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Comparing Sugammadex in the Adult and Geriatric Population

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A COMPARISON OF NEUROMUSCULAR BLOCKADE REVERSAL USING SUGAMMADEX IN THE ADULT AND GERIATRIC POPULATION: A SYSTEMATIC REVIEW

A Major Paper Presented

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Abstract

Neuromuscular blocking agents are an integral part of anesthesia care, with the inherent necessity of reversing its effects prior to patient emergence from anesthesia. Sugammadex offers a novel approach to neuromuscular blockade reversal, whose mechanism differs from acetylcholinesterase inhibitors traditionally used. However, geriatric patients have multiple physiologic age-related changes that can make this population at risk to a variety of adverse events during anesthesia care. The purpose of this systematic review is to determine if the geriatric population, compared to the adult population, requires an altered dose of sugammadex to reduce the incidence of residual neuromuscular blockade during the postoperative period. A literature review was completed using the databases CINAHL, MEDLINE, and Academic Search Complete on Ebscohost. PRISMA framework was used to guide this review. Six studies were identified that met inclusion and exclusion criteria. The Critical Appraisal Skills Programme checklist was used to systematically assess each study. A data collection table was used to organize each study's methodology and results, with a cross-study analysis table to facilitate comparison of included studies. Overall, results showed that increased age was associated with increased time to reversal of neuromuscular blockade after sugammadex administration. However, there were few adverse events reported and a higher incidence of residual neuromuscular blockade and adverse events in the geriatric population related to longer recovery time could not be determined using the included studies. Further research is needed to determine factors which affect the relationship between age and neuromuscular blockade recovery after sugammadex.

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A Comparison of Neuromuscular Blockade Reversal Using Sugammadex in the Adult and Geriatric Population: A Systematic Review

Background/Statement of the Problem

Neuromuscular blockade (NMB) agents are integral in anesthesia practice and widely used for decades. NMB agents are medications which block skeletal muscle movements and are frequently used in surgery to facilitate endotracheal intubation and to optimize surgical conditions without relying on higher doses of anesthetic agents which may increase risk of adverse reactions (Nagelhout, 2014; Naguib, Lien, & Meistelman, 2015). Several NMB agents exist in clinical use with varying pharmacokinetic and pharmacodynamic properties and the anesthesia provider can choose which is best based on intended duration of NMB, patient comorbidities, and goals of anesthesia care.

Antagonism of the effects of NMB using reversal agents is an essential element of anesthesia practice because changes in patient or surgical conditions may require faster resolution of NMB, such as NMB effects extending beyond time needed for surgery. Incomplete antagonism of NMB continues to be a problem in anesthesia practice, leaving patients in a state with partial NMB, also called residual NMB, and potentially exposing patients with partially weakened muscle function to complications (Nagelhout, 2014). Saager et al. (2019) have found that incidence of residual NMB was observed in nearly 65% of patients. Adverse events resulting from inadequate antagonism of NMB include impaired airway protective reflexes, impaired swallowing, hypoxemia, upper airway obstruction, and reduced hypoxic ventilatory drive (Murphy & Brull, 2010).

Until relatively recently in anesthesia care, antagonism of NMB was primarily accomplished by waiting for the NMB agent effect to dissipate and by using

acetylcholinesterase inhibitors, such as neostigmine, for NMB antagonism. Sugammadex offers a different mechanism of action that avoids potential complications and limitations of using acetylcholinesterase inhibitors. Sugammadex is a newer agent for the antagonism of neuromuscular blockade and has the advantage of rapid reversal of deep levels of neuromuscular blockade (Chingmuh et al., 2009). As the geriatric population increases and their health care and surgical needs increase, review of sugammadex efficacy to reverse NMB in geriatric patients as a unique population is needed.

The purpose of this systematic review was to determine if the geriatric population, compared to the adult population, requires an altered dose of sugammadex to reduce the incidence of residual neuromuscular blockade during the postoperative period. A systematic review was conducted to further examine the topic of sugammadex use in geriatric surgical patients to reduce incidences of residual neuromuscular blockade compared to the adult, to ensure safe and effective use in geriatric patients to reverse NMB. The research question to guide this systematic review was: What is the relationship of sugammadex dosing in the geriatric population compared with the adult population in preventing the incidence of residual NMB in the postoperative period?

Next, a review of literature will be presented.

Literature Review

A review of the literature was completed on Ebscohost using the databases CINAHL, MEDLINE, and Academic Search Complete. Search terms used include: sugammadex, elder*, geriatric, aged, neuromuscular block*, NMB. Articles were limited to English language. No date limit was imposed on search results.

Neuromuscular Junction Physiology

The interface between efferent motor neurons and skeletal muscles is called the neuromuscular junction. Despite this junction being one of the most studied areas of nervous system, complete understanding of its workings is not known (Jeevendra Martyn, 2015). The axon terminal branches out as it reaches toward the skeletal muscle fiber cell membrane. The axon terminal branches of the motor neuron do not contact the muscle fiber cell membrane, leaving a junctional space or cleft. Within the axon terminal of the motor neuron, acetylcholine is synthesized and stored in vesicles in preparation for release into the junctional space. Once an electrical signal (action potential) travels to the axon terminal endings, the electrical signal of the nervous system is converted into a chemical signal, in the form of acetylcholine release into the junctional space. The action potential activates calcium ion channels at the axon terminal, allowing an influx of calcium ions into the axon terminal, where vesicles storing acetylcholine await. Calcium ion influx allows for the complex interaction of several proteins which ultimately allow vesicles to migrate to the axon terminal releasing zones and then exocytosis of acetylcholine into the junctional space (Jeevendra Martyn, 2015).

Once released into the junctional space, acetylcholine diffuses toward the skeletal muscle fiber cell membrane and nicotinic acetylcholine receptors (nAChR). There are

several varieties of nAChRs, but in adults without neuromuscular disease the predominate nAChR is composed of five subunits: two alpha, one beta, one delta, and one epsilon (Jeevendra Martyn, 2015). Both alpha subunits must have an acetylcholine molecule bound to activate the nAChR, allowing the influx of predominantly sodium ions but also calcium ions into the muscle fiber sarcoplasm and the efflux of potassium ions out to the junctional space. If enough nAChRs are stimulated by acetylcholine, the electrical gradient of the muscle fiber membrane can reach threshold and produce an end-plate potential. The end-plate potential will propagate into the muscle fiber via transverse tubules to ultimately produce a muscle contraction.

Neuromuscular Blockade

Pharmacologic agents are available that establish neuromuscular blockade (NMB), which is the interference with physiologic processes at the neuromuscular junction and inhibition of muscular contraction. The primary site of action that enables NMB is the alpha subunit of nAChRs. Skeletal muscles are all susceptible to the effects of NMB but not all skeletal muscles are equally affected.

Variability of blood flow and sensitivity of different muscle groups produces patterned responses during onset and recovery of NMB (Nagelhout, 2014). During onset of NMB, extraocular movement muscles and extremities are affected first, followed by muscles in the neck, chest, abdomen, and lastly diaphragm. During recovery, this pattern is reversed, with diaphragm recovering first and extremities and eyes muscles recovering last. For this reason, measuring the onset of NMB is best done using a facial nerve, commonly observing for stimulation of the orbicularis oculi. Blood flow and drug distribution to facial muscles more closely mirrors that of larynx and diaphragm, thus

more closely measures onset of muscle relaxation desired prior to intubation. Measuring recovery from NMB is best measured in the periphery, commonly ulnar nerve stimulation eliciting a contractile response of the adductor pollicis (adduction of the thumb). If adequate recovery can be measured in the more sensitive extremities, then recovery of the less sensitive larynx and diaphragm is better ensured. A prospective observational study of 150 subjects by Thilen et al. (2012) found an increased incidence of residual NMB effects in postanesthesia care unit (PACU) when the orbicularis oculi site was used to determine NMB recovery compared to using the adductor pollicis (n=51/99 vs n=11/51, respectively, $p<0.01$).

Neuromuscular Blockade Agents

NMB agents inhibit muscle contraction by interfering with the physiologic process occurring in the neuromuscular junction, resulting in the inability for muscles to contract and produce movement. There are several drugs clinically available and are divided into different categories: depolarizing agents and nondepolarizing agents. It is the nondepolarizing agents that will be reviewed in detail, as the depolarizing agents will have no bearing on the focus of this systematic review.

Nondepolarizing agents. Nondepolarizing agents can be divided into two classes according to their molecular structure: steroidal and benzoisoquinoliniums. Rocuronium, vecuronium, and pancuronium are examples of steroidal nondepolarizing agents. Steroidal nondepolarizing agents all have a characteristic structure of four hydrocarbon rings that is similar to cholesterol and other endogenous steroids, such as androgens and corticosteroids. Benzoisoquinoliniums have a different molecular structure which does

not have a steroidal ring structure. Atracurium and cisatracurium are examples of benzoisoquinoliniums (Naguib, 2015).

All nondepolarizing agents are competitive antagonists with acetylcholine, binding to an alpha subunit of the nAChR and blocking acetylcholine action at the alpha subunit receptor site. Nondepolarizing agents need only to block one alpha subunit to prevent activation of the nAChR by acetylcholine. By blocking the alpha subunit of the nAChR, nondepolarizing agents do not allow adequate depolarization of the muscle fiber cell membrane to reach threshold and produce an end-plate potential needed for initiating muscle contraction. As concentration of nondepolarizing agent in the blood plasma decreases due to drug metabolism, clearance, and excretion, a concentration gradient causes nondepolarizing agent to diffuse from the neuromuscular junction to the plasma. As concentration of nondepolarizing agent decreases within the neuromuscular junction, acetylcholine then increasingly predominates, and neuromuscular junction physiology increasingly returns to normal (Naguib, 2015).

Neuromuscular Blockade Reversal Agents

Reversal of NMB effects is an important part of anesthesia clinical practice. NMB duration and surgical times do not necessarily coincide. Ongoing NMB into the postoperative period can impair protective airway reflexes if not appropriately reversed. Also, patients should not experience awareness while immobile from the effects of NMB, as this can be psychologically distressful.

Multiple medications are available to antagonize the effects of nondepolarizing agents. Acetylcholinesterase inhibitors includes drugs such as neostigmine and edrophonium to inhibit acetylcholinesterase from breaking down acetylcholine, thus

increasing the concentration of acetylcholine at the neuromuscular junction (Murphy, De Boer, Eriksson, & Miller, 2015). The increased concentration of acetylcholine can compete with nondepolarizing drugs at the active site on nAChRs. However, acetylcholinesterase is inhibited not just at nAChRs but also at other locations in the nervous system, such as muscarinic acetylcholine receptors (mAChRs). Stimulation of mAChRs at sites such as the heart and lungs can produce undesirable effects such as bradycardia, bradyarrhythmia, and bronchoconstriction. Anticholinergic drugs such as atropine and glycopyrrolate are administered with acetylcholinesterase inhibitors to counter the effects of increased acetylcholine at mAChR. Sugammadex is not an acetylcholinesterase inhibitor, offering a different approach to NMB antagonism that avoids potential complications involving acetylcholinesterase inhibitors.

Sugammadex. Sugammadex, classed as a selective relaxant binding agent, offers a new approach to NMB antagonism without affecting acetylcholinesterase (Murphy, De Boer, et al., 2015). Sugammadex is made of eight dextrose units in a circular or donut shaped configuration. Hydrophobic functional groups are configured toward the hollow center of the donut configuration, allowing for binding of hydrophobic compounds. The outer portion of the donut configuration is hydrophilic, increasing its water solubility. Sugammadex is a modified version of this ring of eight dextrose units to enhance electrostatic binding and to physically accommodate the steroidal nondepolarizing drug. Of all the NMB agents, sugammadex is only capable of interacting with the steroidal class of nondepolarizing agents. The steroidal nondepolarizing drug is bound within the dextrose ring structure of sugammadex and reduces the concentration of free steroidal nondepolarizing drug available in the plasma. As more drug is bound by sugammadex, a

concentration gradient is created, facilitating diffusion of nondepolarizing drug away from the neuromuscular junction and toward the plasma, where additional sugammadex can bind more nondepolarizing drug. The complex of sugammadex and bound nondepolarizing drug is primarily eliminated from the body in urine.

Unlike acetylcholinesterase inhibitors, sugammadex can reverse deep states of NMB. In a randomized clinical trial by Chingmuh et al. (2009), the reversal of 1.2 $mg \cdot kg^{-1}$ rocuronium with 16 $mg \cdot kg^{-1}$ sugammadex was compared to spontaneous recovery after 1 $mg \cdot kg^{-1}$ of succinylcholine, a short-acting depolarizing NMB agent. Results from 108 subjects was provided and showed faster recovery ($p<0.001$) with the sugammadex group (mean time 6.2 minutes) compared to succinylcholine (mean time 10.9 minutes). Mean times of the sugammadex group start from time of rocuronium administration. If timed from sugammadex administration, mean time until recovery is 2.9 minutes.

Sugammadex does not bind with equal affinity to all drugs. A study by Zwiers, van den Heuvel, Smeets, and Rutherford (2011) used isothermal titration calorimetry to investigate the binding affinity of sugammadex with over 300 medications. Rocuronium has the highest association constant ($1.79 \cdot 10^7$) of all drugs tested, nearly three times higher than vecuronium ($5.72 \cdot 10^6$), the drug with second highest association constant. Pancuronium also has binding affinity for sugammadex, but approximately half that of vecuronium ($2.62 \cdot 10^6$). However, it is important to note that the interaction of sugammadex and pancuronium does not result in significant NMB reversal (Murphy, De Boer, et al., 2015). Zwiers et al. calculated that fusidic acid, floxacillin, and toremifene (a selective estrogen receptor modifier) theoretically can displace rocuronium and delay

reversal of NMB. However, no evidence of any clinically significant effect on NMB reversal was noted. In prescribing information released by the manufacturer Merck, Sharpe, and Dohme Corp (2018), in vitro studies suggest binding affinity of sugammadex and progesterone, possibly leading to reduced progesterone levels. No clinically significant effect on effectiveness of NMB reversal was stated with this interaction.

Effective dose ranges have been suggested for a variety of NMB depths by Naguib (2015). Effective doses range from 2 $mg \cdot kg^{-1}$ to 16 $mg \cdot kg^{-1}$. Lower doses (2$mg \cdot kg^{-1}$ and 4 $mg \cdot kg^{-1}$) are used for patients with partial spontaneous recovery from NMB. Larger doses (8-16 $mg \cdot kg^{-1}$) are used for more profound NMB, when patients have little or no measurable recovery from NMB. Effective doses for obese patients continue to be investigated. A prospective observational study found sugammadex doses based on ideal body weight insufficiently antagonized NMB in 39.5% (17/43) and 23.4% (18/77) of obese patients in deep and moderate NMB block, respectively (Lauradó et al., 2012). Van Lancker et al. (2011) found that moderate NMB can be antagonized using a sugammadex dose based on ideal body weight +40%. Sugammadex dose calculation based on ideal body weight in obese patients could risk insufficient NMB antagonism and risk relapse of NMB effect due to insufficient dosing (Murphy, De Boer, et al., 2015).

Effective dose was also investigated in those with severe renal impairment. Renal excretion is the primary elimination route for sugammadex. Despite rocuronium having a primarily biliary excretion route, rocuronium will primarily be excreted in urine once bound to sugammadex. Consequently, patients with severe renal impairment present with a unique situation. Panhuizen et al. (2015) investigated the reversal of deep NMB using sugammadex 4 $mg \cdot kg^{-1}$ in patients with severe renal impairment who received

rocuronium 0.6 mg·kg^{-1} with subsequent doses of 0.1-0.2 mg·kg^{-1} to maintain NMB. Thirty-five patients with creatinine clearance below 30ml/min were compared to 35 patients with creatinine clearance above 80ml/min as a control group. From time of sugammadex administration in the renal impairment group, time to achieve adequate recovery was 3.1 minutes. In the control group, time to achieve adequate recovery was 1.9 minutes. The renal impairment group showed statistically significant slower recovery times (p=0.0002). Although recovery times were prolonged by 1-2 minutes, all renal impairment patients achieved adequate recovery following sugammadex administration. During follow-up after sugammadex administration, six subjects in the renal impairment group continued to have detectable levels of rocuronium in plasma, bound to sugammadex, after seven days. Despite effective NMB recovery, there is not enough information to recommend routine sugammadex use in patients with creatinine clearance less than 30 ml/min due to the potential prolonged exposure to sugammadex-rocuronium complex and the potential risk such exposure could entail. Twelve patients did receive hemodialysis during this study, but variations in hemodialysis protocols among involved facilities did not allow for evaluation of hemodialysis effectiveness in removing sugammadex-rocuronium complex in this study.

Measuring Neuromuscular Blockade

Several methods have been employed by anesthesia providers for monitoring NMB for the purpose of determining adequate NMB recovery. Physical assessment or clinical bedside testing, qualitative measurement using a peripheral nerve stimulator (PNS) to assess train of four (ToF), and quantitative measurement devices to measure train of four ratio (ToFR) are all examples of NMB monitoring methods.

Quantitative measurement. Quantitative measurement is a type of objective measurement using a device to measure NMB and numerically displays the ToFR for the user. ToF is the delivery of four consecutive electrical stimuli to elicit a muscle twitch with each electrical stimulus. The ToFR is the ratio of the quantitative measurement of fourth muscle twitch response to the first muscle twitch response during ToF. Full complete recovery without any NMB effect is represented as a ToFR equal to one, meaning the fourth and first twitches are equal strength. Increasing NMB effect will progressively lower the ToFR closer to zero, meaning the fourth twitch is nearing absent while the first twitch is still present. If the fourth twitch is absent, then ToFR is not measurable. Eventually, as NMB effect further deepens, all muscle twitches during ToF progressively fade, with the first twitch being last to fade. Several quantitative devices are described in the literature using various mechanisms to measure NMB. Mechanomyography (MMG) measures the force of contraction of the adductor pollicis. MMG is often referred to as a "gold standard" of quantitative measurement of NMB. MMG is no longer commercially available for clinical use and the complex set-up limits the use of MMG to research purposes only (Brull & Kopman, 2017; Murphy, 2018; Naguib et al., 2018). Electromyography (EMG) measures the electrical response of a muscle in proportion to the contraction force. Naguib et al. (2018) state EMG to be an alternative gold standard, with EMG values and MMG values largely interchangeable with only minor variations. EMG is not commercially available as a portable device for clinical use but is available integrated in a limited number of other monitoring systems. (Brull & Kopman, 2017; Murphy, 2018; Naguib et al., 2018). Acceleromyography (AMG) is a quantitative measuring device used in practice. AMG uses the piezoelectric

effect to measure the acceleration of muscle tissue in response to nerve stimulation. AMG devices are susceptible to factors which may produce inconsistent measurements that do not always allow AMG to be equivalent to the gold standard MMG or EMG (Murphy, 2018; Naguib et al., 2018). AMG can often measure baseline ToFR values exceeding 1.0, leading to a need to computationally convert or "normalize" AMG data values to allow comparison to EMG or MMG. To complicate this issue, some AMG devices may only display a maximum value of 1.0 regardless of actual value, which may lead to a false assumption by the user that the ToFR value is automatically normalized by the AMG device to be comparable to MMG or EMG results. More recent AMG devices can measure thumb movement in multiple directions to provide more consistent measurements, but many of these recent devices have not yet been validated against EMG or MMG and increased accuracy has yet to be demonstrated. Hypothermia, a constant threat to patients with surgical fields exposed in cold operating suites, may alter measurements. Also, the thumb must be freely moveable, which can be a challenge to ensure in various surgical positions, where arms may be tucked in or surgical drapes and equipment restrict access.

Qualitative measurement. Qualitative measurement is a type of subjective measurement and involves the use of a PNS to deliver an electric impulse to elicit a muscle contraction. The user must interpret the muscle responses for adequate effect or recovery of NMB through visual or tactile means. Several patterns of nerve stimulation are described by Murphy (2018) when used to monitor NMB effect of nondepolarizing agents: ToF, double burst stimulation, tetanic stimulation, and post-tetanic count (PTC). ToF is commonly used and involves delivering four consecutive electrical stimuli using 2

Hz and the user subjectively compares the first muscle twitch to the fourth muscle twitch, visually and tactilely. Increasing fade of the fourth twitch compared to the first twitch indicates increasing depth of NMB. Double burst stimulation involves two consecutive short tetanic bursts of electrical stimuli using 50 Hz and may facilitate easier comparison of the two sequential muscle twitches. Increasing fade of muscle contraction strength during the second burst compared to the first burst indicates increasing depth of NMB. Tetanic stimulation delivers a sustained electrical impulse of 50 Hz for 5 seconds while observing for sustained muscle contraction. Tetanic muscle contraction which fades during the duration of stimulus indicates presence of NMB. PTC, used when NMB is deep enough to produce no response at all to ToF stimulation, delivers a tetanic stimulation of 50 Hz for 5 seconds followed by 10-20 single stimuli. Fewer muscle twitches noted in response to these single stimuli corresponds to deeper NMB and longer time until ToF response will return.

Capron et al. (2006) compared tactile assessment monitoring of one site to a control of mechanomyography (MMG) monitoring of the contralateral hand in 32 patients who received rocuronium and sevoflurane anesthesia. Out of 203 MMG measurements of ToFR 0.4-0.9, only 15 qualitative measurements using ToF could detect fade (presence of NMB). Using double burst stimulation, fade was detected by providers in 111 of 203. Using 50-Hz tetanic stimulation, fade was detected in 9 out of 84 patients with ToFR 0.4-0.9. Capron et al. have shown qualitative monitoring to potentially miss many patients who still have continued effects of NMB.

Physical assessment. Certain physical assessment findings have been used to assess NMB recovery, such as sustained head-lift of five seconds. However, studies in

previous decades have demonstrated that physical assessment findings are not sensitive in assessing NMB recovery. Kopmann, Yee, and Neuman (1997) found that all ten of their volunteer subjects can maintain a head-lift and leg-lift of 5 seconds at all tested levels of NMB (ToFR 0.48-0.75). But physical assessment and bedside clinical testing may still have value in detecting residual NMB in the PACU, when patients have already recovered from anesthesia and are extubated. Unterbuchner et al. (2017) were able to develop an algorithm consisting of multiple physical assessment and bedside tests, such as head and arm lift, swallow water, and others, to detect residual NMB in a study of 165 healthy subjects' assessment results compared to AMG measurements. Results were only sensitive for detecting residual NMB with ToFR <0.7 in a non-geriatric population with few or no comorbidities. Unterbuchner et al. concluded that use of quantitative monitoring devices during anesthesia and before extubation remains a gold standard.

Quantitative measurement, when compared with qualitative measurement and physical assessment, allows for detection of more patients with ongoing NMB effects when assessing for adequate recovery/antagonism. Naguib et al. (2018) states there is no consensus on the definition of terms describing the depth of NMB. Naguib et al. in a professional statement proposes definitions of various degrees of NMB. Minimal block is defined as ToFR 0.4-0.9, while shallow block is ToFR <0.4. Moderate block begins when there are more than zero but fewer than four muscle twitch responses during ToF. Deep and then complete block begin when ToF produces no muscle response and PTC must then be used.

Residual Neuromuscular Blockade

Residual skeletal muscle weakness may persist after administration of reversal agents. Kopman, Yee, and Neuman (1997) studied the effects of NMB on ten volunteers without comorbidities. After performing control measurements of sustained head lift of 5 seconds, sustained leg lift of 5 seconds, hand grasp strength measured with a dynamometer, and strength to hold onto tongue depressor with mouth, a $5mg \cdot kg^{-1}$ bolus of nondepolarizing agent mivacurium followed by continuous infusion was given. The tests were repeated at predetermined ToFR measurements, and again when ToFR was stable between 0.85 and 0.9 following controlled NMB recovery. All 10 volunteers could maintain leg-lift of 5 seconds with ToFR 0.50-0.65 and head-lift of 5 seconds at ToFR 0.48-0.75. Grip strength at ToFR 0.7 was a mean 57% of control strength value ($p<0.01$), and masseter muscle strength allowing retention of tongue depressor recovered at ToFR 0.86 (range 0.68-0.95). This small study demonstrated that previous methods used to determine adequate NMB recovery, such as sustained head lift, could be performed by volunteers with a ToFR 0.7. Indeed, some volunteers never lost the ability to sustain head or leg lift during the observation period, despite ToFR in some volunteers as low as 0.48. Kopman, Yee, and Neuman demonstrated that common subjective physical assessments were not sensitive to assess adequate NMB recovery but reported an unexpected result that masseter muscle strength to retain a tongue depressor seemed to correlate with more complete NMB recovery. Despite the volunteers' ability to perform many tests at ToFR 0.7 and to maintain airway without intervention, investigators all agreed that volunteers were insufficiently recovered due to a number of other observations, such as inability to

sit up without assist, inability to sip water through a straw, diplopia and visual disturbance, and general feeling of weakness.

Eriksson et al. (1997) studied effects of nondepolarizing agent vecuronium on pharyngeal constrictor muscle tone, upper esophageal sphincter tone, bolus transit time, muscle coordination, and aspiration monitoring in 14 healthy volunteers using videomanometry, fluoroscopy, and ToFR measurements at the adductor pollicis. Control measurements were done prior to initiating NMB. Esophageal sphincter resting tone had statistically significant reduction at ToFR 0.6, 0.7, and 0.8 ($p<0.05$). Misdirected swallowing and aspiration were observed at ToFR 0.6 (n=4/14), ToFR 0.7 (n=3/14), and ToFR 0.8 (n=1/14). Aspirations did not penetrate level of vocal cords into the trachea and no volunteers demonstrated signs of aspiration such as cough or respiratory discomfort. No aspirations were observed at ToFR 0.9.

In this investigation by Eriksson et al. (1997), despite the limited sample and inability determine any central dysfunction of swallowing, demonstrated incidences of aspiration when ToFR was below 0.9. Airway protection and safety is of paramount importance in anesthesia care. ToFR greater than 0.9 has demonstrated satisfactory return of pharyngeal function and reduced risk of aspiration in the setting of residual NMB.

Currently, surgeries are increasingly performed with the expectation of discharging patients home the same day. This places increasing importance on surgical patients having sufficient recovery from NMB prior to discharge without relying on a hospital admission to provide additional time and monitoring. To better ensure complete recovery with least risk to adverse events associated with residual NMB, the currently

accepted standard of ToFR ≥0.9 for NMB recovery has replaced the previous standard (Naguib et al, 2018).

Residual neuromuscular blockade incidence and complications. Fourtier et al. (2015) conducted a prospective observational study over one year at eight Canadian hospitals on adults undergoing open or laparoscopic abdominal surgery expected to last less than 4 hours using at least one dose of nondepolarizing agent for intubation or maintenance of NMB. An AMG device was used at 10 specific time points starting prior to nondepolarizing agent administration and ending with a final measurement upon arrival to PACU. Attending anesthesiologist and all nurses were masked to the measurements of the AMG device and were not allowed other means of quantitative assessment of NMB. Practitioners could provide care using a qualitative device consistent with usual practice. No medication doses were standardized and decision to extubate was at the discretion of the attending anesthesiologist.

Data was available for 241 patients at tracheal extubation and 207 patients on arrival to PACU. Fourtier et al. found the incidence of residual NMB (defined as normalized ToFR <0.9) at time of extubation and on arrival to PACU were 63.5% and 56.5%, respectively. A positive association was found between incidence of residual NMB and higher dose of rocuronium per minute of surgery at time of extubation and at time of PACU arrival (p=0.021 and 0.007 respectively). A low incidence of postoperative complications did not allow for an assessment of the impact of residual NMB on postoperative complications. Three patients were diagnosed with pneumonia or atelectasis, one patient required assisted ventilation, and one was reintubated. A qualitative device was used in approximately 66% of surgeries, while neostigmine was

used for NMB antagonism in approximately 72% of surgeries. The use of neostigmine without using a PNS was not associated with reduced incidence of residual NMB at extubation and on arrival to PACU (p=0.543 and 0.135, respectively). The use of a PNS was associated with reduced incidence of residual NMB at arrival to PACU (p=0.028) but not at extubation (p=0.273). Fourtier et al. observed that usual anesthesia practice resulted in many patients measuring to have residual NMB, despite use of reversal agent neostigmine and a PNS, and brought attention to a need to examine practices in anesthesia regarding reducing incidences of residual NMB. Although in this study, despite high incidences of residual NMB, a relatively small number of complications were reported.

Saager et al. (2019) conducted a similar year-long, prospective observational study at ten hospitals in U.S.A. on 255 adults undergoing open or laparoscopic abdominal surgery. An AMG device was used to determine residual NMB, defined as ToFR <0.9. Anesthesia providers could provide routine clinical practice using reversal agent and a qualitative device at their discretion while masked to AMG results. Residual NMB incidence was 64.7% (n=165/255), while 31% (n=79/255) had ToFR as low as <0.6 despite routine clinical judgment determining suitability for extubation. Shorter surgery times, shorter times between administration of NMB agent and extubation, and shorter times between administration of reversal agent and extubation were all associated with increased incidence of residual NMB (p=0.003, 0.001, and 0.02, respectively). Many patients had residual NMB at extubation regardless if providers used neostigmine without PNS or in combination with a PNS, 64% (n=52/81) and 65% (112/171) respectively.

Again, low incidence of complications did not allow sufficiently powered statistical analysis of residual NMB impact on incidences of complications in this study.

In a quality improvement project, Murphy et al. (2008) observed high incidences of residual NMB in patients with critical respiratory events (CREs) in the first 15 minutes of arrival to PACU. Of the 7,459 patients over a one-year period who received general anesthesia, 61 developed a CRE and 42 cases were matched with a control for statistical analysis. Only one of the 61 patients who experienced a CRE did not receive a NMB agent. ToFR <0.7 was measured in 31 of 42 CRE cases. Mean ToFR 0.62 (SD ± 0.2) was measured in patients experiencing a CRE, significantly less than control patients (mean ToFR 0.98, SD ±0.07, p=<0.0001). Most frequent CRE criterion observed were SpO_2<90% on 3 liters/minute oxygen via nasal cannula (59.0%), upper airway obstruction requiring jaw thrust, oral airway or nasal airway intervention (34.4%), and SpO_2 90%-93% on 3 liters/minute oxygen via nasal cannula (19.7%). Reintubation occurred in 6.2% of CRE events. Multiple CRE criteria was observed in 34.4% of cases. None of the control patients displayed any criteria of CRE. Murphy et al. states limitations as inability to suggest causal relationship, possible unknown confounding variables when determining control group, and long-term consequences of residual NMB were not assessed and remain unaccounted. Despite these limitations, this study highlights possible adverse outcomes of residual NMB.

Geriatric Perioperative Considerations

The geriatric population is a fast-growing segment of the population in many countries, requiring increased healthcare needs and resources due to cumulative organ

function decline associated with aging. Geriatric persons can have unique risks that predispose to perioperative complications when anesthetic care involves NMB agents.

Cedborg et al. (2014) observed pharyngeal dysfunction in 17 geriatric subjects (aged 65 years and older without stated history of dysphagia, diabetes, gastric reflux, or surgery to pharynx, larynx or esophagus) using videoradiography and manometry, prior to administration of NMB agent and during minimal NMB states with ToFR of 0.7, 0.8, and spontaneous recovery to >0.9. A rocuronium drip was used to attain desired steady states of NMB measured using an MMG device for a total of 669 swallowing maneuvers, with and without contrast. Prior to administering rocuronium, 37% of swallows showed at least one criterion for pharyngeal dysfunction. Pharyngeal dysfunction incidence increased, compared to control measurement, to 67% ($p=0.014$) and 71% ($p=0.009$) at ToFR 0.7 and 0.8, respectively. After spontaneous recovery to ToFR >0.9, no statistically significant difference was noted in pharyngeal function compared to control (45%, $p=0.44$). No effect was observed in the coordination of breathing and swallowing throughout the study. The use of NMB agents was associated with increased pharyngeal dysfunction, even at minimal NMB levels in this study. It was also concerning the percentage of geriatric subjects with observable criteria for dysphagia, even prior to the use of rocuronium and without stated history of dysphagia.

Flood (2015) describes several geriatric physiologic and pharmacologic considerations affecting NMB. Decreased chest wall compliance reduces effectiveness of intercostal breathing muscles and reduces vital capacity, requiring more work by the diaphragm and abdominal muscles for breathing. Declining diaphragm function and a mechanical disadvantage of a more flattened diaphragm position places the elderly in a

more vulnerable situation. Liver function is generally preserved, although protein synthesis may be reduced, especially in setting of poor nutrition. Decreased plasma proteins that bind drugs and decreased plasma cholinesterase can increase free unbound drug to circulate to effect sites. Glomerular filtration rate decreases by 1 mL/min/year after 40 years of age, potentially affecting renal clearance of drugs and metabolites. Reduced skeletal muscle mass alters drug disposition with redistributed blood flow to other body compartments and reduces neuromuscular reserve, potentially exposing geriatric patients to increased risk of NMB complications.

Murphy, Szokol, et al. (2015) conducted a prospective observational cohort study comparing the incidence of residual NMB in geriatric individuals (70 to 90 years old) to younger adult individuals (18 to 50 years old) groups. Anesthetic care and medications were standardized in each cohort. An AMG device was used for ToFR measurement for the 300 subjects, 150 subjects in each cohort. A higher incidence of residual NMB (ToFR <0.9) was observed in the geriatric cohort (57.7% versus 30.0%, p=<0.001). The geriatric cohort was observed to have an increased incidence of airway obstruction during transport to PACU (18.58% vs. 7.3%, p=0.003), increased incidence of SpO_2 90 to 94% in PACU (38.3% vs 17.3%, p=<0.001), and increased incidence of atelectasis or pneumonia on chest radiograph during hospitalization (15.4% vs 2%, p=<0.001). No statistically significant difference in total rocuronium dose or time from reversal to extubation was observed among the cohorts. It is not clear whether the cause of these increased incidences is caused by use of NMB agents and reversal agents, normal physiologic changes associated with aging, complication of hospitalization, or combination of factors.

Geriatric population may take several medications for multiple comorbidities, increasing the likelihood of possible medication interactions. Naguib (2015) describe several medications that can alter the potency of nondepolarizing agents. Antibiotics such as aminoglycosides, clindamycin, and tetracycline can enhance NMB effect. Antidysrhythmic drug quinidine can also increase potency of nondepolarizing drugs. Chronic anticonvulsant therapy can decrease potency, leading to earlier recovery from NMB and a need for higher doses to establish adequate NMB. Naguib (2015) also states several drugs routinely used by anesthesia providers, such as inhaled anesthetics and large doses of locally injected anesthetic, can increase potency of nondepolarizing drugs.

Studies and literature reviews have examined sugammadex use in the geriatric population, but no systematic reviews were found which methodically examined the available evidence. Given the unique risks to the geriatric population, a systematic review was conducted to determine if the geriatric population, compared to the adult population, requires an altered dose of sugammadex to reduce the incidence of residual neuromuscular blockade during the postoperative period. A systematic review was conducted to determine what is the relationship of sugammadex dosing in the geriatric population compared with the adult population in preventing the incidence of residual NMB in the postoperative period.

Next, the theoretical framework will be presented.

Theoretical Framework

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) is the framework for this systematic review. PRISMA guides the transparent and standardized reporting of systematic reviews and assists in the evaluation of systematic reviews by other readers (Liberati et al., 2009). PRISMA expanded upon prior Quality of Reporting of Meta-analyses (QUOROM) guidelines in response to a growing use of systematic reviews of randomized controlled trials to summarize evidence (Liberati et al., 2009). QUOROM guidelines also increase standardization and rigor to the systematic review process and desire to include systematic reviews with meta-analyses in the guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). While the focus of PRISMA is to aid in the reporting of systematic reviews of randomized trials, PRISMA can be used for systematic reviews with basis in other research (Moher, Liberati, Tetzlaff, & Altman, 2009).

PRISMA utilizes a checklist and a flow diagram to provide a standardized approach to completing and reporting systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009; PRISMA, 2015). The checklist (Appendix A) contains 27 required elements of a systematic review and organized into the categories of title, abstract, introduction, methods, results, discussion, and funding. The flow diagram (Figure 1) graphically details the process of obtaining studies for a systematic review through four phases: Identification, Screening, Eligibility, and Included. The checklist and flow diagram were both used to guide the completion of this systematic review using a standardized approach.

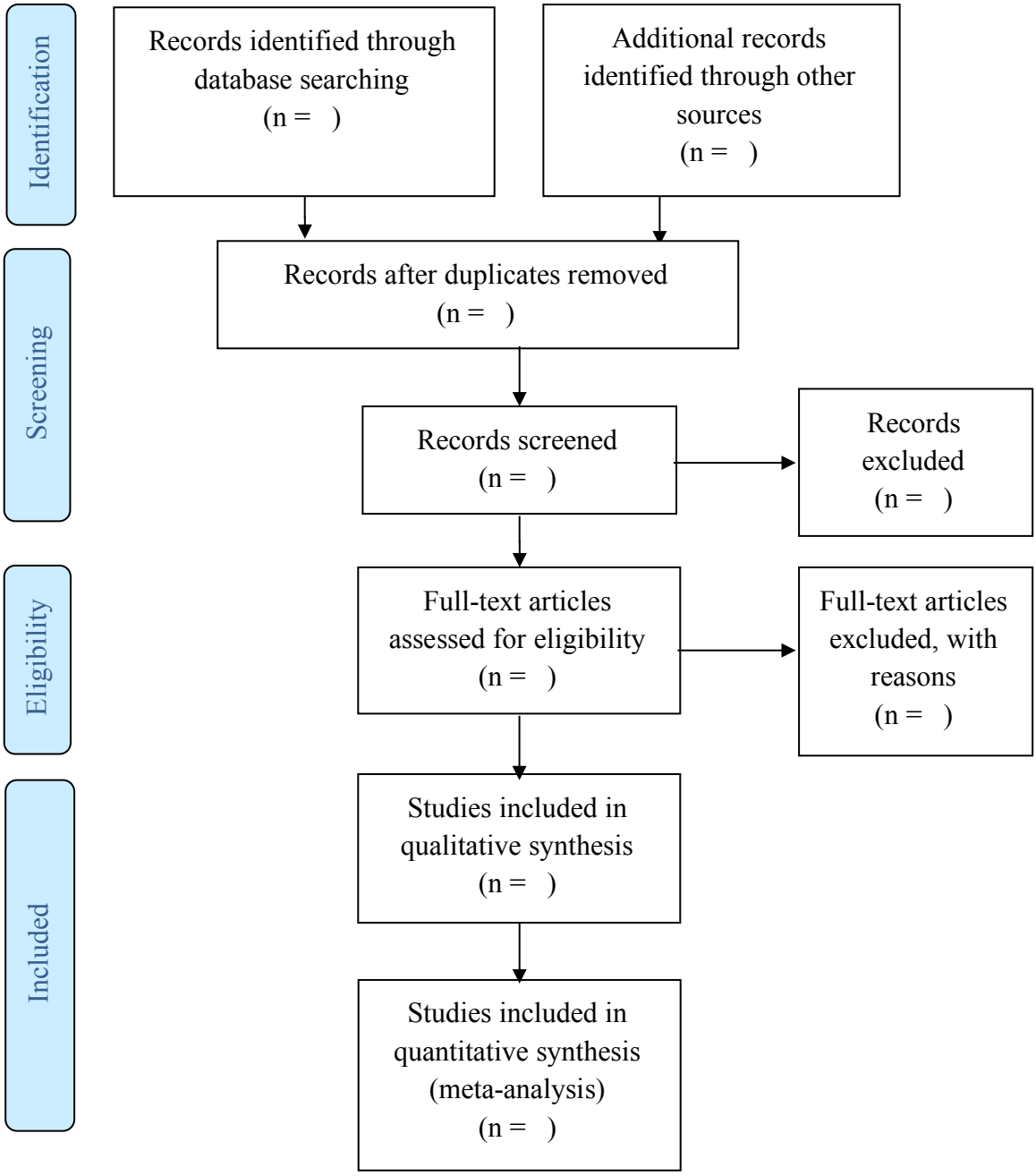

Figure 1. PRISMA 2009 Flow Diagram. From http://www.prisma-statement.org/PRISMAStatement/FlowDiagram

A Critical Appraisal Skills Programme (CASP) checklist was used to assist with systematic evaluation of studies included in the systematic review. The CASP checklist is a critical appraisal tool that contains 12 questions to evaluate and identify limitations of a

study's results and assess research integrity and trustworthiness (Critical Appraisal Skills Programme, 2018a). The checklist is divided into the following three sections: Are the results valid? What are the results? Will the results help locally? (Critical Appraisal Skills Programme, 2018b).

Next, the methods will be presented.

Method

Purpose

The purpose of this systematic review was to determine if the geriatric population, compared to the adult population, requires an altered dose to reduce incidences of residual neuromuscular blockade during the postoperative period.

Inclusion/Exclusion Criteria

Studies considered for inclusion were those examining sugammadex use in the geriatric population and adult population with outcomes regarding residual NMB compared between the two populations. Geriatric population was defined as adults aged 65 years and older. Adult population was defined as those aged 18 years and above but less than 65 years. Quantitative measurement data of residual NMB in the postoperative period is needed to facilitate comparison between studies. Postoperative period was defined as beginning from time of extubation (or from time of entry into PACU or critical care unit if not extubated). Included studies must also involve sugammadex for reversal of nondepolarizing NMB agent rocuronium. Exclusion criteria included studies primarily involving pediatric subjects (less than 18 years old) and studies involving subjects with neuromuscular diseases and limitations, such as myasthenia gravis and hemiparesis due to cerebral vascular accident. Studies not written in English or without English translation were excluded. No date limit was imposed.

Search Plan

Databases used on Ebscohost were CINAHL, MEDLINE, and Academic Search Complete. Search terms used include: sugammadex, elder*, geriatric, aged, neuromuscular block*, NMB. Titles and abstracts were used to screen search results as

part of the search strategy. This systematic review considered the inclusion of randomized controlled trials. However, no randomized controlled trials that meet the inclusion criteria and allowed the comparison of geriatric and adult populations were noted. This systematic review then considered prospective non-randomized cohort studies for inclusion.

Critical Appraisal

The CASP Cohort Study checklist (2018b) was utilized to systematically appraise studies for research integrity and trustworthiness and to assist with identification of any limitations that may impact the strength of research results. All studies eligible for inclusion was subjected to this appraisal tool. The CASP Cohort Study Checklist was chosen for this systematic review as no randomized controlled studies which met inclusion criteria were identified at the time of literature search, which necessitated the inclusion of prospective nonrandomized studies for systematic review. The CASP Cohort Study Checklist is shown below (Table 1).

Data Collection

After critical appraisal, data collection tables were used to organize data regarding specific studies included into the systematic review. These tables (Table 2) include purpose, sample, site, method, limitations, and results.

Cross-Study Analysis

After critical appraisal and data collection, a cross-study analysis table (Table 3) was used to compare pertinent results across all included studies. NMB agent and sugammadex dose, time to recovery of ToFR to >0.9 for each age group, and any adverse events was included in the cross-study analysis table.

Table 1

CASP Cohort Checklist

Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?			
2. Was the cohort recruited in an acceptable way?			
3. Was the exposure accurately measured to minimise bias?			
4. Was the outcome accurately measured to minimise bias?			
5a. Have the authors identified all important confounding factors?			
5b. Have the taken account of the confounding factors in the design and/or analysis?			
6a. Was the follow up of the subjects complete enough?			
6b. Was the follow up of subjects **long** enough?			
Section B. What are the results?			
7. What are the results of this study?			
8. How precise are the results?			
9. Do you believe the results?			
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?			
11. Do the results of this study fit with other available evidence?			
12. What are the implications of this study for practice?			

Table 2

Data Collection Table

Citation				
Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*

Table 3

Cross-Study Analysis

Study	*NMB dose*	*Sugammadex dose*	*Geriatric time to recovery*	*Adult Time to recovery*	*Adverse Events*

Next, the results will be discussed.

Results

A total of 316 articles were identified in the literature search, 30 of which were excluded due a pediatric focus. Using the inclusion and exclusion criteria, six studies were included for analysis in this systematic review. The PRISMA flow diagram illustrating the search results is shown in figure 2. Critical appraisal for each study using the CASP checklist is presented in Appendix B. Data collection tables for each included study are in Appendix C. Appendix D presents the cross-study analysis for outcomes comparison.

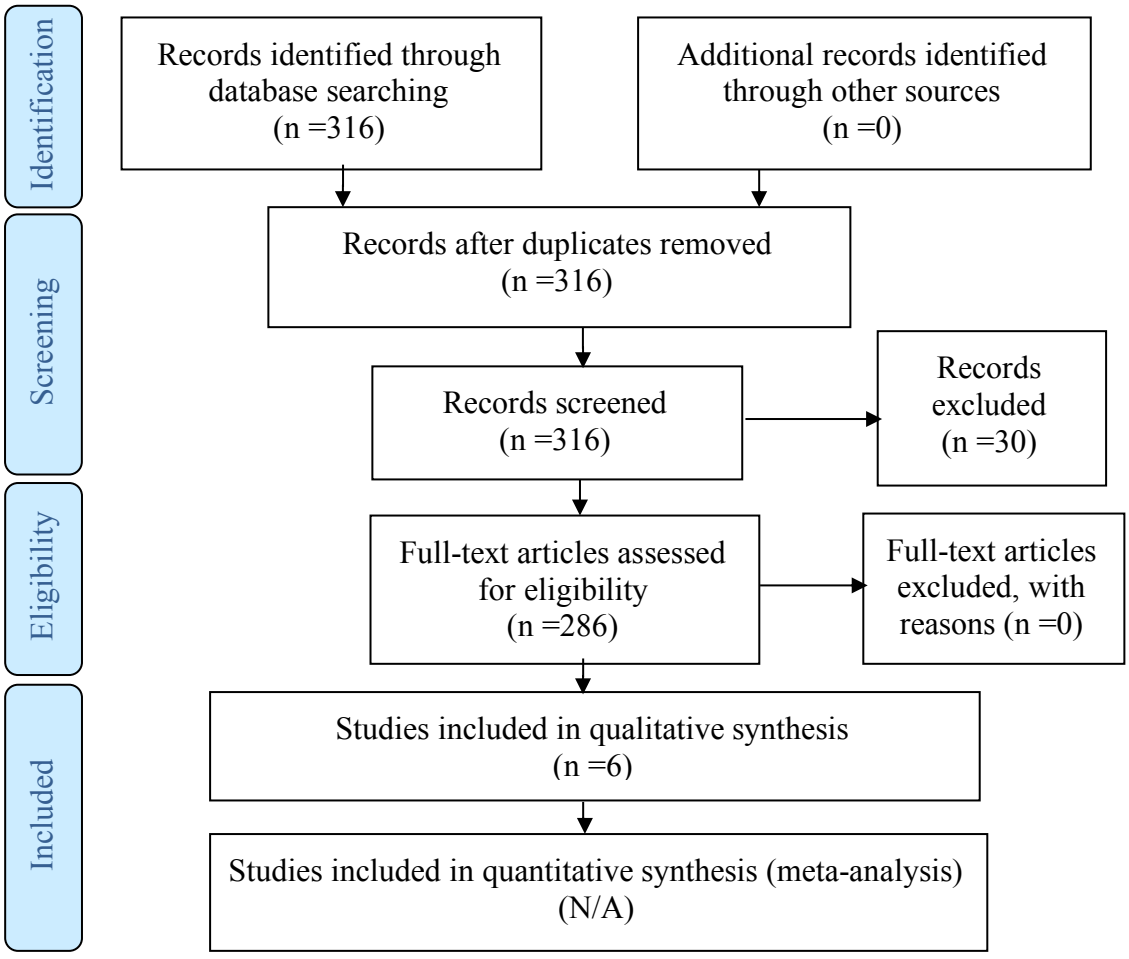

Figure 2. PRISMA flow diagram of search results.

The study by Kadoi, Nishida, and Saito (2013) sought to compare the recovery times from rocuronium-induced NMB using sugammadex between two groups receiving electroconvulsive therapy: young (≤50 years old) and elderly (≥70 years old). This study also investigated the existence of a correlation between cardiac index and reversibility of rocuronium-induced NMB using sugammadex. Seventeen subjects were recruited (young group, n=8; elderly group, n=9) in this prospective observational study. Induction of general anesthesia and NMB was standardized in both groups with weight-based dosing of propofol and rocuronium. Sugammadex dosing was standardized in both groups also. Procedure and location of NMB monitoring was standardized in all subjects. All patients were noted to have no response to ToF stimulation at time of sugammadex administration, due to short time elapsed since rocuronium administration.

The results for this study are shown in Appendix C, Table C-1. All subjects were accounted for this study. The young group had a recovery time of 403±37 seconds (mean± standard deviation [SD]). The elderly group had a longer recovery time of 443±36 seconds (mean±SD). This finding was considered statistically significant (P= 0.04). This study also reported a longer time to loss of ToF response after administration of rocuronium in the elderly group, with the young group requiring 102±10 seconds (mean±SD) and elderly group requiring 139±32 seconds (mean±SD). A statistically significant correlation between cardiac index and onset of NMB was reported (P<0.01) but no statistically significant correlation was found between recovery time to ToFR 0.9 and cardiac index (P= 0.80). No postoperative events related to relapse of NMB or respiratory events were reported. Limitations in this study include small sample size and a dose of sugammadex larger than typically used in clinical practice. Kadoi, Nishida, and

Saito (2013) discussed that recovery times reported in this study were also comparatively longer than reported NMB recovery times in other studies after administration of sugammadex. This finding was attributed to the timing of sugammadex relatively soon after rocuronium administration, when NMB was likely profound with little spontaneous recovery. Although 8 $mg \cdot kg^{-1}$ would be considered appropriate in this study given that only a few minutes have elapsed since a large dose of rocuronium, this is different from routine clinical scenarios where a smaller dose of sugammadex is often given a significant time after rocuronium administration and significant spontaneous recovery of NMB may have occurred. Chronic psychiatric illness and its effects on overall physical health may have also contributed.

The CASP appraisal for this study can be seen in Appendix B, Table B-1. The study compared age populations desired for this systematic review. While the results are generally congruent with other studies, the sugammadex dose used and timing of sugammadex relative to a large dose of rocuronium may limit generalization to typical clinical situations outside of electroconvulsive therapy.

A multicenter prospective observational study by McDonagh et al. (2011) investigated the impact of age on the pharmacokinetics of sugammadex for the reversal of rocuronium-induced NMB. Subjects were stratified into three groups: Adult (aged 18-64 years, n=45), Elderly (aged 65-74 years, n=57), and Old-elderly (aged ≥75 years, n=35). All patients were American Society of Anesthesiologists (ASA) Physical Status 1-3, undergoing elective surgery in supine position requiring general anesthesia and muscle relaxation. Rocuronium dose was standardized to 0.6 $mg \cdot kg^{-1}$ with induction and subsequent rocuronium doses of 0.15 $mg \cdot kg^{-1}$ whenever the ToF stimulation revealed at

least two twitches. Sugammadex dose was standardized at 2 $mg \cdot kg^{-1}$ and given at the end of surgery upon reappearance of the second twitch using ToF.

Results are described in Appendix C, Table C-2. Time from sugammadex administration to recovery of ToFR 0.9 was reported. The Adult group had a time of 2.3 minutes (mean, standard deviation [SD] 1.0 minutes) to recover to ToF 0.9, Elderly group with 2.7 minutes (mean, SD 1.4 minutes), and Old-elderly group with reported time of 3.7 minutes (mean, SD 1.6 minutes). Combined data of Elderly and Old-elderly groups (all subjects ≥65 years old) had a reported recovery time of 3.1 minutes (mean, SD 1.6 minutes). A statistically significant difference was found between the Adult group and the combined elderly data group (P=0.017). Thirteen additional subjects had quantitative monitoring data that was unavailable or considered unreliable. The above results excluded these thirteen subjects. The investigators used data in the 95th percentile to incorporate these thirteen subjects and reported these results separately. Overall, results were similar, with combined Elderly and Old-elderly groups showing statistically significant (P=0.022) longer recovery to ToFR 0.9 than Adult group (3.3 minutes [mean, SD 1.7 minutes] versus 2.5 minutes [mean, SD 1.4 minutes], respectively). Investigators reported all adverse events and felt that two patients in the Elderly group had adverse events that may be related to sugammadex. One patient experienced tachycardia, pyrexia, dizziness, and oliguria. Another patient experienced procedural hypotension. Also, one patient in the Old-elderly group had reported mild muscle weakness, but recurrence of NMB could not be definitively ruled out by investigators as NMB monitoring had ceased by that point postoperatively. No respiratory events or reintubations attributed to incomplete recovery or relapse of NMB were reported. Limitations include a lack of

discussion regarding standardizing inhalational anesthetics to age-adjusted dosages. The Old-elderly group (mean age 80.1 years old [SD 4.1 years]) may have received relatively more inhalational anesthetic than the adult group (mean age 45.5 years old [SD 11.3 years]) if age-adjusted dosage was not accounted in this study.

CASP appraisal for this study is found in Appendix B, Table B-2. Results and aim of this study are pertinent to this systematic review. Rocuronium and sugammadex dosages more closely resemble clinical use and a larger sample across multiple centers improves generalizability of results. However, a lack of discussion regarding standardizing and use of age-adjusted dosing of inhalational agents may introduce a potential threat to validity. Volatile inhalational anesthetics are known to potentiate NMB effect, but it is difficult to estimate its significance in this study without additional information such as length of surgery and inhalation dosages used.

Muramatsu et al. (2018) tested the hypothesis that recovery from deep NMB with low dose sugammadex is slower in elderly patients than in nonelderly patients and that elderly patients would experience a higher incidence of relapse of NMB. Their observational study included 40 subjects (Nonelderly <70 years old [n=20] and Elderly ≥70 years old [n=20]) undergoing surgery with general anesthesia using only intravenous anesthetics propofol and remifentanil infusions. All patients received rocuronium 0.6 $mg \cdot kg^{-1}$ after induction and confirmed to have no response to ToF stimulation prior to intubation. Spontaneous recovery to ToFR >0.5 was then allowed. Then, rocuronium 0.4 $mg \cdot kg^{-1}$ was given with additional doses of 0.2 $mg \cdot kg^{-1}$ if needed to deepen NMB to a PTC range of 2 through 10. Once target NMB attained, sugammadex infusion 50 mcg/kg/min was initiated until ToF count of 3 achieved. Once ToF count of 3 was

achieved, the sugammadex infusion was discontinued. ToFR was measured for at least 30 minutes after sugammadex infusion was discontinued. The subjects were maintained on mechanical ventilation and in general anesthesia using only intravenous anesthetics during this period. Once study was completed, additional sugammadex was administered prior to emergence and extubation.

Results can be found in Appendix C, Table C-3. Spontaneous recovery to ToF count of 1 after the initial rocuronium dose was slower in the Elderly group compared to Nonelderly group (45.4 minutes and 30.2 minutes, respectively, *P*=0.016). Recovery time to ToF count of 3 after initiation of sugammadex infusion was also slower in the Elderly group than the Nonelderly group (15.3 minutes and 11.7 minutes, respectively, *P*=0.018). The investigators also noted two phases of recovery after initiation of sugammadex infusion. Early-phase recovery was characterized by a more rapid recovery and increase in ToFR soon after initiation of sugammadex infusion. Late-phase then followed, characterized by a slower recovery rate of ToFR. No significant difference was noted between the two groups during the early-phase recovery (*P*=0.607). A significant difference was noted during late-phase recovery (0.006), with Elderly group having a slower rate of recovery than the Nonelderly group. Relapse of NMB, defined in this study as a negative change in ToFR after sugammadex infusion was discontinued, was more frequent in the Elderly group (n=7, *P*= 0.044) than the Nonelderly group (n=1).

The CASP critical appraisal tool for this study is found in Appendix B, Table B-3. This study used total intravenous anesthesia, which removed inhalational anesthetics as a possible confounding variable. This study used a sugammadex infusion in the design, which is not usual clinical practice. While it served to experimentally replicate situations

of low sugammadex dosing, it is not known how accurately this reflects actual clinical situations of low sugammadex doses leading to relapse of NMB. No follow-up monitoring postoperatively was stated. It is not known if any incidences of NMB relapse occurred after the study completed, during recovery in the PACU. Although incidences of NMB relapse were not likely due to additional sugammadex given to all subjects at the conclusion of the observation period.

A study by Shin et al. (2016) investigated the dose of sugammadex needed to recover from deep NMB within two minutes for the geriatric and adult populations. Forty-four subjects, ASA Physical Status 1 or 2, undergoing elective ear nose throat surgery under general anesthesia were enrolled. Subjects were separated into two groups: Young Adult (n=22, aged 20-40 years) and Elderly Adult (n=22, aged ≥70 years). Rocuronium dose with induction was 0.6 $mg \cdot kg^{-1}$ and maintenance doses of 0.2 $mg \cdot kg^{-1}$ used to maintain a PTC of 1 or 2 until the end of surgery. Sugammadex 4 $mg \cdot kg^{-1}$ was given to the first subject and observed if recovery to ToFR ≥0.9 occurred within 2 minutes. Sugammadex dose for subsequent subjects was increased or decreased by 0.5 $mg \cdot kg^{-1}$ depending on the previous subject's failed or successful rapid recovery to ToFR ≥0.9 within 2 minutes. Anesthesia providers were masked to the sugammadex dose given during the study. The isotonic regression method was used to determine the effective dose for 50 percent of subjects (ED_{50}) and 95 percent of subjects (ED_{95}) for the Young Adult and Elderly Adult groups. General anesthesia was provided with propofol and remifentanil infusions and without the use of inhalational anesthetics.

Results are displayed in Appendix C, Table C-4. For the Adult group, ED_{50} and ED_{95} for sugammadex is 3.3 $mg \cdot kg^{-1}$ (83% confidence interval [CI], 3.2-3.4) and 4.4

$mg \cdot kg^{-1}$ (95% CI, 3.9-4.5), respectively. The Elderly Adult group ED_{50} for sugammadex is 4.5 $mg \cdot kg^{-1}$ (83% CI, 4.2-5.0) and ED_{95} is 5.4 $mg \cdot kg^{-1}$ (95% CI, 4.9-5.5). Statistical significance was determined by non-overlapping CI between the two groups for ED_{50} and ED_{95}. The investigators discussed limitations, which include baseline ToFR values often exceeding 1.0. The investigators chose not to normalize the ToFR values for this study and instead limited baseline ToFR values to be within 0.95 and 1.05 to minimize the potential of overestimation of recovery from NMB. No postoperative events due to respiratory complications or NMB relapse were reported in any subjects.

CASP appraisal can be found in Appendix B, Table B-4. Overall, results are congruent with other studies. Masking the anesthesia provider from the sugammadex dose and removing inhalational anesthetics from general anesthesia were efforts to improve validity of results by limiting elements of bias and confounding variables. All subjects were ASA Physical Status 1 or 2, which help limit excessive comorbidity differences between the two groups. This study focused on outcomes and age populations desired for this systematic review.

Suzuki et al. (2011) investigated the reversibility of profound rocuronium-induced NMB using sugammadex in younger and older subjects. Younger subjects (aged 20-50 years, n=15) and older subjects (aged ≥70 years, n=15) were undergoing gynecological surgery under general anesthesia and of ASA Physical Status 1 through 3. All subjects received rocuronium 1 $mg \cdot kg^{-1}$ with subsequent doses of 0.02 $mg \cdot kg^{-1}$ whenever a PTC of 1 or 2 was observed. General anesthesia was maintained using sevoflurane 1%-1.5% and remifentanil infusion 0.02-0.05 mcg/kg min. All subjects at the end of surgery were given sugammadex 4 $mg \cdot kg^{-1}$ when spontaneous recovery to PTC of 1 or 2 was observed.

Time to recovery of ToFR 0.9 was recorded while sevoflurane and remifentanil were continued. Subjects were monitored for 24 hours after surgery for respiratory events.

Results can be found in Appendix C, Table C-5. For the younger adult group, recovery to ToFR 0.9 after administration of sugammadex was 1.3 minutes (SD 0.3 minutes, range 0.8-2.0 minutes). The older adult group had a mean recovery time of 3.6 minutes (SD 0.7, range 2.4-4.5 minutes, $P<0.0001$). Duration of surgery was significantly longer for the older adult group (mean 177.5 minutes, $P=0.0015$) than the younger adult group (mean 118.5 minutes). Total rocuronium dose and weight were similar between the younger adult (mean 57.2kg, mean 93.4 mg rocuronium) and older adult (mean 55.9 kg, mean 97.5 mg rocuronium) groups. The investigators reported no postoperative events attributable to relapse of NMB after reversal with sugammadex.

The CASP critical appraisal tool for this study can be found in Appendix B, Table B-5. This study contained only female subjects who underwent gynecological surgery, which may limit generalizability to other populations. The use of inhalational agent and along with longer duration of surgery for the older adult group may prolong the NMB effect in the older adult group. ASA physical status 3 subjects may have also introduced additional comorbidities to this study, but all subjects were free from neuromuscular, renal, and hepatic disease as part of the inclusion criteria. It is unknown from the data reported if ASA Physical Status 3 subjects were overrepresented in the older adult group. Overall, this study investigated the age groups and outcomes desired for this systematic review.

An investigation by Yazar et al. (2016) compared the effects of sugammadex on the duration of recovery from rocuronium and incidence of NMB relapse between the

young elderly (65-74 years old, n=30) and middle-aged elderly (≥75 years old, n=29) groups. All subjects were undergoing laparoscopic cholecystectomy and were ASA Physical Status 1 through 3. All subjects received rocuronium 0.6 $mg \cdot kg^{-1}$ with subsequent doses of 0.15 $mg \cdot kg^{-1}$ whenever ToF count of 2 or more was observed. General anesthesia was maintained using 50% nitrous and 1.5% sevoflurane (end-tidal concentration). Sugammadex 2 $mg \cdot kg^{-1}$ was given at the end of surgery upon spontaneous recovery to ToF count of 2. Recovery time to ToFR 0.9 and incidences of ToFR returning to <0.9 after NMB recovery were recorded. Patients were monitored for adverse events for 60 minutes postoperatively while ToFR was reassessed 5 minutes into the postoperative period to evaluate for relapse of NMB effect.

Results can also be found in Appendix C, Table C-6. The middle-aged elderly group had a longer recovery time to ToFR 0.9 than the young elderly group (mean 5.5 minutes [range 2.47-9.54 minutes] versus mean 3.27 minutes [range 1.41-5.37 minutes, $P<0.001$], respectively). Yazar et al. reported no significant difference between the two groups regarding gender, ASA Physical Status, BMI, duration of surgery, duration of anesthesia, and total amount of rocuronium used in surgery. Time for rocuronium to produce zero twitches in ToF stimulation was longer in the middle-aged elderly group than the young elderly group (2.4 minutes and 1.48 minutes, $P=0.009$). One subject in the young elderly group was determined to have a relapse of NMB and was reintubated.

The CASP critical appraisal for this study is found in Appendix B, Table B-6. This study compared two geriatric populations without comparing an adult group aged <65 years. Overall, findings are congruent in other studies, that increased age of subjects is associated with increased time to recovery of ToFR 0.9 after administration of

sugammadex. While inhalational anesthetics were used and potentially a confounding variable, its impact may be lessened by the limited duration of surgery to less than two hours, less disparity of age when comparing two geriatric groups, and similar duration of anesthesia between the two groups. While sevoflurane was limited to end-tidal measurement of 1.5%, there was no discussion of age-adjusted dosing.

The cross-study analysis which details rocuronium and sugammadex dosage, results, and adverse events, can be found in Appendix D. Five out of six studies examined the use of sugammadex in reversal of rocuronium-induced NMB in both adult and geriatric age groups. Yazar et al. did not include non-geriatric subjects but stratified the aged population into young-elderly and middle-aged elderly in their study. There was also variation in the methodology among the six studies, such as level of NMB being reversed and dose of sugammadex administered. Four studies (Kadoi et al., McDonaugh et al., Muramatsu et al., and Suzuki et al.) all generally found a longer recovery time for the geriatric population compared to non-geriatric population. Yazar et al., who did not include non-geriatric subjects, found that older age was associated with longer recovery time after sugammadex administration within the geriatric population. Shin et al., who investigated the sugammadex dose required for NMB recovery within two minutes, found that the geriatric group required a higher dose of sugammadex to achieve NMB recovery within targeted time compared to the non-geriatric group. Adverse events related to incomplete recovery or relapse of NMB were reported. Among all studies included, one subject experienced relapse of NMB and required reintubation (Yazar et al.). One subject experienced muscle weakness, but relapse of NMB was unable to be definitively ruled out beyond quantitative monitoring period (McDonaugh et al.). In the study by

Muramatsu et al., a negative change in ToFR was noted in eight subjects after receiving low dose sugammadex via infusion that was discontinued prior to NMB recovery to ToFR 0.9. Muramatsu et al. did not report any adverse events.

Next, the summary and conclusions will be discussed.

Summary and Conclusions

Sugammadex offers a novel approach to NMB reversal without the limitations and potential side effects associated with neostigmine. However, there is a lack of systematic reviews that examine the use of sugammadex among different age groups, specifically the geriatric population. The purpose of this systematic review was to determine if the geriatric population, compared to the adult population, requires an altered dose to reduce incidences of residual neuromuscular blockade during the postoperative period.

A literature review which discussed definitions and measurement of recovery from NMB, incidence of incomplete recovery, and geriatric considerations was done. The theoretical framework outlined the use of PRISMA checklist and flow diagram to complete a systematic review. A search for studies meeting the inclusion criteria was completed using Ebscohost databases CINAHL, MEDLINE, and Academic Search Complete.

An individual analysis was performed by completing a data collection table and a CASP checklist for each included study. The CASP checklist allowed for systematic appraisal of each study to identify limitations and assess the validity of an included study's results. A cross-study analysis was then done to compare results and methods across all included studies.

Overall, results of the cross-analysis show that the geriatric population, when receiving an equal weight-based dose of sugammadex, required a longer time to achieve NMB reversal than a younger adult population. Increased age was associated with longer recovery from NMB after sugammadex, even within the geriatric population. Adverse

events associated with residual NMB were infrequent amongst all included studies. In one study using low dose sugammadex infusion, a negative change in ToFR was observed in eight subjects but no adverse events were reported. It was not possible to assess if there was an increased risk of adverse events associated with residual NMB with the limited number of adverse events in the included studies for this systematic review.

Several limitations were noted in this systematic review. First, the included studies had varied methodology in the dose of sugammadex, method of sugammadex administration, level of NMB that was reversed, and varied stratification of geriatric population. However, regardless of methodology, each study found that the group with increased age was associated with increased recovery time. Second, there were few reported adverse events that were associated with residual NMB amongst all included studies. Out of 340 subjects across all six included studies, one subject (65-74 years old) required reintubation postoperatively and one subject (≥75 years old) experienced muscle weakness but unable to definitively rule out residual NMB since the event occurred beyond the observation period of the study. A transient negative change in ToFR was observed in one subject <70 years old and seven subjects ≥70 years old following a low dose sugammadex infusion, but no adverse events were reported. With so few adverse events, it is not possible to assess if increased age was associated with increased adverse events from residual NMB. However, the infrequency of adverse events in this systematic review seems to agree with previous studies by Fourtier et al. (2015) and Saager et al. (2019) that found infrequent adverse events despite a high incidence of residual NMB. Third, the absence of randomized controlled trials limits the strength of concluding that increased age is a causative factor in prolonged recovery from NMB after sugammadex

administration. Several physiologic factors in the geriatric population discussed in the literature review can account for variations in response to NMB drugs and NMB reversal drugs compared to a younger adult population. Also, while all included studies standardized the dose of rocuronium and sugammadex according to weight, not all studies limited or standardized the use of inhalational anesthetic, used age-adjusted dose of inhalational anesthetic, or controlled for duration of surgery (which may expose the geriatric population to all anesthetic drugs for a longer duration).

Next, the recommendations and implications for advanced nursing practice will be discussed.

Recommendations and Implications for Advanced Nursing Practice

Many surgical procedures require the use of NMB agents during anesthesia. The use of NMB agents also come with the need to reverse the effects of NMB. While acetylcholinesterase inhibitors have long been used to reverse NMB, they require anticholinergic drugs to manage side effects such as bradycardia, bronchoconstriction, and increased salivation. Sugammadex is a new class of NMB reversal agent showing some benefits over acetylcholinesterase inhibitors, but it is not without limitation and should be used with consideration to the patient's specific needs.

The results of this systematic review show a correlation between increased age and increased time of NMB recovery after sugammadex administration. The prolonged recovery time following sugammadex bolus varied from less than 1 minute to more than 2 minutes. The clinician should anticipate this response in the aged population and respond appropriately. Recovery from NMB should be confirmed using peripheral nerve stimulation, even after the administration of sugammadex. While residual NMB is associated with low dose sugammadex, incidence of residual NMB is rare if an appropriate dose of sugammadex is used relative to the depth of NMB to be reversed (McDonaugh et al., 2011).

With a lack of randomized controlled trials and the limitations of this systematic review, there is insufficient evidence in this systematic review to support a recommendation to adjust the dose of sugammadex for the geriatric population. Further research is needed to investigate the underlying cause of prolonged NMB recovery in the geriatric population. Shin et al. (2015) suggested that tools to measure peripheral and muscle blood flow may help determine underlying cause. Suzuki et al. (2011) suggest

lower cardiac index may explain prolonged recovery time following sugammadex administration. Kadoi et al (2013) monitored cardiac output in their study but did not find a relationship between cardiac output and NMB recovery time after sugammadex. However, Kadoi et al. discuss that these results do not agree with other studies and suggest that a lack of inhalational agents (having vasodilating properties) and a release of catecholamines during ECT may explain their results.

Certified Registered Nurse Anesthetists can play a vital role in education and expanding research needed to optimize anesthesia care for geriatric patients, a population that is rapidly growing and living longer. The geriatric population have many physiologic age-related changes which potentially alter responses to many aspects of anesthesia care. Ongoing research will be needed as anesthesia practice changes to ensure the geriatric population continues to receive optimal anesthesia care.

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Appendix A

Section/ topic	#	Checklist item	Reported on page#
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix B

Table B-1

CASP Cohort Checklist

Study 1. Kadoi, Y, Nishida, A., & Saito, S. (2013). Recovery time after sugammadex reversal of rocuronium-induced muscle relaxation for electroconvulsive therapy is independent of cardiac output in both young and elderly patients. *Journal of ECT, 29*(1), 33-36.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors?	**X**		
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?	**X**		
Section B. What are the results?			
7. What are the results of this study?	Elderly group had longer recovery to ToFR 0.9 and not associated with CI.		
8. How precise are the results?	Confidence intervals not provided. P values given.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence? *Comment: ECT procedure necessitated reversal shortly after administration of rocuronium*		**X**	
12. What are the implications of this study for practice? *Comment: Large dose sugammadex (8mg·kg^{-1}) used in a situation unique to ECT with small sample size. May not be able to generalize to other clinical scenarios.*		**X**	

CI, cardiac index; ECT, electroconvulsive therapy; ToFR, train of four ratio

Table B-2

CASP Cohort Checklist

Study 2. McDonagh, D. L., Benedict, P. E., Kovac, A. L., Drover, D. R., Brister, N. W., Morte, J. B., & Monk, T. G. (2011). Efficacy, safety, and pharmacokinetics of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in elderly patients. *Anesthesiology, 114*(2), 318-329.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors? *Comment: Authors did not specifically mention temperature control of ToFR monitoring site. Only core temperature control mentioned. Age-adjusted dosing of volatile anesthetics not discussed.*		**X**	
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?	**X**		
Section B. What are the results?			
7. What are the results of this study?	Old-elderly (≥75 years old) and elderly (65-74 years old) groups had longer recovery time to ToFR 0.9 after sugammadex compared to adult (18-64 years old) group		
8. How precise are the results?	Confidence intervals and p-values given.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice? *Comment: Larger sample size in multiple sites increases generalizability of results.*	**X**		

ToFR, Train of Four Ratio

Table B-3

CASP Cohort Checklist

Study 3. Muramatsu, T., Isono, S., Ishikawa, T., Nozaki-Taguchi, N., Okazaki, J., Kitamura, Y., Murakami, N., & Sato, Y. (2018). Differences in recovery from rocuronium-induced deep paralysis in response to small doses of sugammadex between elderly and nonelderly patients. *Anesthesiology, 129*, 901-911.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors?	**X**		
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?		**X**	
Comment: No discussion of PACU monitoring for adverse events. Additional sugammadex after observation ended and prior to subject entering PACU likely reduced risk of adverse events and done prudently to avoid risk of insufficient sugammadex dosing inherent to study design.			
Section B. What are the results?			
7. What are the results of this study?	Increase incidence of relapse and slower recovery of NMB after low dose sugammadex in elderly.		
8. How precise are the results?	p-values and confidence intervals given.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?		**X**	
Comment: Use of sugammadex infusion followed by bolus is not usual clinical practice and may not accurately reflect outcomes in clinical practice.			
12. What are the implications of this study for practice?		**X**	
Comment: Supportive evidence but altered sugammadex administration may impact generalizability of results.			

NMB, neuromuscular blockade; PACU, postanesthesia care unit

Table B-4

CASP Cohort Checklist

Study 4. Shin, S., Han, D. W., Lee, H S., Song, M. K., Jun, E., & Kim, S. Y. (2016). Elderly patients require higher doses of sugammadex for rapid recovery from deep neuromuscular block. *Basic & Clinical Pharmacology & Toxicology, 118*, 462-467.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors?	**X**		
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?	**X**		
Section B. What are the results?			
7. What are the results of this study?	Difference between adult (20-40 years old) and elderly (≥70 years old) ED_{50} and ED_{95} of sugammadex for rapid NMB recovery within 2 min was statistically significant.		
8. How precise are the results?	p-values and confidence intervals given.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice? *Comment: Elderly group may require a higher sugammadex dose to achieve same recovery time as Adult group.*	**X**		

NMB, neuromuscular blockade

Table B-5

CASP Cohort Checklist

Study 5. Suzuki, T., Kitajima, O., Ueda, K., Kondo, Y., Kato, J., & Ogawa, S. (2011). Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients. *British Journal of Anaesthesia, 106*(6), 823-826.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors? *Comment: No age-adjusted dose of sevoflurane discussed but limited to 1%-1.5%. Unknown if elderly group overrepresented with ASA Physical Status 3 subjects.*		**X**	
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?	**X**		
Section B. What are the results?			
7. What are the results of this study?	Longer recovery from PTC 1-2 to ToFR 0.9 in elderly (≥70 years old) compared to adult (20-50 years old).		
8. How precise are the results?	p-values and data ranges given without confidence intervals.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population? *Comment: Sample was only women. No male subjects. Limited demographic information given.*		**X**	
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice? *Comment: Increased age correlated with increased recovery time from deep NMB.*	**X**		

ASA, American Society of Anesthesiologists; NMB, neuromuscular blockade; PTC, post-tetanic count; ToFR, Train of Four Ratio

Table B-6

CASP Cohort Checklist

Study 6. Yazar, E., Yilmaz, C., Bilgin, H., Karasu, D., Bayraktar, S., Apaydin, Y., & Sayan, H. E. (2016). A comparison of the effect of sugammadex on the recovery period and postoperative residual block in young elderly and middle-aged elderly patients. *Balkan Medical Journal, 33*, 181-187.			
Section A. Are the results of the study valid?	**Yes**	**Can't Tell**	**No**
1. Did the study address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimise bias?	**X**		
4. Was the outcome accurately measured to minimise bias?	**X**		
5a. Have the authors identified all important confounding factors? *Comment: Sevoflurane was limited to 1.5% but age-adjusted dose of inhalational agent not discussed. This variable may have less impact due to exclusion of adults <65 years old and less age disparity among subjects.*	**X**		
5b. Have the taken account of the confounding factors in the design and/or analysis?	**X**		
6a. Was the follow up of the subjects complete enough?	**X**		
6b. Was the follow up of subjects **long** enough?	**X**		
Section B. What are the results?			
7. What are the results of this study?	Time to recovery of ToFR was longer with group 2 (≥75 years old) than group 1 (65-74 years old).		
8. How precise are the results?	p-values given with medians and ranges. No standard deviation or confidence intervals with time to recovery results.		
9. Do you believe the results?	**X**		
Section C. Will the results help locally?	**Yes**	**Can't Tell**	**No**
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice? *Comment: Even within the geriatric group, older age is associated with longer recovery time.*	**X**		

ToFR, Train of Four Ratio

Appendix C

Table C-1

Data Collection Table

Study 1. Kadoi, Y, Nishida, A., & Saito, S. (2013). Recovery time after sugammadex reversal of rocuronium-induced muscle relaxation for electroconvulsive therapy is independent of cardiac output in both young and elderly patients. *Journal of ECT, 29*(1), 33-36.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
1. To compare recovery times from rocuronium-induced NMB using sugammadex between young and elderly groups undergoing ECT. 2. To investigate the existence of a correlation between cardiac index and the reversibility of rocuronium-induced NMB using sugammadex after ECT.	Site not discussed. 17 subjects. Elderly group (n=9, age ≥70 years) and young group (n=8, age ≤50 years). ASA PS not discussed. Exclusion: patients with renal, hepatic, cardiovascular, neuromuscular disease, or BMI >35kg·m^{-2}	General anesthesia induced with propofol 1 mg·kg^{-1} and rocuronium 0.6 mg·kg^{-1}. ECT initiated after ToF count of zero. Sugammadex 8 mg·kg^{-1} given immediately after seizure cessation. ToF SX watch used for NMB monitoring.	Young Group: Time to ToFR 0.9 after sugammadex was 403±37 seconds. Elderly Group: Time to ToFR 0.9 after sugammadex was 443±36 seconds (P=0.04)	A large dose of sugammadex was given immediately after cessation of seizure activity, during an ongoing state of deep NMB. Recovery times after sugammadex was longer in this study compared to other reports, with may have been influenced by timing of rocuronium, ECT, sugammadex, and overall physical health

	status during chronic psychiatric illness.

ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; ECT, electroconvulsive therapy; NMB, neuromuscular blockade; ToF, train of four; ToFR, train of four ratio

Table C-2

Data Collection Table

Study 2. McDonagh, D. L., Benedict, P. E., Kovac, A. L., Drover, D. R., Brister, N. W., Morte, J. B., & Monk, T. G. (2011). Efficacy, safety, and pharmacokinetics of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in elderly patients. *Anesthesiology, 114*(2), 318-329.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
To assess the impact of age (≥65 years old) on efficacy, safety, and pharmacokinetics of sugammadex for reversal from moderate rocuronium-induced NMB	14 medical centers in the United States. 150 patients stratified into 3 groups: adult (18-64 years old), elderly (65-74 years old), and old-elderly (≥75 years old). ASA PS 1-3 undergoing elective supine surgery under general anesthesia requiring muscle relaxation. Exclusion: neuromuscular disorder, anticipated difficult	Rocuronium 0.6mg·kg^{-1} initially followed by maintenance doses of 0.15 mg·kg^{-1} as needed upon reappearance of second twitch in ToF. Sugammadex 2 mg·kg^{-1} given at end of surgery upon reappearance of second twitch in ToF. ToF Watch SX used for NMB monitoring.	Adult group (n=45) mean time to recover ToFR 0.9 was 2.3 min. Elderly group (n=57) mean time to recover ToFR 0.9 was 2.7 min. Old-elderly (n=35) mean time to recover ToFR 0.9 was 3.7 min. P value 0.017 Data from 13 subjects were considered unreliable or unavailable. Results with these subjects were reported separately and	No masking or randomization.

	intubation due to anatomy, creatinine clearance ≤30ml/min, family or personal history of malignant hyperthermia, known allergy to medication used in general anesthesia, or receiving medications known to interfere with NMB agents.	by imputing in the above data using 95th percentile information.

NMB, neuromuscular blockade; ToFR, train of four ratio

Table C-3

Data Collection Table

Study 3. Muramatsu, T., Isono, S., Ishikawa, T., Nozaki-Taguchi, N., Okazaki, J., Kitamura, Y., Murakami, N., & Sato, Y. (2018). Differences in recovery from rocuronium-induced deep paralysis in response to small doses of sugammadex between elderly and nonelderly patients. *Anesthesiology, 129*, 901-911.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
To test hypothesis that recovery from deep NMB with low dose sugammadex is slower in elderly patients than in nonelderly patients, and also a higher incidence of recurarization in elderly.	Single center. Nonelderly group (<70 years old, n=20) and elderly group (≥70 years old, n=20) undergoing surgery with general anesthesia using total intravenous anesthetic. Exclusion: severe comorbidities, high risk aspiration, allergy to NMB agents, propofol, or sugammadex, surgery that is undesirable for administration of	Nonrandomized observational study. Rocuronium 0.6mg·kg^{-1} with induction. After spontaneous recovery to ToFR > 0.5, rocuronium 0.4 mg·kg^{-1} given with additional dose 0.2 mg·kg^{-1} if needed to attain PTC 2-10. Once PTC range achieved, sugammadex infusion 50 mcg·kg^{-1}·min until ToF count of 3 achieved and sugammadex infusion stopped. ToF Watch SXTM	Spontaneous recovery time to ToF count 1 after initial rocuronium: nonelderly group 30.2 min, elderly group 45.4 min (P value 0.016). Recovery time to ToF count 3 after initiation of sugammadex infusion: nonelderly group 11.7 min, elderly group 15.3 min (P value 0.018). Slower rate of late-phase recovery from NMB in Elderly group	Use of sugammadex infusion experimentally does not reflect actual practice and results may not reflect actual clinical incidences.

	rocuronium or sugammadex, and patients taking medications with known interaction of rocuronium or sugammadex.	(0.6%/min vs 1.7%/min, *P*=0.006)

NMB, neuromuscular blockade; PTC, post-tetanic count; ToF, train of four; ToFR, train of four ratio

Table C-4

Data Collection Table

Study 4. Shin, S., Han, D. W., Lee, H S., Song, M. K., Jun, E., & Kim, S. Y. (2016). Elderly patients require higher doses of sugammadex for rapid recovery from deep neuromuscular block. *Basic & Clinical Pharmacology & Toxicology, 118*, 462-467.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
To compare the dose of sugammadex needed in elderly and young adults to recover from deep NMB within 2 min.	Single center. 44 subjects: young adult group (n=22, age between 20 and 40 years old) and elderly adult group (n=22, ≥70 years old) undergoing elective ENT surgery under general anesthesia in supine position. ASA PS 1-2. Exclusion: anticipated difficult airway, history of malignant hyperthermia or neuromuscular disease, significant renal or hepatic dysfunction,	Initial dose rocuronium 0.6 $mg \cdot kg^{-1}$ with maintenance dose of 0.2 $mg \cdot kg^{-1}$ to maintain target depth of NMB at 1 or 2 PTC until end of operation. First patient received sugammadex 4 $mg \cdot kg^{-1}$ with dose for subsequent increased/decreased 0.5 $mg \cdot kg^{-1}$ based on previous dose failure/success to recover ToFR ≥0.9 within 2 min. ToF Watch SX	ED_{50} and ED_{95} of sugammadex in young adult group is 3.3 $mg \cdot kg^{-1}$ and 4.4$mg \cdot kg^{-1,}$ respectively. ED_{50} and ED_{95} of sugammadex in elderly adult group is 4.5 $mg \cdot kg^{-1}$ and 5.4 $mg \cdot kg^{-1}$, respectively. Determined statistically significant by non-overlapping confidence interval method.	Unable to determine cause of delayed recovery in elderly. Comorbidity differences between the two groups may be a confounding factor.

	allergy to opioids, muscle relaxants, or general anesthetics, pregnant, breastfeeding, using medications with known interaction with NMB agents, and BMI <17 kg·m^2 or ≥30 kg·m^2.	Sugammadex dose prepared into 5 mL unmarked syringe by nurse unaffiliated with study.

ASA PS, American Society of Anesthesiologists Physical Status; BMI, body mass index; ED_{50}, effective dose for 50% of subjects (83% confidence interval); ED_{95}, effective dose for 95% of subjects (confidence interval 95%); NMB, neuromuscular blockade; PTC, post-tetanic count; ToF, train of four; ToFR, train of four ratio

Table C-5

Data Collection Table

Study 5. Suzuki, T., Kitajima, O., Ueda, K., Kondo, Y., Kato, J., & Ogawa, S. (2011). Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients. *British Journal of Anaesthesia, 106*(6), 823-826.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
To compare the reversibility of profound rocuronium-induced neuromuscular block with sugammadex between younger and older patients.	Younger adult group (n=15, age between 20 and 50 years) and Older adult group (n=15, ≥70 years old) undergoing gynecological surgery under general anesthesia. ASA PS 1-3, patients without neuromuscular, renal, or hepatic disorders, or taking medications with known interaction with NMB agents. Exclusion: BMI ≥25 or BMI ≤18.5.	Initial rocuronium dose 1 $mg \cdot kg^{-1}$ with subsequent doses of 0.02 $mg \cdot kg^{-1}$ whenever a PTC of 1 or 2 was observed. Sugammadex 4 $mg \cdot kg^{-1}$ given at end of surgery after spontaneous recover to PTC 1-2 since previous rocuronium dose. ToF watch SX	Time to recovery of ToFR 0.9 after sugammadex dose: younger adult group 1.3 min (SD 0.3, 0.8-2.0 min), older adult group 3.6 min (SD 0.7, 2.4-4.5 min). P value <0.0001. ToFR data was normalized.	Only female subjects. May limit generalizability to other populations. Use of volatile anesthetic in general anesthesia may have enhanced NMB effect. Dose was not age-adjusted and older adult group may have received greater dose of sevoflurane. Longer duration of surgery for older adult group, which increases duration of sevoflurane exposure.

ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; NMB, neuromuscular blockade; PTC, post-tetanic count; SD, standard deviation; ToF, train of four; ToFR, train of four ratio

Table C-6

Data Collection Table

Study 6. Yazar, E., Yilmaz, C., Bilgin, H., Karasu, D., Bayraktar, S., Apaydin, Y., & Sayan, H. E. (2016). A comparison of the effect of sugammadex on the recovery period and postoperative residual block in young elderly and middle-aged elderly patients. *Balkan Medical Journal, 33*, 181-187.

Purpose	*Site/Sample*	*Method*	*Results*	*Limitations*
To investigate the effects of sugammadex on the duration of recovery from NMB agents and relapse of NMB effect in young elderly and middle-aged elderly groups.	Young elderly (n=30, age 65-74 years) and middle-aged elderly (n=29, age ≥75 years) undergoing laparoscopic cholecystectomy. ASA PS 1-3. Exclusion: renal or hepatic failure, neuromuscular disease, history of malignant hyperthermia, BMI >30. Patients with failed laparoscopic intervention, surgery duration >2 hours, or	Initial dose rocuronium 0.6 $mg \cdot kg^{-1}$ with subsequent rocuronium doses 0.15 $mg \cdot kg^{-1}$ when ToF count 2 or more. Sugammadex 2 $mg \cdot kg^{-1}$ given when ToF count was 2 and surgery is finished. Recovery time to ToFR 0.9 and incidences of ToFR returning to <0.9 postoperatively recorded. ToF Watch SX	Young elderly group recovery to ToFR 0.9 was 3.27 min. Middle-aged elderly group recovery to ToFR 0.9 was 5.5 min (P value <0.001).	Inhalational anesthetic used in this study, which may enhance NMB agent effect. Controlling inhalation agent to end-tidal 1.5% sevoflurane between groups attempted to limit this confounding variable, as did the limitation of surgery to less than 2 hours also.

	admitted to ICU intubated were also excluded.

ASA PS, American Society of Anesthesiologists; BMI, body mass index; NMB, neuromuscular blockade; ToF, train of four; ToFR, train of four ratio

Appendix D

Cross-Study Analysis

Study	*NMB dose*	*Sugammadex dose*	*Geriatric time to recovery*	*Adult time to recovery*	*Adverse Events*
1	Rocuronium 0.6 $mg \cdot kg^{-1}$	8 $mg \cdot kg^{-1}$ with ToF being zero and immediately after seizure stopped	≥70 years old: 443 ±36 sec (mean ± SD)	≤50 years old: 403 ± 37 sec (mean ± SD)	No postoperative events related to recurarization or respiratory events reported.
2	Rocuronium 0.6 $mg \cdot kg^{-1}$ with maintenance dose of 0.15 $mg \cdot kg^{-1}$ as needed with reappearance of second twitch in ToF.	2 $mg \cdot kg^{-1}$ upon reappearance of second twitch in ToF at end of surgery.	65-74 years old: time to recover ToFR 0.9 was 2.7 min (mean, SD 1.4 min). ≥75 years old: time to recover ToFR 0.9 was 3.7 min (mean, SD 1.6 min). all subjects ≥65 years old: time to recover ToFR 0.9 was 3.1 min (mean, SD 1.6 min). P value 0.017	18-64 years old: time to recover ToFR 0.9 was 2.3 min (mean, SD 1.0 min).	Two subjects in 65-74 years old group had adverse events that investigators felt may be related to sugammadex. One experienced tachycardia, pyrexia, dizziness, and oliguria. The other experienced procedural hypotension. One subject in Old-elderly group reported mild muscle weakness, but unable to definitively rule out relapse of NMB as quantitative monitoring had ceased by this point.

3	Rocuronium 0.6mg·kg^{-1} with induction. After spontaneous recovery to ToFR > 0.5, rocuronium 0.4 mg·kg^{-1} given with additional dose 0.2 mg·kg^{-1} if needed to attain PTC 2-10.	Once PTC range 2-10 achieved, sugammadex infusion 50 mcg/kg/min until ToF count of 3 achieved and sugammadex infusion stopped.	≥70 years old: spontaneous recovery to ToF count 1 after initial rocuronium was 45.4 minutes. Recovery to ToF count of 3 after sugammadex infusion was 15.3 minutes.	<70 years old: spontaneous recovery to ToF count 1 after initial rocuronium was 30.2 minutes. Recovery to ToF count 3 after sugammadex infusion was 11.7 minutes.	A transient negative change in ToFR recovery was noted in 1 subject <70 years old and 7 subjects ≥70 years old.
4	Rocuronium 0.6 mg·kg^{-1} with maintenance dose of 0.2 mg·kg^{-1} to maintain target depth of NMB at 1 or 2 PTC	First patient received 4 mg·kg-1, with dose for subsequent subject increased/decreased 0.5 mg·kg^{-1} based on previous subject failure/success to recover ToFR ≥0.9 within 2 min.	≥70 years old: ED_{50} and ED_{95} of sugammadex is 4.5 mg·kg^{-1} and 5.4 mg·kg^{-1}, respectively.	20-40 years old: ED_{50} and ED_{95} of sugammadex is 3.3 mg·kg^{-1} and 4.4 mg·kg$^{-1,}$ respectively.	No postoperative events related to recurarization or respiratory events reported.
5	Rocuronium dose 1 mg·kg^{-1} with subsequent doses of 0.02 mg·kg^{-1} whenever a PTC	4 mg·kg^{-1} given at end of surgery after spontaneous recover to PTC 1-2	≥70 years old: Time to recovery of ToFR 0.9 after sugammadex was 3.6	20-50 years old: Time to recovery of ToFR 0.9 after sugammadex was 1.3	No postoperative events related to recurarization or respiratory events reported.

	of 1 or 2 was observed.	since previous rocuronium dose.	min (SD 0.7, 2.4-4.5 min).	min (SD 0.3 min, 0.8-2.0 min).	
6	Rocuronium 0.6 $mg \cdot kg^{-1}$ with subsequent rocuronium doses 0.15 $mg \cdot kg^{-1}$ with ToF count 2 or more.	2 $mg \cdot kg^{-1}$ given when ToF count was 2 and surgery is finished.	65-74 years old: recovery to ToFR 0.9 was 3.27 min (median, range 1.41-5.37 min). ≥75 years old: recovery to ToFR 0.9 was 5.5 min (median, 2.47-9.54 min).	No subjects <65 years old were included in this study.	Postoperative recurarization was reported in 1 subject in the 65-74 years old group with subsequent reintubation performed.