note about the survey design. The survey was easily accessible and convenient. Participants completed the survey by scanning a QR code from any mobile device, laptop, or desktop computer. The average time to complete the survey was six minutes and three seconds. The survey guaranteed anonymity, as there was no attempt to elicit any personally identifiable information. The survey allowed for the collection of quantifiable data

Limitations

The survey results cannot be generalized to a broader population because they do not represent the clinical practice of all anesthesia providers. The quality improvement project was limited to a single facility, and a convenience sampling method was used to select participants. Although the tailored approach helped increase the usefulness and relevance of the cognitive aid

at the identified facility, it also reduced the relevance to other healthcare facilities. Only descriptive statistics were used to evaluate the survey outcomes—omitting the ability to determine a cause-and-effect relationship. The inclusion of true/false and multiple-choice style survey questions rather than open-ended responses or the use of a focus group restricted the depth of information that could be gathered with each question.

There are a limited number of published studies evaluating the knowledge anesthesia providers possess relating to the intraoperative management of neuromuscular blockade. A state or national performance benchmark for the knowledge-based questions does not exist. This precluded the use of comparative analysis between facilities or geographical locations.
The questions and topics included in the survey were not determined according to any published standardized approach. The variability in the structure and language of the questions included may detract from the reliability and reproducibility of the survey. The unclear wording of a question leaves room for respondents to interpret the meaning differently. The final participation rate of 36.3% of all anesthesia providers fell well below the goal participation rate of 50% participation.

Recommendations

This quality improvement project delivered key insights into the practice habits and areas that warranted educational emphasis among anesthesia providers at the selected institution. Future work may consider examining what central elements anesthesia providers use to guide their daily practices. Results from the current QI project should be interpreted as a high-level first step to audit neuromuscular blockade management strategies. Future research should seek ongoing feedback from anesthesia providers on the proposed cognitive aid and work towards implementation and adoption of the cognitive aid as a facility-specific clinical decision-making

adjunct. Additionally, future work should continually survey the usability of the cognitive aid as an intraoperative reference tool.

It would be beneficial for future investigations to aim to capture the true burden of residual muscle paralysis by quantifying the incidence. This would provide a measurable foundation to extrapolate results to explore the financial implications of postoperative pulmonary complications associated with residual paralysis. It could also serve as supporting evidence to advocate for using quantitative neuromuscular monitoring devices.

Practical suggestions for future work include increased engagement of stakeholders to promote further buy-in, distribution of the survey during a timeline unique from other student registered nurse anesthetists (SRNAs) and forming a focus group that includes a member with formal education in item-writing.

REFERENCES

Abola RE, Romeiser J, Rizwan S, Lung B, Gupta R, Bennett-Guerrero E, et al. (2020). A randomized controlled trial of sugammadex versus neostigmine: impact on early postoperative strength Journal Canadien d'anesthesie [Canadian journal of anaesthesia], 67(8), 959-969. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-02120331.

Aytac, I., Postaci, A., Aytac, B., Sacan, O., Alay, G. H., Celik, B., Kahveci, K., & Dikmen, B. (2016). Survey of postoperative residual curarization, acute respiratory events and approach of anesthesiologists. *Brazilian journal of anesthesiology (Elsevier)*, *66*(1), 55–62. https://doi.org/10.1016/j.bjane.2012.06.011

Badaoui, R., Cabaret, A., Alami, Y., Zogheib, E., Popov, I., Lorne, E., & Dupont, H. (2016). Reversal of neuromuscular blockade by sugammadex in laparoscopic bariatric surgery: In support of dose reduction. Anaesthesia, critical care & pain medicine, 35(1), 25–29. https://doi-org.ahecproxy.ncahec.net/10.1016/j.accpm.2015.09.003

Barash, P. G. (2017). Clinical Anesthesia, 8e: eBook with Multimedia (8th Edition). Wolters Kluwer Health.

Bhananker, S. M., Treggiari, M. M., Sellers, B. A., Cain, K. C., Ramaiah, R., & Thilen, S. R. (2015). Comparison of train-of-four count by anesthesia providers versus TOF-Watch® SX: A prospective cohort study. Canadian Journal of Anesthesia/Journal Canadien D'anesthésie, 62(10), 1089–1096. https://doi.org/10.1007/s12630-015-0433-9

Bonnel, W., & Smith, K. (2018). Proposal writing for nursing capstones and clinical projects (2nd ed.). New York: Springer Publishing Company.

Bruintjes, M. H., van Helden, E. V., Braat, A. E., Dahan, A., Scheffer, G. J., van Laarhoven, C. J., & Warlé, M. C. (2017). Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: a systematic review and meta-analysis. British journal of anaesthesia, 118(6), 834–842. https://doi.org/10.1093/bja/aex116

Brull, S. J., & Kopman, A. F. (2017). Current status of neuromuscular reversal and monitoring. Anesthesiology, 126(1), 173–190. https://doi.org/10.1097/aln.0000000000001409

Brull, S.J. & Murphy, G. S. (2010) Residual Neuromuscular Block: Lessons Unlearned. Part II. *Anesthesia & Analgesia*, *111*(1) 129-140 doi: 10.1213/ANE.0b013e3181da8312

Brull, S. J., & Silverman, D. G. (1993). Visual and tactile assessment of neuromuscular fade. Anesthesia & Analgesia, 77(2), 352–355. https://doi.org/10.1213/00000539-199308000-00024

Bulka, C. M., Terekhov, M. A., Martin, B. J., Dmochowski, R. R., Hayes, R. M., & Ehrenfeld, J. M. (2016). Nondepolarizing Neuromuscular Blocking Agents, Reversal, and Risk of Postoperative Pneumonia. *Anesthesiology*, *125*(4), 647–655. https://doi.org/10.1097/ALN.0000000000001279

Caldwell JE. (2009). Clinical limitations of acetylcholinesterase antagonists. *J Crit Care,* 24:21–8.

Chandrasekhar K, Togioka BM, Jeffers JL. Sugammadex. [Updated 2021 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www-ncbi-nlm-nih-gov.ahecproxy.ncahec.net/books/NBK470263/

Cheng, C. R., Sessler, D. I., & Apfel, C. C. (2005). Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting?. *Anesthesia and analgesia*, *101*(5), 1349–1355. https://doi.org/10.1213/01.ANE.0000180992.76743.C9

Lien, A. (2010). Neostigmine: How Much Is Necessary for Patients Who Receive a Non-depolarizing Neuromuscular Blocking Agent?. *Anesthesiology*, 112:16–18 doi: https://doi.org/10.1097/ALN.0b013e3181c5388f

de Kam, P. J., Nolte, H., Good, S., Yunan, M., Williams-Herman, D. E., Burggraaf, J., Kluft, C., Adkinson, N. F., Cullen, C., Skov, P. S., Levy, J. H., van den Dobbelsteen, D. J., van Heumen, E., van Meel, F., Glassner, D., Woo, T., Min, K. C., & Peeters, P. (2018). Sugammadex hypersensitivity and underlying mechanisms: a randomised study of healthy non-anaesthetised volunteers. British journal of anaesthesia, 121(4), 758–767. https://doi-org.ahecproxy.ncahec.net/10.1016/j.bja.2018.05.057

Ehrenwerth, J., Eisenkraft, J. B., & Berry, J. M. (2013). In Anesthesia equipment principles and applications (pp. 314–315). essay, Elsevier Saunders.

Flood P, Rathmell JP, & Shafer S. Stoeltings Pharmacology and Physiology in Anesthetic Practice. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2015: 334-335.

Fortier, L. P., McKeen, D., Turner, K., de Médicis, É., Warriner, B., Jones, P. M., Chaput, A., Pouliot, J. F., & Galarneau, A. (2015). The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade. *Anesthesia and analgesia*, *121*(2), 366–372. https://doi.org/10.1213/ANE.0000000000000757

Fuchs-Buder T. (2016). Neostigmine: Timing and dosing in 2016. Anaesthesia, critical care & pain medicine, 35(4), 245–247. https://doi-org.ahecproxy.ncahec.net/10.1016/j.accpm.2016.06.004

Gan T. J. (2006). Risk factors for postoperative nausea and vomiting. *Anesthesia and analgesia*, *102*(6), 1884–1898. https://doi.org/10.1213/01.ANE.0000219597.16143.4D

Geldner, G., Niskanen, M., Laurila, P., Mizikov, V., Hübler, M., Beck, G., Rietbergen, H., & Nicolayenko, E. (2012). A randomised controlled trial comparing sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparoscopic surgery. Anaesthesia, 67(9), 991–998. https://doi-org.ahecproxy.ncahec.net/10.1111/j.1365-2044.2012.07197.x

Howard, J., Wigley, J., Rosen, G., & D'mello, J. (2017). Glycopyrrolate: It's time to review. *Journal of clinical anesthesia*, *36*, 51–53. https://doi.org/10.1016/j.jclinane.2016.09.013

Hristovska, A. M., Duch, P., Allingstrup, M., & Afshari, A. (2017). Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. The Cochrane database of systematic reviews, 8(8), CD012763. https://doi-org.ahecproxy.ncahec.net/10.1002/14651858.CD012763

Ji, W., Zhang, X., Liu, J., Sun, G., Wang, X., Bo, L., & Deng, X. (2021). Efficacy and safety of neostigmine for neuromuscular blockade reversal in patients under general anesthesia: a systematic review and meta-analysis. Annals of translational medicine, 9(22), 1691. https://doi.org/10.21037/atm-21-5667

Kent, N. B., Liang, S. S., Phillips, S., Smith, N. A., Khandkar, C., Eikermann, M., & Stewart, P. A. (2018). Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers: a double-blind, placebo-controlled, randomised volunteer study. Anaesthesia, 73(9), 1079–1089. https://doi.org/10.1111/anae.14386

Kheterpal, S., Vaughn, M. T., Dubovoy, T. Z., Shah, N. J., Bash, L. D., Colquhoun, D. A., Shanks, A. M., Mathis, M. R., Soto, R. G., Bardia, A., Bartels, K., McCormick, P. J., Schonberger, R. B., & Saager, L. (2020). Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER):

A Multicenter Matched Cohort Analysis. Anesthesiology, 132(6), 1371–1381. https://doi.org/10.1097/ALN.0000000000003256

Kim, K. S., Cheong, M. A., Lee, H. J., & Lee, J. M. (2004). Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or Sevoflurane Anesthesia. Anesthesia & Analgesia, 99(4), 1080–1085. https://doi.org/10.1213/01.ane.0000130616.57678.80

Kim, N. Y., Koh, J. C., Lee, K. Y., Kim, S. S., Hong, J. H., Nam, H. J., & Bai, S. J. (2019). Influence of reversal of neuromuscular blockade with sugammadex or neostigmine on postoperative quality of recovery following a single bolus dose of rocuronium: A prospective, randomized, double-blinded, controlled study. Journal of clinical anesthesia, 57, 97–102. https://doi.org/10.1016/j.jclinane.2019.02.014

Kim, Y. S., Lim, B. G., Won, Y. J., Oh, S. K., Oh, J. S., & Cho, S. A. (2021). Efficacy and Safety of Sugammadex for the Reversal of Rocuronium-Induced Neuromuscular Blockade in Patients with End-Stage Renal Disease: A Systematic Review and Meta-Analysis. Medicina (Kaunas, Lithuania), 57(11), 1259. https://doi-org.ahecproxy.ncahec.net/10.3390/medicina57111259

Kirkegaard, H., Heier, T., & Caldwell, J. E. (2002). Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. Anesthesiology, 96(1), 45–50. https://doi.org/10.1097/00000542-200201000-00013

Kirmeier, E., Eriksson, L. I., Lewald, H., Jonsson Fagerlund, M., Hoeft, A., Hollmann, M., Meistelman, C., Hunter, J. M., Ulm, K., Blobner, M., & POPULAR Contributors (2019). Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a

multicentre, prospective observational study. The Lancet. Respiratory medicine, 7(2), 129–140. https://doi.org/10.1016/S2213-2600(18)30294-7

Kotake, Y., Ochiai, R., Suzuki, T., Ogawa, S., Takagi, S., Ozaki, M., Nakatsuka, I., & Takeda, J. (2013). In the absence of monitoring, reversal with sugammadex did not preclude residual neuromuscular block. *Anesthesia and analgesia*, *117*(2), 345–351. https://doi.org/10.1213/ANE.0b013e3182999672

Leslie, K., Chan, M., Darvall, J. N., De Silva, A. P., Braat, S., Devlin, N. J., Peyton, P. J., Radnor, J., Lam, C., Sidiropoulos, S., & Story, D. A. (2021). Sugammadex, neostigmine and postoperative pulmonary complications: an international randomised feasibility and pilot trial. Pilot and feasibility studies, 7(1), 200. https://doi.org/10.1186/s40814-021-00942-9

Li, G., Freundlich, R. E., Gupta, R. K., Hayhurst, C. J., Le, C. H., Martin, B. J., Shotwell, M. S., & Wanderer, J. P. (2021). Postoperative Pulmonary Complications' Association with Sugammadex versus Neostigmine: A Retrospective Registry Analysis. Anesthesiology, 134(6), 862–873. https://doi.org/10.1097/ALN.0000000000003735

Luo, J., Chen, S., Min, S., & Peng, L. (2018). Reevaluation and update on efficacy and safety of neostigmine for reversal of neuromuscular blockade. Therapeutics and clinical risk management, 14, 2397–2406. https://doi.org/10.2147/TCRM.S179420

McLean, D. J., Diaz-Gil, D., Farhan, H. N., Ladha, K. S., Kurth, T., & Eikermann, M. (2015). Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology*, *122*(6), 1201–1213. https://doi.org/10.1097/ALN.0000000000000674

McBride, S. & Tietze, M. (2018). Nursing Informatics for the Advanced Practice Nurse, Second Edition: Patient Safety, Quality, Outcomes, and Interprofessionalism. New York: Springer Publishing Company.

Miller, R. D., Eriksson, L. I., Fleisher, L. A., Wiener-Kronish, J. P., Cohen, N. H., & Young, W. L. (2014). *Miller's anesthesia e-book*. Elsevier Health Sciences.

Min, K. C., Bondiskey, P., Schulz, V., Woo, T., Assaid, C., Yu, W., Reynders, T., Declercq, R., McCrea, J., Dennie, J., Adkinson, F., Shepherd, G., & Gutstein, D. E. (2018a). Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial. British journal of anaesthesia, 121(4), 749–757. https://doi-org.ahecproxy.ncahec.net/10.1016/j.bja.2018.05.056

Moon, Y. J., Kim, S. H., Kim, J. W., Lee, Y. K., Jun, I. G., & Hwang, G. S. (2018). Comparison of postoperative coagulation profiles and outcome for sugammadex versus pyridostigmine in 992 living donors after living-donor hepatectomy. Medicine, 97(11), e0129. https://doi-org.ahecproxy.ncahec.net/10.1097/MD.0000000000010129

Mostoller, K., Wrishko, R., Maganti, L., Herring, W. J., & van Zutphen-van Geffen, M. (2021). Pharmacokinetics of Sugammadex Dosed by Actual and Ideal Body Weight in Patients With Morbid Obesity Undergoing Surgery. Clinical and translational science, 14(2), 737–744. https://doi-org.ahecproxy.ncahec.net/10.1111/cts.12941

Murphy, G. S. (2018). Neuromuscular monitoring in the perioperative period. Anesthesia & Analgesia, 126(2), 464–468. https://doi.org/10.1213/ane.0000000000002387

Murphy, G. S., Szokol, J. W., Avram, M. J., Greenberg, S. B., Shear, T. D., Deshur, M. A., Benson, J., Newmark, R. L., & Maher, C. E. (2018). 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. *Anesthesiology*, *128*(1), 27–37. https://doi.org/10.1097/ALN.0000000000001893

Murphy, G. S., & Kopman, A. F. (2016). “to reverse or not to reverse?” Anesthesiology, 125(4), 611–614. https://doi.org/10.1097/aln.0000000000001280

Nagelhout, John J., and Sass Elisha. Nurse Anesthesia. Sixth edition. St. Louis, Missouri: Elsevier, 2018.

Naguib, M., Brull, S. J., Kopman, A. F., Hunter, J. M., Fülesdi, B., Arkes, H. R., Elstein, A., Todd, M. M., & Johnson, K. B. (2018). Consensus Statement on Perioperative Use of Neuromuscular Monitoring. *Anesthesia and analgesia*, *127*(1), 71–80. https://doi.org/10.1213/ANE.0000000000002670

Neely GA, Sabir S, Kohli A. Neostigmine. (2021). Neostigmine. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470596/

Plaud, B., Debaene, B., Donati, F., & Marty, J. (2010). Residual paralysis after emergence from anesthesia. Anesthesiology, 112(4), 1013–1022. https://doi.org/10.1097/aln.0b013e3181cded07

Preault, A., Capron, F., Chantereau, C., Donati, F., & Dimet, J. (2016). Under sevoflurane anaesthesia, a reduced dose of neostigmine can antagonize a shallow neuromuscular block: A double-blind, randomised study. Anaesthesia, critical care & pain medicine, 35(4), 269–273. https://doi.org/10.1016/j.accpm.2015.11.008

Rudolph, M. I., Chitilian, H. V., Ng, P. Y., Timm, F. P., Agarwala, A. V., Doney, A. B., Ramachandran, S. K., Houle, T. T., & Eikermann, M. (2018a). Implementation of a new strategy to improve the peri-operative management of neuromuscular blockade and its

effects on postoperative pulmonary complications. Anaesthesia, 73(9), 1067–1078. https://doi.org/10.1111/anae.14326

Ruetzler, K., Li, K., Chhabada, S., Maheshwari, K., Chahar, P., Khanna, S., Schmidt, M. T., Yang, D., Turan, A., & Sessler, D. I. (2022). Sugammadex Versus Neostigmine for Reversal of Residual Neuromuscular Blocks After Surgery: A Retrospective Cohort Analysis of Postoperative Side Effects. *Anesthesia and analgesia*, *134*(5), 1043–1053. https://doi.org/10.1213/ANE.0000000000005842

Saager L, Maiese EM, Bash LD, Meyer TA, Minkowitz H, Groudine S, Philip BK, Tanaka P, Gan TJ, Rodriguez-Blanco Y, Soto R, Heisel O. (2019). Incidence, risk factors, and consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECITE-US study. J Clin Anesth 2019; 55:33–41

Sasaki, N., Meyer, M. J., Malviya, S. A., Stanislaus, A. B., MacDonald, T., Doran, M. E., Igumenshcheva, A., Hoang, A. H., & Eikermann, M. (2014). Effects of neostigmine reversal of non-depolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. Anesthesiology, 121(5), 959–968. https://doi.org/10.1097/ALN.0000000000000440

Schaller, S. J., Fink, H., Ulm, K., & Blobner, M. (2010). Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. *Anesthesiology*, *113*(5), 1054–1060. https://doi.org/10.1097/ALN.0b013e3181f4182a

Shaydenfish, D., Scheffenbichler, F. T., Kelly, B. J., Lihn, A. L., Deng, H., Nourmahnad, A., Xu, X., Houle, T. T., Eikermann, M., & Forman, S. A. (2020). Effects of Anticholinesterase Reversal Under General Anesthesia on Postoperative Cardiovascular Complications: A

Retrospective Cohort Study. *Anesthesia and analgesia*, *130*(3), 685–695. https://doi.org/10.1213/ANE.0000000000004099

Stratton, S. (2021). Population Research: Convenience Sampling Strategies. *Prehospital and Disaster Medicine, 36*(4), 373-374. doi:10.1017/S1049023X21000649

Tajaate, N., Schreiber, J. U., Fuchs-Buder, T., Jelting, Y., & Kranke, P. (2018). Neostigmine-based reversal of intermediate acting neuromuscular blocking agents to prevent postoperative residual paralysis: A systematic review. European journal of anaesthesiology, 35(3), 184–192. https://doi.org/10.1097/EJA.0000000000000741

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International journal of medical education, 2*, 53–55. https://doi.org/10.5116/ijme.4dfb.8dfd

Thilen, S. R., & Bhananker, S. M. (2016). Qualitative Neuromuscular Monitoring: How to Optimize the Use of a Peripheral Nerve Stimulator to Reduce the Risk of Residual Neuromuscular Blockade. Current anesthesiology reports, 6, 164–169.

Tramèr, M. R., & Fuchs-Buder, T. (1999). Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. *British journal of anaesthesia*, *82*(3), 379–386. https://doi.org/10.1093/bja/82.3.379

US Food and Drug Administration, Center for Drug Evaluation and Research. (2015) Sugammadex.022225Orig1s000. Approval Letter, December 15, 2015. Retrieved November 25, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022225Orig1s000Approv.pdf

APPENDIX A: INSTITUTIONAL REVIEW BOARD APPROVAL

Office of Research
Institutional Review Board

MEMORANDUM

To: Lorraine Schoen
Atrium/Carolinas Healthcare System

From: Jeannie Sekits, Senior Protocol Analyst
Institutional Review Board

Date: 7/27/2022

Subject: Not Human Subjects Research: IRB00086560
Implementation of a cognitive aid to guide intraoperative neuromuscular blockade reversal strategies

The Wake Forest University School of Medicine Institutional Review Board has reviewed your protocol and determined that it does not meet the federal definition of research involving human subject research as outlined in the federal regulations 45 CFR 46. 45 CFR 46.102(f) defines human subjects as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."

The information you are receiving is not individually identifiable. In recent guidance published by the Office of Human Research Protections (OHRP) on the Guidance on Research Involving Coded Private Information or Biological Specimens, OHRP emphasizes the importance on what is being obtained by the investigator and states "if investigators are not obtaining either data through intervention or interaction with living individuals, or identifiable private information, then the research activity does not involve human subjects."

Note that only the Wake Forest University School of Medicine IRB can make the determination for its investigators that a research study does not meet the federal definition of human subject research. Investigators do not have the authority to make an independent determination that a study does not meet the federal requirements for human subject research. Each project requires a separate review and determination by the Board. The Board must be informed of any changes to this project, so that the Board can determine whether it continues to not meet the federal requirements for human subject research. If you have any questions or concerns about this information, please feel free to contact our office at 716-4542.

Medical Center Boulevard, Winston-Salem, NC 27157-1023 (336) 716-4542 / fax (336) 716-4480

APPENDIX B: NEUROMUSCULAR BLOCKADE MANAGEMENT SURVEY

1. I commonly administer less than the recommended 0.2 mg per 1 mg of neostigmine during pharmacologic reversal of neuromuscular blockade.
    a. True
    b. False
    (Howard et al., 2017)

2. Which of the following side effects, if any, influence your decision to use neostigmine for reversal of neuromuscular blocking agents (Select all that apply).
    a. Bronchoconstriction
    b. Bradyarrhythmias
    c. Propensity for PONV
    d. Urinary retention
    (Li et al., 2021)

3. I routinely re-assess the train-of-four count at least 10 minutes and up to 15 minutes after neostigmine administration and prior to extubating patients.
    a. True
    b. False
    (Kim et al., 2019)

4. When monitoring neuromuscular blockade depth at the facial nerve intraoperatively, I routinely move the peripheral nerve stimulator electrodes to the adductor pollicis before extubation.
    a. True
    b. False
    (Brull & Kopman, 2017; Murphy, 2018)

5. I use clinical indicators such as the ability to initiate and sustain spontaneous respirations of an adequate tidal volume to assess patients' recovery from neuromuscular blocking agents.
    a. True
    b. False

6. Sugammadex as a reversal agent is typically not used in patients with a creatinine clearance less than 30 ml/min.
    a. True
    b. False
    (Chandrasekhar et al., 2021).

7. I am hesitant to administer sugammadex in coagulopathic patients.
    a. True
    b. False
    (Moon et al., 2018)

8. When monitoring the facial nerve, I place the electrodes closest to the tragus and corner of the eye, directly above one another.
    a. True
    b. False
    (Naguib et al., 2018)

9. Sugammadex is dosed according to the patients'_____ in order to achieve a faster reversal of neuromuscular blockade.
    a. Actual Body Weight
    b. Ideal Body Weight
    c. Adjusted Body Weight
    d. It does not make a difference
    (FDA, 2015) (Badaoui et al., 2016) (Duranteau et al., 2021) (Mostoller et al., 2021)

10. Which of the following clinical indicators for the use of sugammadex are not currently listed in the Omnicell?
    a. Unable to assess TOF due to surgical limitations
    b. Can't intubate/Can't ventilate
    c. Clinical concern documented in EHR
    d. Failure to intubate after rocuronium or vecuronium when ventilation without airway protection is contraindicated
    e. Inadequate reversal using neostigmine/glycopyrrolate.

11. Neostigmine is a competitive, reversible acetylcholinesterase inhibitor. At doses greater than 0.07 mg/kg, further administration of neostigmine may result in NMJ dysfunction causing paradoxical weakness.
    a. True
    b. False
    (Preault et al., 2016).

12. Tracheal extubation should occur following neostigmine's peak action at 5-6 minutes.
    a. True
    b. False
    (Neely et al., 2021).

13. The maximum recommended dose of neostigmine is 0.07 mg/kg regardless of if the calculated dose exceeds 5 mg.
    a. True
    b. False
14. Match the correct dose of neostigmine according to the clinically assessed train-of-four count:
    a. 1 twitch → a. Use of neostigmine for reversal is not recommended
    b. 2 twitches → b. 0.05-0.07 mg/kg
    c. 3 twitches → c. 0.05 mg/kg
    d. 4 twitches → d. 0.03 mg/kg
    (Caldwell, 2009)

15. Current literature recommends a train-of-four ratio of at least 0.8 to reduce the incidence of residual neuromuscular blockade.
    a. True
    b. False
    (Kirmeier et al., 2019) (Miller and Ward, 2010).

16. When assessing a qualitative train-of-four ratio, current research shows that the majority of clinicians overestimate the value, resulting in underdosing pharmacologic reversal.
    a. True
    b. False
    (Bhananker et al., 2015)

17. Seventy percent of the receptors at the nicotinic neuromuscular junction can still be occupied by a muscle relaxant with a train-of-four count of 4.
    a. True
    b. False
    (Nagelhout, 2018)

18. A patient's ability to sustain a 5-second head lift corresponds to a train of four ratio of 0.50-0.60.
    a. True
    b. False
    (Miller and Pardo, 2011)

19. Following a 5-second tetanic stimulation, any subsequent stimulation(s) will be amplified for approximately 2-5 minutes, resulting in an underestimated degree of neuromuscular blockade.
    a. True
    b. False
    (Brull & Kopman, 2017; Ehrenwerth et al., 2013)

20. Monitoring train-of-four at the facial nerve best indicates readiness of extubation as it most closely reflects recovery of the pharyngeal muscles, thereby decreasing the risk for upper airway obstruction and aspiration.
    a. True
    b. False
    (Brull & Kopman, 2017)

21. The train-of-four count is most beneficial to inform anesthesia providers about the:
    a. Dosing of reversal agent
    b. Timing of reversal agent
    c. Depth of neuromuscular block
    d. Time to spontaneous recovery
    (Thilen & Bhananker, 2016)

22. Patients using hormonal birth control methods who have received sugammadex should be advised to use an alternate form of birth control for seven days:
    a. True
    b. False
    (US Food and Drug Administration., 2015)

23. Hemodialysis can effectively remove a rocuronium/sugammadex molecular complex.
    a. True
    b. False
    (Kim et al., 2021)

24. A greater degree of clinically significant bradycardia occurs with sugammadex administration compared to neostigmine.
    a. True
    b. False
    (Hristovska et al., 2017)

25. Recent data suggest that the incidence of a hypersensitivity reaction to sugammadex increases with (select all that apply):
    a. Repeated administration
    b. Doses of 16 mg/kg
    c. Renal impairment
    d. Pediatric patients
    (de Kam et al., 2018) & (Min et al., 2018a)