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Abstract

Neuromuscular blocking agents (NMBAs) are frequently utilized in anesthetic practice to relax the vocal cords in preparation for endotracheal intubation and to facilitate optimal operating conditions for various surgical procedures. Residual muscle paralysis in the postoperative period is a serious consequence of NMBAs that can lead to severe consequences including airway obstruction, hypoxia, reintubation, aspiration, and pneumonia. Neuromuscular blockade (NMB) is overcome either by spontaneous recovery or, in most cases, with the use of a reversal agent. Two of the most common reversal agents are neostigmine, a cholinesterase inhibitor, and sugammadex, a modified gamma-cyclodextrin. Of the two medications, sugammadex is a significantly more expensive option per dose, which creates budgetary concerns and leads to restrictions on its usage. However, sugammadex provides a markedly faster, more reliable, and more effective reversal of neuromuscular blockade compared to neostigmine with fewer side effects. By accelerating recovery from NMB with fewer adverse effects, patients spend less time in the operating room (OR) and post-anesthesia care unit (PACU) with fewer respiratory complications. Taking these factors into consideration, the higher medication cost of sugammadex can potentially be justified and/or offset by its superior safety profile and savings in OR and PACU time.

Keywords: Neuromuscular blocking agent, Reversal, Sugammadex, Neostigmine, Cost

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Since their introduction in 1942, neuromuscular blocking agents (NMBAs) have been used routinely in anesthesia practice to facilitate endotracheal intubation and optimize surgical conditions (Boon et al., 2018). NMBAs cause muscle relaxation by blocking signal transmission at the acetylcholine receptor in the neuromuscular junction, rendering it inactive (Boon et al., 2018). Along with analgesia and amnesia, muscle relaxation is a fundamental component of general anesthesia, yet there are disadvantages that anesthesia providers must consider when administering neuromuscular blocking agents. Despite the use of NMBA reversal drugs, a dangerous side effect of neuromuscular blockade can occur when muscle weakness extends beyond the period of general anesthesia, otherwise known as a residual neuromuscular blockade (rNMB) (Money et al., 2019).

Muscle weakness associated with rNMB can precipitate many anesthesia-related respiratory complications including airway obstruction, hypoxia, atelectasis, aspiration, pulmonary edema, and need for reintubation (Money et al., 2019). The complications associated with rNMB can negatively affect the health and wellbeing of patients postoperatively. rNMB can also lead to additional resource utilization, such as increased recovery time, minutes spent in the OR and PACU settings, and treatment of postoperative pulmonary complications (PPC) associated with persistent muscle weakness. To minimize the occurrence of rNMB and its negative effects, anesthesia providers must ensure patients have regained appropriate muscle strength before extubation by administering an NMBA reversal agent or allowing enough time for spontaneous recovery (Money et al., 2019).

Reversal agents are used in millions of cases annually to antagonize the effects of NMBAs (Hurford et al., 2020). Two of the most common reversal agents used are neostigmine, a cholinesterase inhibitor, and sugammadex, a modified gamma-cyclodextrin (Zaouter et. al, 2017). These medications vary significantly in their mechanisms of action, speeds of onset, side effects, clinical effectiveness, and costs. Historically, neostigmine has been the medication of choice for NMB reversal, while the more expensive sugammadex, introduced in 2016, is relatively newer to clinical practice (Hurford et al., 2020). Since its introduction, sugammadex established itself as the superior medication in terms of its efficacy and particular ability to quickly antagonize rocuronium-induced neuromuscular blockade, which accelerates recovery time (Carron et al., 2016). Sugammadex is also generally well tolerated by patients with minimal side effects, contributing to its favorable safety profile (Keating, 2016). What remains unclear is whether faster recovery times and a lesser risk of respiratory complications are worth the higher cost of sugammadex overall.

The purpose of this review is to investigate the various advantages of sugammadex in the clinical setting, and whether these advantages justify its cost per vial compared to neostigmine. While the pharmacoeconomic implications of sugammadex are complex, this literature review will investigate the comparative costs and economic impact of each reversal medication, considering not only the cost per vial but also the additional expenses related to the speed of recovery and frequency of adverse complications affecting length of stay in the OR and PACU settings.

Review of Neuromuscular Blocking Reversal Agents

AChE Inhibitors: Neostigmine

NMBAs act at the neuromuscular junction (NMJ), where an electrical impulse travels along the motor neuron and causes the release of the neurotransmitter acetylcholine (Ach) from the presynaptic membrane. Ach travels across the synaptic cleft to the postsynaptic membrane of the muscle fiber, where it acts on nicotinic receptors to cause muscle contraction. Nondepolarizing NMDAs such as rocuronium block Ach by competing for the binding site on nicotinic receptors, establishing neuromuscular blockade. Neostigmine, an acetylcholinesterase (AChE) inhibitor drug, reverses NMB by inactivating the enzyme that hydrolyzes acetylcholine. High levels of acetylcholine in the NMJ allow the neurotransmitter to competitively antagonize NMBAs at the postsynaptic receptor and restore skeletal muscle function (Boon et al., 2018).

AChE inhibitors are effective at antagonizing both aminosteroid and benzylisoquinoline types of non-depolarizing NMBAs. Aminosteroid NMBAs include the drugs rocuronium, vecuronium, and pancuronium. Common types of benzylisoquinoline NMBAs include mivacurium, atracurium, and cisatracurium. AChE inhibitors carry significant muscarinic side-effects (e.g., hypersalivation, bradycardia, bronchoconstriction, nausea). As such, an appropriately dosed anticholinergic medication (e.g. glycopyrrolate or atropine) must be co-administered to mitigate these effects (Keating, 2016). A caution with administration of neostigmine is a ceiling effect when AChE inhibition has reached 100%. As such, a limitation of neostigmine is its inability to reverse a deep or profound level of neuromuscular blockade (Keating, 2016).

Sugammadex

Sugammadex is a novel, synthetically modified gamma-cyclodextrin that reverses non-depolarizing aminosteroid muscular blockade from rocuronium, and, to a lesser extent, vecuronium, but does not antagonize benzylisoquinoline blockade (Boon et al., 2018). Free plasma NMBA molecules are irreversibly encapsulated by sugammadex in a one-to-one ratio and eliminated via the urine, effectively reversing NMBA activity at the NMJ (Boon et al., 2018). With this mechanism of action, sugammadex produces a rapid and effective reversal of non-depolarizing NMBAs independent of the depth of blockade (Krause et al., 2019). Likewise, because of molecular encapsulation of the NMBA, its onset of action is prompt and muscarinic side effects are exceedingly rare. Moreover, it can be administered at any stage of the surgical procedure, including immediately after an intubating dose of rocuronium, which is especially useful in an emergency cannot-intubate, cannot-ventilate situation (Boon et al., 2018).

Complications of NMB Reversal Agents

rNMB extending beyond the period of general anesthesia is strongly linked to pulmonary complications such as upper airway obstruction, hypoxemia, atelectasis, pneumonia, increased airway secretions, bronchospasm, and laryngospasm, necessitating the need for reintubation (Togioka et al., 2020). According to a study by Cammu (2018), 73% of patients who experienced critical respiratory events in the PACU, such as airway obstruction, hypoxemia, signs of respiratory distress, or reintubation, also had significant levels of residual neuromuscular blockade on train of four monitoring. There is a clear association between rNMB and respiratory complications postoperative, so to minimize this risk, NMBA reversal medications are used to antagonize NMB. Quantitative monitoring is used to assess the level of NMB and aids in NMBA reversal agent dosing. Quantitative monitoring can be an effective strategy to prevent rNMB when used appropriately in the clinical setting. Tools to monitor neuromuscular blockade include train of four (TOF) and post-tetanic count (PTC) monitoring.

Tools for Monitoring NMB

Train of Four

The most common method to assess level of NMB is with a TOF peripheral nerve monitor (Boon et al., 2018). With this method, the monitor is applied either at the distal forearm to stimulate the ulnar nerve or on the face to stimulate the facial nerve. Four consecutive electrical stimuli are administered to evoke muscle contractions (Boon et al., 2018). At baseline, all four muscle contractions will be present and equal and are denoted as one twitch (T1), second twitch (T2), third twitch (T3), and fourth twitch (T4) (Boon et al., 2018). With an increasing degree of NMB, the amplitude of the latter twitches decreases relative to the first twitches, an occurrence known as fade, and can then disappear entirely (T0) (Boon et al., 2018). The number of detectable muscle twitches corresponds with the depth of the NMB, and the degree of fade is expressed as a ratio comparing the strength of the fourth twitch with the strength of the first twitch, otherwise known as the T4:T1 ratio or TOF ratio (Boon et al., 2018).

Post-Tetanic Count

When high doses of NMB are administered, and the TOF measurement is zero, a tetanic stimulus of 50 Hz for five seconds may be applied to the nerve, releasing a large amount of acetylcholine from the neuromuscular junction (Boon et al, 2018). The tetanic stimulus is then followed by 15 additional electrical stimuli delivered at one-second intervals. The number of measured twitches makes up the PTC (Boon et al., 2018). The depth of the NMB is classified based on the TOF and the PTC. For example, a moderate block corresponds with T2-T3 on TOF with a PTC > zero, while a deep block is T0 on TOF and a PTC > zero. An intense block is T0 on TOF with a PTC of zero (Boon et al., 2018). These measurements of NMB depth are used to guide clinical management of patients such that if the TOF ratio is greater than 0.9 (or 90%), NMB is considered resolved, and therefore it is safe to extubate (Boon et al., 2018). Additionally, an accurate assessment of the degree of NMB is required before the decision to use neostigmine or sugammadex can be made. Neostigmine is not effective for reversal of deep or profound NMB (Cammu, 2018). Thus, it is suggested practice to administer neostigmine when ≥ 2 twitches are present on TOF monitoring (Cammu, 2018).

Quantitative monitoring is essential for guiding appropriate timing and dosage of NMB reversal, and aids providers in determining when sugammadex versus neostigmine should be chosen. Despite cost differences between sugammadex and neostigmine, there are instances such as a deep or profound NMB where sugammadex is the only appropriate medication choice if it is available. This literature review will explore the costs of each reversal agent and costs associated with recovery time including minutes spent in the OR and PACU and occurrence of postoperative respiratory complications.

Literature Review

Clinical Inquiry

To review the pharmacoeconomic implications of the choice of a reversal agent for neuromuscular blockade (NMB), the following PICOT question was used to direct the literature review:

> For patients requiring reversal of NMB, is the increased cost of routine sugammadex usage compared to neostigmine justified by the cost savings gained from reduced recovery time and post-operative complications?

Methodology

A comprehensive search was conducted using PubMed, the Cochrane Library, Google Scholar, and CINAHL databases. Systematic reviews, randomized controlled trials (RCTs), and non-randomized controlled trials were preferentially included. Peer and narrative reviews, economic assessments, prospective observational studies, and review articles were also assessed for relevance. Search terms included: sugammadex, neostigmine, cost, and economic implications. Additional search criteria were adult population, English language, and full-text availability. Relevant studies from 2011 to 2021 were prioritized. 30 articles were reviewed, and 23 were selected based on overall quality of the evidence.

Synthesis of Findings

Incidence of rNMB

rNMB and its resulting respiratory manifestations can occur in the PACU after general anesthesia when NMBAs are used, and the incidence is likely grossly underestimated by providers in current practice (Romano et al., 2016). To assess and quantify the impact of rNMB on critical respiratory events in the PACU, Murphy et al. (2008) conducted a prospective, case-controlled observational trial including 7,459 patients in a one-year period who received a general anesthetic and experienced a CRE within the first 15 minutes of arrival in the PACU. A CRE was defined as upper airway obstruction, mild to moderate or severe hypoxia, signs of respiratory distress, reintubation, or evidence of aspiration (Murphy et al., 2008). In all cases, patients received a balanced anesthetic consisting of a volatile agent, opioids, and a neuromuscular blocking agent.

Peripheral TOF monitoring was conducted intraoperatively, and NMB was reversed with neostigmine and glycopyrrolate at the conclusion of the surgery. CREs were identified in 61 patients (0.8%) and the most prevalent events were hypoxemia (59%) and upper airway obstruction (34.4%). To have a comparison group, each case with a CRE in the PACU was matched with a patient of the same age and sex who underwent the same surgical procedure under general anesthesia with NMBA but did not experience a CRE (Murphy et al., 2008). Results showed that a significant rNMB, defined as TOF ratio value of 0.62 ± 0.20) was present in the majority (73.8%) of cases with a CRE within 15 minutes of PACU admission, while, in contrast, near-complete recovery was noted in the control group (Murphy et al., 2008).

Incidence of rNMB using sugammadex versus neostigmine

A randomized, controlled study conducted in 2016 by Brueckmann et al. aimed to investigate the impact of sugammadex on rNMB and readiness for OR discharge. Study participants included patients over age 18 of ASA class I-III undergoing elective laparoscopic or open abdominal surgery during a one-year period at Massachusetts General Hospital. Anesthesia was maintained with intravenous (IV) induction agents, opioids, inhaled anesthetics, and rocuronium to facilitate intubation (Brueckmann et al., 2016). The anesthesiologist was un-blinded to the study drug, and administered either sugammadex (n = 74) or neostigmine (n = 76) at the conclusion of the procedure to antagonize the effects of NMB based on TOF monitoring data. According to the study design, sugammadex 2mg/kg was to be administered if spontaneous recovery had reached moderate (TOF count 1 to 3) or deep (no response to TOF stimulation, but a response to post-tetanic count) neuromuscular blockade (Brueckmann et al., 2016). Administration and dosing of neostigmine/glycopyrrolate was dosed according to the facility's usual care practices and the product labels.

The primary endpoint of the study was rNMB (defined as a TOF ratio < 0.9) upon arrival to PACU. rNMB was present in 22% of patients, all of whom were in the neostigmine group (Brueckmann et al., 2016). Limitations to this study include restriction to a single facility and a relatively low number of participants. Additionally, the study design may have influenced findings because anesthesiologists were un-blinded to the reversal drugs, and neostigmine dosing was discretionary.

A similar study by Domenech and colleagues (2019) sought to estimate the incidence of rNMB with or without a NMBA reversal agent and quantitative neuromuscular monitoring. This retrospective, observational cohort study of 240 patients undergoing elective procedures requiring NMB that was conducted during a 3-month period in 2015 at a hospital in Buenos Aires, Argentina. Retrospective data was collected from each surgery, including the duration, type of NMBA used, dose, time from medication administration to TOF ratio > 0.9, and the use of intraoperative quantitative monitoring. All patients were monitored with TOF measurements within 5 minutes of PACU arrival. Primary endpoint was presence of clinically significant rNMB, defined by a TOF ratio < 0.9.

Results revealed zero incidence of rNMB (TOF ratio < 0.9) in patients who received intraoperative quantitative monitoring, regardless of whether sugammadex or neostigmine was used for reversal. rNMB was observed in the non-monitored group of patients, with TOF ratio < 0.9 present in 16% of the sugammadex group and 40% of the neostigmine group (Domenech et al., 2019). These results suggest that rNMB was likely due to an insufficient reversal agent dosage, assuming the anesthesiologists' underestimation of NMB depth (Domenech et al., 2019).

Although this was an observational, single-center study whose results may be difficult to generalize to all facilities, results suggest that the combination of NMB monitoring and administration of either reversal agent is essential for the prevention of rNMB and that sugammadex administration in the absence of TOF monitoring is not an effective strategy in eliminating rNMB. Limitations include lack of blinding as to type of NMBA that was used and small sample size.

A randomized controlled trial (RTC) of 240 patients by Togioka et al. (2020) sought to explore the associations between rNMB in older patients and potentially related variables, including use of NMB monitoring, duration of surgery, type of NMB medication, type of reversal agent, and time between the last dose of NMB and TOF ratio in PACU. Eligible patients included those greater than 70 years old, scheduled for surgeries lasting longer than 3 hours, and lack of medical or surgical contraindication to neuromuscular blockade (Togioka et al., 2020). Patient variables, including age, sex, ASA classification score, height, weight, and body mass index, were recorded for all participants, as was surgery-related data including duration of surgery, NMB medication and dosage used, and use of TOF monitoring (Togioka et al., 2020).

All patients were monitored with TOF measurements within 5 minutes of arrival to PACU. Incidence of rNMB defined by TOF < 0.9 was 24% and present in only 10% of the sugammadex group compared to 49% of the neostigmine group (Togioka et al., 2020). There was a 7% reduction in PPC, the primary endpoint, in the sugammadex group, which is consistent with previous studies, and not statistically significant (Togioka et al., 2020). The most common complication observed in the study was atelectasis, occurring in 25% of the neostigmine group and 19% of the sugammadex group, which was not statistically significant (Togioka et al., 2020). A notable finding, however, was in hospital readmission rates: there was a threefold increase in 30-day hospital readmission rates in the neostigmine group (15%) compared to the sugammadex group (5%). Authors hypothesized the improved efficacy of sugammadex and elimination of negative cardiovascular and upper airway effects with neostigmine may contribute to the reduced 30-day hospital readmission rate (Togioka et al., 2020).

A study by Cho et al. (2017) compared NMB reversal with either sugammadex or pyridostigmine, an AChE inhibitor medication with a mechanism of action similar to neostigmine, in 50 patients undergoing video-assisted thoracoscopic surgery (VATS) lobectomy. Primary endpoints included incidence of PPC, duration of chest tube insertion, and length of hospital stay. Overall incidence of PPC was found to be lower in patients who received sugammadex than pyridostigmine (26.3% versus 54.8%, respectively) (Cho et al., 2017). Authors hypothesized this finding was due to the rapid restoration of normal skeletal muscle function, achievement of deep breathing, and decrease in atelectasis when sugammadex was used (Cho et al., 2017).

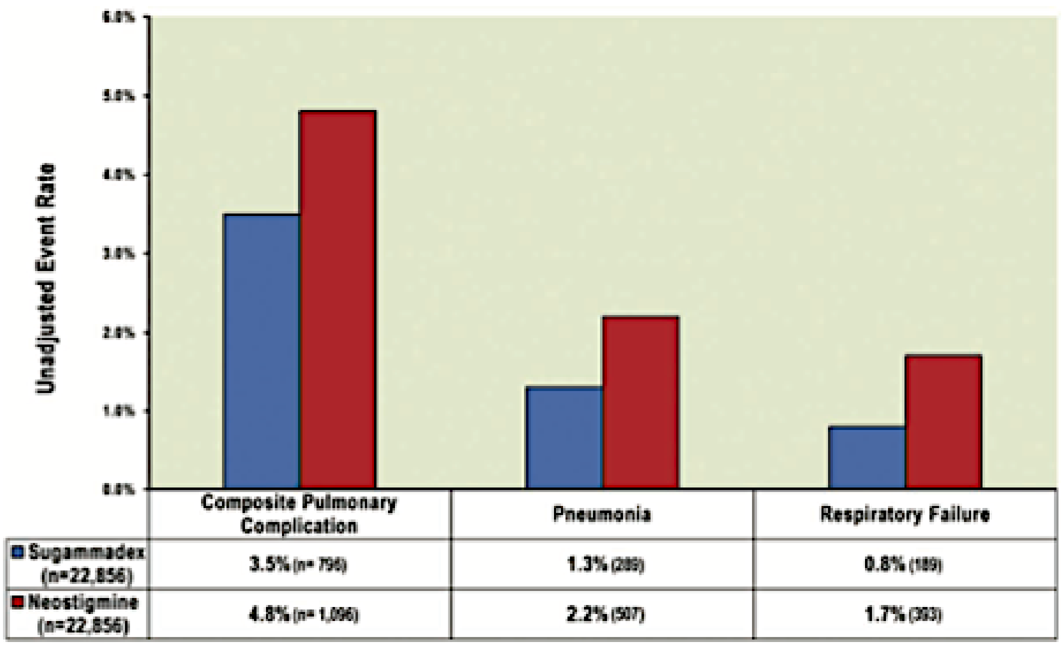
A 2017 Cochrane Review regarding the efficacy and safety of using sugammadex versus neostigmine for reversal of neuromuscular blockade was conducted by Hristovska et al. 28 RTCs (n = 2298) were included for meta-analysis. Participants were age > 18 with ASA classification I-IV who received non-depolarizing NMBs for elective surgical procedures. All trials compared recovery times and adverse events with sugammadex and neostigmine (Hristovska et al., 2017). Secondary outcomes of the study included risks of adverse events and serious adverse events (Hristovska et al., 2017).

Meta-analysis revealed significantly fewer overall composite adverse events in the sugammadex group than in the neostigmine group (283 per 1000 in the neostigmine group and 159 per 1000 in the sugammadex group). A review of specific adverse events revealed significantly less risk in the sugammadex group compared to the neostigmine group for the following parameters: desaturation, need for transient oxygen supplementation, and the ability to perform a 5-second head lift (Hristovska et al., 2017). Furthermore, an analysis of the number needed to treat for an additional beneficial outcome revealed that eight patients should be treated with sugammadex rather than neostigmine to avoid one patient experiencing any single adverse event (Hristovska et al., 2017). Overall, this 2017 Cochrane review provides a strong assessment of the efficacy of sugammadex, as it includes a sizable number of RTCs and a large sample size.

Kherpetal et al. (2020) conducted a multicenter matched cohort analysis to determine if patients who received sugammadex after general anesthesia with NMB were at a lower risk of PPC than those who received neostigmine. The study consisted of over 45,000 patients age > 18 undergoing general anesthesia and NMB with rocuronium for inpatient noncardiac elective surgery. Figure 1 shows that patients who received sugammadex compared to those who received neostigmine for NMB reversal had 30% reduced risk of major pulmonary complications, 47% reduced risk of pneumonia, and 55% reduced risk of respiratory failure (Kherpetal et al., 2020). The overall findings of this study suggest that using sugammadex has a strong advantage at reducing postoperative pulmonary complications and improving patient outcomes, however, there were limitations to the research. Natural advancements in the medical management of pulmonary care protocols may have accounted for some of the reductions in pulmonary complications during the four years that the study was conducted.

Figure 1.

Major Pulmonary Complication Rates with Sugammadex versus Neostigmine



Note: Major pulmonary complication rates in patients undergoing noncardiac inpatient surgery. The composite pulmonary complication primary outcome included pneumonia, respiratory failure, and other major complications. (Kherpetal et al., 2020).

Speed of Recovery With Sugammadex Versus Neostigmine for Reversal of NMB

Recovery Time from T2 Reappearance

Many studies have compared the clinical effectiveness of sugammadex and neostigmine as it relates to time to recovery from NMB at the reappearance of T2. The Cochrane review by Hristovska had a primary outcome measurement that compared recovery time from T2 to TOF > 0.9 between sugammadex 2 mg/kg versus neostigmine 0.5 mg/kg in 10 RCTs where varying doses of rocuronium were used for both intubation and maintenance. A meta-analysis of the results showed that sugammadex reversed NMB in 1.96 minutes, compared to 12.87 minutes for neostigmine; as such, sugammadex is on average 10.22 minutes (or 6.6 times) faster than neostigmine in reversing NMB at T2 reappearance (Hristovska et al., 2017).

A retrospective study by Romano et. al (2016) aimed to compare the recovery times in patients who received NMB after either sugammadex or neostigmine administration to estimate the time spent in the OR and the possible economic impact of a faster recovery in morbidly patients undergoing laparoscopic bariatric surgery. Inclusion criteria for this study were as follows: age < 18 and < 45 years, BMI ≥ 40 kg/m^2, ASA class III, and no planned ICU admission. Anesthesia was maintained per a standard protocol with propofol, remifentanil, and sevoflurane, and neuromuscular monitoring was performed using acceleromyography. At the conclusion of the surgery, either sugammadex 2 mg/kg or neostigmine 50 mcg/kg plus atropine 0.01 mg/kg was given at the reappearance of T2. Patients were extubated in the OR when a TOF ratio of 0.9 was achieved. Patients were then transferred to the PACU (Romano et al., 2016).

The primary endpoint of the study was to compare the time to achieve a TOF ratio of 0.9, mean time to achieve an Aldrete score of 10, and the associated costs of each medication (Romano et al., 2016). Ninety-nine patients were included in the study and were divided into two groups (50 in the sugammadex group and 49 in the neostigmine group). In the sugammadex group, the mean recovery time from reversal agent administration to TOF > 0.9 was 1.4 minutes, compared to 26.4 minutes in the neostigmine group (Romano et al., 2016). Operating room occupancy was found to be 93.3 minutes for the sugammadex group and 116 minutes for the neostigmine group, a significant difference (Romano et al., 2016). The results of this retrospective analysis conclude that sugammadex accelerates recovery time, decreases overall time spent in the operating room, and may have favorable economic implications compared to neostigmine when cost savings per minute of OR occupancy are evaluated

Time Spent in the OR and PACU.

Similar to the Romano (2016) study, other researchers have investigated OR and PACU occupancy when sugammadex versus neostigmine was used to reverse NMB after general anesthesia. A systematic review and meta-analysis of 518 patients by Carron et al. (2016) sought to determine whether the clinical superiority of sugammadex could lead to faster discharge from the OR, PACU, and surgical ward compared to neostigmine. The results of this study showed that sugammadex was associated with a significant reduction in discharge time from OR to PACU compared to neostigmine, with a mean difference of 22.4 minutes (Carron et al., 2016). Sugammadex was also associated with a significantly faster discharge from the PACU to the surgical ward (mean difference 16.95 minutes) (Carron et al., 2016).

A retrospective observational study by Min et al. (2020) analyzed post-anesthetic recovery times, hospital charges, and unplanned readmissions for patients undergoing robot-assisted laparoscopic prostatectomy who received general anesthesia and rocuronium. Results indicated that for the 1,430 patients enrolled, there was a 6% decrease in hospital length of stay, an 8% decrease in post-anesthetic recovery time, and no change in 30-day readmission rates for patients who received sugammadex compared to neostigmine (Min et al., 2020). Although this study was limited to a single-center analysis and cannot be generalizable, it supports the findings of similar studies in that sugammadex accelerates recovery and decreases time spent in the OR and the PACU settings.

Recovery Time from Profound Neuromuscular Blockade

In the clinical setting, there are instances where a profound neuromuscular blockade must be antagonized. The Cochrane review investigated recovery time from a PTC 1 to 5 to TOF > 0.9 by combining two trials, both of which used a single intubating dose of rocuronium 0.6 mg/kg and a maintenance dose of 0.15 mg/kg. The studies administered either neostigmine 0.07 mg/kg or sugammadex 4mg/kg at the reappearance of PTC 1 to 5 (Hristovska et al., 2017). Meta-analysis of trial results showed that sugammadex reversed this level of the blockade in 2.9 minutes, while neostigmine reversed it in 48.8 minutes (Hristovska et al., 2017). Therefore, the data shows that sugammadex reverses neuromuscular blockade 45.78 minutes (or 16 times), faster than neostigmine at the reappearance of PTC 1 to 5 (Hristovska et al., 2017). Overall results of the Cochrane review suggest that the speed of sugammadex for reversal of any level of the neuromuscular blockade offers a serious potential advantage. A faster recovery from NMB ultimately reduces overall anesthesia time, OR occupancy, and potentially reduces overall healthcare costs.

Cost-Effectiveness of Neostigmine and Sugammadex

Actual Costs of Reversal Agents

Medications to reverse NMB are used in millions of surgical cases each year, and the decision to routinely use a more expensive medication over a traditional one has significant financial implications for health systems (Hurford et al., 2020). To analyze the specific costs associated with the choice of reversal drug, Hurford et al. (2020) constructed a decision model for sugammadex versus neostigmine for reversal of NMB with rocuronium in adult patients.

Costs of both medications vary widely, but Hurford et al. used the Federal Supply Schedule (FSS) pricing from 2019 to determine medication costs for this analysis (Figure 2). Drug pricing was as follows: high-dose sugammadex (4mg/kg) was valued at $171.06, while low-dose sugammadex (2 mg/kg) was $93.40, and neostigmine with glycopyrrolate was $21.21 (Hurford et al., 2020). Hurford et al. created a fictional, mid-sized health system in the Midwest United States for this cost analysis. In a facility of this size and location, drugs to reverse NMB are used in an estimated 18,000 cases annually, so even a small incremental cost increase has a large economic impact on the institution (Hurford et al., 2020). Based on the cost of each medication alone, the decision to use sugammadex would cost a hospital nearly one million dollars annually (Hurford et al, 2020). Authors included downstream costs, such as costs of OR time, unplanned postoperative mechanical ventilation, and postoperative nausea and vomiting, in their analysis to determine if the use of sugammadex can be justified, or even have a financial benefit, through these mechanisms.

Figure 2.

Federal Supply Schedule Pricing, 2019

Key data used in the base-case decision model.

Parameter	Value	Data source
Drug Pricing		
Neostigmine/glycopyrrolate	$ 21.21	FSS 2019
Sugammadex - high dose	$ 171.06	FSS 2019
Sugammadex - low dose	$ 93.40	FSS 2019
Nothing	$ -	FSS 2019
Downstream costs		
OR direct costs/min	$ 32.49	Childers 2018 [8]
Incremental MV costs/day	$2631.85	Dasta 2005 [9]
PONV costs	$ 98.62	Parra-Sanchez 2012 [11]
OR reversal times (minutes)		
Neo/glyco - deep block	13.1	Meta-analysis [10]
Moderate block	10.5	
Sugammadex - deep block	2.1	
Moderate block	1.5	
Nothing - deep block	68.4	
Moderate block	31.5	
Patient-related parameters		
Prop. of deep blocks	0.21	Carron 2016 [3]
Prop. of high risk (ASA ≥3)	0.51	UC Health 2017
Prop. UPMV in high risk	0.0015	UC Health 2017
Prop. UPMV in low risk	0.0004	UC Health 2017
Prop. PONV	0.207	UC Health 2017
Relative risks of complications (versus neostigmine)		
Relative risk of UPMV		
Sugammadex	0.112	Carron 2016 Martinez-Ubieto 2016 Olesnicky 2017 [3,41,42]
Nothing	2.2	Murphy 2018 [43]
Relative risk of PONV	0.74	Meta-analysis [10]

Note: Data used in the base-case decision model for cost analysis. (Hurford et al., 2020).

The Value of OR and PACU Time

Hurford et al. (2020) discovered that the cost of OR time varies extensively, ranging from $10 to $62 per minute. Certain costs are fixed and unaffected by changes in unproductive (non-operative) time, such as the cost of surgical supplies for a specific case, but other costs are variable upon location, day of the week, and type of surgical procedure performed. Opportunity costs are difficult to quantify, for example whether time saved translates into personnel being allocated additional cases (Hurford et al., 2020). Authors discovered that reductions in OR time with sugammadex offer the most significant savings in their base-case analysis, and that sugammadex use is preferable when a health system values OR time more than $8.65/minute

(Hurford et al., 2020). OR costs are notoriously difficult to value, therefore if OR costs are deemed negligible or excluded from the analysis, neostigmine is preferably to sugammadex (Hurford et al., 2020).

A study by Zaouter et al. (2017) sought to discover how a decrease in OR and PACU occupancy could translate into potential cost savings when sugammadex is used to reverse NMB compared to neostigmine. Zaouter et al. conducted an economic evaluation to determine the value of each minute of OR time saved when using sugammadex in the United States. The authors calculated an operating room time cost of $30 per minute, and the price of sugammadex is approximately $100 for a 200 mg vial (Zaouter et al., 2017). The authors' calculations were based on a 75 kg patient. Results of the study showed that in patients with a superficial blockade (reappearance of T4), a 2mg/kg dose of sugammadex reduces mean time to achieve TOF ratio > 0.9 by 17 minutes compared to neostigmine (Zaouter et al., 2017). In this case, sugammadex lowers the costs related to surgery by $410 ($30.00/minute x 17 minutes saved - $100 = $410). Similar calculations were performed for scenarios with moderate and deep NMB, and the cost savings were $358 and $1,225, respectively (Zaouter et al., 2017). By these calculations, sugammadex offers the greatest cost savings for a patient with a deep level of NMB.

The purpose of this economic assessment was to investigate whether the faster recovery times associated with sugammadex can make it cost-effective if these time savings were translated into productive workplace activities. The authors used their calculations to determine how many additional cases could be performed in a day based on the minutes saved by using sugammadex to reverse NMB rather than neostigmine (Figure 3). This evaluation assumes that time saved with sugammadex would be used productively, and that the institution does, in fact, have additional surgeries to perform that day. The economic evaluation revealed that the use of sugammadex lowers operating room costs and allows a larger number of surgical operations to be performed in the same day, suggesting that although it is more expensive per vial, sugammadex is cost-effective if time savings can be translated into productive activity (Zaouter et al., 2017).

Figure 3.

The Value of Each Minute of OR Time Saved Using Sugammadex

Clinical Case scenarios	Number of additional cases performed per day	Budget balance per OR day in Canada ($Can)	Budget balance per OR day in United States ($US)
Short surgery with moderate NMB	2	-28	716
Long surgery with moderate NMB	1	-14	358
Short surgery with deep NMB	2	550	2450

Note: Overview of the value of each minute of OR time saved with sugammadex. (Zaouter et al., 2017).

Similar results were found in the retrospective study by Romano et al. (2016) analyzing morbidly obese patients undergoing elective bariatric laparoscopic surgery. Patients who received sugammadex at reappearance of T2 showed shorter times to achieve a TOF ratio > 0.9 and Aldrete score of 10, and a significant reduction in OR theater occupancy (mean time of 23 minutes). While sugammadex accounted for 2.58% of the total cost of surgery (as opposed to 0.06% with neostigmine), the total time saved by using sugammadex was 19.4 hours, which could potentially be used to perform 12 additional surgeries (Romano et al., 2016). The authors concluded that there is a clear economic advantage to the use of sugammadex if the time saved could be utilized for additional productivity (e.g., more surgeries) as well as cost savings associated with OR occupancy (e.g., personnel salaries) (Romano et al., 2016). A major limitation to this study is that it assumes that time saved in the OR would be automatically translated into productive activities, such as additional surgeries.

Carron et al. (2016) also conducted a retrospective analysis to evaluate the economic impact of sugammadex. Their findings showed that although sugammadex has a higher direct cost, it contributes to overall cost-savings by allowing a rapid, safe recovery in high-risk patients and expediting extubation at the end of general anesthesia, which speeds workflow (Carron et al., 2016). The authors estimated the economic benefits of sugammadex at 6.6. euros per minute gained in the OR, and 0.3 euros per minute gained in the PACU, confirming that sugammadex is cost-effective for reversal of moderate or deep NMB and has the potential to increase OR productivity with subsequent economic benefit (Carron et al., 2016). Through multiple studies, the works of Carron et al. and Zaouter et al. (2017) suggest that sugammadex has the potential to accelerate patient discharge, especially from OR to PACU, possibly due to the differences in the mechanism of action to reverse NMB and superiority of recovery of respiratory function with sugammadex. It can be concluded from these results that faster turnover times using sugammadex may outweigh its higher cost.

The Value of Decreasing Postoperative Complications

To approximate both the clinical and economic impact of the use of sugammadex for routine reversal of NMB with rocuronium, Martinez-Ubieto et al. (2021) analyzed 537,931 patients in Spain comparing two hypothetical scenarios: one where sugammadex is available for reversal of moderate or deep NMB, and one where it is not. In the scenario where sugammadex was not available, comparators included neostigmine or no reversal agent (Martinez-Ubieto et al., 2021). The authors studied clinical parameters of atelectasis and pneumonia and found that the increase in drug cost with sugammadex was offset by savings in post-operative events (52% reduction in cases of pneumonia and 84% reduction in atelectasis) and that the total cost of complications avoided was projected to 70.4 million euros (Martinez-Ubierto et al., 2021).

A 2020 economic analysis conducted in China by Ren et al., (2020) had similar findings when comparing the cost-effectiveness of sugammadex versus neostigmine for 2,000 patients undergoing laparoscopic surgery. The authors' decision tree model projected that the use of sugammadex for NMB reversal would lead to 673 fewer complications (including rNMB-related complications, hospitalizations, and other adverse events) compared to neostigmine (Ren et al., 2020). Despite the additional medication cost of sugammadex, 93.6% of that increased cost was offset by the cost savings attributed to the treatment of rNMB-related complications (Ren et al., 2020). In summary, the authors concluded that the greater costs of sugammadex are almost entirely balanced by the costs saved in the treatment of complications and that sugammadex offers a good value as a reversal agent.

Impact of Provider Attitudes Regarding Sugammadex Use

Although it has been established that sugammadex is more clinically effective and has a better safety profile than neostigmine, the impact of pharmacoeconomics on sugammadex use is not fully understood. To assess global patterns of clinical practice and the use of sugammadex amongst providers, O'Reilly-Shah et al. (2017) developed a tool to deploy a survey to 11,863 anesthesia providers worldwide. Results of the survey showed that 40% of the respondents self-limited administration of sugammadex, primarily due to cost concerns, even in the absence of an institutional policy restricting its use (O'Reilly-Shah et al., 2019). Despite the benefits of sugammadex over neostigmine, O'Reilly-Shah et al. deduced the primary limiting factor for sugammadex use was cost, with secondary factors being limited drug supply and concerns for adverse events.

The authors extrapolated that although anesthesia providers appear to be making patient care decisions with economic concerns in mind, the pharmacoeconomic implications may be more complex than acquisition costs alone, and that the higher drug costs of sugammadex may be offset by other factors such as faster recovery times and decreased rates of complications related to rNMB (O'Reilly-Shah et al., 2019). Based on the survey results, it is evident that providers weigh direct medication costs heavily when it comes to the choice of NMBA reversal agent, however, indirect costs savings and quality advantages must absolutely be considered as well (O'Reilly-Shah et al., 2019).

Discussion

NMBAs are an essential component of a general anesthetic, used not only to facilitate endotracheal intubation, but to provide surgeons with satisfactory operating conditions. A well-known, but unfortunate complication of NMBAs occurs when there is inadequate reversal of the paralytic medication, a phenomenon otherwise known as rNMB. RNMB can lead to hypoxia, upper airway obstruction, aspiration, pneumonia, and ultimately necessitate reintubation. In fact, according to Murphy et al. (2008), rNMB was present in the majority of cases where a respiratory event occurred within 15 minutes PACU arrival. This evidence suggests that rNMB is a significant contributor of respiratory complications in the PACU setting, and as such, anesthesia providers have a strong incentive for eliminating this risk for patients.

There is a large body of research investigating the incidence of rNMB and pulmonary complications in PACU, and whether using sugammadex versus neostigmine makes a significant difference in mitigating this risk. Studies by Brueckmann et al. (2016), Togioka et al. (2020), Kherpetal et al. (2020) and Cho et al. (2017) showed that sugammadex reduced risk of pulmonary complications in PACU compared to AChE inhibitor medications. Additionally, the Cochrane review by Hristovska et al. (2017) found significantly fewer adverse events, including desaturation and need for oxygen supplementation, in patients who received sugammadex compared to neostigmine.

Conversely, a similar study by Domenech et al. (2019) found no evidence of rNMB for any patients in their study, whether they received sugammadex or neostigmine. Based on the results of this study, authors concluded that when NMB monitoring is used and either reversal agent is administered, rNMB and its subsequent pulmonary populations can effectively be prevented. Based on the literature, it is evident that sugammadex is the more effective NMB reversal agent in terms of preventing rNMB and respiratory complications, especially when NMB monitoring is used to guide dosage.

Still, the decision to administer neostigmine versus sugammadex for the reversal of NMB is a complex one based on a myriad of factors. Another important consideration when choosing an agent to antagonize the effects of NMB is the speed at which the reversal can be performed, as this has both clinical and economic implications, even affecting hospital workflow. Hristovska et al. (2017) and Robertis et al. (2016) both studied recovery times from T2 reappearance and found that sugammadex restored TOF ratio > 0.9 in under 2 minutes compared to over 10 minutes for neostigmine. The evidence is clear that sugammadex accelerates neuromuscular recovery time, which can also translate into decreased time spent in OR and PACU settings.

Robertis et al. (2016) found that sugammadex decreased OR time by 23 minutes, while Carron et al. (2016) had similar results with 22 minutes saved. Sugammadex is also associated with significantly faster discharge from PACU times and an 8% overall decreased anesthesia recovery time (Min et al., 2020). Recovery times are important not only for improving hospital workflow and efficiency, also in emergency situations. Sugammadex can reverse profound neuromuscular blockade in 2.9 minutes, where neostigmine cannot reverse this level of NMB at all (Hristovska et al., 2017). This is especially advantageous in a cannot-intubate-cannot-ventilate scenario. While sugammadex has been established as the superior medication to reverse NMB in terms of clinical effectiveness, speed of neuromuscular recovery, and safety, the high costs of unrestricted sugammadex are significant and cannot be readily ignored.

Decreasing recovery time, OR, and PACU occupancy can be translated into costs savings when analyzing the value of each minute in the OR and PACU settings and considering the increased workplace productivity that could result. When sugammadex is administered over neostigmine, it has been proven that a TOF ratio > 0.9 will be achieved sooner, and the patient can be extubated and transferred to the PACU with less risk of rNMB and, therefore, less risk of PPC. Based on these advantages, patients who are treated with sugammadex will ultimately spend less time in the OR, which potentially decreases turnover time and helps with overall workflow and productivity, assuming the extra time is used for productive activities. Taking all these factors into consideration, sugammadex is potentially a cost-effective, safer alternative to using neostigmine for the reversal of NMB.

Finally, provider attitudes and perceptions regarding the pharmacoeconomic implications of sugammadex use also play a role in how it is used in current practice. O'Reilly-Shah and colleagues (2019) found that cost concerns are likely the primary factor limiting sugammadex use in the clinical setting, even in the absence of institutional policies that restrict such practices. Anesthesia providers make care decisions with economic concerns in mind, even if they do not impact the provider directly. While it important to consider healthcare costs for both patients and hospitals, the pharmacoeconomics of sugammadex and neostigmine are clearly complex, and decisions should not just be made on cost per vial alone.

Literature Gaps/Limitations

Cost-effectiveness is a complex, multifactorial subject, and it is difficult to conduct research that firmly determines whether a medication, although clearly superior in many ways, is worth the additional costs it incurs. In addition, sugammadex remains still a relatively new medication, and there is a lack of comprehensive, prospective cost-effective studies in North America. While sugammadex use is justified for reversal of deep and profound NMB, additional research is needed to determine if sugammadex is cost-effective for routine reversal of superficial and moderate NMB.

Conclusion

Overall, the literature provides evidence that sugammadex, while definitively more expensive, is a superior alternative to neostigmine for the reversal of NMB in terms of safety, efficacy, and efficiency. With a faster onset time and fewer side effects, the studies analyzed in this review show that patients who received sugammadex had faster discharge from the OR and PACU settings with fewer rNMB-related complications. Faster recovery times can ultimately be translated into costs savings in terms of potential increased productivity in the OR, such as completing additional surgeries in a day, as well as money saved on staff salaries and resources per minute of time saved. Additionally, a lower incidence of respiratory complications such as atelectasis and pneumonia saves money that hospitals would otherwise have to spend on the diagnosis and treatment of such conditions, as well as additional recovery time. By looking at the larger picture of the two medications, and the broader clinical and financial impacts of each one, it is reasonable to conclude that the extra cost of using sugammadex for the routine reversal of

NMB may be justified not only by its superior safety profile but also the indirect cost savings associated with the improved clinical outcomes. While additional research is needed to solidify these findings and strengthen the evidence for this conclusion, there is a large enough body of research that currently exists to make a strong argument for unrestricted sugammadex use.

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