Residual Neuromuscular Blockade, Antagonism & Quantitative Monitoring

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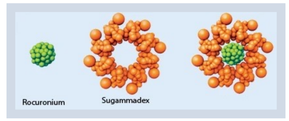
Introduction

Residual neuromuscular blockade poses significant risks, with up to a 64% incidence rate at the end of surgery or in the PACU.[1] The American Society of Anesthesiologists (ASA) has taken a significant step by issuing guidelines that emphasize the critical importance of vigilant monitoring and the utilization of quantitative devices. These steps are an important direction in ensuring patient safety and better outcomes. While these guidelines offer valuable insights, recent research has uncovered additional nuances that clinicians should consider as improvements to practices will continue to evolve.

Background

Non-Depolarizing Neuromuscular Blocking Agent: Rocuronium

- Monoquaternary steroid analogue.
- Dosage: 0.6mg/kg for intubation. It can have a prolonged effect in elderly and liver disease patients.
- Onset like succinylcholine but with a much longer duration of action. It's also effective for precurarization before succinylcholine administration.[2]



Reversal: Neostigmine

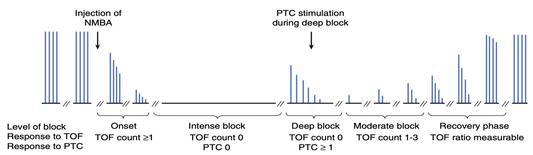
- Cholinesterase Inhibitor.
- Dosage: 0.02-0.05 mg/kg, max 5 mg.
- Side effects: salivation, lacrimation, bradycardia, bronchoconstriction.
- Side effect management: glycopyrrolate (antimuscarinic) at 0.2:1 ratio.
- Onset: 7-10 minutes, Duration: ~1 hour.[2]

Reversal: Sugammadex

- γ-cyclodextrin-based agent for reversing nondepolarizing neuromuscular blockade.
- It forms a 1:1 water-soluble complex with drugs like rocuronium, effectively terminating their neuromuscular blocking effects.
- Sugammadex may interfere with hormonal contraceptives, require caution in patients with severe kidney dysfunction, and is most effective against steroidal neuromuscular blockers like rocuronium.[2]

Neuromuscular Monitoring (NMM) – Train of Four (TOF)

- TOF stimulation consists of four stimuli spaced at intervals of 0.5 seconds (equivalent to a frequency of 2 Hz) and is typically repeated every 10 to 20 seconds.
- When there are four responses to TOF stimulation, the **Train-of-Four Ratio (TOFr)** is determined by comparing the strength of the fourth response (T4) with the strength of the first response (T1).
- When the height of the fourth twitch equals or closely matches that of the first twitch (TOFR ≥0.9 or no fade), it signifies full neuromuscular function recovery.
- Extubation should not occur until the TOFR is ≥0.9 to prevent the risk of residual paralysis. In patients, a TOFR <0.9 is associated with increased morbidity and mortality.[2]



Forms of Neuromuscular Monitoring

Clinical Signs – Clinicians use clinical signs to infer adequate return of neuromuscular function such as

- 5-second head lift
- Tidal Volume
- Grip Strength

Qualitative Monitoring – Clinicians use subjective visual or tactile assessments with a peripheral nerve stimulator (PNS) to estimate the strength of muscle contractions in response to TOF stimulation.

Quantitative Monitoring

Mechanomyography (MMG)

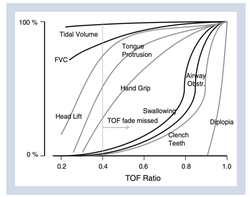
- MMG measures muscle contraction in response to nerve stimulation, but it has limitations such as bulky equipment and fixed arm position requirements.
- MMG is highly accurate, but there are no practical clinical devices available, and this is unlikely to change due to technical challenges.

Acceleromyography (AMG)

- AMG measures thumb acceleration in response to ulnar nerve stimulation using a piezo-electric ceramic wafer.
- Raw AMG data may display TOFR values above 1.00 (100%), requiring a mathematical correction for precise assessment. Most AMG units lack validation against MMG.

Electromyography (EMG)

- EMG measures muscle action potential intensity, with similarities to MMG.
- EMG can be utilized even when thumb movement is restricted or when the arms are tucked
- Accessibility is increasing due to commercial availability and advancements.[2]



Notable TOFr, Physiological Markers

- At TOFr of ≤ 0.1 – Tidal volume while intubated possible.
- TOFr between 0.3–0.5 – Head lift and hand grip possible.
- At TOFr of 0.6 – Normal vital capacity achievable.
- Experienced clinicians employing peripheral nerve stimulation can identify fade when the TOF ratio is at or below 0.4, but they may not detect it when the TOF ratio falls between 0.5 and 0.9.[3]

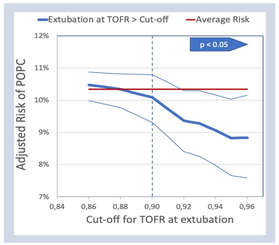
ASA Recommendations (published January 2023)

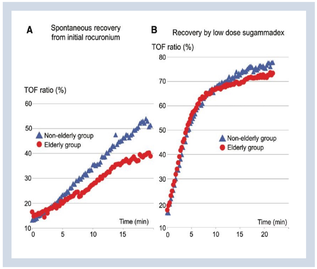
	Strength of Recommendation	Strength of Evidence
1. When neuromuscular blocking drugs are administered, we recommend against clinical assessment alone to avoid residual neuromuscular blockade, due to the insensitivity of the assessment	Strong	Moderate
2. We recommend quantitative monitoring over qualitative assessment to avoid residual neuromuscular blockade.	Strong	Moderate
3. When using quantitative monitoring, we recommend confirming a train-of-four ratio greater than or equal to 0.9 before extubation.	Strong	Moderate
4. We recommend using the adductor pollicis muscle for neuromuscular monitoring.	Strong	Moderate
5. We recommend against using eye muscles for neuromuscular monitoring.	Strong	Moderate
6. We recommend sugammadex over neostigmine at deep, moderate, and shallow depths of neuromuscular blockade induced by rocuronium or vecuronium, to avoid residual neuromuscular blockade.	Strong	Moderate
7. We suggest neostigmine as a reasonable alternative to sugammadex at minimal depth of neuromuscular blockade.	Conditional	Low
8. To avoid residual neuromuscular blockade when atracurium or cisatracurium are administered and qualitative assessment is used, we suggest antagonism with neostigmine at minimal neuromuscular blockade depth. In the absence of quantitative monitoring, at least 10 min should elapse from antagonism to extubation. When quantitative monitoring is utilized, extubation can be done as soon as a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation.[4]	Conditional	Very Low

Review of Literature

Extubation at TOFR ≥0.95 Reduces Postoperative Pulmonary Complications (POPC)

The suggestion to aim for a TOFr greater than 0.95 is based on findings from a post hoc examination of the POPULAR trial. This analysis revealed a noteworthy reduction in the risk of postoperative pulmonary complications (POPC) when TOFR exceeded 0.95. Specifically, the adjusted absolute risk reduction for POPC was 3.5% in the complete case population and 3.4% in the propensity score matched population.[5]



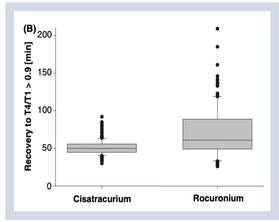


Elderly at Greater Risk of POPC with Underdosed Sugammadex

Elderly patients face slower recovery and a higher risk of recurarization when sugammadex is underdosed for deep rocuronium-induced paralysis.[6]

Faster Recovery in Morbidly Obese Patients with ABW-Dosed Sugammadex

The study found that dosing based on ideal body weight (IBW) caused a significant delay in the recovery of neuromuscular function compared to dosing based on actual body weight (ABW) in morbidly obese patients. While the median time to clinical recovery was 1.5 minutes faster with ABW dosing, the slowest 10% of patients took at least 3.7 minutes longer to recover when dosed by IBW compared to ABW dosing.[7]



Rocuronium's Variable Duration of Action & Accumulation Effect

Rocuronium had a longer and more variable duration of action compared to cisatracurium after repeated administration, likely due to differences in their chemical structures. Rocuronium's duration of action increased with repeated doses, while cisatracurium remained consistent.[8]

Variability in Sugammadex Dosing and the Importance of Quantitative Monitoring

Sugammadex dosing varies widely among patients, with doses ranging from 0.43 mg/kg to 5.55 mg/kg to achieve a train-of-four ratio of at least 0.9. This variability underscores the importance of quantitative twitch monitoring to assess Sugammadex's effectiveness, as a one-size-fits-all approach may not guarantee the desired outcome.[9]

Conclusion

Clinical Significance 1 – Quantitative Monitoring is Recommended

Reversal dosing varies widely among patient populations. Therefore, quantitative twitch monitoring is essential to confirm successful reversal.[4]

Clinical Significance 2 – Clinical Budget Impacts

The reduced POPC events with the use of Sugammadex compared to Neostigmine (+/-Glycopyrrolate) overall leads to a savings by reduced OR time and faster recovery from NMBD in PACU. Therefore, appropriate dosing of Sugammadex for full reversal (TOFr of 0.95–1) will financially be beneficial as well as improved patient outcomes and satisfaction.[10]

Clinical Significance 3 – Emergency NMBA Reversal

In a cannot ventilate cannot intubate airway emergency, where NMBA was used, reversal with Neostigmine takes approximately 7-10min (mild-to-light paralysis) and at least 1 twitch is needed. Whereas, with Sugammadex 16mL/kg, it takes 1.3-1.9 min to fully reverse NMBA and no return of muscle twitches are needed.[2]

Clinical significance 4 – Generic Sugammadex Release in the Works

Merck, the producers of Bridion, has a patent that expires in January 2026. This allows a generic brand to be released on the market. Aspiro has been working on a generic, Sugammadex Sodium, that was approved on June 9th, 2023. The FDA tentatively approved a generic sugammadex, ANDA, from Syneos Health, LLC U.S. Agent for Gland Pharma Limited in 2021.[11]

References

1. Saager L, Maiese EM, Bash LD, et al. Incidence, risk factors, and consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECITE-US study. J Clin Anesth. 2019;55:33-41. doi:10.1016/j.jclinane.2018.12.042
2. Brull, Sorin J. "Neuromuscular Blocking Agents." Clinical Anesthesia, edited by Paul G. Barash et al., 8th ed., Lippincott Williams & Wilkins, 2017, pp. 527–63.
3. Donati F. Residual paralysis: a real problem or did we invent a new disease?. Can J Anaesth. 2013;60(7):714-729. doi:10.1007/s12630-013-9932-8
4. Stephan R. Thilen, Wade A. Weigel, Michael M. Todd, Richard P. Dutton, Cynthia A. Lien, Stuart A. Grant, Joseph W. Szokol, Lars I. Eriksson, Myron Yaster, Mark D. Grant, Madhulika Agarkar, Anne M. Marbella, Jaime F. Blanck, Karen B. Domino; 2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade. Anesthesiology 2023; 138:13–41 doi: https://doi.org/10.1097/ALN.0000000000004379
5. Blobner M, Hunter JM, Meistelman C, et al. Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. Br J Anaesth. 2020;124(1):63-72. doi:10.1016/j.bja.2019.08.023
6. Muramatsu T, Isono S, Ishikawa T, et al. Differences of Recovery from Rocuronium-induced Deep Paralysis in Response to Small Doses of Sugammadex between Elderly and Nonelderly Patients. Anesthesiology. 2018;129(5):901-911. doi:10.1097/ALN.0000000000002412
7. Horrow JC, Li W, Blobner M, et al. Actual versus ideal body weight dosing of sugammadex in morbidly obese patients offers faster reversal of rocuronium- or vecuronium-induced deep or moderate neuromuscular block: a randomized clinical trial. BMC Anesthesiol. 2021;21(1):62. Published 2021 Feb 27. doi:10.1186/s12871-021-01278-w
8. Maybauer DM, Geldner G, Blobner M, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. Anaesthesia. 2007;62(1):12-17. doi:10.1111/j.1365-2044.2006.04862.x
9. Bowdle TA, Haththotuwegama KJ, Jelacic S, Nguyen ST, Togashi K, Michaelsen KE. A Dose-finding Study of Sugammadex for Reversal of Rocuronium in Cardiac Surgery Patients and Postoperative Monitoring for Recurrent Paralysis. Anesthesiology. 2023;139(1):6-15. doi:10.1097/ALN.0000000000004578
10. Jiang Y, Bash LD, Saager L. A Clinical and Budgetary Impact Analysis of Introducing Sugammadex for Routine Reversal of Neuromuscular Blockade in a Hypothetical Cohort in the US. Adv Ther. 2021;38(5):2689-2708. doi:10.1007/s12325-021-01701-1
11. Court Rules in Favor of Merck in Patent Case. thepharmaletter. https://www.thepharmaletter.com/article/court-rules-in-favor-of-merck-in-patent-case. Published June 14, 2023.