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CURRENT OPINION

Optimizing Reversal of Neuromuscular Block in Older Adults: Sugammadex or Neostigmine

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Abstract

Residual neuromuscular paralysis, the presence of clinically significant weakness after administration of pharmacologic neuromuscular blockade reversal, is associated with postoperative pulmonary complications and is more common in older patients. In contemporary anesthesia practice, reversal of neuromuscular blockade is accomplished with neostigmine or sugammadex. Neostigmine, an acetylcholinesterase inhibitor, increases the concentration of acetylcholine at the neuromuscular junction, providing competitive antagonism of neuromuscular blocking drug and facilitating muscle contraction. Sugammadex, a modified gamma-cyclodextrin, antagonizes neuromuscular blockade by encapsulating rocuronium and vecuronium in a one-to-one ratio for renal clearance, a pharmacokinetic property that led to the recommendation that sugammadex not be administered to those with end-stage renal disease. While data are limited, reports suggest sugammadex is efficacious and well tolerated in individuals with reduced renal function. Sugammadex provides a more rapid and complete reversal of neuromuscular blockade than neostigmine. There is also accumulating evidence that sugammadex may provide a protective effect against the development of postoperative pulmonary complications, nausea, and vomiting, and that it may have beneficial effects on the rate of bowel and bladder recovery after surgery. Accordingly, sugammadex administration is beneficial for most older patients undergoing surgery.

Key Points

Residual neuromuscular paralysis is common in older patients after surgery and it is associated with postoperative pulmonary complications.

Pharmacologic neuromuscular blockade reversal during surgery is accomplished with neostigmine or sugammadex treatments in older adults.

This paper summarizes the current treatments and emphasizes the importance of using quantitative neuromuscular monitoring and careful consideration of surgical and patient characteristics to guide selection and dosing of neostigmine and sugammadex.

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1 Introduction

An estimated 300 million surgical procedures are performed globally each year [1]. The proportion of major surgeries involving older patients continues to increase; one-third of all surgical patients are aged > 65 years [2, 3]. Further, 20% of individuals aged ≥ 75 years undergo surgery each year [4]. These trends are driven by the development of less invasive techniques, new methods of diagnosis, and an aging population. Unfortunately, advanced age is independently associated with postoperative morbidity and mortality [5].

Neuromuscular blockade is administered during most major surgeries to provide immobilization. This improves operating conditions, facilitates endotracheal intubation, and reduces patient-ventilator dyssynchrony [6]. Residual neuromuscular blockade (rNMB), common after surgery [7], is clinically diagnosed when patients exhibit neuromuscular weakness postoperatively. Associated with poor postoperative outcomes, the risk for rNMB increases with age [8, 9]. However, rNMB is a modifiable risk factor for postoperative complications, and can be avoided by the administration of pharmacologic reversal. In contemporary practice, pharmacologic reversal of neuromuscular

blockade is accomplished with the drugs neostigmine or sugammadex.

The objective of this article is to review literature comparing neostigmine to sugammadex for reversal of neuromuscular blockade, and to provide a framework for choosing between neostigmine and sugammadex in geriatric surgical patients. Throughout this review, although the focus is on age as a risk factor, it should be noted that there are geriatric syndromes that confer a higher risk for postoperative complications than age itself. For example, frailty predicts postoperative outcomes in older surgical patients better than chronological age alone. Frailty is a biologic syndrome of multi-system impairment that leads to decreased reserve and vulnerability to adverse postoperative outcomes. Unfortunately, studies are lacking regarding the contribution of frailty to residual neuromuscular blockade.

2 Neuromuscular Monitoring and the Problem with Residual Neuromuscular Paralysis

The train-offour (TOF) pattern of nerve stimulation is most commonly used by clinicians to detect rNMB. It involves four equally spaced supramaximal nerve stimulations at 0.5 s intervals [10]. Train of four count is the number of twitches (0–4) subjectively counted by the clinician via tactile or visual assessment of muscle contraction. The TOF count is measured with a peripheral nerve stimulator. Peripheral nerve stimulators are common in anesthetizing locations worldwide and are relatively inexpensive [11].

The TOF ratio is the ratio of the amplitude of the 4th twitch to the amplitude of the 1st twitch, rNMB is defined by this ratio [10]. A TOF ratio < 0.9 indicates the presence of clinically significant rNMB [12]. Assessment of the TOF ratio requires a device that provides both nerve stimulation and measurement of the evoked muscle action potential or contraction. The two categories of devices used clinically to assess TOF ratio are electromyographs and acceleromyographs [10]. Unfortunately, these devices are significantly more expensive than standard peripheral nerve stimulators, require more advanced training, and consequently have not become standard throughout the world. As a result, rNMB is underappreciated and vastly underdiagnosed [7, 11].

The impact of rNMB on organ dysfunction is clear in pharmaco-physiological interaction studies, which are conducted without the confounding effects of surgery and anesthesia. In these studies, neuromuscular blocking agent (NMBA) is slowly titrated into healthy awake volunteers via intravenous infusion to achieve low-level blockade (TOF ratio 0.7–0.95) resulting in oropharyngeal muscle dysfunction [13–16]. Specifically, tensor palatine and genioglossus muscle firing is interrupted with low-level neuromuscular blockade (TOF ratio of 0.5–0.8) [14]. These muscles normally contract 100 milliseconds before diaphragm contraction [17]. In the presence of low-level blockade, tensor palatine and genioglossus muscle dysfunction ensues, the diaphragm generates negative pressure, and the retronasal and retroglossal airway collapse [17]. In addition, low-level neuromuscular blockade is associated with delayed initiation of swallowing after the introduction of a liquid bolus, impaired pharyngeal muscle coordination, and an increased incidence of misdirected swallowing [15, 16]. In individuals aged > 65 years, low-level neuromuscular blockade (TOF ratios of 0.7–0.8) increases the incidence of pharyngeal dysfunction by 30% [18]. Finally, respiratory center response to acute hypoxemia and hypercarbia is depressed in the presence of low-level neuromuscular blockade (TOF ratio 0.7) [19–21]. The NMBAs dose dependently inhibit acetylcholine-mediated transmission at the synaptic junction between the glossopharyngeal nerve and the carotid body –the primary peripheral chemoreceptor that drives respiratory response to acute hypoxia and hypercarbia [19].

The evidence from these volunteer studies translates to post-surgical patients. Residual neuromuscular paralysis is associated with postoperative upper airway obstruction [22, 23], hypoxemia [22–24], atelectasis [24, 25], pneumonia[24–26], prolonged hospital length of stay [27], and a higher rate of intensive care unit admission [28]. While temporary postoperative pulmonary complications, such as episodic hypoxemia, and prolonged post-anesthesia care unit oxygen therapy, may seem inconsequential, they are associated with significant patient morbidity and greater hospital resource utilization [29].

A rare side effect that is often not included in the list of complications associated with residual neuromuscular blockade is accidental awareness under general anesthesia. One-fifth of accidental awareness cases are attributed to failure to completely reverse neuromuscular blockade at the time of emergence. These events, which are described as experiencing trauma and distress due to being partially paralyzed, are highly correlated with the administration of NMBA and lack of pharmacologic reversal [30].

Aged patients appear to be at greater risk for rNMB [8], in part because they are less likely to receive pharmacologic reversal due to concern for side effects [31]. Unfortunately, rNMB is more likely to cause postoperative complications in aged individuals, likely due to a higher prevalence of comorbid conditions [8]. In one prospective, cohort-matched, observational study, rNMB was associated with a higher rate of postoperative airway obstruction, hypoxemia, atelectasis, and pneumonia in older patients compared to a younger cohort [8].

3 Pharmacokinetics and Pharmacodynamics of Neostigmine and Sugammadex

3.1 Neostigmine

Synthesized in 1931, neostigmine has been the standard medication for reversal of neuromuscular blockade for decades [32]. Neostigmine provides effective pharmacologic reversal of neuromuscular blockade produced by the nondepolarizing NMBAs rocuronium, vecuronium, pancuronium, and cisatracurium [32]. Neostigmine does not provide effective pharmacologic reversal created by the depolarizing agent succinylcholine, and may actually potentiate it [33].

Neostigmine forms a covalent bond to the active site of acetylcholinesterase, thus, inhibiting it. Acetylcholinesterase is an enzyme localized predominantly in the neuromuscular junction. It hydrolyzes acetylcholine, the primary neurotransmitter that causes muscle movement in the neuromuscular junction. By inhibiting the breakdown of acetylcholine, neostigmine increases neuromuscular junction acetylcholine concentration, allowing acetylcholine to competitively displace NMBA from the post-synaptic nicotinic receptor and facilitating muscle contraction [34]. Neostigmine does not inactivate NMBA; reparalysis can occur if acetylcholine concentration drops faster than NMBA elimination [32]. Because neostigmine increases acetylcholine concentrations throughout the body, unopposed neostigmine activity is associated with bradyarrhythmias, bronchospasm, pupil constriction, nausea, abdominal cramping, urinary urgency, and increased oropharyngeal secretions and bowel peristalsis [35]. Therefore, anticholinergic medications (typically glycopyrrolate or atropine) must be co-administered with neostigmine.

Neostigmine does not provide effective pharmacologic reversal from deep neuromuscular blockade (TOF count 0 or 1) [36]. In addition, neostigmine has a maximal pharmacologic effect at 5 mg, or 0.07 mg/kg (actual body weight), whichever is less [35]. Excess neostigmine administration has been shown to paradoxically provoke muscle weakness, impaired respiration, and upper airway obstruction [37, 38].

Neostigmine is 20% bound to albumin in plasma. Approximately half of administered neostigmine is eliminated unchanged through the kidney, while the remainder is eliminated via hepatic metabolism. Dose adjustments are not recommended for individuals with hepatic or renal dysfunction [35]. Neostigmine does not require dose adjustment in older patients [39]. Neostigmine effectively reverses neuromuscular blockade provided by cisatracurium, the primary NMBA administered during surgery to individuals with a creatinine clearance < 30 mL/min [40].

3.2 Sugammadex

Sugammadex is a newer drug developed to reverse neuromuscular blockade due to neuromuscular junction antagonism provided by rocuronium and vecuronium. Sugammadex, synthesized in 1999, received European Union approval in 2008 and United States Food and Drug Administration (FDA) approval in 2015 [41, 42]. Sugammadex was introduced into US clinical practice in December 2015, immediately changing NMBA use patterns. Since 2016, pharmacologic reversal with sugammadex has steadily increased, along with use of rocuronium and vecuronium, NMBAs that can be reversed safely with sugammadex [31, 43, 44]. The use of sugammadex has increased particularly among older patients. In outpatient [31] and inpatient settings [43, 45], older patients are now more likely to receive sugammadex than neostigmine.

Sugammadex has a different mechanism of action than neostigmine. It is a modified gamma-cyclodextrin with a torus shape that contains a hydrophobic core and a hydrophilic outer surface [46]. The hydrophobic core noncovalently binds to rocuronium and with lesser affinity to vecuronium, in a one-to-one ratio [46]. Once encapsulated, rocuronium and vecuronium are bound to the sugammadex molecule forming water-soluble inclusion complexes in plasma. Thus, the plasma concentration of free NMBA decreases, which creates a concentration gradient that drives NMBA from the neuromuscular junction to plasma. The concentration of NMBA in the nicotinic acetylcholine receptor rapidly declines and neuromuscular activity is allowed to resume. Because sugammadex does not inhibit acetylcholinesterase like neostigmine, co-administration of anticholinergic medications such as glycopyrrolate and atropine are not required to offset muscarinic effects on the heart (bradyarrhythmias) and airway (bronchospasm).

Sugammadex is considered biologically inactive and is associated with fewer adverse effects than neostigmine [46]. As a medication administered during general anesthesia and surgery, it is associated with postoperative nausea and vomiting, pain localized to areas of surgical trauma, and dysgeusia [47, 48]. The FDA approval was denied twice over concerns for anaphylaxis and bleeding dyscrasia [46]. Higher doses of sugammadex, used to reverse deeper levels of neuromuscular blockade, appear to increase the risk for anaphylaxis [49–51]. Postmarketing surveillance provided reassurance that the incidence of sugammadex

anaphylaxis is equivalent to the accepted risk associated with NMBA [52]. Repeat exposure to sugammadex does not appear to increase risks for anaphylaxis. In vitro and in vivo studies have associated sugammadex exposure in healthy individuals to a temporary (1-h) 25% prolongation in prothrombin time and activated partial thromboplastin time [46]. However, sugammadex administration has not been linked to increased bleeding during surgery and the extension in clotting times is now hypothesized to be a laboratory artifact [53].

Sugammadex undergoes no metabolism in plasma and has negligible protein binding. Sugammadex is excreted through the kidney, typically as a water-soluble complex bound to NMBA. Dose adjustments are not required for individuals with hepatic dysfunction or those with a creatinine clearance $\geq$ 30 mL/min [49]. Sugammadex administration is not recommended for individuals with a creatinine clearance $<$ 30 mL/min [54]. Administration of rocuronium and vecuronium is also not recommended for individuals with significant renal dysfunction.

3.3 Comparative Effectiveness of Neostigmine versus Sugammadex for Reversal of Neuromuscular Blockade

Several factors must be considered when choosing between neostigmine and sugammadex for pharmacologic neuromuscular blockade reversal. While specific clinical scenarios clearly favor one drug over the other, for the majority of surgeries reversal may be accomplished with either drug. Sugammadex is on patent and more expensive than neostigmine; however, it provides faster, more reliable and more complete reversal of neuromuscular blockade than neostigmine [55]. For moderate blockade, a TOF count of 2, sugammadex provides full reversal 10 min faster than neostigmine [36]. For deep blockade, a TOF count of 0 or 1, sugammadex provides full reversal 45 min faster than neostigmine [36, 56, 57]. Sugammadex was associated with 60% fewer postoperative residual paralysis events than neostigmine in a meta-analysis of 15 studies, that included ($n = 1500$) individuals administered neuromuscular blockade reversal with sugammadex or neostigmine at levels of deep block (3 studies), moderate block (6 studies), light block (3 studies), and variable depth of block (3 studies) [36]. Administering sugammadex to 13 patients prevented one postoperative residual paralysis event that would have occurred with neostigmine.

4 Neostigmine Versus Sugammadex: Clinically Important Outcomes

4.1 Central Nervous System

As the brain ages, there are changes in structure, function, and metabolism. The volume and weight of the brain declines after the age of 40, and the decline is thought to accelerate after the age of 70. In addition to brain atrophy, certain cognitive functions such as short-term memory also slowly decline with aging. Neurotransmitter changes also occur with age, as well as increasing blood-brain-barrier permeability. Cerebrovascular changes include decreasing dense areas of capillaries, arterial intimal thickening, and increased micro-vessel deformities. These changes lead to arteriosclerosis, increased vascular resistance, and decreased perfusion pressure, with patients with comorbidities and lifestyle risk factors experiencing greater disease burden [58]. Taken together, these changes increase the risk of neurocognitive dysfunction.

Neostigmine does not readily cross the blood-brain barrier and thus has little direct effect on the central nervous system. Neostigmine increases acetylcholine plasma concentration, which may cause undesirable parasympathetic effects including bradycardia, salivation, nausea, and vomiting. As mentioned above, reversal of neuromuscular blockade with neostigmine requires co-administration of an anticholinergic, such as glycopyrrolate. While glycopyrrolate has minimal blood-brain-barrier penetrance compared to other anticholinergics, it does cross into the central nervous system [59], and administration has been associated with impaired human learning and memory [60]. Further, the blockade of muscarinic receptors by glycopyrrolate may result in complications such as constipation, urinary retention, and vision changes, which have been associated with postoperative delirium.

Like neostigmine, sugammadex does not readily cross the blood-brain barrier. An advantage to sugammadex is that it is biologically inert, having no receptors in the human body. Administration of sugammadex eliminates the need for perioperative anticholinergic agents, which is advantageous in geriatric surgical patients, who are more susceptible to anticholinergic adverse effects. The American Geriatrics Society (AGS) maintains a list of Potentially Inappropriate Medications (PIMs) that are not recommended for use in individuals aged $>$ 65 years [61], anticholinergic medications are featured on this list. Recent guidelines recommend avoiding PIMs in geriatric patients in the perioperative period to prevent delirium [62–64].

Postoperative delirium and postoperative neurocognitive dysfunction are among the most common surgical complications experienced by geriatric surgical patients, and are associated with increased hospital length of stay, functional disability, mortality, and risk for developing dementia, including Alzheimer's disease. Identifying strategies to prevent perioperative neurocognitive disorders would improve patient outcomes and reduce healthcare costs. It has been hypothesized that sugammadex administration may reduce the development of perioperative neurocognitive disorders, compared to neostigmine.

A recent prospective pilot study on patients undergoing aortic valve replacement compared sugammadex ($n = 14$) and neostigmine ($n = 7$) on postoperative cognitive function and recovery at varying time points (preoperative baseline, 30 min, 24 h, 72 h, and 30 days, postoperatively) using the Postoperative Quality Recovery Scale [65]. While there was no difference in global cognitive recovery between the two groups at the early time points, the sugammadex group showed improved global cognitive recovery at 30 days when compared to the neostigmine group (85.7 vs 42.9%, $p = 0.04$). The percentage of patients oriented to person, place, and time 30 min after surgery was significantly higher in the sugammadex group. The sugammadex group also performed better at a "word list" memory task and a "word generation" task at 72 h and 30 days postoperatively.

The same investigators performed an experiment to determine whether rats exposed to sugammadex versus saline had a difference in postoperative cognitive level based on performance in the Morris water maze. They found postoperative cognitive impairment in the saline group that was not present in the sugammadex group. They further explored neuroinflammatory markers in rat hippocampi; immunohistochemistry data indicated a possible beneficial role of sugammadex in altering neuroinflammation postoperatively [65].

To date, only a few small pilot studies have investigated whether sugammadex is associated with a decreased incidence of postoperative neurocognitive disorders, compared to glycopyrrolate. Larger more definitive studies are necessary to shed light on this topic.

4.2 Cardiovascular System

The foundation for providing safe anesthesia in older adults with cardiovascular disease is avoiding hemodynamic perturbations and arrhythmias, which are associated with renal and cardiac morbidity [66, 67]. Aged patients have a higher prevalence of clinically significant coronary atherosclerosis, increasing risk for intra- and postoperative myocardial ischemia. They also have increased fibrosis of the cardiac conduction system, increasing the risk for arrhythmia development.

While rocuronium and vecuronium have minimal effects on blood pressure, heart rate, and plasma noradrenaline and adrenaline concentrations [68], neostigmine and glycopyrrolate can impact propensity for arrhythmias and blood pressure volatility. Neostigmine (cholinergic) decreases and glycopyrrolate (anticholinergic) increases inotropy and chronotropy. The net effect depends on the ratio of neostigmine to glycopyrrolate administered. An administration ratio that favors anticholinergic effects increases risk for tachyarrhythmia, myocardial ischemia, hypertension, and heart failure [69]. An administration ratio that favors cholinergic effects increases risk for bradyarrhythmia, atrioventricular heart block, and hypotension [70]. Sugammadex has no effect on the cardiac conduction system or arterial resistance and avoids cardiovascular risks associated with neostigmine and glycopyrrolate [71].

In a prospective randomized trial comparing sugammadex to neostigmine (coadministered with atropine) in patients with mean age of 60 years and New York Heart Association class 2 or 3 disease, mean heart rate and systolic blood pressure were significantly higher in the neostigmine group for 5 min after reversal administration [72]. The authors concluded that sugammadex is preferred in patients with preexisting cardiac disease due to more stable hemodynamic parameters.

4.3 Respiratory System

Age is an independent risk factor for the development of a postoperative pulmonary complication (PPC) [73]. Compared to patients aged < 60 years, patients aged 60–69 have twice the chance and patients aged ≥ 70 years have three times the chance of developing a PPC [74]. For each 10-year increase in subject age, risk of PPC increases 1.6 times [24]. Further, development of a PPC in older adults is associated with decreased 3-month survival [75].

A number of age-related physiological changes predispose to PPCs. Chest wall compliance decreases, respiratory muscle strength decreases, and hypoxic ventilatory drive is blunted, thus increasing risk for hypoxia and hypercarbia. Lung elasticity decreases, increasing closing capacity and predisposing small airways to collapse, forming areas of atelectasis. Pharyngeal dysfunction becomes more common, increasing risk for postoperative aspiration and pneumonia. The aforementioned physiologic changes are exacerbated in the presence of rNMB and residual postoperative inhalational anesthetic agent, with some agents, such as sevoflurane, having a lesser effect upon carotid body response to acute hypoxemia [19, 76]. Accordingly, it is hypothesized

that the combination of sevoflurane and sugammadex may awaken the carotid body hypoxic chemoreflex and reduce the incidence of postoperative pulmonary complications.

Several trials have assessed whether the avoidance of negative effects on upper airway dilator muscles associated with neostigmine, combined with improved carotid body hypoxic chemoreflex and respiratory muscle function from sugammadex could reduce the incidence of PPCs (Table 1). Observational studies tended to capture significant pulmonary outcomes that could be easily retrieved through chart review, such as reintubation, pneumonia, and initiation of non-invasive ventilation [77–81]. Randomized controlled trials, which had a much smaller sample size, tended to capture less significant pulmonary complications such atelectasis, bradypnea, desaturation, and upper airway obstruction [47, 82–87]. The result was fairly consistent across observational and randomized controlled trials –sugammadex provided a protective effect, with the majority of studies showing 20%–30% lower relative odds of PPCs for patients who received sugammadex [47] For older patients with pulmonary co-morbidities, we recommend considering neuromuscular blockade reversal with sugammadex [47].

4.4 Hepatorenal System

With normal aging, lean body mass (the target for NMBAs), plasma volume [88], and albumin protein production declines (increasing the free-fraction of protein bound drugs) [89, 90]. These changes were hypothesized to increase the potency of NMBAs. However, the dosage of drug required to produce maximal block (effective dose 95%) [91–93], and time of onset were not found to be altered in the older population [92, 94, 95].

Normal physiologic changes of aging associated with the hepatorenal system have been shown to increase the duration of effect for NMBA. Glomerular filtration rate decreases 1% per year beyond 40 years of age, up to 30% loss by age 80 years, reducing the elimination rate for NMBAs [96, 97]. Hepatic blood flow decreases and there is a reduction in hepatocyte mass and function [97], reducing metabolism of NMBAs. The net effect of these physiologic changes is slower metabolism and clearance of NMBAs [95], prolonged pharmacodynamic effect [94, 98], and longer time to spontaneous recovery [95, 99, 100]. Consequently, in older individuals, a lower dose of NMBA is required, and the interval between administrations may be prolonged (intermittent bolus administration) or the infusion rate reduced (continuous infusion administration) [91].

When NMBAs are administered, there is greater interindividual variability in clearance and duration of action in older patients, which in turn, increases risk for adverse events related to rNMB [100]. This variability is attributed to differences in renal and hepatic function [101], and may be exacerbated by coadministration of inhaled fluorinated anesthesia drug [100]. Careful quantitative neuromuscular monitoring may ameliorate some of this risk and is strongly recommended. Sugammadex administration provides additional protection against rNMB. Although time to full reversal after sugammadex administration is longer in older individuals [102], sugammadex still provides faster, more complete, and more reproducible reversal of neuromuscular blockade than neostigmine [103]. The effectiveness of

Table 1 Comparative impact of sugammadex and neostigmine on the incidence of postoperative pulmonary complications

Study	Sugammadex		Neostigmine		Odds ratio	95% CI
	Events	Total	Events	Total		
Observational studies						
Cammu (2012) [77]	1	44	11	139	0.27	0.03–2.16
Kheterpal (2020) [78]	796	22856	1096	22856	0.71	0.64–0.78
Krause (2020) [79]	164	3896	209	3420	0.80	0.52–1.20
Li (2021) [80]	114	2691	461	7800	0.70	0.57–0.87
Yu (2021) [81]	44	237	93	237	0.35	0.23–0.54
Randomized controlled trials						
Alday (2019) [82]	18	61	24	61	0.65	0.30–1.37
Evron (2017) [83]	0	32	1	24	0.24	0.01–6.18
Ledowski (2021) [84]	2	85	8	83	0.23	0.05–1.10
Lee (2021) [85]	15	46	19	47	0.71	0.31–1.67
Leslie (2021) [86]	5	59	5	61	1.02	0.28–3.67
Togioka (2020) [47]	33	100	40	100	0.74	0.40–1.37
Unal (2015) [87]	5	37	12	37	0.33	0.10–1.05

CI confidence interval

sugammadex is not altered in older adults with mild to moderate renal dysfunction or hepatic dysfunction [49].

Clearance of sugammadex and the sugammadex-NMBA complex is significantly prolonged amongst individuals with creatinine clearance < 30 mL/min [54], a pharmacokinetic property that led to the recommendation that sugammadex not be administered to those with end-stage renal disease [49]. This recommendation was based upon the theoretical concern that prolonged exposure to the sugammadex-NMBA complex may increase risk for hypersensitivity reaction and reoccurrence of neuromuscular blockade, should the sugammadex-NMBA complex dissociate [104]. However, retrospective studies [104, 105], and one small prospective study [106], did not find an increased incidence of hypersensitivity reaction or postoperative neuromuscular paralysis amongst patients with reduced renal function. Further, there are reports illustrating the potential ability of sugammadex to rescue individuals with end-stage renal disease from rNMB after reversal with neostigmine [107] and after an inadvertent subcutaneous injection of rocuronium [108].

4.5 Gastrointestinal System

Aging is associated with a modest increase in gastric emptying time and colonic transit time [109, 110]. Electrogastrophy has shown that gastric motor activity is reduced after a meal [110] and colon neuron density is reduced by one-third in older adults [111]. These physiologic changes translate to an increased risk for postoperative constipation in older patients [112]. Several studies were recently published on the comparative effect of sugammadex and acetylcholinesterase inhibitors, such as neostigmine, on bowel recovery. They hypothesized that the avoidance of anticholinergic effects (provided by glycopyrrolate) on gastrointestinal smooth muscle may facilitate faster gastric recovery and earlier return of bowel function in patients receiving sugammadex. In these studies, bowel recovery was assessed by measuring time to first flatus and bowel movement [113–116]. Interestingly, only one of these studies included a population having colorectal surgery [116]. The other trials included patients having cholecystectomy or head and neck surgery [113–115]. While the sample size is small and time of first flatus may be an imprecise and poorly reproducible outcome, these studies tended to demonstrate sugammadex was associated with earlier return of bowel function (Table 2) [113–116].

Postoperative nausea and vomiting (PONV) is one of the most common complications after general anesthesia. While advancing age may be a protective factor against the development of PONV [117–119], the avoidance of PONV in older patients is essential for enhancing patient comfort. The comparative impact of sugammadex versus neostigmine on the incidence of PONV has been assessed in several trials (Table 3) [47, 116, 120–123]. The authors hypothesized that the avoidance of emetogenic effects from neostigmine may reduce the incidence of PONV. In these studies, PONV was generally assessed for the first few hours after surgery. The consistent observation was that sugammadex provided a protective effect against the development of PONV.

4.6 Urinary System

Postoperative urinary retention (POUR), or the inability to micturate with a full bladder, is a common complication after surgery. Advanced age appears to increase risk for POUR [124]. POUR Postoperative urinary retention can cause suprapubic pain, abdominal discomfort, overflow incontinence, and postoperative delirium in older patients. Two investigations assessed the comparative impact of sugammadex versus neostigmine on the incidence of POUR (Table 4) [125, 126]. The authors hypothesized that the avoidance of anticholinergic inhibitory effects (provided by glycopyrrolate) on bladder detrusor muscle may reduce POUR (defined as the unplanned postoperative insertion of a urinary catheter). Both studies found a significantly lower incidence of POUR in patients administered sugammadex.

Table 2 Comparative impact of sugammadex and acetylcholinesterase inhibitors on bowel recovery after surgery

Study	Type of surgery	Sugammadex		Acetylcholinesterase inhibitor		*p*-value
		Time in hours (IQR or SD)	*n*	Time in hours (IQR or SD)	*n*	
Time to first flatus						
An (2020) [113]	Laparoscopic cholecystectomy	15.0 (16.3–25.9)	49	20.9 (6.4–25.3)	53	0.001
Sen (2016) [114]	Total thyroid	24 (18–29)	36	24 (18–32)	36	> 0.05
Time to first bowel movement						
An (2020) [113]	Laparoscopic cholecystectomy	38.0 (25.1–64.7)	28	47.3 (38.7–68.5)	28	0.09
Deljou (2022) [115]	Craniotomy	49.6 (30.8, 74.1)	408	59.6 (41.0, 78.3)	323	0.02
Hunt (2020) [116]	Laparoscopic colorectal	41.7 (29.7)	96	53.4 (30.4)	128	0.004
Sen (2016) [114]	Total thyroid	32 (24–40)	36	26 (18–36)	36	> 0.05

IQR interquartile range, *n* number, *SD* standard deviation

Table 3 Comparative impact of sugammadex and neostigmine on the incidence of postoperative nausea and vomiting

Study	Sugammadex		Neostigmine		Odds ratio	95% CI
	Events	Total	Events	Total		
Hunt (2020) [116]	50	96	61	128	1.19	0.71–2.03
Paech (2018) [120]	74	151	78	153	0.92	0.59–1.45
Togioka (2020) [47]	14	100	17	100	0.79	0.37–1.71
Tuna (2017) [121]	24	40	31	40	0.44	0.16–1.15
Woo (2013) [122]	3	60	6	60	0.47	0.11–1.99
Yagan (2017) [123]	4	50	13	48	0.23	0.07–0.78

CI confidence interval

Table 4 Comparative impact of sugammadex and neostigmine on the incidence of postoperative urinary retention

Study	Sugammadex		Neostigmine		Odds ratio	95% CI
	Events	Total	Events	Total		
Han (2021) [125]	1	39	6	38	0.14	0.02–1.23
Valencia Morales (2021) [126]	2	75	16	106	0.15	0.03–0.69

CI confidence interval

5 Conclusion

The goal of neuromuscular blockade reversal for older adults undergoing surgery is to minimize postoperative residual paralysis. Postoperative residual paralysis is associated with complications involving the respiratory system, as well as prolonged hospital length of stay and a higher rate of intensive care unit admission.

Sugammadex provides reversal of neuromuscular blockade that is more rapid, more reliable, and more complete than neostigmine. Evidence is mounting that sugammadex may protect against the development of PPCs, and that it may facilitate bladder and bowel recovery after surgery. However, trials have failed to show that sugammadex completely eliminates rNMB and postoperative complications [47], or that sugammadex administration is associated with a shorter hospital length of stay [47, 80, 82–86, 115, 116, 120, 125]. This is summarized in Table 5.

These findings emphasize the importance of using quantitative neuromuscular monitoring (electromyographs and acceleromyographs) to guide the dosing of both neostigmine and sugammadex for all procedures that include the administration of NMBA, a recommendation that was recently added to the Association of Anaesthetists standards for monitoring during anaesthesia and recovery [127]. Sugammadex remains more costly than neostigmine in most countries; cost-benefit analysis continues to dictate institutional polices governing the availability of sugammadex. Until sugammadex becomes closer in price to neostigmine, we recommend careful consideration of surgical and patient characteristics in the context of evidence from comparative outcome studies to guide the decision of which reversal agent to select, sugammadex or neostigmine.

Table 5 Comparative impact of sugammadex and neostigmine on hospital length of stay

Study	Type of surgery	Sugammadex		Acetylcholinesterase inhibitor		*p*-value
		Time in days (IQR or SD)	*n*	Time in days (IQR or SD)	*n*	
Observational studies						
Li (2021) [80]	Varied	3 (1–5)	2691	3 (1–6)	7800	Not provided
Deljou (2022) [115]	Craniotomy	4 (3–8)	408	5 (3–10)	323	0.22
Hunt (2020) [116]	Laparoscopic colorectal	6.4	96	3.3	128	0.66
Randomized controlled trials						
Alday (2019) [82]	Abdominal	12.9 (10.6)	62	11.4 (8.4)	64	> 0.05
Evron (2017) [83]	Laparoscopic sleeve gastrectomy	3.5 (0.8)	32	3.5 (1.0)	25	0.7
Han (2021) [125]	Laparoscopic cholecystectomy	3.7 (1.0)	39	3.5 (0.95)	38	0.29
Ledowski (2021) [84]	Varied	7.5 (5–10)	85	9 (6–13)	83	> 0.05
Lee (2021) [85]	Video-assisted thoracoscopic surgery	8 (7–10)	46	7 (6–10)	47	0.43
Leslie (2021) [86]	Varied	5.1 (3.1–9.2)	59	5.1 (3.2–8.2)	61	Not provided
Paech (2018) [120]	Laparoscopic gynecologic	0.23 (0.17–0.30)	151	0.22 (0.18–0.31)	153	0.15
Togioka (2020) [47]	Varied	4.0 (3.4)	100	4.5 (5.0)	100	0.42

IQR interquartile range, *n* number, *SD* standard deviation

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Declarations

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Conflict of interest Brandon Togioka has received two investigator-initiated research grants from Merck & Co., the company that owns and sells ugammadex. The opinions expressed in this article are those of the authors and do not necessarily reflect those of Merck & Co. Katie Schenning declares no conflicts of interest.

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