7-12-2018

Anesthetic Considerations for the Parturient with Idiopathic Intracranial Hypertension

Levi G. La Porte

The Safety and Efficacy in Reversal of Neuromuscular Blockades with Sugammadex versus Neostigmine

by

Nicole L. Landen

Bachelor of Science in Nursing, University of Minnesota, 2014

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December 2019

PERMISSION

Title	The Safety and Efficacy in Reversal of Neuromuscular Blockades with Sugammadex versus Neostigmine
Department	Nursing
Degree	Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing and Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in her absence, by the chairperson of the department or the dean of the School of Graduate Studies. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Signature_____

Date_____

Abstract

Title: The Safety and Efficacy in Reversal of Neuromuscular Blockades with Sugammadex versus Neostigmine

Background: Neuromuscular blockade (NMB) is utilized for skeletal muscle paralysis during surgery to facilitate mechanical ventilation and prevent undesired patient movement intraoperatively. The depth of the NMB must be monitored to ensure optimal surgical conditions, as well as to determine when it is safe to extubate without placing the patient at risk for residual neuromuscular blockade. A recent survey from the 2017 Anesthesia Patient Safety Foundation (APSF) has shown that 64-72% of the respondents perceived the incidence of residual NMB to be only 1-10% (Murphy, 2018). However, Brull and Kopman (2017), determined the incidence of residual NMB to be 30-50% in the patients admitted to the Post Anesthesia Recovery Unit (PACU) following surgery. The use of reversal agents can help reduce the incidence of residual NMB; however, some agents are not effective at all depths of paralysis. Traditionally, neostigmine has been utilized to antagonize the effects of a neuromuscular blockade elicited by non-depolarizing agents. In December 2015, the Federal Drug Administration (FDA) approved sugammadex as a new medication that does not interfere with the acetylcholinesterase receptor system and ultimately avoids the undesirable side effects commonly seen with traditional reversal agents.

Purpose: To determine the safety and efficacy of sugammadex and neostigmine on NMB reversal, a literature review was conducted to provide current, supporting evidence comparing their use in NMB reversal.

Process: A literature review was conducted utilizing the CINAHL and PubMed databases, all of which were accessed from the University of North Dakota's Health Sciences Library. All

literature was evaluated extensively and applied to this paper or rejected due to substandard information.

Results: The evidence-based literature verified that sugammadex reverses any level of neuromuscular blockade within 5 to 10 minutes. The research also supports that sugammadex is associated with less adverse effects compared to neostigmine.

Implications: Sugammadex can safely be administered to adults with any level of neuromuscular blockade and efficiently reverses paralysis. Whereas, neostigmine can only reverse a neuromuscular block that has shown to have some spontaneous recovery before its administration. Additionally, the literature supports less side-effects with the use of sugammadex compared to neostigmine.

Keywords: Sugammadex, Neostigmine, Neuromuscular Blockade (NMB), Rocuronium, Train of Four (TOF), Post-tectonic count (PTC)

The Safety and Efficacy in Reversal of Neuromuscular Blockades with Sugammadex versus Neostigmine

Neuromuscular blockade (NMB) is utilized for the purpose of skeletal muscle paralysis during surgery to facilitate mechanical ventilation and prevent undesired movement by the patient intraoperatively. Paralysis is achieved by using depolarizing (i.e., succinylcholine) or nondepolarizing neuromuscular blocking agents. The nondepolarizing agents can be divided into two categories, the benzylisoquinolones, and the aminosteroidal agents. The benzylisoquinolones include atracurium and cis-atracurium. Whereas, the steroidal agents include vecuronium and rocuronium (Nagelhout & Elisha, 2018). The depth of the NMB must be monitored to ensure optimal surgical conditions, as well as help determine when it is safe to extubate without placing the patient at risk for residual neuromuscular blockade.

A recent survey from the 2017 Anesthesia Patient Safety Foundation (APSF) has shown that 64-72% of the respondents perceived the incidence of residual NMB to be only 1-10% (Murphy, 2018). However, Brull and Kopman (2017), determined the incidence of residual NMB to be 30-50% in the patients admitted to the PACU following surgery. These patients experience residual NMB that can lead to various complications, not limited to: "upper airway obstruction from pharyngeal muscle weakness, hypoxemia, increased risk of aspiration, decreased ventilatory response to hypoxia, unpleasant muscle weakness, and delay in tracheal extubation" (Nagelhout & Elisha, 2018, p. 436). All of which, can ultimately lead to an increase in perioperative morbidity and longer hospital stays (Batistaki et al., 2016).

The use of reversal agents can help reduce the incidence of residual NMB. However, some agents are not effective at all depths of paralysis. Traditionally, neostigmine has been utilized to antagonize the effects of neuromuscular blockades elicited by nondepolarizing agents.

However, it must be used in combination with a muscarinic antagonist, such as glycopyrrolate, to compensate for the cholinergic side-effects associated with cholinesterase inhibitor administration. Recently, sugammadex has been approved by the FDA as a new medication that does not interfere with the acetylcholinesterase receptor system. Thus it avoids the undesirable muscarinic side effects associated with cholinesterase inhibitors. To determine the safety and efficacy of sugammadex and neostigmine on NMB reversal, a literature review was conducted to provide current, supporting evidence comparing their use in reversal of NMBs.

Purpose

The purpose of this independent project is to present a successful case report of an adult patient undergoing general anesthesia who was safely administered a dose of sugammadex intraoperatively and monitored for effects postoperatively. Additionally, this independent project will provide anesthetic providers with evidence-based research regarding the safety and use of sugammadex compared to neostigmine in reversal of various depths of NMBs.

Case Report

A 157 centimeters, 98.5 kilogram (kg), 73-year-old female presented for a ventral hernia repair for recurrent ventral hernias. Past medical history included: hypertension (HTN), chronic kidney disease-stage 3, gastroesophageal reflux disease (GERD), cerebral vascular accident due to emboli of cerebral artery, former smoker (quit in 1997), osteoarthritis, diverticulosis, iron deficiency anemia, obesity (BMI 39), sacroiliac (SI) joint pain, dyslipidemia, adjustment disorder, and neuropathic pain. Past surgical history included gastric bypass, lumbar fusion, and ventral hernia repairs with no noted complications to anesthesia. She had no known allergies. Current medications included: ferrous sulfate (325mg), carbamazepine (100mg), omeprazole (40mg), amlodipine (5mg), metoprolol (50mg), pravastatin (40mg), and aspirin (81mg). As

needed medications included: acetaminophen, melatonin, and calcium carbonate. She had been NPO for eight hours. Pre-operative labs included: Hemoglobin 11.1g/dL, Hematocrit 24.8 %, Platelet count 289 x 10^3/μL, blood glucose 119mg/dL, BUN 47mg/dL, Creatinine 1.17mg/dL, Sodium 135mEq/L, Potassium 3.8mEq/L, and Chloride 98mEq/L. Using the American Society of Anesthesiologists (ASA) system, the patient was classified as an ASA level three.

Airway assessment included Mallampati class I, full neck range-of-motion, and adequate thyromental distance. Preoperative vitals included: blood pressure 100/64 mmHg, heart rate 78 beats per minute, respirations 16 breaths per minute, oxygen saturations of 97% on room air, and temperature 36.4 degrees Celsius. Auscultation of her heart and lungs revealed clear, bilateral breaths sounds and regular heart rate and rhythm.

The patient was transported to the operating room (OR) via OR cart. An 18-guage, peripheral intravenous (IV) line was inserted in the pre-operative care unit, and a lactated ringer (LR) solution was infusing. A pulse oximetry monitor was applied, and 2-milligrams (mg) of midazolam IV was administered for anxiolysis and amnesia. Additional standard monitors were applied to the patient, including five-lead electrocardiogram (EKG), non-invasive blood pressure cuff, and Bispectral Index (BIS) monitor. The patient was pre-oxygenated with 10-liter (L) of 100% oxygen via face mask with spontaneous ventilation for approximately three minutes. Induction was initiated with 100-micrograms (mcg) fentanyl IV, 40mg lidocaine IV, 5mg priming dose of rocuronium IV, and a dexmedetomidine infusion bolus of 0.25mg/kg IV. Propofol 200mg IV was administered, and cessation of spontaneous respirations was noted along with loss of eyelash reflex. Tape was carefully placed over the patient's eyelids to prevent corneal abrasions, and manual mask ventilation commenced. Forty milligrams of rocuronium IV was administered for paralysis. Manual mask ventilation was provided for an additional one-

minute before a Miller 2 laryngoscope was inserted into the patient's oropharynx, and vocal cord visualization was confirmed. A size 7.0 endotracheal tube (ETT) was passed through the vocal cords successfully and the ETT cuff was inflated to minimal occlusive pressure. Endotracheal placement was confirmed via condensation noted in the ETT with manual breaths, positive end-tidal-carbon-dioxide ($ETCO_2$) measurements, and bilateral breath sounds with equal chest rise. The ETT was then securely taped in place. Supportive ventilation was administered via Drager ventilator on pressure control ventilation (PCV) mode to ensure adequate tidal volumes, oxygenation, and $ETCO_2$. The inhalational agent, Desflurane, was started and fresh gas flows were decreased in increments to provide a 0.8 to 1.0 Minimum Alveolar Concentration (MAC) at one liter of combined oxygen and air flows. The patient was in the supine position for induction with her arms at her side. Following induction her arms were padded and abducted less than 90-degrees. All other pressure points, lines and tubes were adequately padded for the procedure. A nasopharyngeal temperature probe was placed in the right nare for continuous temperature monitoring throughout the surgery. Additional prophylactic medications for nausea and vomiting, ondansetron 4 mg IV and dexamethasone 4 mg IV, were administered. Two-grams of cefazolin IV and 5,000-units of heparin IV were also given before the patient was prepped and draped for surgery. A dexmedetomidine infusion was initated, after the bolus administration, at 0.5 mcg/kg/min IV. Fifty-milligrams of Ketamine IV and 50 mcg of Fentanyl IV were given prior to incision. Throughout the four hour case, an additional 200 mcg of fentanyl IV, 1 mg hydromorphone IV, 3,000 milliliters (mL) of LR solution IV, and 500 mL of 5% albumin IV were administered. Neuromuscular blockade was monitored via Train of Four (TOF) monitor on the orbicularis oculi muscle. Paralysis was maintained with 10 mg boluses of rocuronium IV throughout the case to maintain a TOF ratio 2/4.

At the end of the procedure a final TOF provided 4/4 twitches after a total of 130 mg rocuronium IV was administered. Based on the amount of neuromuscular blocking agent administered, it was decided for the patient's safety to utilize sugammadex 4 mg/kg IV (400 mg) for adequate neuromuscular reversal. An oral airway was placed, Desflurane was discontinued , and high-flow 100% oxygen was administered via pressure control ventilation. Shortly after the sugammadex administration, spontaneous respirations were noted and the patient was withdrawn from mechanical ventilation to allow spontaneous breathing. The patient exhibited positive clinical indicators for extubation (i.e. followed commands, 5-second head lift, adequate tidal volumes, and purposeful movements). The oropharynx was suctioned and the patient was extubated to spontaneous mask ventilations and finally to 3L oxygen via nasal cannula. Adequate air exchange was noted without complication and oxygen saturation (SpO_2) was maintained greater than 94%. The patient was then transferred to the PACU without any complication. The patient woke up comfortably and denied any pain. Her PACU stay was uneventful, and no additional opioid or antiemetic medication were required in the PACU. The patient remained hemodynamically stable throughout her recovery and was successfully transferred to the inpatient unit for an overnight stay.

Literature Search

To conduct a precise literature search a PICO question was formulated to accurately identify relevant literature in various search engines. The PICO process is a technique used to frame and answer health-care related questions to provide evidence-based practice recommendations and interventions. The PICO acronym stands for Population, Intervention, Comparison, and Outcome. The following PICO question was formulated: In adult surgical patients receiving neuromuscular blocking agents, is sugammadex compared to traditional

acetylcholinesterase inhibitors, such as neostigmine, more effective in reversing neuromuscular blockades?

The CINAHL database was searched in order to determine whether sugammadex was superior to traditionally used acetylcholinesterase inhibitors (i.e. neostigmine) in reversing neuromuscular blockades. The first focused keywords searched were "Neostigmine AND Sugammadex" which resulted in 104 articles. Then "Safety" was added to the "Neostigmine AND Sugammadex" search, resulting in 18 articles. Furthermore, the search was limited to, English articles within the last 10 years (2008-2018), resulting in 16 articles. From the 16 results, articles were selected based on topic relevancy as well as limited to adult patient studies, which resulted in 10 studies chosen for initial review.

An additional search of "Neostigmine AND Sugammadex" with "efficacy" produced 19 articles. The search was limited to, English articles within the last 10 years (2008-2018), resulting in 18 articles. From the 18 articles, multiple studies were duplicates identified with the initial search and only three additional studies were added for initial review.

Furthermore, the PubMed database was also utilized for the literature search. Using the advanced search setting the keywords, 'Neostigmine AND Sugammadex,' were searched and resulted in 203 articles. Refining the search by limiting the data to the last five years, English language, and human subjects, 65 articles were generated. Some articles were duplicates, identified in the initial CINAHL database search, which were removed from the article selection and inclusion. Of the 65 PubMed articles an additional 10 articles were selected for initial review.

Overall, 23 articles were reviewed, however 9 articles were of relevance and selected for inclusion in the research of the efficacy of sugammadex compared to neostigmine on the reversal

of neuromuscular blockades. A total of five systematic review/metanalyses and four randomized control trials were identified and used for the evaluation of sugammadex and neostigmine effects on neuromuscular blockades.

Terminology

Neuromuscular Transmission

Neuromuscular transmission occurs between motor neurons and muscle cells at the neuromuscular junction (Butterworth, Mackey, & Wasnick, 2013). A nerve action potential travels along the nerve and releases Acetylcholine (ACh) into the synaptic cleft (Butterworth et al., 2013). ACh then travels toward and binds to the nicotinic receptor sites on the muscle membrane, resulting in depolarization and muscle contraction (Butterworth et al., 2013). Normal neuromuscular transmission ultimately, depends on ACh binding to nicotinic cholinergic receptors on motor-end plates of skeletal muscles (Butterworth et al., 2013).

Neuromuscular Blocking Agents

Skeletal muscle relaxation can be produced by multiple influences, one being neuromuscular blocking agents (muscle relaxants) (Butterworth et al., 2013). There are two categories of muscle relaxants, depolarizing and nondepolarizing agents (Butterworth et al., 2013). The single depolarizing agent, succinylcholine, mimics ACh and binds to the receptor eliciting a continuous depolarization resulting in sustained paralysis for a short duration of time (Butterworth et al., 2013). Nondepolarizing muscle relaxants act by competing with ACh for the nicotinic binding sites on skeletal muscles. By competitive inhibition, nondepolarizing agents occupy the receptor inhibiting depolarization from occurring via ACh, thereby blocking neuromuscular transmission resulting is muscle paralysis (Butterworth et al., 2013).

Cholinesterase Inhibitors - Reversal Agent

Reversal of a nondepolarizing neuromuscular blockades can depend on spontaneous reversal (i.e. gradual diffusion, redistribution, metabolism, and excretion of the drug) or pharmacological reversal (by direct administration of specific reversal agents) (Butterworth et al., 2013). Traditionally, NMBs have been reversed indirectly via cholinesterase inhibitors (also known as acetylcholinesterase inhibitors) (Butterworth et al., 2013). Cholinesterase inhibitors have the ability to increase the amount of ACh available to compete against the nondepolarizing agent, ultimately reestablishing normal neuromuscular transmission (Butterworth et al., 2013). Cholinesterase inhibitors, such as neostigmine, inactivates acetylcholinesterase, thus preventing the breakdown of acetylcholine into acetate and choline (Butterworth et al., 2013). By binding to the enzyme, it allows an increase in the concentration of ACh at the junctional cleft (Butterworth et al., 2013). This rise in ACh, increases the likelihood that ACh will reoccupy the receptor site that was once occupied by the neuromuscular blocking agent, allowing restoration of normal neuromuscular function (Butterworth et al., 2013). Neostigmine also allows the ACh within the cleft to have a longer lifespan because it is not broken down by the enzyme as it normally would (Butterworth et al., 2013). Ultimately, this allows for more antagonistic dissociation time and reactivation of the nicotinic receptor site via ACh (Nagelhout & Elisha, 2018). However, in excessive doses, acetylcholinesterase inhibitors have the ability to potentiate a nondepolarizing neuromuscular blockade due to the excess ACh available (Butterworth et al., 2013). Furthermore, ACh can affect more than the nicotinic receptors of skeletal muscles. The excess ACh can bind to other muscarinic receptors, which are associated with the parasympathomimetic side effects commonly seen following the administration of neostigmine (Butterworth et al., 2013). These unwanted side-effects are usually minimized by prior or co-administration of an

anticholinergic medication, such as atropine or glycopyrrolate (Butterworth et al., 2013). These anticholinergic medications help prevent the muscarinic side-effects associated the with cholinesterase inhibitor administration. Normal reversal doses of neostigmine range from 0.03-0.07 mg/kg IV with an onset of 5-15 minutes and duration of action lasting 45-90 minutes (Nagelhout & Elisha, 2018).

Reversal Agent- Sugammadex

Until recently, neuromuscular blocking agents, such as rocuronium, vecuronium, and pancuronium, were commonly pharmacologically reversed via neostigmine (Butterworth et al., 2013). However, a novel reversal agent, sugammadex, has become available on the United States pharmaceutical market to selectively reverse rocuronium-induced neuromuscular blockades, and less selectively the other steroidal neuromuscular blocking agents (Butterworth et al., 2013). Sugammadex is the first "selective relaxant binding agent" (Nagelhout & Elisha, 2018, p. 163). It is a modified gamma-cyclodextrin molecule that encapsulates and forms a tight water-soluble complex in a 1:1 ratio with steroidal neuromuscular blocking agents, including rocuronium, vecuronium, and pancuronium (Nagelhout & Elisha, 2018). Once the encapsulation occurs there is no dissociation and the sugammadex-relaxant complex is excreted in the urine (Nagelhout & Elisha, 2018). This type of reversal mechanism is independent of the neuromuscular blockade depth (Nagelhout & Elisha, 2018). Thus, a shallow or deep block can be reversed with appropriate doses (Nagelhout & Elisha, 2018). In contrast to neostigmine, where no amount of the medication can immediately reverse a block that is so intense there is no response to tetanic peripheral nerve stimulation (Nagelhout & Elisha, 2018). Sugammadex is most effective against rocuronium, followed by vecuronium and pancuronium, however it is not effective against the benzylisoquinolones like neostigmine is (Nagelhout & Elisha, 2018). Dosing of sugammadex

includes 2 mg/kg IV for moderate neuromuscular block (T2 on TOF), 4 mg/kg IV for a deep block (1-2 PTC), and 16 mg/kg IV for immediate reversal of an induction dose of rocuronium (Herring et al., 2017; Merck Connect, 2018).

Neuromuscular Function Monitoring

Monitoring of neuromuscular blockade is a standard of care (Standard V) during any anesthetic in which muscles relaxant are administered (AANA, 2013). However, it has been noted that clinicians in the United States are not using any type of monitor to assess level of paralysis (Nagelhout & Elisha, 2018).

There are several methods available for monitoring the intensity of a neuromuscular block, but the most commonly used is the visual and tactile responses noted via evoked electrical stimuli (Nagelhout & Elisha, 2018). Contraction of the adductor muscle of the thumb via stimulation of the ulnar nerve is the preferred site to determine the level of neuromuscular blockade (Nagelhout & Elisha, 2018). However, when access to the arm is unavailable, additional monitoring sites include nerves of the feet and face (Nagelhout & Elisha, 2018). Paralysis occurs in the following order: the eye muscles, the extremities and trunk of the body (neck then chest), the abdominal muscles and lastly, the diaphragm (Nagelhout & Elisha, 2018). Conversely, during recovery it returns in the opposite manner with the eyes being last to fully recover (Nagelhout & Elisha, 2018). Using the orbicularis oculi muscle may be applicable to monitor for onset of paralysis because blood and drug distribution to the face muscles mirrors the distribution to airway (larynx and diaphragm), indicating adequate paralysis for intubation (Nagelhout & Elisha, 2018). However, for recovery Nagelhout and Elisha (2018) support the hand to be the best place to measure recovery from NMB, since the hand is more sensitive to

relaxants than the diaphragm. Thus, if there is recovery in the hand, the upper airway muscles should be recovered as well (Nagelhout & Elisha, 2018).

Train-of-Four (TOF). Muscle stimulation via Train-of-Four (TOF), Tetany, and Post-Tetanic Count (PTC) are common methods of measurements of NMB (Nagelhout & Elisha, 2018). The "TOF delivers four separate stimuli every 0.5 seconds at a frequency of 2 Hertz (Hz) for two seconds" (Nagelhout & Elisha, 2018, p. 142). When comparing the four stimulated responses they are classified as twitch, T1 up to T4 (Nagelhout & Elisha, 2018). Upon onset of NMB with a nondepolarizing relaxant there is a progressive reduction of the twitch responses and strength of the twitch (Nagelhout & Elisha, 2018). This decrease in strength is known as fade. Fade is referred to the "inability to sustain a response to repetitive nerve stimulation" (Nagelhout & Elisha, 2018, p. 142). A TOF-ratio compares twitch 4 to twitch 1 and can aid in approximating the degree of paralysis (Nagelhout & Elisha, 2018). According to Nagelhout and Elisha, (2018), when the fourth twitch disappears it indicates 75-80% of receptors are blocked (TOF ratio 3/4). A progressive disappearance of the third twitch correlates with 80-85% block and when the second twitch is lost (T4, T3, and T2 are absence) reflects 90-95% of NMB is present (Nagelhout & Elisha, 2018). When there are no twitches visualized or palpated, it indicates a 100% NMB has been achieved (Nagelhout & Elisha, 2018). Ideally, sufficient paralysis of 85-95%, is adequate for any procedure (Nagelhout & Elisha, 2018). This correlates with one to two twitches present during the TOF stimulus (Nagelhout & Elisha, 2018).

Post-Tetanic Count (PTC). The PTC measurement has not been used commonly, however it is becoming a more utilized test when clinicians have no response to a TOF stimulus (Nagelhout & Elisha, 2018). The PTC is assessed following a 50-Hz tetanic stimulation for five seconds followed by a series of single 1 Hz stimulations (Nagelhout & Elisha, 2018). The

response to the single twitches, correlates with the approximate depth of block and can be indicative of how long it may take for spontaneous reversal to occur (Nagelhout & Elisha, 2018). The physiology behind this test is as follows: the single 50Hz tetanus mobilizes excess ACh and after a three-second pause it is common to see a series of twitches because the extra ACh can transiently reverse the muscle relaxant (Nagelhout & Elisha, 2018). The more twitches following tetany correlates with a less intense block (Nagelhout & Elisha, 2018).

Review of the Literature

For neostigmine to be appropriate for administration, adequate spontaneous recovery must be established (Butterworth et al., 2013). Some evidence of spontaneous recovery, such as a single twitch of the TOF (T1) should be present before reversal is attempted with anticholinesterase medication (Butterworth et al., 2013). However, this rule does not apply to sugammadex. The following research will present the evidence on the safety and efficacy of reversing neuromuscular blockades with neostigmine and sugammadex.

Moderate Block Reversal

The evaluation of a moderate block is indicated by visual or palpable T1 and T2 twitches with fade by the TOF stimulator (Carron, Zarantonello, Tellaroli, & Ori, 2016; Herring et al., 2017; Hristovska, Duch, Allingstrup, & Afshari, 2017; Kaufhold et al., 2016). The primary findings from the many studies conducted, indicate sugammadex to be faster than neostigmine in reversing rocuronium-induced NMB (Carron et al., 2016; Herring et al., 2017; Hristovska et al., 2017; Kaufhold et al., 2016). Hristovska et al., (2017) meta-analysis found sugammadex to be 10.22 minutes, or 6.6 times, faster than neostigmine to produce a TOF ratio of 0.9 or greater following a moderate rocuronium-neuromuscular blockade. Sugammadex was also seen to produce faster recovery to baseline neuromuscular function (Carron et al., 2017; Herring et al.,

2017). Herring et al. (2017) analysis, resulted in 96% and 86% of subjects (respectively for rocuronium and vecuronium induced NMB) to recover to TOF ratio of 0.9 within 5 minutes. In contrast, only 16% and 9% (NMB induced via rocuronium and vecuronium, respectively) of the patients treated with neostigmine recovered to the same TOF ratio within 5 minutes (Herring et al., 2017). Furthermore, Kaufhold et al. (2016) endorses, lower than the approved, recommended doses of sugammadex (2 mg/kg IV) may sufficiently reverse a TOF ratio of 0.2 to baseline neuromuscular function within 5-10 minutes. Whereas, due to the ceiling effect of neostigmine it was unable to reliably reverse the majority of patients within 10 minutes (Kaufhold et al., 2016). Kaufhold et al. (2016) recommends to wait until four twitches in the TOF are visible before using neostigmine for reversal of NMBs due to its unreliable effects. Ultimately, Sugammadex provides a more reliable recovery associated with a higher TOF value post-extubation, thus demonstrating sugammadex to be clearly superior over neostigmine in reversing moderate NMB (Carron et al., 2016; Herring et al., 2017; Hristovska et al., 2017; Kaufhold et al., 2016).

Deep Block Reversal

Deep paralysis is indicated by a PTC of 1 to 4 (Geldner et al., 2012; Herring et al., 2017; Hristovska et al., 2017; Jones, Caldwell, Brull, & Soto, 2008). The following studies have looked at the reversal of a deep neuromuscular blockade with 4 mg/kg IV of sugammadex given at 1-2 PTC: Geldner et al., 2012; Herring et al., 2017; Hristovska et al., 2017; Jones et al., 2008;. Herring et al. (2017) found sugammadex produced an average recovery time of 2.2 minutes and 3.8 minutes following rocuronium and vecuronium induced paralysis, respectively. Within 5 minutes, 95% and 77% (respectively for rocuronium and vecuronium induced NMB) of the sugammadex group had full recoveries while only 7% of the rocuronium-neostigmine group recovered within 5 minutes (Herring et al., 2017). Not one person from the vecuronium group

was able to recover within that 5 minutes following neostigmine administration (Herring et al., 2017). These results were also seen and supported in Jones et al. (2008) randomized comparison study and in the meta-analysis conducted by Hristovska et al. (2017). The research established that the neostigmine group, required 30-60 minutes for majority of its patients to fully recover to TOF ratio of 0.9 or greater following administration at PTC 1-2 (Hristovska et al., 2017; Jones et al., 2008). As with the majority of the studies reviewed, Geldner et al. (2012) also found sugammadex superior to neostigmine despite comparing the reversal of the two medications at different depths of NMB. The evidence produced in this study supported sugammadex to produce a more rapid recovery and establishment of normal neuromuscular function with deep NMB when compared to neostiminge's reversal of a moderate NMB (Geldner et al., 2012).

Immediate reversal of profound NMB following 1.2 mg/kg IV rocuronium administration, sugammadex 16 mg/kg IV was found to produce rapid recovery or neuromuscular function in an average of 1.7 minutes (Herring et al., 2017). Neostigmine was not studied in this setting due to prior recommendations stating that some indication of spontaneous recovery must be seen before it can safely be administered (Herring et al., 2017; Kaufhold et al., 2016).

The faster reversal time associated with sugammadex ultimately allows for earlier tracheal extubation following maintenance of deep NMB. This can aid in earlier discharge times from the OR and PACU (Geldner et al., 2012; Jones et al., 2008). All together, sugammadex is concluded to more rapidly reverse a rocuronium-induced NMB regardless of the depth (Geldner et al., 2012; Herring et al., 2017; Hristovska et al., 2017; Jones et al., 2008).

General Side-effects/Adverse Effects

Hemodynamic changes were minimal between the administration of sugammadex compared to neostigmine throughout all the literature (Geldner et al., 2012; Hristovska et al., 2017; Jones et al., 2008) Some variable changes in heart rates were noted between the neostigmine and sugammadex group; however, the changes were immaterial in comparison (Geldner et al., 2012; Hristovska et al., 2017; Jones et al., 2008). Overall, no statistically significant findings in regards to hemodynamic changes were concluded throughout the literature reviewed.

Sugammadex was found to be associated with significantly lower respiratory and cardiovascular adverse events (AEs), as well as less postoperative weakness (Carron et al., 2016; Hristovska et al., 2017). There were similar risks found between sugammadex and neostigmine for pain scores (Carron et al., 2016; Hristovska et al., 2017). Neostigmine was associated with more respiratory AEs, such as hypoxemia, which can possibly be due to bronchospasm aggravated by an increased level of respiratory secretions (Carron et al., 2016). Neostigmine has also been associated with dose-dependent negative effects on the genioglossus muscle and diaphragmatic function as well as general weakness due to impaired neuromuscular transmission or inadequate reversal (Carron et al., 2016). Other general AEs were directly related to co-administration of cholinesterase inhibitors and anticholinergic medications (dry mouth, visual accommodation disorder, or hyperhidrosis) (Carron et al., 2016; Hristovska et al., 2017). Ultimately, Carron et al. (2016) and Hristovska et al. (2017) found sugammadex provided a more reliable reversal, with significantly less risk of residual paralysis postoperatively, while also having a lower adverse effect profile.

Renal Effects

Sugammadex is renally eliminated thus posing a risk to worsen renal failure. (Herring et al., 2017). Isik, Palabiyik, Cegin, Goktas, and Kati (2016) and Carron et al. (2016) looked specifically at the effects sugammadex and neostigmine have on renal biomarkers. They concluded that both medications minimally affected renal glomerular filtration and tubular function (Carren et al., 2016; Isik et al., 2016). This marginal reduction in renal clearance produced only slightly slower recovery times and were not associated with any clinical evidence of renal dysfunction (Carron et al., 2016; Herring et al., 2017). Additionally, hemodynamic changes that could potentially affect renal function were also similar between the two groups and did not lead to further deterioration in renal function (Isik et al., 2016). In regards to severe renal impairment (i.e. those requiring dialysis), sugammadex is currently not recommended for use due to the limited data available (Herring et al., 2017). It was concluded that renal function may be affected by both medications, however, sugammadex has been established to have more tolerable effects than neostigmine (Carron et al., 2016; Herring et al., 2017; Isik et al., 2016).

Bleeding

Research has shown sugammadex is associated with an increase in Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) occurring within 10 minutes following sugammadex administration (Hristovska et al., 2017; Iwasaki, Renew, Kunisawa, & Brull, 2017). However, this elevation is seen to resolve within 60 minutes (Hristovska et al., 2017; Iwasaki et al.,2017). This short-lived increase was concluded to not be associated with any increased bleeding risk or severity of bleeding (Hristovska et al., 2017, Iwasaki et al., 2017). However, it is still important to monitor those with coagulopathies or on anticoagulation/thromboprophylaxic mediations (Herring et al., 2017). One study determined that the transient effect on PT and aPTT associated with sugammadex was likely attributed to a reaction with phospholipid in the assay

(Carron, Zarantonello, Lazzarotto, Tellaroli, & Ori, 2017). As a whole, the studies support that these increases in PT and aPTT are transient and unlikely to be clinically relevant (Carron et al., 2017; Hristovska et al., 2017; Iwasaki et al., 2017).

Hypersensitivity

Iwasaki et al. (2017) touched on hypersensitivity reactions associated with sugammadex. The most frequent symptoms of sugammadex-induced anaphylaxis are rash, hypotension, and tachycardia (Iwasaki et al., 2017). Also, most reactions were triggered within four minutes after administration. This critical period of hypersensitivity was also confirmed to be within the 5-minute time frame following sugammadex injection in the study conducted by Carron et al. (2017). Thus, it is vital to be vigilant during this critical period to ensure adequate identification of allergic response are managed in a timely manner.

Discussion

Sugammadex has been shown to decrease the time it takes to achieve a TOF 0.9 or greater, reflecting the return of normal neuromuscular function. The approved doses of sugammadex, 2 mg/kg IV for a moderate block or 4 mg/kg IV for a deep block, have been proven superior to even the largest doses of neostigmine in ensuring adequate and timely reversal of paralysis. Throughout all the literature, there was a common theme with the use of neostigmine; it requires some spontaneous recovery from paralysis, such as a single twitch in a TOF reading, to be eligible for administration in attempts to reverse neuromuscular blockades. Additionally, some research has shown that it should not be administered until there are 4/4 twitches in the TOF test (Kaufhold et al., 2016). The quicker reversal times associated with sugammadex has allowed anesthesia providers to maintain a deep level of paralysis for the entirety of a surgery without risking incomplete recovery or other complications (Geldner et al.,

2012). This deep paralysis can improve surgical field conditions, such as better views for laparoscopic cases. It can also allow lower pressures used to create pneumoperitoneum, which similarly, may provide additional benefits following laparoscopic surgery (Geldner et al., 2012; Jones et al, 2008). Largely, the research provides support for sugammadex to provide a faster and more reliable reversal, thus providing a great benefit to its use for patient safety.

As sugammadex has been proven to provide a more reliable reversal of paralysis, it does not come without risk. Side effects and adverse events can occur with all medications and the research shows there are less side-effects and risks associated with sugammadex compared to neostigmine. A significant attribute of sugammadex is that it has been shown to prevent residual neuromuscular blockade due to it mechanism of action. Its encapsulating method inactivates the paralytic agent and then together they are excreted from the body (Nagelhout & Elisha, 2018). Compared to neostigmine, which reverses the neuromuscular blockade via competitive inhibition (Butterworth et al., 2013). Meaning, it allows more ACh to be available to overcome paralytic agents from the receptor sites. Consequentially, this can lead to residual neuromuscular blockade due to paralytic agent remaining in the synaptic cleft; or lead to neuromuscular weakness related to the excess ACh that has been shown to overstimulate the receptors leading to weakness. Both of which are suboptimal for patient outcomes following surgery. Overall, more research is needed to understand the specific side-effects patients experience following surgery with administration of these reversal agents. Some of the reported side effects can be associated with other anesthetic drugs administered throughout surgery and may or may not be associated with the administration of neostigmine or sugammadex. Overall, the most undesirable side-effects associated with paralysis include residual neuromuscular blockade, generalized weakness, and

muscarinic effects resulting from the anticholinergic medication administration with neostigmine. All of which were seen to be minimal in the sugammadex participants' recovery.

Other important considerations to remember when using sugammadex comes from the Merck Connect (2018) package insert. It's important to note that sugammadex can interact with hormonal contraceptives, posing risk of them becoming less effective (Merck Connect, 2018). It is imperative to ensure patients are aware of this risk post-operatively after sugammadex has been administered. It is also important that anesthesia providers are aware that sugammadex is incompatible with verapamil, ondansetron, and ranitidine (Merck Connect, 2018). Thus, confirm the infusion line is adequately flushed with approved solutions before sugammadex is co-administered with one of these incompatible agents. In the end, sugammadex has been shown to be superior to neostigmine in its reversal efficacy and safety profile. Its ability to completely avoid the muscarinic-associated side-effects linked with traditional reversal agents, creates a favored choice in anesthetic management for a majority of patients.

Although the clinical benefits of sugammadex outweigh the support for neostigmine, sugammadex is expensive. The drug patent for sugammadex does not expire until 1/27/2021, and consequently it is still more expensive than the traditional reversal agents. Currently, small vials of sugammadex 100 mg/ml in 2ml vial is approximately 117 Euros which equates to roughly $133 USD (Hristovska, et al., 2017). For a 100 kg patient it would cost between $133 USD to $266 USD for a 2mg/kg IV or 4mg/kg IV dose. Compared to neostigmine which is approximately $23 USD for a 10 mL vial of 0.5mg/mL (Drugs.com, 2019a), plus the cost of glycopyrrolate which is approximately $15 USD for a 5 ml vial of 0.2mg/ml (Drugs, 2019b). For the 100kg patient, the total cost to administer neostigmine with glycopyrrolate is approximately $38 USD (0.05mg/kg IV of neostigmine and 0.01mg/kg IV of glycopyrrolate). However, this

administration comes with a limitation due to the requirement of spontaneous recovery from NMB before neostigmine can safely and effectively be provided.

Despite being more expensive there are several benefits that can justify the excess cost of sugammadex. Hristovska et al. (2017) noted sugammadex offers great differences in reversal time and this extra time has some advantages. One advantage includes, reduced anesthesia time, which could improve recovery and potentially reduce total costs to the patient and hospital. Sugammadex can be administered at any stage of a surgical procedure, independent of the block. Thus, it can reduce patient recovery time perioperatively, which provides staff extra time to work on alternative activities. Carron et al. (2017) meta-analysis found sugammadex to be associated with faster OR to PACU discharge, compared to neostigmine (mean difference [MD] for moderate level blocks was 22.14 minutes and 30.05 minutes for deep NMB). These patients also had faster PACU to surgical ward times (MD of 16.9 minutes) than the neostigmine participants. Paton et al. (2010) systematic review of the cost-effectiveness of sugammadex found that the reduced recovery times associated with sugammadex, economically depends on the 'value of each minute' (Paton et al., 2010, p. 563). It was concluded there is potential for sugammadex to be cost effective if any time saved due to a faster recovery freed staff to work on productive activities (Paton et al., 2010). Due to the time saved in the OR by reversing with sugammadex, those added minutes in turn can be applied to other surgeries, meetings, educational opportunities, etc. This area of research is hard to conduct due to the various hospital and surgery structures; however, the potential is there. It largely depends on how effectively that extra time is being used to understand the net efficiencies.

Conclusion

Neuromuscular blocking agents induce muscle relaxation which is commonly used during surgery for facilitating tracheal intubation and providing optimal surgical conditions by suppressing voluntary skeletal muscle movements. It is important at the end of surgery these medications can be reversed to allow normal neuromuscular function that is vital to spontaneous ventilation allowing emergence through anesthesia to preoperative function. Cholinesterase inhibitors, such as neostigmine have traditionally been the only agents available to counteract the neuromuscular blockade until recently. Sugammadex is a newer medication that selectively inhibits neuromuscular blocking agents from allowing paralysis. Sugammadex works by encapsulating the neuromuscular blocking agent creating a complex that completely inactivates its ability to produce paralysis. Research has shown sugammadex to completely reverse all levels of blockades faster than neostigmine. This includes blocks where neostigmine administration is not favorable due to the depth of the blockade. Overall, the literature supports sugammadex as a safer and more efficacious medication in the reversal of all depths of neuromuscular blockades.

References

American Association of Nurse Anesthetist (AANA). (2013). Standards for nurse anesthesia practice. Retrieved from https://www.aana.com/docs/default-source/practice-aana-com-web-documents-(all)/standards-for-nurse-anesthesia-practice.pdf?sfvrsn=e00049b1_2

Batistaki, C., Tentes, P., Deligiannidi, P., Karakosta, A., Florou, P., & Kostopanagiotou, G. (2016). Residual neuromuscular blockade in a real life clinical setting: Correlation with sugammadex or neostigmine administration. *Minerva Anestesiologica*, *82*(5), 550-558.

Brull, S. J., & Kopman, A. F. (2017). Current status of neuromuscular reversal and MonitoringChallenges and opportunities. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *126*(1), 173-190.

Butterworth, J.F., Mackey, D.C., & Wasnick, J.D. (2013). *Morgan & Mikhail's Clinical Anesthesiology* (5th ed.). McGraw-Hill Medical.

Carron, M., Zarantonello, F., Lazzarotto, N., Tellaroli, P., & Ori, C. (2017). Role of sugammadex in accelerating postoperative discharge: A meta-analysis. *Journal of Clinical Anesthesia*, *39*, 38-44.

Carron, M., Zarantonello, F., Tellaroli, P., & Ori, C. (2016). Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromuscular blockade: A meta-analysis of randomized controlled trials. *Journal of Clinical Anesthesia*, *35*, 1-12.

Drugs.com. (2019a). Neostigmine prices, coupons and patient assistane programs. Retrieved from https://www.drugs.com/price-guide/neostigmine

Drugs.com. (2019b). Robinul prices, coupons, and patient assistance programs. Retreved from https://www.drugs.com/price-guide/robinul

Geldner, G., Niskanen, M., Laurila, P., Mizikov, V., Hübler, M., Beck, G., . . . 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.

Herring, W. J., Woo, T., Assaid, C. A., Lupinacci, R. J., Lemmens, H. J., Blobner, M., & Khuenl-Brady, K. S. (2017). Sugammadex efficacy for reversal of rocuronium-and vecuronium-induced neuromuscular blockade: A pooled analysis of 26 studies. *Journal of Clinical Anesthesia, 41*, 84-91.

Hristovska, A., Duch, P., Allingstrup, M., & Afshari, A. (2017). Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database of Systematic Reviews,* (8)

Isik, Y., Palabiyik, O., Cegin, B. M., Goktas, U., & Kati, I. (2016). Effects of sugammadex and neostigmine on renal biomarkers. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 22*, 803.

Iwasaki, H., Renew, J. R., Kunisawa, T., & Brull, S. J. (2017). Preparing for the unexpected: Special considerations and complications after sugammadex administration. *BMC Anesthesiology, 17*(1), 140.

Jones, R. K., Caldwell, J. E., Brull, S. J., & Soto, R. G. (2008). Reversal of profound rocuronium-induced blockade with SugammadexA randomized comparison with neostigmine. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 109*(5), 816-824.

Kaufhold, N., Schaller, S. J., Stäuble, C. G., Baumüller, E., Ulm, K., Blobner, M., & Fink, H. (2016). Sugammadex and neostigmine dose-finding study for reversal of residual

neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20). *BJA: British Journal of Anaesthesia, 116*(2), 233-240.

Merck Connect. (2018). Dosing for Bridion® (Sugammadex). Retrieved from https://www.merck.com/product/usa/pi_circulars/b/bridion/bridion_pi.pdf

Murphy, G. (2018). Presentation of the APSF Collaborative Panel on Neuromuscular Blockade and Patient Safety at the 2017 ASA Annual Meeting Retrieved from https://www.apsf.org/wp-content/uploads/newsletters/2018/Feb/pdf/APSF201802.pdf#page=12

Nagelhout J. & Elisha, S. (2018). *Nurse Anesthesia* (6th ed.). Elsevier Saunders. ISBN: 978-0-323-44392-0

Paton, F., Paulden, M., Chambers, D., Heirs, M., Duffy, S., Hunter, J. M., . . . Woolacott, N. (2010). Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: A systematic review and economic evaluation. *British Journal of Anaesthesia, 105*(5), 558-567.

Appendix A

The Safety and Efficacy in Reversal of Neuromuscular Blockades with Sugammadex versus Neostigmine

Nicole Landen, SRNA

UND Nurse Anesthesia
University of North Dakota

Introduction

- Neuromuscular blockade is utilized for the purpose of skeletal muscle paralysis during surgery to facilitate mechanical ventilation and provide optimal surgical conditions by suppressing voluntary skeletal muscle movements.
- A survey from the 2017 Anesthesia Patient Safety Foundation (APSF) has shown:
  - Majority of its respondents perceived the incidence of residual NMB to be only 1-10% (Murphy, 2018).
  - Brull and Kopman (2017), determined the incidence of residual NMB to be 30-50% in the patients admitted to the PACU following surgery.

Introduction

- Reversal agents can help reduce the incidence of residual NMB. However, some agents are not effective at all depths of paralysis.
  - Traditionally: cholinesterase inhibitors (neostigmine) with a muscarinic antagonist (glycopyrrolate)
  - Recently: sugammadex
- To determine the safety and efficacy of sugammadex and neostigmine on NMB reversal, a literature review was conducted to provide current, supporting evidence comparing their use in reversal of NMBs.

Case Information

- Surgery: Ventral Hernia Repair
- 73 year old
- 157 centimeters
- 98.5 kg
- Female
- ASA 3

Pre-operative Evaluation

- Pre-op Vitals
  - BP 100/64 mmHg
  - HR 78 bpm
  - RR 16 bpm
  - SpO2 97% on room air
  - 36.4°C
- Airway Assessment
  - Mallampati I with full neck ROM
  - Adequate thyromental distance
- Preoperative labs- unremarkable

Pre-operative Evaluation

- Past Medical History:
  - HTN
  - CKD-stage 3
  - GERD
  - CVA- cerebral artery
  - Former Smoker (quit 1997)
  - OA
  - Diverticulosis
  - Obesity (BMI 39)
  - Neuropathic pain
  - Dyslipidemia
  - Adjustment disorder
  - SI joint pain
  - Iron Deficiency anemia
- Past Surgical History:
  - Gastric Bypass
  - Lumbar Fusion
  - Ventral Hernia Repairs

Anesthetic Course

- Midazolam 2mg IV
- Standard monitors were applied (SpO2, 5 Lead EKG, NIBP, and BIS)
- Pre-oxygenation with 10L of O2 via face-mask ventilation
- Induction with
  - Fentanyl 100mcg IV
  - Lidocaine 40mg IV
  - Rocuronium 5mg priming dose IV
  - Dexmedetomidine infusion bolus of 0.25mg/kg IV
  - Propofol 200mg IV
- Eye lids taped

UND Nurse Anesthesia University of North Dakota

Anesthetic Course Cont'd

- Rocuronium 40mg IV
- 7.0 ETT inserted via Miller 2 laryngoscope
- Desflurane initiated and MAC of 0.8-1.0 via Pressure-control ventilation (PCV)
- Nasopharyngeal temperature monitoring
- PONV Prophylactic medications ondansetron 4mg IV and dexamethasone 4mg IV
- Cefazolin 2g IV and heparin 5000 units SQ

UND Nurse Anesthesia University of North Dakota

Anesthetic Course Cont'd

- Dexmedetomidine infusion 0.5mcg/kg/min IV
- Ketamine 50mg IV and Fentanyl 50mcg IV prior to incision
- Maintenance Phase during four hour case:
  - Additional Fentanyl 200mcg IV
  - Hydromorphone 1mg IV
  - 3L of Lactated Ringer's
  - 5% Albumin 500mL IV
- Paralysis monitored via orbicularis oculi muscle and neuromuscular blockade maintained with 10mg IV boluses of Rocuronium to maintain TOF ratio 2/4
  - Total of 130 mg IV rocuronium was given

UND Nurse Anesthesia University of North Dakota

Intraoperative Issues

- Patient remained hemodynamically stable throughout the case
- Difficultly maintaining 2/4 TOF

UND Nurse Anesthesia University of North Dakota

Anesthetic course Cont'd

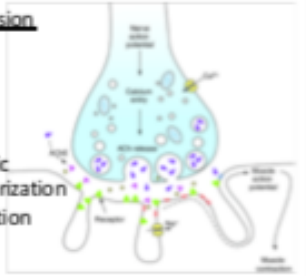
- Emergence:
  - TOF 4/4
  - Reversal with 4mg/kg IV Sugammadex
- Patient extubated without incident
- 3L/min O2 applied via nasal cannula
- Transferred to PACU without complication
- Uneventful PACU and hospital stay

UND Nurse Anesthesia University of North Dakota

Background Information

Neuromuscular Transmission

- Action potential
- Influx Ca^{2+}
- Release ACh
- ACh bind to Nicotinic receptors → depolarization and muscle contraction



UND Nurse Anesthesia University of North Dakota

Background Information

Neuromuscular Blockade:

- Depolarizing
  - Succinylcholine mimics ACh and binds to the receptor eliciting a continuous depolarization resulting in sustained paralysis for a short duration of time.
- Nondepolarizing agents
  - Compete with ACh for the nicotinic binding sites on skeletal muscles blocking the depolarization of the action potential leading to paralysis.

UND Nurse Anesthesia University of North Dakota

Background Information

Neuromuscular Blockade Reversal:

- Spontaneous
- Pharmacological
  - Cholinesterase Inhibitors- Neostigmine
    - Inactivate acetylcholinesterase, preventing the breakdown of ACh → increasing the amount of ACh available to compete against the nondepolarizing agent to reestablish normal neuromuscular transmission.
  - Sugammadex
    - "Selective relaxant binding agent" (Nagelhout & Elisha, 2018, p. 163)
    - Modified gamma-cyclodextrin molecule that encapsulates and forms a tight water-soluble complex in a 1:1 ratio with steroidal neuromuscular blocking agents, including rocuronium, vecuronium, and pancuronium.

UND Nurse Anesthesia University of North Dakota

Background Information

Neuromuscular Blockade Monitoring:

- Train of Four (TOF)
  - Delivery of four stimuli every 0.5 seconds at a frequency of 2 Hertz (Hz) for two seconds.
    - T4 disappearance it indicates 75-80% of receptors are block (TOF ratio 1/4).
    - T1 and T4 disappearance correlates with 80-85% block
    - T2 lost (T4, T3, and T2 are absence) reflects 90-95% of NMB
    - Zero twitches visualized or palpated, it indicates a 100% NMB has been achieved
  - Ideally, one to two twitches present during the TOF stimulus is sufficient for all procedure (85-95% of receptors blocked).
- Post-Tetanic Count (PTC)
  - Assessed following a 50-Hz tetanic stimulation for five seconds followed by a series of single 1-Hz stimulations
    - Correlates with the approximate depth of blockand can be indicative of how long it may take for spontaneous reversal to occur

UND Nurse Anesthesia University of North Dakota

Literature Search

- Databases:
  - CINAHL
    - Keywords: "Neostigmine AND Sugammadex" and "Safety" "Efficacy"
    - Limits: last 10 yeas (2008-2018)
    - 13 studies for initial review
  - Pubmed
    - Keywords: Neostigmine AND Sugammadex
    - Limits: last 5 years, English language, human subjects
    - 10 studies for initial review
- 23 articles reviewed and 9 articles were of relevance and selected for inclusion

UND Nurse Anesthesia University of North Dakota

Moderate Neuromuscular Blockade

- Palpable T1 and T2 twitches with fade via TOF stimulator
  - Hristovska et al. (2017) found sugammadex to be 10.22 minutes, or 6.6 times, faster than neostigmine to produce a TOF ratio of 0.9 or greater following a moderate rocuronium-neuromuscular blockade.
  - Herring et al. (2017) observed 96% and 86% of subjects (respectively for rocuronium- and vecuronium-induced NMB) to recover to TOF ratio of 0.9 within 5 minutes.
    - Only 16% and 9% of the patients treated with neostigmine recovered to the same TOF ratio within 5 minutes.
  - Kaufhold et al. (2016) ordered lower than the approved, recommended doses of sugammadex (2 mg/kg IV) may sufficiently reverse a TOF ratio of 0.2 to baseline neuromuscular function within 5-10 minutes. Whereas, due to the ceiling effect of neostigmine it was unable to reliably reverse the majority of patients within 10 minutes.

UND Nurse Anesthesia University of North Dakota

Deep Neuromuscular Blockade

- PTC of 1 to 4
  - Herring et al. (2017) found sugammadex produced an average recovery time of 2.2 minutes and 3.8 minutes following rocuronium and vecuronium induced paralysis.
    - Within 5 minutes:
      - 91% and 77% the sugammadex group had full recoveries while only 7% of the rocuronium-neostigmine group recovered within 5 minutes.
      - Not one person from the vecuronium group was able to recover within that 5 minutes following neostigmine administration.
  - The research established that the neostigmine group, required 30-60 minutes for majority of its patients to fully recover to TOF ratio of 0.9 or greater following administration at PTC 1-2 (Hristovska et al., 2017; Jones et al., 2008).

UND Nurse Anesthesia University of North Dakota

Profound Neuromuscular Blockade

- Sugammadex 16 mg/kg IV required an average of 1.7 minutes to reverse a profound NMB following 1.2 mg/kg IV rocuronium administration (Herring et al., 2017).
- Neostigmine was not studied in this setting due to recommendations of having some indication of spontaneous recovery before it can safely be administered (Herring et al., 2017; Kaufhold et al., 2016).

UND Nurse Anesthesia University of North Dakota

General Side-effects/Adverse Events

- Hemodynamic changes were minimal between the administration of sugammadex compared to neostigmine throughout all the literature (Geldner et al., 2012; Hristovska et al., 2017; Jones et al., 2008).
- Sugammadex was found to be associated with significantly lower respiratory and cardiovascular adverse events, as well as less postoperative weakness (Carron et al., 2016; Hristovska et al., 2017).

UND Nurse Anesthesia University of North Dakota

Renal Effects

- Sugammadex is renally eliminated (Herring et al., 2017).
- Isik, Palabiyik, Cegin, Goktas, and Kati (2016) and Carron et al. (2016) concluded that both medications minimally affected renal glomerular filtration and tubular function.
- The marginal reduction in renal clearance produced only slightly slower recovery times and were not associated with any clinical evidence of renal dysfunction (Carron et al., 2016; Herring et al., 2017).
- Sugammadex is currently not recommended for use in patients with severe renal impairment due to the limited data available (Herring et al., 2017).

UND Nurse Anesthesia University of North Dakota

Bleeding

- Sugammadex is associated with an increase in PT and aPTT occurring within 10 minutes following administration (Hristovska et al., 2017; Iwasaki, Renew, Kunisawa, & Ikeda, 2017).
  - Resolves within 60 minutes (Hristovska et al., 2017; Iwasaki et al., 2017).
  - Not associated with any increased bleeding risk or severity of bleeding (Hristovska et al., 2017; Iwasaki et al., 2017).
- Carron, Zarantonello, Lazzarotto, Tellaroli, and Ori, (2017) determined that the transient effect on PT and aPTT associated with sugammadex was likely attributed to a reaction with phospholipid in the assay.
- Overall, the increases in PT and aPTT are transient and unlikely to be clinically relevant (Carron et al., 2017; Hristovska et al., 2017; Iwasaki et al., 2017).

UND Nurse Anesthesia University of North Dakota

Hypersensitivity

- The most frequent symptoms of sugammadex-induced anaphylaxis:
  - Rash
  - Hypotension
  - Tachycardia

  (Iwasaki et al., 2017)
- Most reactions were triggered within four minutes after administration (Carron et al., 2017; Iwasaki et al., 2017).

UND Nurse Anesthesia University of North Dakota

Important Sugammadex Information

- Sugammadex can interact with hormonal contraceptives, posing risk of them becoming less effective.
- Sugammadex is incompatible with:
  - verapamil
  - ondansetron
  - ranitidine

UND Nurse Anesthesia University of North Dakota

Cost Comparison

- Sugammadex Drug Patent expires 1/27/2021
  - 100mg/ml in 2mL vial: $52.49 USD
- Neostigmine 0.5mg/ml in 10mL: $22.28 USD
- Glycopyrrolate 0.2mg/mL in 5mL: $15.40 USD
- For a 100kg Patient:
  - Sugammadex 2mg/kg dose = $52.49
  - Neostigmine (0.05mg/kg) + Glycopyrrolate (0.01mg/kg) = $22.28 + $15.40 = $37.68
- Possible Advantages:
  - Reduced Anesthesia Time (Hristovska et al., 2017)
  - Faster OR to PACU discharge (Carron et al., 2017)
  - "Value of each minute" (Paton et al., 2010, p. 563)

(Drugs.com, 2020)

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA

Recommendations

- Sugammadex has been shown to be superior to neostigmine regardless of the depth of the neuromuscular blockade in the time it takes to achieve a TOF 0.9 or greater, reflecting the return of normal neuromuscular function.
- Research supports sugammadex to provide a more reliable reversal of paralysis and is associated with less side-effects and risks compared to neostigmine.
- Patient education on oral contraceptives to ensure the use of back-up methods or non-hormonal contraceptives for 7 days following sugammadex administration.

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA

Conclusion

- Overall, the literature supports sugammadex as a safer and more efficacious medication in the reversal of all depths of neuromuscular blockades when compared to neostigmine.
  - Including blocks where neostigmine administration is not favorable due to the depth of the blockade.

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA

References

[illegible]

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA

References

[illegible]

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA

Thank You
Are There Any Questions?

UND NURSE ANESTHESIA
UNIVERSITY OF NORTH DAKOTA