

## Sugammadex: A Miracle Drug, but is Further Research Needed?

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### LETTER TO EDITOR

Sugammadex is a drug that changes the practice of general anesthesia and is considered a revolutionary drug in neuromuscular physiology [1]. It is modified gamma-cyclodextrin, used as a reversal agent for steroidal non-depolarized muscle relaxants (NDMR). It encapsulates free NDMR drugs like rocuronium and vecuronium at NMJ. The core part of the drug is enough large to encapsulate the NDMR drugs. It is a worldwide available and FDA approved drug.

Sugammadex is commonly used as an NDMR reversal agent (mainly rocuronium) in bariatric surgery for obesity with a BMI greater than 30, patients with compromised respiratory reserve (asthma and COPD), and the geriatric age group. Using sugammadex, the muscarinic S/E of neostigmine (nausea, vomiting, bradycardia, diarrhea, etc.) and the anti-muscarinic S/E (dry mouth, palpitation, urinary retention, constipation, etc.) of glycopyrrolate can be avoided. Sugammadex is approved to be used as an NDMR reversal agent for 2-year-old and older age groups, and studies have demonstrated that it has similar efficacy and S/E in this age group as compared to adults. The cost of sugammadex is a significant consideration that may restrict its use as a regular antagonist of neuromuscular-blocking medications.

There are a few studies that demonstrate sugammadex has a favorable post-operative respiratory outcome. Recently, in 2023, a systemic review and meta-analysis were conducted by Hong-Mei Liu et al. to determine whether reversal with sugammadex was linked to a lower risk of post-operative complications as compared to neostigmine. The study concluded that the incidence of post-operative pulmonary complications (PPC: airway obstruction, requirement of NIV, pleural effusion, pneumonia, and atelectasis) is lower with sugammadex when compared to neostigmine [2]. Another RCT was conducted in 2023 by Huang et al. on sugammadex vs. neostigmine for the evaluation of respiratory muscle strength recovery by using ultrasound in the post-extubation period [3]. They concluded that immediately after extubation, expiratory muscle strength recovery is enhanced with sugammadex than neostigmine. However, they also noticed that the strength of the respiratory muscles in most of the patients did not recover completely for half an hour after their arrival in the post-operative recovery room

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after extubation. Eventually this might lead to post-operative pulmonary complications, as discussed above. Yet another meta-analysis comparing neostigmine versus sugammadex for neuromuscular blockade reversal showed that residual paralysis is decreased with sugammadex as compared to neostigmine [4]. In addition, cases of post-operative recurarization and residual paralysis in surgical patients after sugammadex were also reported [5,6].

Studies suggest that residual (re-curarization) neuromuscular blockade or insufficient respiratory muscle strength are still present with sugammadex as a reversal agent, but to a much lesser extent compared to neostigmine. Residual neuromuscular blockade or re-curarization if TOF ratio is less than 0.9 is one of the known causes of respiratory muscle dysfunction that can lead to complications after surgery. This might lead to atelectasis, aspiration, pneumonia, and reintubation [7]. Ultimately, it may lead to a prolonged hospital stay, nosocomial infection, and financial burden.

In current clinical practice, the recommended dose for sugammadex is 2 to 4 milligrams per kg, which can go up to 16 mg/kg depending on the last dosage of NDMR agents. The exact dose of sugammadex required in altered physiology (ex., pregnancy, patients with critical illness, malnourished patients, elderly patients with renal and liver disease, inborn errors of metabolism, etc.) is still not clear. Recurrence or residual neuromuscular blockade after sugammadex is caused by the redistribution of unbound rocuronium molecules toward the NMJ or an insufficient dose of sugammadex to encapsulate rocuronium molecules. After sugammadex administration, unbound rocuronium molecules move rapidly from the NMJ site to the plasma site due to the concentration gradient difference between these two sites [8]. If the sugammadex dose is inadequate or less than what is needed to encapsulate rocuronium molecules, unbound or free rocuronium molecules move or redistribute towards the NMJ site along with the concentration gradient and produce paralysis. As residual neuromuscular blockade is associated with post-operative pulmonary complications, anesthesiologists should consider using NM monitoring peri-operatively in order to decrease the PPC associated with residual neurological blockade.

Lastly, re-establishment of the NMB after sugammadex is also a bit challenging as free molecules of sugammadex present at the NMJ encapsulate the rocuronium. Therefore, rocuronium's onset of action may be delayed, and its duration

may be reduced [9]. Therefore, a higher dose of rocuronium is required to produce NMB, or we need to search for an alternate group of NDMR drugs.

In summary, post-operative pulmonary complications associated with residual neuromuscular blockade are less common with sugammadex as compared to neostigmine. Sugammadex is rarely associated with serious side effects in clinical practice. Although, raised a few interesting issues, and it's convincing that it's worth further research. A few cases of anaphylaxis have been reported following the administration of sugammadex [10]. Moreover, case reports of bradycardia and asystole [11] and cardiac arrest [12] (due to coronary vasospasm) after sugammadex were also reported. It is acknowledged that sugammadex is a "magic drug" that has changed anaesthesia practice; however, further prospective, large-scale, multi-center trials research are needed to demonstrate that it has a positive impact on anaesthesia practice, particularly in the context of neuromuscular physiology.

#### ABBREVIATIONS

NDMR: Non-Depolarizing Muscle Relaxant; NMJ: Neuromuscular Junction; NMB: Neuromuscular Blockade; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; NIV: Non-Invasive Ventilation; TOF: Train Of Four; S/E: Side Effects; PPC: Post-operative Pulmonary Complications.

#### CONFLICT OF INTEREST

None.

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