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CASE SERIES PHARMACOLOGY

Thinking outside the box: management of sugammadex failure in the operating room; a case series and literature review

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ABSTRACT

Ensuring complete reversal of neuromuscular blockade (NMB) is crucial for safe anesthetic care. Sugammadex, a selective binding agent, is highly effective in reversing steroidal NMB agents like rocuronium, and is often considered superior to standard reversal agents due to its ability to quickly reverse large doses of rocuronium, its increased flexibility in neuromuscular management in the operating room, and its reduced risk of residual neuromuscular blockade in the PACU when appropriately dosed. However, instances of sugammadex failing to achieve adequate reversal pose significant clinical challenges. We present here a case series of three cases in which Neuromuscular block proved resistant to the routine reversal agents.

Abbreviations: CAD: coronary artery disease, NMB: neuromuscular blockade, NASH: non-alcoholic fatty liver disease, PACU: post-anesthesia care unit, SVT: supraventricular tachycardia, TOF: train-of-four

Keywords: sugammadex, neuromuscular blockade, Neuromuscular Blocking Agents, neostigmine, Cholinesterase Inhibitors

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1. INTRODUCTION

Ensuring complete reversal of neuromuscular blockade (NMB) is crucial for safe anesthetic care. Sugammadex, a selective binding agent, is highly effective in reversing steroidal NMB agents like rocuronium. Sugammadex is often considered superior to standard reversal agents due to its ability to quickly reverse large doses of rocuronium, its increased flexibility in neuromuscular management in the operating room, and its reduced risk of residual neuromuscular blockade in the PACU when appropriately dosed.[1] However, instances of sugammadex failing to achieve adequate reversal pose significant clinical challenges.

Our institution encountered several cases where sugammadex failed to provide adequate reversal. We define sugammadex failure as the need for additional doses beyond FDA recommendations to achieve a train-of-four (TOF) ratio >0.9, and the inability to extubate despite recommended doses. These experiences led us to question why sugammadex failed in these scenarios and how to manage patients if sugammadex fails in the future. Understanding these scenarios is vital for improving outcomes, especially in ambulatory surgical settings with limited resources.

2. CASE SERIES

Case 1:

A 40-year-old female (BMI 40 kg/m^2) with obesity, non-alcoholic fatty liver disease (NASH), and recent GLP-1 agonist use underwent surgery at an ambulatory center. Modified rapid sequence induction was performed using rocuronium (80 mg); no additional doses were given during the 2-hour procedure. Neuromuscular blockade was monitored via Senzime TetraGraph® on the right forearm. Anesthesia was maintained with total IV anesthesia. The patient remained normothermic and received no agents known to prolong neuromuscular blockade.

Upon emergence, TOF remained 0/4 and post-tetanic count (PTC) was 0/20 on the Senzime TetraGraph® following initial rocuronium dosing. Full reversal (TOF ratio 100%) was achieved only after staged administration of 1400 mg sugammadex (14 mg/kg) over 30 minutes. Despite this, tidal volumes remained <5 mL/kg and the patient appeared weak during sedation weaning. Neostigmine/glycopyrrolate was considered but deferred due to limited evidence and the surgical center's limited overnight staffing. The patient remained intubated and was transferred to an inpatient facility, where she was successfully extubated on postoperative day 2.

Case 2:

An 81-year-old male (BMI 24.5 kg/m^2) with atrial fibrillation, coronary artery disease (CAD), thoracic aortic aneurysm, and sensorimotor polyneuropathy underwent prostate surgery under general anesthesia. Induction included propofol, rocuronium (50 mg), fentanyl, and lidocaine. Muscle relaxation was maintained with an additional 50 mg rocuronium; none was given in the hour before extubation. TOF showed two twitches prior to reversal with IV neostigmine (5 mg) and glycopyrrolate (0.5 mg). The patient was extubated after the 180-minute procedure.

Within 15 minutes of extubation, the patient desaturated with inadequate ventilation. Propofol and succinylcholine were administered to facilitate LMA placement. TOF showed 3 twitches with fade, suggesting incomplete reversal. Sugammadex was given in two 400 mg in divided doses (total 7.3 mg/kg), with minimal improvement. The patient was reintubated, sedated with propofol in PACU, and gradually regained strength. He was successfully extubated and discharged the next day without complications.

Case 3:

A 66-year-old female (BMI 22 kg/m^2) with ESRD post-kidney transplant (7 months prior), hypertension, and hyperparathyroidism was admitted for evaluation of a pulmonary mass. Home immunosuppressants (including prednisone 5mg) and other medications were continued on the day of her bronchoscopy.

Anesthesia was induced with lidocaine, propofol, and rocuronium (50 mg), and maintained with propofol infusion (100 mcg/kg/min). Dexamethasone (4 mg) was given at induction. Rocuronium was re-dosed (10 mg) two hours before emergence (total 60 mg). Neuromuscular monitoring via Senzime TetraGraph® showed a TOF count 0 and PTC 0/20 at case end (3.5 hours).

Initial sugammadex dose (200 mg) was ineffective; due to concerns about high-dose effects, a staged approach was used with an additional 400 mg over 45 minutes (total 600 mg; 6 mg/kg), resulting in gradual recovery. The patient regained full strength and was extubated without complication.

3. DISCUSSION

3.1. Rocuronium Bromide:

Rocuronium, a nondepolarizing neuromuscular blocking agent, works by competitively binding to nicotinic acetylcholine receptors at the neuromuscular junction, preventing acetylcholine from triggering muscle contractions. It was developed to provide an alternative to succinylcholine for rapid sequence induction in anesthesia.[2] Rocuronium quickly gained popularity in the 1990's due to its rapid onset and intermediate duration of action, making it suitable for both routine and emergency intubations. Though succinylcholine has a shorter duration of action, making it preferable in rapid intubation sequences, rocuronium has a more favorable side effect profile, such as reduced risk of hyperkalemia, myalgias and malignant hyperthermia.[3,4]

Rocuronium has an onset time of approximately 45-60 seconds, providing good intubation conditions within 1-2 minutes. [5] The duration of action typically lasts around 20-35 minutes, though this can vary based on dosage and patient factors. Rocuronium has a half-life of approximately 1.4 to 2.4 hours in adults.[5] There is also heterogeneity among patients' drug metabolization and variability in response to redosing of rocuronium, such as hepatic or renal dysfunction delaying drug clearance. Rocuronium interacts with specific CYP450 enzymes, specifically CYP3A4 and to a lesser degree CYP2C19, and patients with hepatic dysfunction are at risk for a prolonged plasma-half-life of rocuronium, thus potentiating the drugs' effects.[6,7] Renal insufficiency is known to delay clearance of the drug. Rocuronium is

minimally metabolized by the liver, with most of the drug being excreted unchanged in the feces (31%) and urine (26%).[8]

The drug's neuromuscular blocking effects can be significantly influenced by acid-base and electrolyte imbalances, which may either potentiate or cause resistance to its action. The drug's effect is potentiated in acidotic states but reduced in alkalotic states.[9] Additionally, acute or chronic electrolyte imbalances, such as conditions that can cause hypocalcemia, hypokalemia, or hypermagnesemia, are known to potentiate neuromuscular blockade.[10]

3.2. Neostigmine and Glycopyrrolate:

Neostigmine and glycopyrrolate have long histories of use in anesthesia to reverse neuromuscular blockade. Neostigmine was first introduced in the 1940s and has been widely used to reverse the effects of non-depolarizing neuromuscular blocking agents (NMBAs). Neostigmine reverses the effects of rocuronium by inhibiting acetylcholinesterase, increasing acetylcholine levels, acting as a competitive antagonist of rocuronium at muscle receptors. Glycopyrrolate, an anticholinergic drug synthesized in counteracts neostigmine's muscarinic side effects like bradycardia, bronchoconstriction, and excessive salivation. Together, these drugs ensure the safe recovery of patients from muscle relaxants used during surgery.[11,12]

3.3. Neuromuscular monitoring:

Careful monitoring of neuromuscular blockade in intraoperative management is crucial in optimizing patient recovery and improving postoperative patient outcomes. To underscore the importance of monitoring, previous literature has demonstrated postop residual neuromuscular blockade occurred in up to 40% of patients.[13] Historically, neuromuscular blockade recovery was assessed by a variety of clinical tests until 1958, when Christie and Churchill-Davidson described the use of a nerve stimulator to monitor neuromuscular block.[14] In the 1970s, when the TOF pattern was first elucidated, nerve stimulation using electrodes and applying a supramaximal stimulus to peripheral nerves and measuring the associated muscular response became the gold standard of monitoring neuromuscular blockade.[14] This is commonly referred to as mechanography and is a qualitative form of measuring neuromuscular blockade.

Not all neuromuscular blockade sites are created equal. The response to neuromuscular blockade of muscle groups to nondepolarizing neuromuscular blockers occurs at variable rates. The first muscle groups to respond to neuromuscular blockers are the central muscles such as the diaphragm and laryngeal muscles, with response of the peripheral muscles such as adductor pollicis occurring later. This response is quicker for the central muscles due to greater blood flow and therefore greater neuromuscular blocking agent delivery. When nondepolarizing neuromuscular blockers are given, recovery from neuromuscular blockade of these muscle groups occurs in the following order from fastest to slowest: diaphragm, laryngeal muscles, corrugator supercilii, abdominal muscles, orbicularis oculi, geniohyoid, and finally adductor pollicis.[15] The multiple facial muscle groups, corrugator supercilii and orbicularis oculi, can be isolated and monitored which correlate well with recovery of the diaphragm and adductor pollicis muscles respectively, however, clinically can be difficult to distinguish these two muscle groups apart. To avoid this, monitoring at the adductor pollicis is the most preferable site of monitoring as it has the slowest reversal from neuromuscular blockade and adequate reversal at this muscle group ensures adequate recovery of all muscle groups with quicker recovery, namely the diaphragm and laryngeal muscles.[16,17] Other muscle groups, such as leg muscle groups including the tibialis anterior can be used as monitoring sites however demonstrate variable response in reversibility when compared to other muscle groups. Despite this, monitoring each muscle group has its own distinct advantages, such as quick onset and offset of recovery demonstrated by the eye muscle groups, or monitoring the tibialis anterior can be useful in specific surgical positions or when other sites are inaccessible.

Our monitoring has continued to evolve and improve, and we are now shifting away from qualitative monitoring towards quantitative monitoring of neuromuscular blockade. This is primarily due to qualitative monitoring relying on subjective visual or tactile evaluation of muscle responses, which can often be less reliable indicators of adequate reversal. The American Society of Anesthesiologists (ASA) recommends the use of quantitative neuromuscular monitoring over qualitative assessment to avoid residual neuromuscular blockade.[17] Quantitative monitoring provides objective measurements, such as the TOF ratio, ensuring more accurate assessment of neuromuscular function. The Anesthesia Patient Safety Foundation (APSF) has recommended that every patient receiving a muscle relaxant should have at least qualitative, and preferably quantitative monitoring, to assess requirements for reversal agents and adequacy of neuromuscular function prior to tracheal extubation.[13] A recent Consensus Statement on the Use of Perioperative Monitoring recommended that quantitative monitors should be used whenever a nondepolarizing muscle relaxant has been administered.[18] For objective monitors to be widely accepted into clinical practices, the devices

need to be improved as to not to be affected by patient hand position, be self-calibrating and provide reliable and repeatable results, and require minimal monitor setup times. Recently, three-dimensional acceleromyograph (AMG) technology captures muscle contraction in multi-dimensions and provides quantitative data on neuromuscular blockade reversal.[13] Portable electromyographic (EMG) devices have also been recently developed and approved for routine clinical care, allowing for TOF ratio data to be rapidly obtained after placing an electrode strip on the hand and connecting the strip to a cable.[13] EMG monitors provide accurate quantitative data without the need for immobilization of the studied muscle, preload application, or free movement of the thumb (arms can be tucked at the sides).[18]

Overall, quantitative monitoring helps improve patient safety over qualitative monitoring by reducing the risk of complications associated with residual neuromuscular blockade, such as hypoxemia, impaired pulmonary function, and postoperative pneumonia.

3.4. Prolonged Neuromuscular Blockade:

The dissociation of rocuronium from nicotinic acetylcholine receptors at the neuromuscular junction (NMJ) is governed by several key factors: Receptor-Ligand Binding Dynamics, Acetylcholine Concentration, Plasma Concentration Gradient, Physiological Conditions, and Drug Interactions (Table 1).

There are multiple factors that can lead to prolonged neuromuscular blockade. Drug interactions also play a role, potentiating neuromuscular blockade and altering the kinetics of rocuronium dissociation. These include the use of certain antibiotics like tetracyclines, clindamycin, or aminoglycosides and antidepressants such as sertraline and amitriptyline.[19,20] Lithium, local anesthetics, quinidine, and magnesium sulfate can also interfere with neuromuscular transmission. Inhalation anesthetics, particularly enflurane and isoflurane, have also been shown to prolong the duration of neuromuscular block and decrease infusion requirements of neuromuscular blocking agents.

Additionally, physiological factors such as pH and temperature can modulate receptor-ligand interactions; for instance, acidosis may enhance neuromuscular blocker potency by increasing ionization and receptor affinity, while hypothermia can slow dissociation by reducing metabolic activity. Patients who may also be at increased risk for residual neuromuscular block include those with myopathy, particularly in geriatric patients (65 years or older), those with neuromuscular diseases, patients with carcinomatosis, and cachectic or debilitated patients.[21,22] Residual weakness may be attributed to various causes, including patient specific metabolic factors, and lack of neuromuscular monitoring, large dose of rocuronium over a short interval, and the administration of rocuronium an hour before anticipated extubation.[17,23-24]

3.5. Sugammadex:

Sugammadex is a modified gamma-cyclodextrin that works by encapsulating NMBA molecules, rendering them inactive and allowing for their rapid elimination from the body. One molecule of sugammadex can noncovalently bind to one molecule of a steroidal muscle relaxant. Although sugammadex was developed to selectively bind rocuronium, it also binds other steroidal muscle relaxants, such as vecuronium and pancuronium, however with lower affinity.[18]

Sugammadex is believed to bind rocuronium in plasma. Unbound rocuronium exits the NMJ and enters the plasma via a passive gradient, where it is subsequently bound by circulating sugammadex, forming a complex that does not readily dissociate and can thus be excreted from the body.[25] Sugammadex exerts its effect by selectively encapsulating free (unbound) rocuronium molecules in the plasma, forming a stable 1:1 complex. This mechanism does not directly displace rocuronium already bound to nicotinic acetylcholine receptors at the NMJ. Instead, by reducing the concentration of unbound rocuronium in the plasma, sugammadex establishes a concentration gradient that promotes the diffusion of rocuronium away from the NMJ and back into the plasma, thereby facilitating neuromuscular recovery.

3.6. Side effects of Sugammadex:

Sugammadex's side effects are cited as dose dependent. Risks of sugammadex include hypersensitivity reactions, ranging from isolated skin reactions to serious systemic reactions such as anaphylaxis and anaphylactic shock, even in patients with no prior exposure.[26] Symptoms may include conjunctival edema, urticaria, erythema, uvula swelling, nausea, pruritus, and clinically significant hypotension often requiring vasopressors for circulatory support. Pulmonary issues such as bronchospasm, as well as cardiovascular issues such as bradycardia and other dysrhythmias, including supraventricular tachycardia (SVT), ventricular fibrillation, and ventricular tachycardia, have also been reported.

Sugammadex works by encapsulating rocuronium or vecuronium molecules, forming a tight complex that prevents them from binding to nicotinic receptors at the neuromuscular junction. However, if another drug or

compound with a higher affinity for sugammadex is introduced—or if the concentration of free sugammadex decreases—rocuronium or vecuronium may be released from the complex. Once free, these neuromuscular blocking agents can re-bind to acetylcholine receptors, leading to recurarization (the return of muscle paralysis). This is particularly important in patients with renal impairment, where sugammadex and the drug complex are not cleared efficiently. The risk of displacement reactions is highest within a period equivalent to three times the half-life of sugammadex. In adults with normal renal function, the half-life of sugammadex is 2 hours, but this can be prolonged in individuals with renal impairment: approximately 4 hours for mild impairment, 6 hours for moderate impairment, and 19 hours for severe impairment. Additionally, when drugs that potentiate neuromuscular blockade are used in the post-operative phase, special attention should be paid to the possibility of recurrence of neuromuscular blockade.

3.7. Sugammadex Failure:

Sugammadex, while highly successful, may fail to reverse neuromuscular blockade adequately. In clinical trials, a small number of patients experienced a delayed or minimal response to the administration of Sugammadex.[27] We explore the reasons why it may fail, including patient inadequate acetylcholine (ACh) at the NMJ, timing of neuromuscular reversal inadequate sugammadex dosing and concentration gradient of plasma sugammadex, type of anesthesia, NMB dosing and neuromuscular monitoring, and compatibility with other medications and fluids. [17, 23-24]

3.7.1. Adequate Acetylcholine at the NMJ:

Following the administration of sugammadex, a substantial portion of circulating rocuronium is rapidly encapsulated in the plasma, effectively reducing its free concentration and facilitating recovery from neuromuscular blockade. However, in some cases, a clinically significant amount of rocuronium may remain bound at the NMJ, particularly in patients with altered pharmacodynamics or impaired redistribution. Factors such as reduced tissue perfusion, delayed drug diffusion, or receptor-level variability may contribute to persistent receptor occupancy, despite adequate plasma clearance. Certain patients may be more susceptible to this blockade and/or require a higher level of ACh to effectively displace rocuronium. This residual binding can result in incomplete or delayed neuromuscular recovery, even when standard doses of sugammadex are administered.

In such scenarios, the administration of neostigmine may serve as a valuable adjunct. By inhibiting acetylcholinesterase, neostigmine increases the concentration of ACh at the NMJ, thereby enhancing the competitive displacement of rocuronium from nicotinic receptors. This mechanism may be particularly beneficial in patients with borderline or incomplete reversal, where endogenous ACh levels are insufficient to overcome residual blockade.[33-36]. Although sugammadex and neostigmine operate via distinct mechanisms, their sequential or combined use, when carefully considered, may optimize neuromuscular recovery in select patients. Clinical judgment, guided by quantitative neuromuscular monitoring, is essential to determine the appropriateness and timing of such interventions. Further research is warranted to determine whether this approach is effective and safe on a broader scale, rather than relying solely on case-by-case decision-making.

3.7.2. Timing of reversal:

The timing of sugammadex administration is crucial. As mentioned previously, sugammadex facilitates neuromuscular recovery by encapsulating free rocuronium in the plasma, thereby reducing its unbound concentration. This reduction creates a passive concentration gradient that drives rocuronium to diffuse from the NMJ back into the plasma, where it is sequestered by circulating sugammadex. During the arousal phase as patients emerge from anesthesia, the release of catecholamines can increase cardiac output. This elevated cardiac output enhances intravascular flow, allowing more circulating sugammadex to access and bind unbound rocuronium that has entered the plasma, thereby facilitating neuromuscular reversal.[31,32] Administering neuromuscular reversal at a lighter depth of anesthesia (e.g., Stage I versus Stage III) can enhance acetylcholine release and neuromuscular responsiveness. Whether through natural recovery or cholinesterase inhibition, elevated acetylcholine levels more effectively displace rocuronium from nicotinic receptors at the neuromuscular junction, facilitating its transition to an unbound state that can be encapsulated by sugammadex.

3.7.3. Anesthesia Type:

Inhalational agents potentiate the effects of neuromuscular, increasing the risk of prolonged muscle weakness and sugammadex failure.[30] Reducing volatile anesthetic concentrations and lightening anesthetic depth during emergence is essential to minimize this effect. In contrast, total intravenous anesthesia (TIVA) with agents like propofol do not contribute to muscle relaxation, and do not affect neuromuscular blockade. In turn, TIVA can be considered when there is heightened risk for prolonged neuromuscular blockade.

3.7.4. Dosing and Monitoring:

Qualitative neuromuscular monitoring should begin prior to the administration of paralytics and continue throughout the procedure. Rocuronium dosing should be carefully titrated to the desired depth of paralysis, with redosing avoided within one hour of anticipated extubation. Administering rocuronium close to emergence may reduce the effectiveness of sugammadex and increase the risk of incomplete reversal. In cases of very deep blockade, even with appropriate dosing, reversal may be delayed if insufficient time is allowed for redistribution and encapsulation of the neuromuscular blocker. Higher doses of sugammadex may be required to reverse deep blockade, potentially raising the risk of adverse effects, including anaphylaxis.[28] Also, if rocuronium or vecuronium is re-administered soon after sugammadex, the effect may be blunted due to residual sugammadex in plasma, or conversely, residual NMBAs may reoccupy receptors if sugammadex is cleared.

Table 1: Risk Factors for Prolonged Rocuronium-Induced Neuromuscular Blockade and Intraoperative Management Strategies

Conditions with Increased Risk of Prolonged blockade	▪ Advanced age ▪ Neuromuscular disorders ▪ Hepatic Disease ☐ Changes to CYP3A4, CYP2C19 can reduce rocuronium metabolization ▪ Renal Disease ☐ Reduced rocuronium excretion
Drug Interactions:	▪ Be aware of medications that can alter the kinetics of rocuronium dissociation can prolong or potentiate neuromuscular blockade: ☐ Antibiotics: Tetracyclines, clindamycin, or aminoglycosides. ☐ Antidepressants: sertraline and amitriptyline ☐ Lithium ▪ Local anesthetics ☐ Quinidine ☐ Magnesium sulfate ☐ Volatile anesthetics
Rocuronium Dosing and Neuromuscular Monitoring	▪ Neuromuscular Dosing: ☐ Carefully titrate rocuronium to the desired depth of paralysis. ☐ Reduce total cumulative dose of rocuronium, when possible. ☐ Avoid redosing within one hour of anticipated extubation, when possible. ▪ Neuromuscular Monitoring: ☐ Utilize neuromuscular monitoring from case onset. ☐ Quantitative monitor: Train of four ratio ≥ 0.9
Receptor-Ligand Binding Dynamics	▪ Optimize pH ☐ Acidosis can enhance the potency of some neuromuscular blockers by increasing their ionization and receptor affinity ▪ Optimize Temperature ☐ Hypothermia can slow dissociation by reducing metabolic activity ▪ Optimize Electrolyte imbalances ☐ Hypocalcemia, hypokalemia, hypermagnesemia, are known to potentiate neuromuscular blockade

3.7.5. Compatibility:

Table 1 illustrates the multifactorial contributors to prolonged neuromuscular blockade following administration of rocuronium, including patient-specific variables (e.g., advanced age, renal or hepatic impairment, and neuromuscular disorders), pharmacologic factors (e.g., cumulative dose, drug interactions), and intraoperative considerations (e.g., hypothermia, acid-base disturbances).

The compatibility of sugammadex with other intravenous medications is crucial. Sugammadex is compatible with 0.9% sodium chloride, 5% dextrose, 0.45% sodium chloride and 2.5% dextrose, 5% dextrose in 0.9% sodium chloride, Isolyte P with 5% dextrose, Ringer's lactate solution, and Ringer's solution.[29] It is essential to flush the infusion line adequately (e.g., with 0.9% sodium chloride) between the administration of sugammadex and other drugs.[29] It is also important to note medications that may hinder the effectiveness of sugammadex; these medications include dexamethasone, hormonal contraceptives,F Co-administration of these agents compromises the reversal of NMJ blockers via sugammadex.[30] Notably, sugammadex is physically incompatible with ondansetron, ranitidine, and verapamil. Given that ondansetron and sugammadex are typically administered at the conclusion of a case, this physical incompatibility may hinder the effectiveness of sugammadex.

3.7.6. Recommendations for Managing Sugammadex Reversal Failure:

If reversal with sugammadex fails, it is crucial to optimize various factors that may prolong neuromuscular blockade (Table 2, Figure 1). Providers

Table 2 highlights factors that may affect sugammadex reversal, such as acetylcholine levels at the NMJ, sugammadex plasma concentration gradient, anesthesia type, and sugammadex medication compatibility. (ACh-Acetylcholine, NMJ-Neuromuscular junction, TIVA- total intravenous anesthesia) should ensure that sugammadex is administered with compatible medications and fluids, and select the appropriate dosing based on the patient's actual body weight. For routine reversal, when the TOF shows the reappearance of the second twitch, administer 2 mg/kg IV; for moderate blockade, characterized by 1–2 post-tetanic counts with no TOF twitches, administer 4 mg/kg IV. In the case higher doses are required for reversal, such as immediately after a rapid sequence intubation (RSI), titrate sugammadex in a stepwise manner, recognizing that its side effects are dose-dependent, with a maximum dosing limit of 16 mg/kg IV.

Table 2: Risk Factors and Intraoperative Management Strategies to Mitigate Sugammadex Failure

Acetylcholine Concentration	▪ Inadequate ACh at the NMJ ☐ Certain patients may be more susceptible to persistent receptor binding or may have insufficient acetylcholine (ACh) levels to effectively displace rocuronium. ▪ Timing of Reversal: ☐ Administer neuromuscular reversal at a lighter depth of anesthesia (e.g., Stage I versus Stage III) can enhance cardiac output, catecholamine release, acetylcholine release and availability at the NMJ.
Plasma Concentration Gradient	▪ Sugammadex primarily binds to unbound (free) rocuronium in the plasma, not to rocuronium that is already bound to nicotinic acetylcholine receptors at the neuromuscular junction (NMJ). ▪ Increased sugammadex plasma concentration, as well as increased cardiac output and blood flow, can create a concentration gradient that favors the movement of rocuronium from the NMJ back into the plasma, promoting dissociation.
Anesthesia Type	▪ TIVA, rather than volatile anesthesia, can be considered when there is concern for patient susceptibility to residual neuromuscular blockade.
Sugammadex compatibility	▪ Ensure sugammadex is administered with compatible fluid. ▪ Avoid/be aware of medications that can hinder the effectiveness of sugammadex. ☐ Dexamethasone, hormonal contraceptives, and toremifene. ▪ Avoid co-administration of sugammadex with medications it is physically incompatible with. ☐ Ondansetron, ranitidine, and verapamil.

If sugammadex fails to achieve full reversal and the patient remains weak, consider the possibility of persistent receptor-bound rocuronium with insufficient ACh to displace it. In such cases, the use of neostigmine/glycopyrrolate may be considered, although this approach is not well studied and remains controversial. It should be employed only in select cases with close monitoring. If neuromuscular function remains inadequate, the patient should remain intubated. In an outpatient setting, consider transferring the patient to an inpatient facility if extended monitoring or ventilatory support is needed, or if there are limited staff or monitoring capabilities overnight.

4. SUMMARY

While Sugammadex has revolutionized the management of neuromuscular blockade by offering a rapid and reliable reversal agent, it does not eliminate the necessity for vigilant monitoring. Anesthesia providers must remain attentive to the depth of neuromuscular blockade and ensure complete reversal prior to extubation. Importantly, clinicians should recognize that Sugammadex may not be universally effective in all patients, underscoring the continued importance of individualized assessment, neuromuscular monitoring to ensure patient safety, and contingency planning if sugammadex failure occurs.

5. Conflicts of Interest

The authors have no conflict of interest

6. Ethical consideration

7. Authors contribution

TD, GR: concept, manuscript writing and editing

SS, WM: manuscript writing and editing

RRF: concept, manuscript editing

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