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DNP Project: Reversal of Neuromuscular Blockade with Neostigmine: Development of an Evidence-based Practice Protocol

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Reversal of Neuromuscular Blockade with Neostigmine:
Development of an Evidence-based Practice Protocol

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Abstract

**Background/Significance:** A large population of patients entering the post-operative anesthesia care unit (PACU) with residual neuromuscular blockade (NMB), as defined by a Train-of-Four ratio < 0.9, has been reported in the literature. Patients with residual NMB have a higher likelihood of respiratory insufficiency and failure, and many others experience uncomfortable feelings of muscle weakness. Neostigmine is a commonly used agent to reverse NMB, but little is known about factors which affect use and dosing.

**Purpose/Objectives:** The purpose of this Scholarly Leadership Project was to identify the factors being considered by anesthesia providers when using neostigmine as a reversal agent for NMB. The findings from this study and current evidence were utilized in the formulation of a set of evidence-based practice guidelines for the reversal of NMB with neostigmine.

**Design:** This study utilized a descriptive, online survey design.

**Methods:** A survey was sent through the email LISTSERV of the Illinois Association of Nurse Anesthetists (IANA), the official professional organization of certified registered nurse anesthetists (CRNAs) in the state of Illinois. 192 active CRNA members of the IANA participated. A validated, investigator-developed online survey, which examined the factors being considered by anesthesia providers when using neostigmine, was sent to 1,384 members of the IANA.

**Analysis:** Descriptive statistics using means, standard deviation, frequencies, and percentages was used to describe the sociodemographics of respondents and the online responses to the survey. Chi square statistics were utilized to examine different factors considered by CRNAs when administering neostigmine.

**Findings:** This study revealed different factors that anesthesia providers consider when using
neostigmine including: quantity and quality of muscle twitches present during train-of-four monitoring, twitches with and without fade, and time elapsed since the last dose of neuromuscular blocking agent. Furthermore, no statistically significant differences were found in the mean score of the factors being considered for neostigmine use between CRNAs in terms of their years of experience, types of practice, institutional settings, and level of education.

**Practice Implications:** Project results provide an evidence-based practice protocol, which anesthesia providers can use in discerning adequate and appropriate reversal of NMB.

*Keywords:* Neuromuscular blockade, neuromuscular blocking agents, neostigmine, residual, reversal
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Section I: Introduction

Background and Significance

Non-depolarizing muscle relaxants (NDMR) are agents, which cause temporary musculoskeletal paralysis through competitive inhibition of acetylcholine at the motor end plate (Butterworth, Mackey, & Wasnick, 2013b). Intraoperative use of NDMRs allows for reliable, reversible muscle relaxation, which facilitates surgical access to the operative site. Drugs that reverse the effects of NDMRs are known as cholinesterase inhibitors (Kruidering-Hall & Campbell, 2012). Cholinesterase inhibitors that are currently available include neostigmine, edrophonium, pyridostigmine, and physostigmine, with neostigmine and edrophonium being the most commonly used in anesthesia practice in the United States. This study focused only on neostigmine.

Neostigmine is a common agent used to reverse the effects of NDMRs through inhibition of the enzyme, acetylcholinesterase (Butterworth, Mackey, & Wasnick, 2013a). Through inhibition of acetylcholinesterase, acetylcholine (ACh) levels increase, which results in the stimulation of both nicotinic and muscarinic receptors (Butterworth, Mackey, & Wasnick, 2013a). Nicotinic receptors are found in the neuromuscular junction of skeletal muscles and increased stimulation of these receptors results in stronger contractions of muscle fibers (Pappano, 2012). Conversely, muscarinic receptors are found in mucous membranes, lining of the lungs, atrioventricular (AV) node of the heart, eyes, and central nervous system (Pappano, 2012). Stimulation of muscarinic receptors by ACh results in bradycardia, prolongation of the QT interval, increased mucous secretion, bronchoconstriction, pupillary constriction, and smooth muscle contraction of the intestines and bladder (Butterworth, Mackey, & Wasnick, 2013a).
Glycopyrrolate, an anti-muscarinic agent, is routinely administered concomitantly with neostigmine, which abates the side effects associated with muscarinic agonism (Butterworth, Mackey, & Wasnick, 2013a).

Within the practice of anesthesia there is a wide variance in the dosing and administration practices of neostigmine (Duvalentin, Cunin, Plaud, & Maisön, 2008; Gray & Wilson, 1959; Naguib et al., 2010; Videira & Vieira, 2011). Anesthesia providers often base dosing preferences on several factors that include age, quality of muscle relaxation, timing of the last administration of NDMR, disease processes affecting drug metabolism and excretion, such as liver and kidney disease). Currently, there are no universally accepted guidelines for reversal of neuromuscular blockade with neostigmine. Moreover, several published articles have called for the development of a set of guidelines for NMB reversal based on the negative effects of residual NMB (Cedborg et al., 2014; Saur, Stahn, Soltesz, Noeldge-Schomburg, & Mencke, 2011; Sundman, et al., 2000). A synthesis of the adverse effects of residual NMB can be found in Table 1.

Neuromuscular monitoring allows the anesthesia provider to assess the status of muscle paralysis through electrical stimulation of nerve fibers. Train-of-four (TOF) neuromuscular monitoring consists of four separate electrical impulses delivered at intervals of 0.5 seconds, which in non-paralyzed will result in four brief muscle contractions, also known as twitches (Dorsch & Dorsch, 2011). The number and intensity of twitches obtained is correlated to the intensity of the neuromuscular block. Train-of-four ratio (TOFR) compares the amplitude of the fourth muscle twitch divided by the amplitude of the first muscle twitch (Dorsch & Dorsch, 2011). A TOFR of 1 (100%) signifies the absence of NMB. Conversely, a lower TOFR signifies a more intense NMB (Dorsch & Dorsch, 2011).
According to Murphy and Brull (2010), 40% of postoperative patients whom received intraoperative muscle relaxation have residual NMB with a train-of-four (TOF) ratio < 0.9 and 1-3% will experience an adverse event due to residual paralysis. A study by Debaene, Plaud, Dilly, & Donati (2003) identified 45% of postoperative patients had residual neuromuscular blockade after receiving a single dose of intermediate-acting NDMR. Cedborg et al. (2014) identified an increased incidence of pharyngeal dysfunction in patients with partial NMB, resulting in aspiration.

**Problem Statement**

A wide variation exists among anesthetists in the dosing and administration of NMB reversal agents. Additionally, no universally published guidelines exist for the reversal of NMB. As a result of the large variation in dosing and administration of NMB reversal agents, a significant number of post-operative patients have residual NMB. Patients with residual NMB may experience hypoventilation, leading to hypoxia, and possible apnea (Kruidering-Hall & Campbell, 2012).

**Study Purpose**

This project identified the factors in which anesthesia providers currently use to dose and administer neostigmine and examine the types of neuromuscular monitoring used by CRNAs during the reversal of NMB using neostigmine. The findings from this study can aid in the development of an evidence-based practice protocol for the reversal of NMB using neostigmine. This study aimed to answer the following research questions:

1. **What factors do anesthesia providers consider when administering neostigmine?**
2. **What are the significant factors that anesthesia providers use to determine neostigmine dosing?**
3. What are the types of neuromuscular monitoring are used by anesthesia providers during the reversal of NMB using neostigmine?

4. Are there significant differences in the factors considered by anesthesia providers according to practice type (academic versus non-academic practice), years of experience (less than 5 years versus 5 years of more), level of education (Bachelors versus Masters versus Doctoral degree), and type of institution in which anesthesia is practiced.

**Conceptual Framework**

The conceptual basis for the development of an evidence-based practice (EBP) protocol for safe NMB reversal and implementing the protocol into the practice of anesthesia providers is consistent with the Stetler model of Evidence-based Practice. The model is grounded in the conceptual framework of research utilization (RU), which according to Stetler (2001), “is the process of transforming research knowledge into practice” (p. 282). Furthermore, RU dominates the early steps of the Stetler model, and results in the acceptance of evidence-based practice found in the latter stages of the model (Stetler, 2001).

The Stetler model of evidence-based practice, describes five phases of how practitioner analyze and use study findings to implement evidence-based nursing practice change (Dang et al., 2015). As described by Stetler (1994; 2001) the five phases are as follows:

**Phase I: Preparation.** During the preparation phase the practitioner defines the purpose and outcomes for each issue (Stetler, 2001). In addition, influencing factors (i.e. internal, external), which may interfere with research progress or validity, should be identified (Stetler, 2001). Furthermore, various sources of research evidence are collected and sorted.

**Phase II: Validation.** During the validation phase the practitioner evaluates evidence in the form of a critique and synopsis (Stetler, 2001). Furthermore, sources are rated based on the
strength of the findings (Stetler, 2001). If sufficient evidence exists the researcher moves into phase III of the model (Stetler, 1994). Conversely, if there is insufficient evidence the study ends at phase II (Stetler, 1994).

**Phase III: Comparative evaluation/Decision making.** During the comparative evaluation or decision making phase the practitioner uses a set of four criteria to determine if study findings can be applied to practice (Stetler, 1994). First, the “fit of setting” criterion allows the researcher to investigate similarities between the sample and the study setting, and the population and setting of which EBP is being implemented (Stetler, 2001). Second, the “feasibility: r, r, r” criterion assesses the risk, resources, and readiness for implementation of EBP (Stetler, 2001). Third, the “current practice” criterion assesses the effectiveness of current practice and the relevance for EBP in the current practice (Stetler, 1994). Fourth, the “substantiating evidence” criterion assesses the overall strength of the research evidence (Stetler, 2001). Evidence is then labeled as either “to not use,” “to use,” or “to consider use” (Stetler, 2001, p. 277). If the evidence is labeled “to use” or “to consider use” the practitioner progresses to phase IV, however if the evidence is labeled “to not use” the study is stopped (Stetler, 2001).

**Phase IV: Translation/application.** The translation or application phase focuses on the integration of the developed EBP (Stetler, 2001). The research findings are converted into practice change or recommendations (Dang et al., 2015).

**Phase V: Evaluation.** During the evaluation phase the practitioner assesses the various outcomes of the practice change (Stetler, 2001).

The use of a theoretical framework helped to guide planning and implementation stages of the Scholarly Leadership Project. The Stetler model of evidence-based practice as developed by Stetler (1994; 2001) enhances the strength of the evidence-based guidelines for
neuromuscular blockade reversal using neostigmine by guiding the acquisition and application of evidence. Phase V, evaluation, will not be conducted in this project, however evaluation of protocol dissemination may be the focus of follow up studies.

**Section II: Literature Review**

A search of the literature regarding neostigmine dosing and administration, and the incidence of neuromuscular blockade was conducted. The literature search was performed using the following computerized databases: Web of Science, PubMed, and ScienceDirect. The following Medical Subject Heading (MeSH) terms “neuromuscular blockade” and “neostigmine” plus common search term, "residual" were utilized during the computer-based literature search. The search results were filtered by removing studies that contained the term “sugammadex” as this NMB reversal agent lacked FDA approval at the time the literature review was written and is not included in the subject of this study. The database search generated 290 articles. Journal articles included in the literature review were scholarly papers meeting the following criteria: demonstrated a knowledge deficit in the area of neuromuscular block (NMB) reversal; contained information that is important in the creation of best practice guidelines and/or objectives aimed at improving practice and patient outcomes.

**Residual Neuromuscular Blockade**

**Incidence.** Residual neuromuscular blockade is defined as a train-of-four ratio (TOFR) < 0.9. A study performed by Murphy et al. (2005) demonstrated that the vast majority of patients (87.5%) have residual NMB immediately before tracheal extubation despite passing standard methods of extubation criteria - TOF 4/4 without fade (incremental decrease in the amplitude of each consecutive twitch), eye opening, adequate spontaneous ventilation, and five-second head
lift or hand grasp. The findings of this study suggest that the standard methods of evaluating the effectiveness of NMB reversal are ineffective in identifying residual NMB.

Several similar studies have demonstrated the presence of residual NMB, which progressed into the postoperative phase of recovery. In a study by Gaszynski, Szlachcinski, Jakubiak, and Gaszynski (2009), 48% of patients entering the post-anesthesia care unit (PACU) had residual NMB (TOF Ratio <0.9). Furthermore, 26% of the patients had a TOF ratio less than 0.7. Adamus, Koutna, and Neoral (2007) performed a study in which no neuromuscular monitoring was used during the anesthetic. The study demonstrated a 34% incidence of residual neuromuscular blockade upon arrival to the PACU. The researchers compared the patients with postoperative residual NMB to those that had fully recovered; they discovered that the patients with residual NMB received larger doses of rocuronium, given less neostigmine, and there was less time between the last dose of rocuronium and the administration of neostigmine.

Sauer, Stahn, Soltesz, Noeldge-Schomburg, and Mencke (2011) conducted a study in which one group received a standardized weight-based dose of neostigmine and the other received a placebo. Patients who received neostigmine were allowed to return to a TOF ratio of 1.0 before tracheal extubation, whereas the placebo group were tracheal extubated at a TOF ratio less than 1.0, but without fade in TOF and double-burst nerve stimulation. Double-burst stimulation is a set of three electrical stimuli at 50 Hz followed by another set of two or three electrical stimuli timed 0.75 seconds later. Fifty-percent of the placebo group developed hypoxemia, compared to 28% in the neostigmine group. This study demonstrated that neostigmine was effective in antagonizing rocuronium versus placebo, however a large population of patients still developed adverse respiratory outcomes despite full reversal of NMB.
**Complications.** The diaphragm is a skeletal muscle therefore NMBAs impair diaphragm excursion. Impairment of diaphragm may result in shortness of breath, atelectasis (collapse of alveoli resulting in intrapulmonary shunting), respiratory distress, or respiratory failure. Furthermore, skeletal muscles are involved in swallowing, movement of the vocal cords, epiglottis, and tongue, and for stenting open the structures of the upper airway (i.e. laryngopharynx, oropharynx, and nasopharynx). For patients with neuromuscular paralysis the anesthesia provider is tasked with controlling ventilation, and protecting the airway from aspiration. Therefore it can be hypothesized that a patient with residual NMB may also require airway management to maintain adequate ventilation and to prevent aspiration. In fact, a study by Eikermann et al. (2007) demonstrated that patients with partial NMB have decreased upper airway volumes during inspiration. Additionally, expiratory volume and respiratory rate were not affected by partial NMB (Eikermann et al., 2007). In a similar study, Eriksson et al. (1997) demonstrated that patients with partial neuromuscular paralysis had a higher likelihood of aspiration due to pharyngeal dysfunction if the TOFR was less than 0.9. In fact, six out of 14 volunteers aspirated with a TOFR less than 0.9, while no volunteers aspirated with a TOFR greater than 0.9 (Eriksson et al., 1997).

Cedborg et al. (2014) performed a study involving elderly patients with partial neuromuscular paralysis and the inability to protect their airway from aspiration. They concluded that partial neuromuscular paralysis increases pharyngeal dysfunction with aspiration from 37% (control) to 71% (study). A similar study by Sundman et al. (2000) compared the incidence of pharyngeal dysfunction in a control group with patient with partial neuromuscular paralysis at TOFR 0.6, 0.7, 0.8 and 0.9. The control group had a pharyngeal dysfunction rate of
6% compared to 28% at a TOFR of 0.6; 17% at a TOFR of 0.7; 20% at a TOFR of 0.8; and 13% for patients with a TOFR greater than 0.9 (Sundman et al., 2000).

Neostigmine

**Administration.** Studies have demonstrated that the majority of anesthesia providers do not routinely reverse NMB (Naguib et al., 2010; Osmer, Vogele, Zickman, & Hempelman, 1996). However current studies recommend the routine reversal of NMB (Miller & Ward, 2010; Kopman & Eikermann, 2009). However, if objective neuromuscular monitoring can demonstrate a TOFR $\geq 0.9$ neostigmine is not recommended, nor is it required (Lien, 2010).

When administering neostigmine to reverse NMB the goal is to time the dose of the reversal agent so that the peak effect of the drug occurs closely before tracheal extubation. Buder et al. (2010) concluded that a reduced dose of neostigmine adequately reverses a shallow NMB (TOFR > 0.4) caused by atracurium within 10 minutes. Murphy (2006) suggests practitioners are administering the reversal agent too late and thus not allowing sufficient time for the reversal agent to act. Furthermore, full reversal of an intense NMB may require 20-30 minutes, and thus Brull & Murphy (2010) recommends reversal be given 15-30 minutes before tracheal extubation.

**Dosing.** The standard dosing of neostigmine when reversing NMB is 25-75 mcg/kg (Nagelhout, 2014). A study by Buder et al. (2010) evaluated the dose-effect relationship of neostigmine. Results of the study determined the NMB recovery time from the start of the neostigmine administration to a TOFR of 0.9 and 1.0 with starting TOFR of 0.4 and 0.6 (Buder, 2010). NMB recovery time for a starting TOFR of 0.4 to an end point of TOFR 0.9 are as follows: six minutes for a neostigmine dose of 10 mcg/kg, six minutes for a neostigmine dose of 20 mcg/kg, and four minutes for a neostigmine dose of 30 mcg/kg (Buder, 2010). NMB
recovery time for a starting TOFR of 0.6 to an end point of TOFR 0.9 are as follows: four minutes for a neostigmine dose of 10 mcg/kg, three minutes for a neostigmine dose of 20 mcg/kg, and four minutes for a neostigmine dose of 30 mcg/kg (Buder, 2010). Furthermore, the probability of successful reversal within 10 minutes of neostigmine administration increased as the dosage increased with 30 mcg/kg near 100% at TOFR of 0.4 and 0.6 (Buder, 2010). These results suggest that moderate degrees of NMB may be adequately antagonized with neostigmine dosages of 20 – 30 mcg/kg. There is a lack of research for a dose-effect relationship at higher intensity of NMB.

**Age.** It is a well known that pharmacokinetics and pharmacodynamics vary significantly across the age spectrum and should be given special consideration when dosing neostigmine. A study by Bevan et al. (1999) demonstrated significant variation between adults, aged 20-65 years old, and children, aged 2-12 years old, in the recovery time from NMB after reversal with neostigmine. Children with NMB due to rocuronium administration recovered to a TOFR of 0.9 in 12.1 minutes versus adults who recovered in 37.1 minutes when neostigmine is administered five minutes after relaxant (Bevan et al., 1999). However, when neostigmine is administered with a TOFR of 0.25, children recovered from NMB from rocuronium in 4.8 minutes versus adults who recovered in 4.5 minutes (Bevan et al., 1999). This study demonstrates that age is an important factor when reversing an intense NMB as evidenced by the large age group variation in time when neostigmine was administered five minutes after NDMR. However, if reversing when a TOFR is \(\leq 0.25\) it seems age becomes less of a factor.

**Body Composition.** Studies have shown that obesity increases the duration of NMB (Schwartz, Matteo, Ornstein, & Halevy, 1992; Weinstein et al., 1988). As a result of these study conclusions, it could be hypothesized that obesity also affects the reversal of NMB. In fact, a
study by Suzuki, Masaki, & Ogawa (2006) demonstrated that obese patients with NMB reversed by neostigmine required a significantly longer time to reach a TOFR of 0.9 in comparison with the normal weight and overweight patient populations. In fact, obese patients required 25.9 minutes to obtain a TOFR of 0.9, whereas overweight patients required 14.6 minutes and normal weight patients required only 6.9 minutes (Suzuki, Masaki, & Ogawa, 2006). The results from this study demonstrate that the obese patient requires a significantly longer time to recover from NMB and thus the anesthesia provider should consider early administration of neostigmine.

**Monitoring**

Neuromuscular monitoring is essential for effective reversal of NMB. Without the use of monitoring the anesthesia provider is blindly administering additional muscle relaxant and reversal agent. Despite the importance of neuromuscular monitoring several studies have demonstrated that a large number of anesthesia practitioners do not routinely use neuromuscular monitoring in their practice (Grayling & Sweeney, 2007; Sorgenfrei, Mogensen & Swiatek, 2005; Buder et al, 2003). Brull and Murphy (2010) assert, “perioperative monitoring of evoked neuromuscular responses that guides the administration of anticholinesterases and documents return of neuromuscular function should be a standard of care” (p. 135).

Qualitative or subjective nerve monitoring uses an electrical impulse to stimulate an evoked potential along a peripheral motor nerve, which results in a brief contraction or twitch of the muscle that the nerve innervates. The anesthesia provider observes the muscle twitch and notes the quality (fade versus no-fade) and the quantity (twitch count). Peripheral nerves commonly used for twitch monitoring include the facial, ulnar, and tibial nerves, however reliability of twitch monitoring varies amongst the nerves. Thilen et al. (2012) concluded that train-of-four nerve monitoring of the facial nerve was associated with a higher incidence of
residual neuromuscular block when compared to nerve monitoring at the ulnar nerve (incident rate of 52% versus 22% respectively). Thus, the ulnar nerve is the preferred site for qualitative (subjective) nerve monitoring.

Monitoring of clinical signs is a common method used by practitioners to assess for residual NMB. These clinical signs include patient responsiveness, subjective measurements of muscle strength (i.e. 5-second head lift, hand grasp), eye opening, and tongue extrusion, however studies have demonstrated these tests do not reliably predict adequate reversal of neuromuscular blockade (Eikermann, Groeben, Hussing, & Peters, 2003; Hayes, Mirakhur, Breslin, Reid, & McCourt, 2001; Fruergaard, Mogensen, Berg, & El Mahdy, 1998; Mogensen & Claudius, 2010). According to Grayling & Sweeney (2007), the majority of anesthesia providers primarily rely on clinical signs when assessing the status of neuromuscular blockade.

Section III: Methods

Design

This study utilized a descriptive, online survey design.

Setting

The online survey was distributed to all certified registered nurse anesthetists (CRNAs) who are members of the Illinois Association of Nurse Anesthetists (IANA), the official professional organization of CRNAs in the state of Illinois.

Sample

The sample for this study included CRNAs who are members of the IANA. Student registered nurse anesthetists (SRNAs) were excluded from this study whether members of the IANA or not. Additionally, anesthesiologists and anesthesia residents were excluded from the survey by means of the survey distribution.
Sample Size

There are approximately 1,384 CRNA members of the IANA. A convenience sampling of the population described above was utilized in this study. Online surveys can have a wide range of responsiveness. Based on a study by Cook, Health, and Thompson (2000), an average 30% response rate was found when 39 separate online surveys were analyzed (Pan, 2010). Therefore, for this study the targeted response rate was 30%. The number of complete responses was 192 (13.7%).

Recruitment Procedure

The subjects for this study were CRNAs recruited from the IANA. Institutional Review Board (IRB) approval was obtained from DePaul University. A form letter was emailed to the administrator of IANA requesting to send out the web link for the online Qualtrics survey to all CRNAs (Appendix A). The IANA distributed the survey to all CRNA members by means of an email LISTSERV. A web link in the email directed the study participant to the anonymous online Qualtrics survey. The email template used for survey dissemination by the IANA can be found in Appendix B.

Test-retest reliability was conducted using a subgroup of CRNAs who volunteered to retake the survey by providing their email address to determine the reliability of the investigator-developed online survey. An email with the survey retest link was sent to all volunteers and a reminder email was sent two weeks later. A total of 44 CRNA volunteers responded, however only 28 CRNAs completed the retest survey.
Instrument

The instrument included brief demographic questions and an investigator-developed online survey that examined the factors that are considered by anesthesia providers when using neostigmine as a reversal agent for NMDR such as the age, gender, and weight of patients among others (Appendix C). The survey questions were related to neostigmine administration practices among CRNAs. The demographic questions of the survey included years of experience, education level, type of institution and practice type (academic or non-academic). Face validity of the survey tool was established through the review of the survey questions by ten content experts including CRNAs and attending anesthesiologists. Content validity was established through a comprehensive literature review on the content domains of neostigmine use. Reliability of the survey was established using test-retest reliability testing using Pearson's r correlation statistics. A Pearson's r value of .70 or greater indicates adequate reliability of the online survey. The reliability of the survey was established by sending the survey twice at one-week intervals to only those participants who volunteered to complete the test-retest.

Human Subjects Protection

Training of Research Personnel on Human Subject Protections was completed May 19, 2015. The researcher of this study completed the following Collaborative Institutional Training Initiative (CITI) courses: CITI Health Information Privacy and Security (HIPS) for students, Responsible Conduct of Research, and Students – Class Projects. Approval was received from the DePaul IRB on November 23, 2015 (Appendix F).

The study survey was distributed to CRNA members of the IANA via an email from the IANA. Informed consent was implicit through voluntary completion of the survey. Survey
responses were collected anonymously via Qualtrics and no IP addresses were associated with the
collected surveys. Data will be destroyed three years after study completion.

Analysis

Descriptive statistics were used to describe the sociodemographics of respondents and the
online responses to the survey. Chi square statistics were performed to examine significant
differences in the factors considered by anesthesia providers when administering neostigmine.
Dichotomous, independent groupings (academic versus non-academic practice type, low level of
years of clinical experience less than five years versus clinical experience of five years or more,
lower level of education with Bachelor’s degree versus higher level of education with Doctoral
degree) of CRNAs were used in the analysis.

Project Design

Assessment. In the assessment phase, an electronic survey was distributed to the target
population to collect demographic data and obtain data related to the current practices of
reversing NDMRs with neostigmine. A Practice protocol for reversing NDMRs using
neostigmine was developed utilizing the study results and the information obtained through the
review of the literature.

Implementation. In the implementation phase, a practice protocol for reversal of
NDMRs using neostigmine will be developed and submitted to the IANA and/or the American
Association of Nurse Anesthetists (AANA) for white paper consideration.

Evaluation. This study leaves the evaluation process of the practice protocol for future
research. A future study could evaluate practice change among the anesthesia providers by
submitting a follow-up survey after implementation of the NDMR reversal protocol. The study
could be expanded to include attending anesthesiologists, anesthesia residents, and SRNAs to
analyze variance in dosing and administration of neuromuscular blockade reversal amongst the groups.

Section IV: Findings

Survey Tool

In order to determine content validity the survey was graded by 10 content experts consisting of six CRNAs and four physician anesthesiologists. The experts comprehensively graded each of the three categories: “factors for use,” factors for dosing,” and “neuromuscular monitoring.” In addition, the content experts graded the individual survey questions. The questions that were graded were specific to the practice of reversing neuromuscular blockade (Neostigmine Factors Scale) using questions six through 19, and thus excluding questions related to demographics, provider readiness for practice change, and questions regarding survey retesting for validity. Each item was graded for clarity, relevance, simplicity, and consistency using a 10-point Likert-type scale.

- Clarity: score of 1 = unclear, score of 10 = very clear
- Relevance: score of 1 = not relevant, score of 10 = high relevance
- Simplicity: score of 1 = very complex and confusing, score of 10 = simple and easy to understand
- Consistency: score of 1 = inconsistent, score of 10 = high consistency

The results revealed a statistically significant correlation between survey grades by content experts (r = 0.913, p < 0.000), therefore providing sufficient evidence of survey content validity.
Table 2. Content Validity

Numbers expressed as **Average Score**

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</tr>
<tr>
<td>Clarity</td>
<td>9.9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9.8</td>
<td>9.6</td>
<td>9.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Relevance</td>
<td>9.2</td>
<td>9.8</td>
<td>9.3</td>
<td>9.5</td>
<td>9.5</td>
<td>9.9</td>
<td>9.5</td>
<td>9.5</td>
<td>9.5</td>
<td>9.7</td>
<td>9.8</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Simplicity</td>
<td>10</td>
<td>10</td>
<td>9.5</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
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<tr>
<td>Consistency</td>
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<td>9.3</td>
<td>10</td>
<td>10</td>
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<td>10</td>
<td>9.5</td>
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<td>9.8</td>
<td>9.8</td>
<td>9.8</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Clarity: score of 1 = unclear up to a score of 10 = very clear question items.
Relevance: score of 1 = not a relevant question items up to a score of 10 = highly relevant question items
Simplicity: score of 1 = very complex, confusing question items up to a score 10 = simple, easy to understand question items
Consistency: score of 1 = inconsistent question items up to a score of 10 = highly consistent question items

**Survey tool reliability.** Reliability of the online survey tool was tested using the results from survey questions six through 19 (Neostigmine Factors Scale). The results revealed the survey tool was reliable in measuring the opinions of CRNA on the various factors influencing the use of neostigmine (Cronbach's alpha = 0.711). Additionally, test-retest was also performed to measure the reliability of the online survey. A total of 44 CRNAs volunteered to complete a
retest survey, however only 28 participants completed the retest, which contained identical
survey questions to that of the original survey. Using the Pearson intraclass correlation
coefficient test the results of the original survey were correlated with the results of the retest. A
statistically significant correlation was revealed between the two surveys \( r = 0.84, p < 0.000 \),
thereby providing adequate evidence of test-retest reliability.

**Descriptive Statistics**

Complete survey results were collected from 192 (13.9%) out of 1,384 CRNA members
of the IANA. Survey completion was voluntary and all participants met the inclusion criteria.
Each subject completed an online survey regarding factors used when dosing and administering
neostigmine for reversal of neuromuscular blockade. The majority of the participants had >20
years (n=53, 27.6%) of experience as a CRNA, 23.4% had 0-4 years (n= 45), 22.4% had 5-10
years (n=43), 13.5% had 11-15 years (n=26), 13.0% had 16-20 years (n=25). The majority of
participants held a Masters degree (n=145, 75.5%), 11.5% held a Bachelors degree (n= 22), and
13.0% held a Doctorate degree (n=25). The majority of participants deliver anesthesia in private
hospitals (n=108, 56.3%) followed by public (county) hospitals (n = 53, 27.6%), outpatient
surgical centers (n=29, 15.1%), and Veteran Affairs (V. A.) Hospitals (n=2, 1.0%). Participants
primarily delivered anesthesia in a non-academic facility (n=113, 58.9%) compared to an
academic facility (n=79, 41.1%).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many years have you been a Certified Registered Nurse Anesthetist?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>45</td>
<td>23.4</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>43</td>
<td>22.4</td>
</tr>
<tr>
<td>11 – 15 years</td>
<td>26</td>
<td>13.5</td>
</tr>
<tr>
<td>16 – 20 years</td>
<td>25</td>
<td>13.0</td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td>53</td>
<td>27.6</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td>What is the highest degree you hold related to anesthesia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelors</td>
<td>22</td>
<td>11.5</td>
</tr>
<tr>
<td>Masters</td>
<td>145</td>
<td>75.5</td>
</tr>
<tr>
<td>Doctorate</td>
<td>25</td>
<td>13.0</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td>What type of institution do you primarily administer anesthesia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Surgical Center</td>
<td>29</td>
<td>15.1</td>
</tr>
<tr>
<td>Public (County) Hospital</td>
<td>53</td>
<td>27.6</td>
</tr>
<tr>
<td>Private Hospital</td>
<td>108</td>
<td>56.3</td>
</tr>
<tr>
<td>V.A. Hospital</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td>How would you describe your anesthesia practice?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>79</td>
<td>41.1</td>
</tr>
<tr>
<td>Non-academic</td>
<td>113</td>
<td>58.9</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td>I routinely reverse muscle paralysis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>151</td>
<td>78.6</td>
</tr>
<tr>
<td>Neutral</td>
<td>16</td>
<td>8.3</td>
</tr>
<tr>
<td>Disagree</td>
<td>25</td>
<td>13.0</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td>Implementation of a best practice protocol for the reversal of neuromuscular blockade using neostigmine would be beneficial to my practice.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>114</td>
<td>59.4</td>
</tr>
<tr>
<td>Neutral</td>
<td>51</td>
<td>26.6</td>
</tr>
<tr>
<td>Disagree</td>
<td>27</td>
<td>14.1</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Due to the heterogeneous nature of responses to the question, “How many years have you been a Certified Registered Nurse Anesthetist?,” the variables were grouped together to create two homogenous variables. The new grouping includes the following variables: 0-10 years (n=88) and 11-29 years (n=104) (Table 4). Similarly, variables for the survey question, “What type of institution do you primarily administer anesthesia?,” were regrouped by combining variables “V.A Hospital” with “Public (County) Hospital.”. The new grouping includes the
following variables: outpatient surgical center (n=29), public hospital (n=55), and private hospital (n=108) (Table 4).

**Table 4. Regrouped Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many years have you been a Certified Registered Nurse Anesthetist?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 10 years</td>
<td>88</td>
<td>45.8</td>
</tr>
<tr>
<td>11 – 29 years</td>
<td>104</td>
<td>54.2</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100</td>
</tr>
<tr>
<td>What type of institution do you primarily administer anesthesia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Hospital</td>
<td>108</td>
<td>56.3</td>
</tr>
<tr>
<td>Public Hospital</td>
<td>55</td>
<td>28.6</td>
</tr>
<tr>
<td>Outpatient Surgical Center</td>
<td>29</td>
<td>15.1</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 5. Survey Question Frequencies**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage</th>
<th>$M$</th>
<th>$SD$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I routinely reverse muscle paralysis.</td>
<td>Agree</td>
<td>151</td>
<td>78.6</td>
<td>2.66</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>16</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>25</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider the age of the patient as an important factor in the administration of neostigmine.</td>
<td>Agree</td>
<td>56</td>
<td>29.2</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>56</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>80</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Overall, I consider the number of muscle twitches present during train-of-four testing as an important factor in the administration of neostigmine.</td>
<td>Agree</td>
<td>152</td>
<td>79.2</td>
<td>2.68</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>18</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>22</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Overall, I consider the quality of the muscle twitches during train-of-four testing as an important factor in the administration of neostigmine.</td>
<td>Agree</td>
<td>158</td>
<td>82.3</td>
<td>2.74</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>18</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>16</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider twitches with fade during train-of-four testing as an important factor in the administration of neostigmine.</td>
<td>Agree</td>
<td>146</td>
<td>76.0</td>
<td>2.68</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>30</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>16</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider twitches without fade during train-of-four testing as an important factor in the administration of neostigmine.</td>
<td>Agree</td>
<td>114</td>
<td>59.4</td>
<td>2.45</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>51</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>27</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider the time elapsed since the last dose of neuromuscular blocking agent when administering neostigmine.</td>
<td>Agree</td>
<td>168</td>
<td>87.5</td>
<td>2.80</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>10</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>14</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider increasing the dose of neostigmine when the twitches have fade in train-of-four testing.</td>
<td>Agree</td>
<td>105</td>
<td>54.7</td>
<td>2.31</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>41</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disagree</td>
<td>46</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>I consider decreasing the dose of neostigmine when the twitches have fade in train-of-four testing.</td>
<td>Agree</td>
<td>89</td>
<td>46.4</td>
<td></td>
</tr>
</tbody>
</table>
The body of the survey inquired if CRNAs “agree,” are “neutral,” or “disagree” with specific factors relating to the dosing and administration of neostigmine, and monitoring of neuromuscular blockade status to assess readiness for reversal. Factors considered by CRNAs were defined as those questions having greater than 50% of the CRNAs selecting “agree.” Factors not considered by CRNAs are those with less than 50% of the CRNAs selecting “agree.” Factors considered by CRNAs include: number of muscle twitches present during train-of-four testing (agree=152, 79.2%; neutral=18, 9.4%; disagree=22, 11.5%), quality of muscle twitches present during train-of-four testing (agree=158, 82.3%; neutral=18, 9.4%; disagree=16, 8.3%), twitches with fade (agree=146, 76.0%; neutral=30, 15.6%; disagree=16, 8.3%), twitches without fade (agree=114, 59.4%; neutral=51, 26.6%; disagree=27, 14.1%), time elapsed since the last neostigmine when the twitches have no fade in train-of-four testing.

<table>
<thead>
<tr>
<th></th>
<th>Neutral</th>
<th></th>
<th>Disagree</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td>53</td>
<td>192</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.0</td>
<td></td>
<td>27.6</td>
<td></td>
<td>2.19</td>
</tr>
</tbody>
</table>

Overall, I consider the patient body mass index as an important factor for dosing of neostigmine.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72</td>
<td>54</td>
<td>66</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37.5</td>
<td>28.1</td>
<td>34.4</td>
<td></td>
<td>2.03</td>
<td>0.849</td>
</tr>
</tbody>
</table>

I routinely use subjective neuromuscular monitoring (i.e. Train-of-four, Tetanus) to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>165</td>
<td>14</td>
<td>13</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.9</td>
<td>7.3</td>
<td>6.8</td>
<td></td>
<td>2.79</td>
<td>0.549</td>
</tr>
</tbody>
</table>

I routinely use train-of-four nerve monitoring to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>167</td>
<td>14</td>
<td>11</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>87.0</td>
<td>7.3</td>
<td>5.7</td>
<td></td>
<td>2.81</td>
<td>0.518</td>
</tr>
</tbody>
</table>

I routinely use tetanus nerve monitoring to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83</td>
<td>49</td>
<td>60</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.2</td>
<td>25.5</td>
<td>31.3</td>
<td></td>
<td>2.12</td>
<td>0.857</td>
</tr>
</tbody>
</table>

I routinely use objective neuromuscular monitoring (i.e. TOF Watch) to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>91</td>
<td>38</td>
<td>63</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>47.4</td>
<td>19.8</td>
<td>32.8</td>
<td></td>
<td>2.15</td>
<td>0.886</td>
</tr>
</tbody>
</table>

Implementation of a best practice protocol for the reversal of neuromuscular blockade using neostigmine would be beneficial to my practice.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>114</td>
<td>51</td>
<td>27</td>
<td>192</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.4</td>
<td>26.6</td>
<td>14.1</td>
<td></td>
<td>2.45</td>
<td>0.729</td>
</tr>
</tbody>
</table>
A factor considered by CRNAs was identified as increasing the dose of neostigmine when the twitches have fade (agree=105, 54.7%; neutral=41, 21.4%; disagree=46, 24.0%). Neuromuscular monitoring used by CRNAs when assessing patient readiness for reversal includes routine use of subjective neuromuscular monitoring (agree=165, 85.9%; neutral=14, 7.3%; disagree=13, 6.8%) and routine use of train-of-four monitoring (agree=167, 87.0%; neutral=14, 7.3%; disagree=11, 5.7%). Factors not considered by CRNAs include age of the patient (agree=56, 29.2%; neutral=56, 29.2%; disagree=80, 41.7%), patient body mass index (agree=89, 37.5%; neutral=54, 28.1%; disagree=66, 34.4%), decreasing the neostigmine dose when twitches have no fade (agree=89, 46.4%; neutral=50, 26.0%; disagree=53, 27.6%), routine use of tetanus nerve monitoring (agree=83, 43.2%; neutral=49, 25.5%; disagree=60, 31.3%), and routine use of objective neuromuscular monitoring (agree=91, 47.4%; neutral=38, 19.8%; disagree=63, 32.8%).

**Inferential Statistics**

A chi-square test was conducted to determine statistically significant associations between categorical variables in terms of years of CRNA experience, level of education, type of practice, and institutional setting and patient age when administering neostigmine. No statistically significant associations were found between patient age and years of CRNA experience ($\chi^2 (2, N = 192) = 4.210, p = 0.122$) or CRNA level of education ($\chi^2 (4, N = 192) = 0.525, p = 0.971$) or type of institution CRNA is employed ($\chi^2 (4, N = 192) = 4.841, p = 0.304$) or type of practice ($\chi^2 (2, N = 192) = 2.648, p = 0.266$).

Results from several survey questions were combined to create two variables: neuromuscular twitch monitoring and subjective nerve monitoring. The neuromuscular twitch monitoring variable combines all survey questions regarding practitioner clinical decision
making in regards to twitch count and quality (questions 8, 9, 10, 11, 13, and 14). The subjective nerve monitoring variable combines survey questions regarding the use of subject nerve monitoring including train-of four and tetanus (questions 16, 17, and 18).

An independent-samples t-test was conducted to compare years of CRNA experience and type of practice to neuromuscular twitch monitoring and the use of subjective nerve monitoring (i.e. TOF, twitch quality). There was no significant difference in the scores for 0-10 years of CRNA experience \((M = 14.76, SD = 3.49)\) and 11-29 years of CRNA experience \((M=15.27, SD=2.42)\), \(t(190) = -1.206, p = 0.229\), compared to neuromuscular twitch monitoring practice. There was no significant difference in the scores for academic practice type \((M = 14.93, SD = 3.02)\) and non-academic practice type \((M = 15.11, SD = 2.93)\), \(t(190) = -0.409, p = 0.683\), compared to the use of subjective nerve monitoring. There was no significant difference in the scores for 0 – 10 years of CRNA experience \((M = 7.67, SD = 1.31)\) and 11-29 years of CRNA experience \((M = 7.76, SD = 1.54)\), \(t(190) = -0.474, p = 0.683\), compared to the use of subjective nerve monitoring. These results suggest that CRNA experience and type of practice are not influential factors in the practice of twitch interpretation or subjective neuromuscular monitoring practices.

**Test-retest Reliability**

A total of 44 CRNAs volunteered to complete a retest survey, however only 28 participants completed the retest, which contained identical survey questions to that of the original survey. Using the Pearson correlation coefficient test the results of the original survey were correlated with the results of the retest. A statistically significant correlation was revealed between the two surveys \((r = 0.84, p < 0.000)\), thereby providing adequate evidence of test-retest reliability.
Section V: Discussion

This study is the first investigation that assessed the various factors that CRNAs use in NMB reversal with neostigmine. Moreover, the differences in factors considered by CRNAs were also examined for statistically significant associations in terms of the years of CRNA experience, level of education in anesthesia, type of practice, and institutional setting. First, there were no statistically significant difference between years of CRNA experience and consideration of patient age when reversing neuromuscular blockade with neostigmine. Second, there was no statistically significant difference between years of CRNA experience, CRNA level of education, type or practice and type of institution when compared to the use of neuromuscular twitch monitoring, and use of subjective nerve monitoring. Overall, no statistically significant differences were found in the mean score of the factors considered for neostigmine use between CRNAs in terms of years of experience, types of practice, institutional settings, and levels of education. These findings reconfirm the discord present in the practice of NMB reversal, which was noted in previous studies (Naguib et al., 2010; Videira & Vieira, 2011).

This study also assessed the factors considered by CRNAs when dosing and administrating neostigmine, and monitoring of neuromuscular blockade status to assess readiness for reversal. Factors reportedly considered by CRNAs when administering neostigmine include: number and quality of muscle twitches present during train-of-four testing, twitches with fade, twitches without fade, and time elapsed since the last dose of NDMR. These factors include the eight most commonly used factors used for reversal of NDMR identified by Videira and Vieira (2011). One factor considered by CRNAs when dosing neostigmine is increasing the dose of neostigmine when the TOF demonstrate fade. According to Kopman and Eikermann (2009), management of a twitch count of four with fade requires an increased dose of neostigmine.
NEOSTIGMINE

(0.04mg/kg) compared to a twitch count of four without fade (0.02mg/kg). Nerve monitoring used by CRNAs when assessing patient readiness for reversal includes routine use of subjective nerve monitoring and routine use of train-of-four monitoring. Anesthesia providers in the US commonly use subjective nerve monitoring (includes train-of-four-monitoring) (Naguib et al., 2010). Factors not commonly used by CRNAs included age of the patient, patient body mass index, decreasing neostigmine dose when twitches have no fade, routine use of tetanus nerve monitoring, and routine use of objective neuromuscular monitoring.

This study defined factors used by CRNAs when deciding to reverse NMB as those having a percentile greater than 50%, however there was significant disagreement amongst CRNAs regarding these factors. The results of this study duplicate the studies by; Duvalestin, Cunin, Plaud, and Maison (2008), Gray & Wilson (1959), Naguib et al. (2010), and Videira and Vieira (2011) which identified a large variation in the practice of dosing and administering neostigmine amongst anesthesia providers. Evidenced by the overwhelming lack of statically significant data this study highlights the dissonance present amongst anesthesia providers in the dosing and administration practices of neostigmine. With residual NMB affecting upwards of 40% of post-operative patients who received intra-operative neuromuscular blocking agents, it is evident that the current practice of neostigmine use is inadequate (Murphy & Brull, 2010). A set of universally excepted evidence-practice guidelines for the reversal of NMB with neostigmine is necessary to aid anesthesia providers in safe and consistent NMB reversal practices.

Residual NMB occurs far too often in post-operative patients and results in an increased morbidity and mortality. As seen in the results of this study, the current practice of reversing muscle paralysis remains unstandardized resulting in a large variation in the practice of dosing and administering neostigmine, and NMB status when reversing with neostigmine. This
unstandardized approach promotes residual NMB and endangers patient safety and should be addressed immediately.

**Limitations**

Limitations of the study were identified. First, the survey tool did not include a gender differentiation question. Analyzing variances between genders is typically standard, albeit there is no difference in the clinical training or didactic course work between male and female nurse anesthetists, therefore it is unlikely gender has a role in dosing and administering neostigmine. Second, this survey had a small population and was restricted only to CRNA members of IANA; excluded were attending anesthesiologists, anesthesia residents, and SRNAs, thereby limiting generalizability of study findings to the overall anesthesia provider population. Future studies on this topic could include these anesthesia providers populations. Third, the study focused only on the most commonly used cholinesterase inhibitor, neostigmine; results must be interpreted with caution as there are other agents being used in the clinical setting.

**Recommendations**

Development of a universally accepted evidence-based practice protocol for the reversal of NMB using neostigmine is necessary to improve patient safety and reduce post-operative morbidity and mortally related to residual NMB. The evidence obtained from this study was be used to develop an evidence-based protocol for the safe reversal of NMB. A protocol incorporating key factors in the reversal of NMB identified in this study is outlined below. The investigators of this study plan to submit this protocol to the IANA and/or the AANA for white paper consideration.
## Evidence-based Guidelines - Neuromuscular Blockade Reversal With Neostigmine

<table>
<thead>
<tr>
<th>TOF Ratio</th>
<th>TOF</th>
<th>Neostigmine</th>
<th>Timing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOFR &lt; 0.4</td>
<td>0 – 1 Twitch</td>
<td>Wait on Reversal</td>
<td>15-30 min before extubation²</td>
<td>Monitoring is a standard of care¹</td>
</tr>
<tr>
<td>TOFR ≥ 0.4</td>
<td>2-3 Twitches</td>
<td>Administer 50 mcg/kg³</td>
<td>15-30 min before extubation²</td>
<td>Objective monitoring is preferred over subjective as it most reliably monitors status of NMB¹, ¹²</td>
</tr>
<tr>
<td></td>
<td>4 Twitches w/ Fade</td>
<td>Administer 40 mcg/kg³</td>
<td>15-30 min before extubation²</td>
<td>The preferred site for peripheral nerve stimulation is the adductor pollicis¹³ (ulnar nerve stimulation).</td>
</tr>
<tr>
<td></td>
<td>4 Twitches w/o Fade</td>
<td>Administer 20 mcg/kg³</td>
<td>15-30 min before extubation²</td>
<td>Do not rely on clinical signs/test (i.e. headlift, hand grasp, eye opening) as they do not accurately represent status of neuromuscular recovery⁴, ⁵, ⁶, ⁷</td>
</tr>
</tbody>
</table>

**Clinical Considerations:**

- **Neostigmine:**
  - Dose: 20-50 mcg/kg³
  - Administer concomitantly with anticholinergic (i.e Glycopyrrolate)¹¹
  - No reversal recommended for TOFR ≥ 0.9
  - Obesity⁹ and increased age¹⁰ lengthens reversal time to TOF ratio ≥ 0.9

- **Monitoring:**
  - Monitoring is a standard of care¹
  - Objective monitoring is preferred over subjective as it most reliably monitors status of NMB¹, ¹²
  - The preferred site for peripheral nerve stimulation is the adductor pollicis¹³ (ulnar nerve stimulation).
  - Do not rely on clinical signs/test (i.e. headlift, hand grasp, eye opening) as they do not accurately represent status of neuromuscular recovery⁴, ⁵, ⁶, ⁷

It is important to note that improvement of the practice of neuromuscular blockade reversal is not a substitute for interdisciplinary communication. In fact, effective communication is equally as important as following the evidence-based practice guidelines. There has to be an exchange of communication between the anesthesia provider and the surgeon to assess post-operative plans, estimated duration to the end of surgery, and whether maintenance of neuromuscular blockade is required throughout the case. Each of these discussion points has the potential to affect the neuromuscular blockade plan, and if proper communication does not take place there is an increased risk of harm to the patient.

**Implications for Future Research**

This study defers the evaluation process for future research. After initiation of the evidence-based guidelines for neuromuscular blockade reversal with neostigmine at the
institutional, state, or national level, evaluation of possible change in practice could take place. Resubmission of the survey tool (Appendix C) to the same population would allow for comparisons between neuromuscular block reversal practices pre-EBP protocol and post. In addition, surveillance of residual neuromuscular blockade incidence rates could assess the effects of practice change, although this issue is multifactorial and it may be difficult to determine the cause of any incidence rate changes. Additional follow-up studies could include additional anesthesia providers including attending anesthesiologists, anesthesia residents, and student nurse anesthetists. Furthermore, these follow up studies should compare the dosing and administration practices of neostigmine between attending anesthesiologists, anesthesia residents, student nurse anesthetists, and CRNAs.

Conclusion

This study described the various factors used by CRNAs when dosing and administering neostigmine. There are no significant associations in any of these factors with CRNAs' subgroupings according to their years of anesthesia experience, level of education in anesthesia, type of practice, and institutional setting. The overall factors used by CRNAs include the number and quality of muscle twitches present during train-of-four testing, twitches with and without fade, time elapsed since the last dose of NDMR, increased dosing of neostigmine when the twitches have fade, and routine use of subjective neuromuscular monitoring, including TOF.

Residual neuromuscular blockade occurs far too often in post-operative patients and results in an increased morbidity and mortality. The current practice of reversing muscle paralysis is not standardized, resulting in a large variation in the neostigimine dosing practice, and evaluation of NMB status when reversing with neostigmine. This nonstandardized approach promotes residual NMB and endangers patient safety. This study presented a set of evidence-
based guidelines with the goal of standardizing NMB reversal. The standardization of practices related NMB reversal will improve patient safety and reduce the incidence of residual neuromuscular blockade.
References


neuromuscular block in the elderly: Effects on airway protection. *Anesthesiology, 120*(2), 312-325.


<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Purpose</th>
<th>Design</th>
<th>Sample/Population</th>
<th>Statistical Analysis</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Debaene, Plaud, Dilly, &amp; Donati, 2003)</td>
<td>Evaluate incidence of residual paralysis (TOF Ratio &lt; 0.9) in the PACU after a single intubating dose of an intermediate-acting NDMR is administered at a dosage twice the ED$_{95}$.</td>
<td>-Non-randomized, observational study. -Anesthetic management was provider specific. -Groups: -Vecuronium -Rocuronium -Atracurium</td>
<td>526 patients</td>
<td>-Probability values were used to reject null hypotheses. -No other statistical calculations were reported.</td>
<td>-Patients with a TOF ratio &lt;0.7: 16% -Patients with a TOF ratio &lt; 0.9: 45% -10% of patients had a TOF ratio &lt;0.7 2 hours or more after administration of MR. -Traditional clinical tests (head lift, tongue depressor) and manual assessment of twitch fade demonstrated a poor sensitivity to detect residual block (11-14%).</td>
</tr>
<tr>
<td>(Cedborg et al., 2014)</td>
<td>Evaluate the effects of partial NMB on pharyngeal function, coordination of breathing and swallowing, and airway protection in the elderly.</td>
<td>-Non-randomized, controlled Study. -Study intervals: TOF 0.7, 0.8, and &gt;0.9</td>
<td>Study Group: 17 volunteers over 65 years old Control Group: 6 volunteers over 65 years old -Local Ethics Board Approved.</td>
<td>-ANOVA -Generalized linear model -Wilcoxon test -Mann-Whitney U test</td>
<td>-Positive correlation between partial NMB and increased pharyngeal dysfunction. -No correlation between partial NMB and coordination of breathing and swallowing.</td>
</tr>
<tr>
<td>(Hayes, Mirakhur, Breslin, Reid, &amp; McCourt, 2001)</td>
<td>Compare incidence of postoperative residual NMB in patients entering the PACU after use of intermediate-acting NMBDs.</td>
<td>-Randomized, controlled study -Provider unaware that patient is in study. -Four Groups: -Control -Vecuronium -Atracurium -Rocuronium -Data collected on randomized days.</td>
<td>160 patients -LRB Approved -Written and informed consent obtained</td>
<td>-One-way ANOVA -Kruskal-Wallis test -Chi-squared Test</td>
<td>-A large proportion of patients entering the PACU, whom have received intermediate-acting NMBDs, have a TOF ratio &lt; 0.8.</td>
</tr>
<tr>
<td>(Murphy et al., 2008)</td>
<td>1) Compare effectiveness of objective</td>
<td>-Randomized, controlled, single blind Study</td>
<td>185 patients undergoing elective surgery requiring intraop NMB.</td>
<td>-One-sided Chi squared test</td>
<td>-Intraoperative management of NMB did not differ significantly. -No statistical significance of the time from...</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Methodology</td>
<td>Sample Details</td>
<td>Statistical Methods</td>
<td>Key Findings</td>
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<tr>
<td>Sundman et al., 2000</td>
<td>1) Evaluate swallowing using fluoroscopy to record and understand the mechanism behind pharyngeal dysfunction during partial NMB. 2) Evaluate the effects of Atracurium on pharyngeal function.</td>
<td>-Non-randomized, controlled Study. -A total of 444 swallows analyzed. -Counted each swallow as 1 data point &amp; Compared TOF ratio (0.6, 0.7, 0.8, &gt; 0.9) to area of penetration (pharynx, larynx, or bolus remained in mouth)</td>
<td>Sample Size: 20 healthy volunteers (12 men, 8 women) -LRB approved</td>
<td>-Regression -T-test -Wilcoxon signed rank test</td>
<td>-Partial NMB by Atracurium is associated with an increased incidence of misdirected swallowing. -The MOA of pharyngeal dysfunction was identified as a delayed initiation of the swallowing reflex, impaired function of pharyngeal muscles, and impairment of coordination. -The majority of misdirected boluses penetrated the laryngeal inlet.</td>
</tr>
<tr>
<td>Suzuki, Masaki, &amp; Ogawa, 2006</td>
<td>Compare reversal of vecuronium by neostigmine in normal weight, overweight, and obese female patients.</td>
<td>Non-randomized, controlled study. -Three Groups: -Normal Weight -Overweight -Obese -Normal weight group is control.</td>
<td>-45 female patients. -ASA physical status I or II -Age 27-57 years old -Elective gynecologic surgery. -Approval by Hospital Ethics Committee on Human Rights in Research.</td>
<td>-ANOVA -Bonferroni post hoc test</td>
<td>-When using RBW to dose vecuronium, recovery to a TOF ratio of 0.9 is slow in overweight and obese (female) patient population. -Time to TOF ratio of 0.9: -Obese: 25.9 minutes -Overweight: 14.6 minutes -Normal Weight: 6.9 minutes</td>
</tr>
<tr>
<td></td>
<td>Vecuronium dosing using real body weight (RBW).</td>
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</tbody>
</table>
Appendix A. Letter to IANA Administrator

Dear IANA Administrator,

My name is Kyle Mayer and I am a Nurse Anesthesia Trainee from DePaul University and NorthShore University School of Nurse Anesthesia. I am conducting a research study on the current practice of dosing and administration of the neuromuscular blockade reversal agent, neostigmine. I am writing to request an email containing a web link to the survey be emailed to all CRNA members of the IANA.

Participation in the study is voluntary. All responses are anonymous and IP addresses will not be tracked.

I have attached the email message with the link to the survey. The survey is now available and the survey invitation email can be distributed at your soonest convenience. Please contact me with any questions or concerns.

Thank you very much.

Sincerely,

Kyle Mayer, BSN, RN, NAT
DePaul University
NorthShore University – School of Nurse Anesthesia
mayerkyle427@hotmail.com

Attachment: (See Appendix B)
Appendix B. Email Template for Survey Dissemination

Dear Illinois CRNA,

My name is Kyle Mayer and I am a Nurse Anesthesia Trainee from DePaul University. I am writing to invite you to participate in my research study regarding the current practice of neuromuscular blockade reversal dosing and administration. This study is only available to members of the Illinois Association of Nurse Anesthetists.

All responses are anonymous and IP addresses will not be tracked. Study participation is completely voluntary, and it will take about 5 minutes of your time to complete the survey. If you would like further details regarding this study, I have attached a study information sheet.

If you'd like to participate in this study please click the following link – http://depaul.qualtrics.com/SE/?SID=SVcPatJOquqeRYRtr

Thank you very much.

Sincerely,

Kyle Mayer, BSN, RN, NAT
DePaul University
mayerkyle427@hotmail.com

Attachment: Study Information Sheet
Appendix C. Survey of the Current Practice of Muscle Paralysis Management and Reversal

1. You are invited to participate in a web-based online survey on the development of practice guidelines for the reversal of neuromuscular blockade using neostigmine. Your participation in this survey is voluntary. You may refuse to take part in the research or exit the survey at any time without penalty. You are free to decline to answer any particular question you do not wish to answer for any reason.

This online survey will not collect identifying information such as your name, email address, or IP address; therefore, your responses will remain anonymous. If you agree to participate in the second follow-up survey, we will ask for your email address in order to send you another survey. In this case your responses will not be anonymous, but we will keep them confidential.

Consent: If you would like to take part in this brief survey click “Accept.” If you choose to not participate in this survey click “Decline,” and close your browser window.

☐ Accept  ☐ Decline

2. How many years have you been a Certified Registered Nurse Anesthetist?

0-4  5-10  11-15  16-20  >20

3. What is the highest degree you hold related to anesthesia?

Bachelors  Masters  Doctorate

4. What type of institution do you primarily administer anesthesia?

Outpatient Surgical Center  Public (County) Hospital  Private Hospital  VA Hospital

5. How would you describe your anesthesia practice?

Academic  Non-academic

6. I routinely reverse muscle paralysis.

Disagree  Neutral  Agree

7. I consider the age of the patient as an important factor in the administration of neostigmine.

Disagree  Neutral  Agree

8. Overall, I consider the number of muscle twitches present during train-of-four testing as an important factor in the administration of neostigmine.
9. Overall, I consider the **quality** of the muscle twitches during train-of-four testing as an important factor in the administration of neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

10. I consider twitches **with** fade during train-of-four testing as an important factor in the administration of neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

11. I consider twitches **without** fade during train-of-four testing as an important factor in the administration of neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

12. I consider the **time elapsed since the last dose** of neuromuscular blocking agent when administering neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

13. I consider increasing the dose of neostigmine when the twitches have fade in train-of-four testing.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

14. I consider decreasing the dose of neostigmine when the twitches have no fade in train-of-four testing.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

15. Overall, I consider the patient **body mass index** as an important factor for dosing of neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

16. I routinely use subjective neuromuscular monitoring (i.e. Train-of-four, Tetanus) to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>

17. I routinely use train-of-four nerve monitoring to assess patient readiness for reversal with neostigmine.

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
</table>
18. I routinely use tetanus nerve monitoring to assess patient readiness for reversal with neostigmine.
   
   Disagree    Neutral    Agree

19. I routinely use objective neuromuscular monitoring (i.e. TOF Watch) to assess patient readiness for reversal with neostigmine.

   Disagree    Neutral    Agree

20. Implementation of a best practice protocol for the reversal of neuromuscular blockade using neostigmine would be beneficial to my practice.

   Disagree    Neutral    Agree

Would you be willing to take the same survey again in 1 week to assess consistency of survey responses?

   YES (Repeat survey link will be sent in 1 week)
   If YES, please type your email address:________________________

   NO (no repeat survey link will be sent)
Appendix D. Email Template for Test/Re-test Survey Validity

Dear Illinois CRNA,

My name is Kyle Mayer and I am a Nurse Anesthesia Trainee from DePaul University. I am writing you because you recently participated in a research and volunteered to retake a portion of the survey. As a reminder, the research study is regarding the current practice of neuromuscular blockade reversal dosing and administration.

Again, all responses are anonymous and IP addresses will not be tracked. Study participation is completely voluntary; you have the choice to participate in this study or not. If you'd like to participate in this follow up survey please click the following link – [weblink to survey].

Thank you very much.

Sincerely,

Kyle Mayer, BSN, RN, NAT
DePaul University
mayerkyle427@hotmail.com
Appendix E. SLP Committee Members

De Paul University
College of Science and Health/School of Nursing
Doctor of Nursing Practice Program

This is to certify that I have agreed to serve as a chair/member of the DNP Evidence-based Scholarly Leadership Project by

Kyle Mayer

and I have discussed all aspects of the project proposal.

Chair of the DNP Scholarly Project Committee:

(Name of faculty member) (Date)

DNP Scholarly Project Committee Members:

(Name of faculty member) (Date)
Appendix F. IRB Approval Letter

DePaul University

Research Involving Human Subjects
NOTICE OF INSTITUTIONAL REVIEW BOARD ACTION

To: Kyle Mayer, BSN, Graduate Student, School of Nursing

Date: November 23, 2015

Re: Research Protocol # KM100115NUR
“Reversal of Neuromuscular Blockade Using Neostigmine: Development of Evidence-based Practice Protocol – A Scholarly Leadership Project”

Please review the following important information about the review of your proposed research activity.

Review Details
This submission is an initial submission.

Your research project meets the criteria for Exempt review under 45 CFR 46.101 under the following category:

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.

Approval Details
Your research was originally reviewed on October 27, 2015 and revisions were requested. The revisions you submitted on November 17, 2015 were reviewed and approved on November 23, 2015.

Number of approved participants: 420 Total
You should not exceed this total number of subjects without prospectively submitting an amendment to the IRB requesting an increase in subject number.

Funding Source: 1) None.

Approved Performance sites: 1) DePaul University.

Reminders
- Under DePaul’s current institutional policy governing human research, research projects that meet the criteria for an exemption determination may receive administrative review by the Office of Research
Services Research Protections staff. Once projects are determined to be exempt, the researcher is free to begin the work and is not required to submit an annual update (continuing review). As your project has been determined to be exempt, your primary obligation moving forward is to resubmit your research materials for review and classification/approval when making changes to the research, but before the changes are implemented in the research. All changes to the research must be reviewed and approved by the IRB or Office of Research Services staff. Changes requiring approval include, but are not limited to, changes in the design or focus of the research project, revisions to the information sheet for participants, addition of new measures or instruments, increasing the subject number, and any change to the research that might alter the exemption status (either add additional exemption categories or make the research no longer eligible for an exemption determination).

- Once the project is complete, you should submit a final closure report to the IRB.

The Office of Research Services would like to thank you for your efforts and cooperation and wishes you the best of luck on your research. If you have any questions, please contact me by telephone at (312) 362-6168 or via email at jblooom8@depaul.edu.

For the Board,

Jessica Bloom, MPH
Research Protections Coordinator
Office of Research Services

Cc: Bernadette Roche, Ed.D., Faculty, School of Nursing
Appendix G. SLP Final Approval Form

DePaul University
School of Nursing
Doctor of Nursing Practice Program
DNP Evidence-Based Scholarly Leadership Project
Final approval Form

DNP student Name: Kyle Mayer

DNP Scholarly Leadership Project Title: Reversal of Neuromuscular Blockade with Neostigmine: Development of an Evidence-Based Practice Protocol.

The Evidence-based Scholarly Leadership Project is designed as a clinical scholarship project allowing students to demonstrate synthesis and mastery of an advanced specialty within nursing practice. The project integrates the various role of the DNP in a comprehensive health care environment that includes utilization of leadership, consultation, advocacy, and collaboration and in depth work with experts from nursing and other disciplines.

By the completion of the DNP program, the student must complete the project, culminating in a presentation of the project. Following the final presentation, this form must be signed to verify successful completion of the project. The DNP project committee chair will forward the signed form to the School of Nursing program Director.

DNP Scholarly Leadership Project Final Approval

Date

Date

Date