ORIGINAL ARTICLE

Efficacy of Sugammadex as a Reversal with an Optimized Train of Four Stimulation Parameters

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ABSTRACT

Residual neuromuscular blockades are a potentially dangerous complication after surgery due to administering neuromuscular blocking agents. Sugammadex is a novel neuromuscular blocking agent reversal drug that combats faster reversal times. However, it still needs to be determined how efficient it is compared to neostigmine, particularly with optimal Train of Four monitoring. Sugammadex and neostigmine were analyzed through 11 studies to determine the speed of recovery and postoperative complications. Sugammadex was found to have a quicker recovery time and fewer complications after surgery compared to neostigmine. A train of four stimulation analyses determined that higher voltages do not create as adequate 4/4 responses as at a lower, more reliable voltage. Therefore, our results determine that Sugammadex is a faster, safer drug choice, and the train of four stimulations is most reliable at 30mA. Still, it may be adequate up to 50mA without supramaximal stimulation. Further research should investigate how Sugammadex may differentiate depending on the patient's sex and how muscle relaxant dosages may change recovery time even with adequate train of four responses.

INTRODUCTION

During surgical operations under anesthesia, neuromuscular blocking agents (NMBA) are frequently administered to improve endotracheal intubation and optimize ventilation and patient movement prevention in surgical procedures. These patients receiving an NMBA must always be monitored during surgery. While NMBAs provide routine assistance and essential muscle relaxation, incomplete recovery after anesthesia, called a residual neuromuscular block (NMB), affects between 20-40% of patients in the post-anesthesia care unit (PACU) [1]. Residual NMBs can potentially be dangerous as they have high

incidence rates for postoperative recovery deficit risks such as pulmonary function complications, severe hypoxemia, upper airway obstructions, and residual paralysis [2]. Peripheral nerve stimulation techniques have been argued to be vital for assessing NMBs, yet in cases conducted from 2004 to 2012, only 39% of patients received adequate neuromuscular monitoring [3]. This is concerning, as there is a narrow window for detecting NMB: no blockade is detectable until 65-75% of the receptors in the neuromuscular junction are blocked, yet paralysis becomes complete at 90-95% receptor occupancy [4]. These preventable complications highlight the importance of effective neuromuscular monitoring to ensure full reversal before extubating, safeguarding patient safety.

NMBAs can be classified into two categories: depolarizing agents and non-depolarizing agents. Depolarizing agents have two-phase blocks that can cause sustained depolarization of the neuromuscular junction. Depolarizers do not cause a fade from the continuous stimulus in the first phase as twitches decrease in equal size; however, if given in larger doses, the second phase, like non-depolarizing agents, may develop where a fade is observed [5]. Succinylcholine is an example of a depolarizer with a rapid onset and offset, but it was found to cause fasciculations or momentary muscle excitation before relaxation [6]. Due to the side effect profile, it has been mostly discontinued in favor of non-depolarizing agents. Non-depolarizing agents like vecuronium and rocuronium act as competitive antagonists, blocking neuromuscular transmission and producing fade that may progress to complete paralysis with increasing doses [6]. These NMBs can be defined as light, moderate, deep, or profound. Anticholinesterase agents like neostigmine have traditionally been used to reverse the effects of non-depolarizing NMBAs; however, they are ineffective in reversing profound blockade and may cause transient muscle weakness [7]. Sugammadex, a modified gamma-cyclodextrin, represents a novel approach to rapid and complete NMBA reversal by directly inactivating non-depolarizing agents and being able to reverse all levels of blockades [6]. However, the efficacy of Sugammadex at optimal dosing, potential postoperative deficits, and its effects on neuromuscular monitoring are still being discussed.

Train of Four (TOF) is the most common stimulation pattern for neuromuscular monitoring. Conceptualized by Ali et al. in 1970, TOF was introduced initially as a new monitoring method for the degree of NMB that did not require a comparison to a previously taken control response [8]. The study found that TOF stimulation gave four twitches (T1, T2, T3, and T4) of equal amplitude in a non-paralyzed state, decreasing first from T4 until T1 as NMB developed [8]. The TOF ratio, calculated by comparing the amplitude of the fourth twitch to the first, is the gold standard for assessing neuromuscular function. A TOF ratio <0.70 indicates significant residual blockade, while a ratio >0.90 represents satisfactory recovery [9]. Sometimes, TOF cannot capture everything; for profound non-depolarizing NMBs, post-tetanic count (PTC) may be more beneficial, while more minor light degrees may be easier to detect with double-burst stimulation (DBS) [5]. However, TOF stimulation does not cause pain or subsequent muscle responses after application compared to PTC, and DBS cannot provide accurate measurements for recovery by subjective means [10]. It is essential to have an optimal function for TOF monitoring to interpret responses accurately.

During higher levels of NMB, the stimulation intensity may be increased to reach a 4/4 TOF ratio. However, this does not necessarily indicate that the muscle is no longer paralyzed and that the patient is in the proper recovery window. Optimal TOF monitoring requires careful consideration of stimulation intensity and anesthesia depth to avoid false negatives or positives, as higher stimulation intensities may mask residual paralysis during profound blockade.

This systematic review aims to compile and analyze existing research and clinical studies on the efficacy of Sugammadex for neuromuscular blockade reversal and optimal TOF monitoring stimulation. Understanding these factors may improve the reliability of monitoring for residual neuromuscular weakness and earlier detection of paralysis. These research findings will allow for a proper scope of surgical and post-operative processes to help clinicians make informed decisions prioritizing patient safety and entire functional response outcome.

METHODS

Search Strategy

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed, Google Scholar, and UTD Library for studies on neuromuscular blockades and their agents under TOF monitoring. Our exclusion criteria were as follows: books, single case studies, retrospective studies, pediatric studies, studies on obese patients, patients with co-morbid neurodegenerative disorders, emergency surgeries, studies using non-standard monitoring techniques, or alternative reversal agents. These criteria were selected to provide us with a diverse sample of healthy adult patients, ensuring that our results could be generalized appropriately, with minimal external factors that might affect TOF, thus yielding a reliable response. Only studies published before May 1st, 2023, were included in our search. Preference was given to papers from randomized controlled trials, observational studies, or other analyses, ensuring proper sample selection. Collected papers compared Sugammadex and Neostigmine with Rocuronium under TOF monitoring; other non-depolarizing agents were excluded to maintain efficiency in the search process. The keywords for our search included Train of Four Monitoring, TOF, TOF Stimulation, Sugammadex, and Neuromuscular Blockade.

Study Selection

The Zotero database was used to import and organize studies. Any duplicates were removed first. To screen the remaining studies, we applied the following inclusion criteria: 1) TOF monitoring of neuromuscular block with reversal by Sugammadex, 2) human-monitored studies, 3) patients aged >18 years, and 4) no history of neuromuscular diseases, obesity, or paralysis, focusing only on overall healthy patients. All studies were compared to our inclusion criteria and rejected if they did not meet them. The included studies were categorized into subject-defined sections for easier readability and then divided among group members for full-text review, where relevant data were extracted.

Current Technical Aspects of Train of Four

Technique

The literature review focused on human-based studies that included healthy individuals aged 18 years or older, excluding those with a history of neuromuscular disorders, paralysis, or obesity. Following the establishment of our criteria, we investigated general train-of-four stimulation methods and the use of TOF to assess neuromuscular function at the following peripheral nerve sites: the abductor hallucis and the posterior tibial nerve; the facial nerve and the orbicularis oculi muscle; the median nerve and the abductor pollicis brevis; and the peroneal nerve in the fibular head and the tibialis anterior in the leg.

Electrode placement

Electrode placement is another critical component of TOF that is crucial to eliciting correct and accurate responses. The electrodes must be positioned close to the muscle to accurately stimulate the target muscle and record compound muscle action groups, or CMAPs. In the instance of MEP recording, these needle electrodes were also used to observe the electromyographic responses [11]. Additionally, the recordings would be taken from the anterior tibialis muscle, and the stimulating electrodes would be placed at the fibular head to stimulate the fibular (peroneal) nerve. The electrodes would also be placed near the medial malleolus to stimulate the posterior tibial nerve and record TOF responses from the abductor hallucis muscle.

Stimulation

Stimulation is also a critical component that was examined in relation to TOF. Four repeated impulses would typically stimulate TOF, such as two Hz standard frequencies delivered to a peripheral nerve. This stimulation pattern aimed to trigger twitch responses in the associated muscle group and assess neuromuscular functions, which were recorded using CMAPs. While they vary in performance depending on the patient's comfort, several stimulations, such as supramaximal and ulnar nerve stimulation, can assess the degree of neuromuscular blockade [12]. Changing these simulations, which typically range from 50 to 100 mA, is possible. Usually, the duration, time, and interval between consecutive trains were regulated to minimize hazards and ensure that the reported results were dependable [12].

Recording

Another approach to ensuring accurate assessments of neuromuscular functions across multiple investigations was to compare different recording techniques. We discovered that CMAPs produced by the TOF stimulation were often recorded using EMGs. To see the twitch response from peripheral nerve stimulation, the electrodes must be placed correctly over the muscle group you want to target, such as the anterior tibialis or the abductor hallucis.

Ratios

Ratios are another critical component of TOF that is essential in tracking neuromuscular blockade. The ratios are helpful because they determine the extent of a patient's impairment since they compare the time interval between the fourth twitch response (T4) and the first twitch response (T1). The different levels of TOF ratio are an indication of the level of paralysis, such as T4 = 75-80% block (TOF 3⁄4), T3 = 85% block (TOF 2/4), T2 = 95% block (TOF ¼), and T1 = 100% block (TOF 0/4). Although TOF ratio differs between patients, within-individual variability in TOF ratio recording ranged from 1.5% to 5%, regardless of block level, as observed in one of the studies we looked at, which also indicated that smaller TOF ratios generally linked with greater infusion rates of mivacurium [13].

Current

TOF stimulation often entails the regulated administration of electrical impulses to a peripheral nerve to ensure that the muscle group receives precise and reliable responses. Currents, which generally range from 20 to 100 mA, are a valuable tool in TOF stimulation to guarantee consistent activity of motor units. Furthermore, we can analyze the onset time between muscles and currents depending on the intensity of the current stimulation [14]. This is valuable in ensuring a proper balance between the intensity of the current so we can reduce the risk of any impairments in case the currents are too high. Interestingly, Saitoh et al. (1995) suggest that the most effective stimulating current for identifying twitches in TOF is 30 mA, rather than TOF ratios in patients in the ICU or PACU [12]. They further stated that the ideal stimulating current for TOF in awake patients was not determined by previous research regarding the recovery duration of the individual responses to the stimulation. Their implications for TOF measurement and their variations can be highlighted in several studies that eventually help understand the results.

Drug Mechanisms

Neostigmine

Neostigmine inactivates anticholinesterase by carbamylation by combining with the acetylcholinesterase molecule's anionic and esteratic sites. Reactivation is relatively slow, making neostigmine a reliable reversal agent. However, a muscarinic blocker, e.g., atropine or glycopyrrolate, must be given simultaneously with neostigmine to counteract the parasympathomimetic action of the neostigmine [15]. Due to side effects of atropine, such as tachycardia, dry mouth, and blurred vision, neostigmine may be contraindicated in patients with cardiovascular disease or severe asthma. Another limitation of neostigmine is the relatively slow onset of action, as it does not become efficient before spontaneous recovery [16]. The peak effect of neostigmine occurs approximately 10 minutes after injection, with a duration of action of about 20–30 minutes. These pharmacodynamic properties can lead to residual paralysis in the postoperative period [17].

Sugammadex

Sugammadex is a modified gamma-cyclodextrin. It forms a complex via chemical encapsulation with rocuronium and vecuronium. This subsequently decreases the amount of the moderate or profound neuromuscular blocking agent that can bind to nicotinic receptors in the neuromuscular junction. Due to its unique mechanism of action by encapsulating steroidal paralytic medications, Sugammadex has a rapid onset of two minutes and a half-life of two hours, making it an efficient intraoperative reversal agent [18]. A systemwide transition of the standard pharmacologic reversal agent from neostigmine to Sugammadex has decreased the odds of adverse postoperative respiratory outcomes [17]. During deep levels of the block, with less than two responses at the TOF, neither rocuronium nor vecuronium can be reversed satisfactorily within a short period of time using neostigmine. In humans, profound neuromuscular blocks (post-tetanic count: 1 or 2) can be rapidly and safely reversed with Sugammadex. There are situations in which a deep block must be reversed very rapidly. For example, when tracheal intubation has failed, Sugammadex can completely reverse the block in less than 3 minutes [16].

Anesthesia Use and Impact

Reversal of NMBAs is not uniformly consistent in all body muscle groups. Central muscles, such as the diaphragm and larynx, which have a good blood supply, tend to experience a faster onset and offset of NMB. In contrast, peripheral muscles like the adductor pollicis have a slower recovery time [19]. TOF remains the most valuable stimulation pattern at induction of anesthesia during muscle paralysis [5]. Inhalational anesthesia and intravenous anesthesia are two main types of anesthesia. Inhalation anesthesia is conducted through a mask or endotracheal intubation. There are specific advantages and disadvantages of both types of anesthesia for intraoperative neuromonitoring. Continuous IONM monitoring is feasible during inhalational anesthesia as the depth of anesthesia is precisely controlled due to the easy titration of anesthetic agents [10]. There is a potential risk of respiratory complications in patients with predisposing factors. Intravenous anesthesia reduces the risk of respiratory dysfunction, but dosage adjustment is critical due to the longer half-life of agents [2]. Both types of anesthesia are preferred according to their effectiveness, the underlying factors of patients, and the type of surgical procedure. Neuromuscular relaxants are required for endotracheal intubation, mechanical ventilation, and surgical site manipulation, but they can significantly hamper IONM monitoring if used continuously during the procedure [20].

Data Extraction

To properly assess all studies, we pulled Sugammadex and neostigmine doses and patients' recovery time from the initial reversal drug administration to extubating. We included whether ranges were established and any adverse effects during postoperative recovery.

Assessment of Bias

Randomized controlled trials and prospective studies are the most reliable forms of study as they help reduce the biases associated with accounting for various factors and types of surgeries where these drugs

may be used. We used the Cochrane Collaboration tool to assess the risk of bias in randomized trials [21]. We evaluated random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases not specifically mentioned, such as funding.

Statistical Analysis

The authors performed Statistical Analysis. Data is expressed as mean ± standard deviation. All data assumed a normal distribution, followed by a two-tailed t-test with equal variance to detect group differences. The probability of detecting a significant difference was 5% ($p < 0.05$).

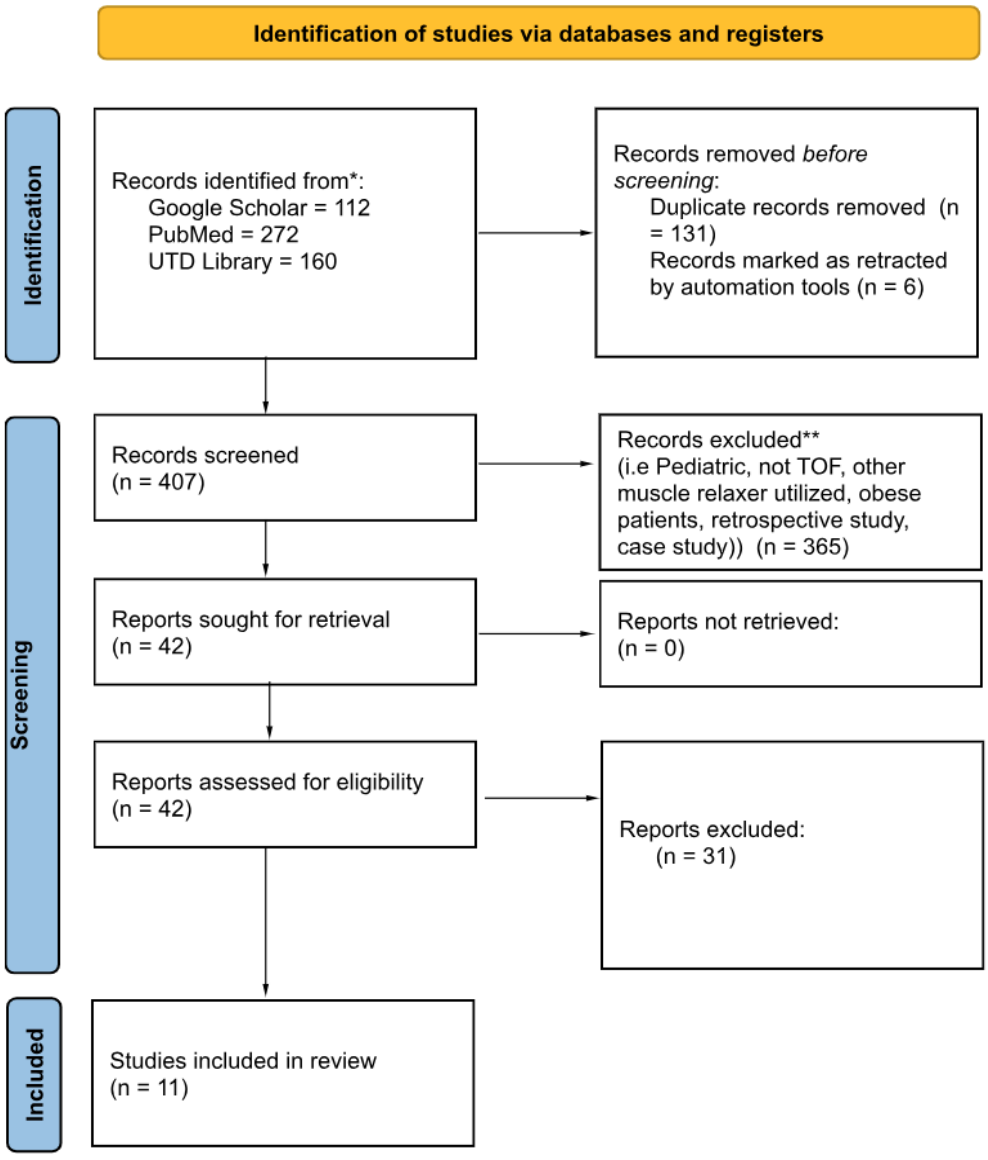

Figure 1. PRISMA Flow Diagram of the study selection. The identification, screening, and inclusion of studies in the review.

RESULTS

Literature Search

We searched PubMed, Google Scholar, and the University of Texas at Dallas Library database for relevant studies, and 542 papers were retrieved. After removing duplicates, 407 papers were left to be screened. After assessing an overview of abstracts, 365 papers were excluded for not meeting our inclusion criteria, leaving 42 papers for review for eligibility. After further review, 11 studies were approved for assessment and analysis. This process is shown by the PRISMA flow diagram (Figure 1).

Data Analysis

Characteristics

All the studies were randomized, with nine controlled trials and two prospective studies (Table 1). Sugammadex was used as the intervention method compared to neostigmine for all studies. There were 869 participants, 435 of whom were in the Sugammadex group and 434 in the Neostigmine group. The age of participants showed no significant difference between Sugammadex or neostigmine groups across any of the studies (57.5 ± 10.43 v. 56.63 ± 10.47, $t(865) = 1.2271$, $p = 0.2201$). Body mass index (BMI) was not significantly different among those in any of the studies (26.86 ± 3.48 v. 26.63 ± 3.06, $t(865) = 1.0345$, $p = 0.3012$). Females comprised 387 individuals; 193 participants received Sugammadex, and 194 received Neostigmine. Males comprised 480 individuals; 241 participants received Sugammadex, and 239 received Neostigmine. Compared to other male participants, male participants had no difference between Sugammadex or Neostigmine (21.91 ± 11.60 v. 21.72 ± 11.17, $t(478) = 0.1828$, $p = 0.8551$). Females had no difference from other females between Sugammadex or Neostigmine (17.55 ± 13.66 v. 17.63 ± 14.87, $t(385) = 0.0551$, $p = 0.9561$). However, comparison between males and females did show a significant outcome in Sugammadex (21.91 ± 11.60 v. 17.55 ± 13.66, $t(432) = 3.5944$, $p = 0.0004$) and Neostigmine (21.72 ± 11.17 v. 17.63 ± 14.87, $t(431) = 3.2662$, $p = 0.0012$). The two-tailed P values indicated no significant difference between age, BMI, or specifically in the same gender (males v. males; females v. females) between those who received Sugammadex and those receiving neostigmine.

Recovery time

All studies reported average surgery time except for Li et al. (2021) and Leslie et al. (2021) [22,23]. Patients who received Sugammadex during surgery showed no statistical significance between surgery times of those who received neostigmine (182.89 ± 160.91 v. 185.28 ± 156.77, $t(867) = 0.1494$, $p = 0.8813$). Recovery time showed to be extremely statistically significant between Sugammadex and neostigmine (8.074 ± 7.57 v. 18.45 ± 11.18, $t(867) = 16.0224$, $p = 0.0001$) (Fig. 3).

STUDIES	STUDY DESIGN	SAMPLE SIZE	REVERSAL DRUGS	AGES	BMI	SEX (MALES/TOTAL)
ABOLA ET AL. 2020	RCT	62	SUGAMMADEX	54.4 ± 13.5	33.6 ± 7.7	15/31
			NEOSTIGMINE	53.1 ± 13	33.9 ± 7.6	14/31
DEANA ET AL. 2020	RCT	41	SUGAMMADEX	54.1 ± 9.8	25.2 ± 4.2	14/21
			NEOSTIGMINE	54.1 ± 10.4	25.3 ± 3.9	12/20
FIORDA DIAZ ET AL. 2022	RCT	37	SUGAMMADEX	56.5	32.5	7/18
			NEOSTIGMINE	48	28.2	11/19
HUANG ET AL. 2023	RCT	58	SUGAMMADEX	44 ± 11	23.3 ± 3.5	20/30
			NEOSTIGMINE	44 ± 12	22.8 ± 2.3	21/28
LESLIE ET AL. 2021	RCT	120	SUGAMMADEX	64.6 ± 11.1	25.6 ± 4.6	33/59
			NEOSTIGMINE	62.7 ± 10.1	27 ± 5.8	37/61
LI ET AL. 2021	RCT	82	SUGAMMADEX	74 ± 4	25 ± 3	28/40
			NEOSTIGMINE	75 ± 5	25 ± 3	24/40
OZCIFTCI ET AL. 2022	RANDOMIZED PROSPECTIVE	60	SUGAMMADEX	53 ± 16	26.6 ± 11	27/30
			NEOSTIGMINE	54 ± 16	26.3 ± 10	29/30
TANG ET AL. 2023	RCT	48	SUGAMMADEX	42 ± 3	27.3 ± 1.5	13/24
			NEOSTIGMINE	46 ± 5	28 ± 1.7	12/24
TOGIOKA ET AL. 2020	RCT	200	SUGAMMADEX	74.8 ± 4.3	28.8 ± 5	48/100
			NEOSTIGMINE	75.1 ± 5	28.4 ± 6.7	44/100
TSAI ET AL. 2023	RCT	61	SUGAMMADEX	58.5 ± 16.7	24.1 ± 3.6	14/31
			NEOSTIGMINE	53.8 ± 14.5	24.3 ± 3.6	12/30
YU ET AL. 2022	RANDOMIZED PROSPECTIVE	100	SUGAMMADEX	56.7 ± 10.3	23.4	22/50
			NEOSTIGMINE	57.2 ± 9.8	23.7	23/50

Table 1. Study Characteristics. Characteristics summary of selected studies and each average participant's age, BMI, and sex. All studies examined fulfilled the inclusion criteria.

STUDIES	REVERSAL DRUG	SURGERY TIME, MIN	TOTAL MUSCLE RELAXANT*, MG	REVERSAL DOSAGE, MG/KG	RECOVERY TIME, MIN
ABOLA ET AL. 2020	SUGAMMADEX	106	89	2	7
	NEOSTIGMINE	119	98	70 GLYCOPYRROLATE 10	8
DEANA ET AL. 2020	SUGAMMADEX	402 ± 54	217± 61	2	9.4
	NEOSTIGMINE	378 ± 102	199 ± 74	0.05 ATROPINE 0.01	34.6
FIORDA DIAZ ET AL. 2022	SUGAMMADEX	61.5	0.3-0.7*	2	3
	NEOSTIGMINE	61		0.05	9
HUANG ET AL. 2023	SUGAMMADEX	34	0.9*	2	0.5
	NEOSTIGMINE	27		5 ATROPINE 2.5	5.3
LESLIE ET AL. 2021	SUGAMMADEX		49	2	9
	NEOSTIGMINE		49	2.5	10
LI ET AL. 2021	SUGAMMADEX		0.3*	2-4	3.6
	NEOSTIGMINE		0.9*	0.02 ATROPINE 0.01	34.6
OZCIFTCI ET AL. 2022	SUGAMMADEX	43	0.6*	2	22
	NEOSTIGMINE	49		0.05 ATROPINE 0.02	30
TANG ET AL. 2023	SUGAMMADEX	488 ± 42	5.98	4	4.8
	NEOSTIGMINE	491 ± 49	6.05	70	23.5
TOGIOKA ET AL. 2020	SUGAMMADEX	215.8	106.3	2	22.8
	NEOSTIGMINE	212.9	104.2	0.07	23.9
TSAI ET AL. 2023	SUGAMMADEX	155.7 ± 40.5	1*	2	3.975 ± 1.94
	NEOSTIGMINE	186.6 ± 69.5		0.05	14.7 ± 4.56
YU ET AL. 2022	SUGAMMADEX	140	80	2	2.74 ± 0.46
	NEOSTIGMINE	143	80	0.05 ATROPINE 0.02	9.38 ± 0.995

Table 2. Average times and dosage amounts. Each study is separated by Sugammadex or Neostigmine and shows the average times of surgery and recovery with muscle relaxant and reversal drug dosage. (*Studies did not specify the total amount, giving normal dosage by kg of body weight mg/kg).

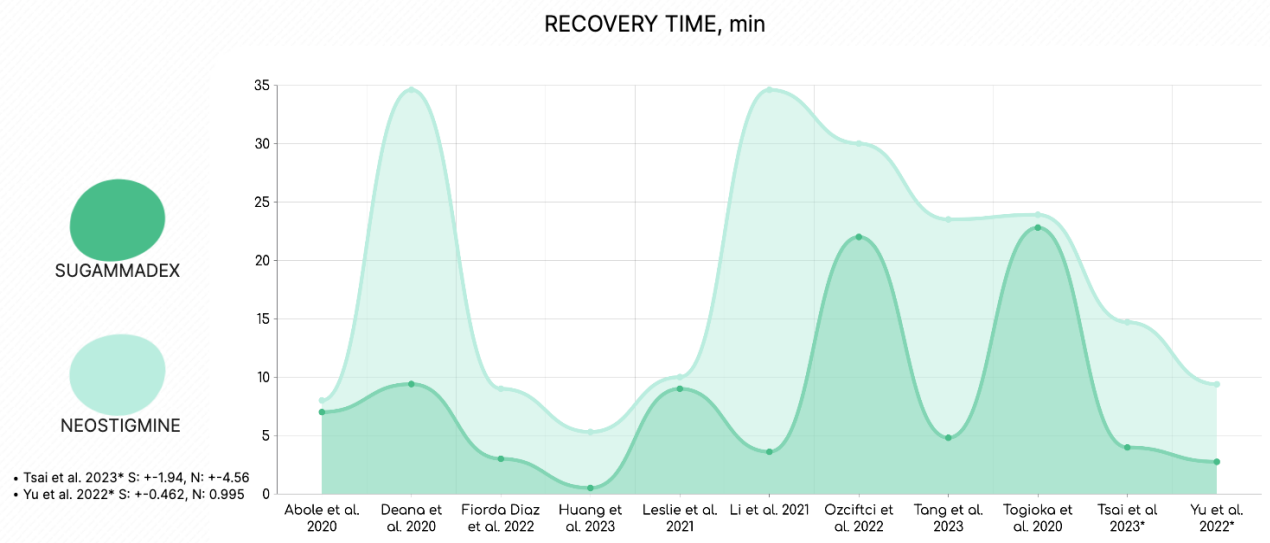

Figure 3. Recovery time by study and drug. Charting Sugammadex and Neostigmine recovery time in minutes in each study compared to each other.

Adverse Complications

Of the studies that reported adverse effects, Sugammadex showed an exceptionally statistically significant less chance of causing complications than Neostigmine (5.8125 ± 8.35 v. 12.188 ± 13.58, $t(286) = 4.1653$, $p = <0.0001$). Specifically, with TOF less than 0.90, Sugammadex was far less likely to have a residual neuromuscular blockade (5.5 ± 4.95 v. 30.5 ± 21.92, $t(70) = 3.7448$, $p = 0.0004$).

Train of Four Parameters

Three hundred eight (308) people were studied in these extra papers to determine TOF parameters. Frequency was homogenous among all studies at 2 Hz, while duration was either not specified or kept at 0.2 msec or 10 seconds. Stimulation ranged from 20mA to 80mA.

Quality of Assessment

After assessing bias, we found our studies at low risk of bias. This would mean they are adequate to provide comparable analysis between the data. All of the studies had good, randomized selection. We could not identify any conflicts of interest or biases regarding the funding source because many of these papers highlighted the limitations and future directions of the research rather than focusing solely on the positive outcomes. Disclosing any limitations in these studies allowed us to identify potential future studies. Although all the studies met our sample size requirements, which included patients at least 18 years old, and our outcome measures were objective, the average age of the studies was between 40 and 50 years old, which limited the study outcomes of younger adolescents.

ADVERSE EFFECTS	STUDIES	SUGAMMADEX	NEOSTIGMINE
HYPOXEMIA	LI ET AL.	1	7
	TANG ET AL.	1	4
	TOGIOKA ET AL.	6	7
NAUSEA/VOMITING	LI ET AL. 2021	0	3
	FIORDA DIAZ ET AL. 2022	4	1
	TOGIOKA ET AL. 2020	14	17
URINARY RETENTION	LI ET AL. 2021	2	10
	FIORDA DIAZ ET AL. 2020	0	2
PNEUMONIA	TANG ET AL. 2023	1	3
	TOGIOKA ET AL. 2020	3	2
	YU ET AL. 2022	7	15
PULMONARY COMPLICATIONS	TANG ET AL. 2023	0	2
	TOGIOKA ET AL. 2020	33	40
	YU ET AL. 2022	10	21
TOF LESS THAN 0.9	TOGIOKA ET AL. 2020	9	46
	YU ET AL. 2022	2	15
TOTAL AMOUNT		93	195

Table 3. Adverse Effects. Complications from Sugammadex or neostigmine administration from selected studies that reported common adverse effects.

STUDIES	SAMPLE SIZE	NEUROMUSCULAR BLOCKADE	STIMULATION SITE	FREQUENCY	DURATION	INTER-STIMULUS INTERVAL	STIMULATION	TOF RESULTS
BRULL ET AL. (1990)	95	VECURONIUM	OLECRANON GROOVE, VOLAR FOREARM	NOT SPECIFIED	NOT SPECIFIED	NOT SPECIFIED	20, 30, 50 MA	T4/T1 RATIO AT 50 MA ≤0.70 (N=28), >0.70, <0.95 (N=25), ≥0.95 (N=30)
BRULL ET AL. (1995)	2	VECURONIUM	THUMB ADDUCTION	2 HZ	0.2 MSEC	12 SEC	30, 60 MA	T4/T1 RATIOS, VISUAL INSPECTION: 48% GREATER THAN,VIDEOTAPE ANALYSIS 56% GREATER THAN. T4 40% LESS THAN BASELINE, T4 OVERSTIMULATION
HEIER ET AL. (2010)	12	MIVACURIUM	ADDUCTOR POLLICIS	2 HZ	NOT SPECIFIED	NOT SPECIFIED	25-35 MA	TOF RATIO BELOW 0.90 -> DECREASE FUNCTION
HELBO-HANSEN ET AL. (1992)	24	ATRACURIUM	ADDUCTOR POLLICIS, ULNAR NERVE	2 HZ	0.2 MSEC	12 SEC	58 MA	"P<0.01 AT CURRENTS LESS THAN 40 MA" TOF WAS EFFICENT AT LOW LEVEL CURRENTS
LAGNEAU ET AL. (2001)	13	CISTRACURIUM	LEFT AND RIGHT ORIBULARIS, LEFT AND RIGHT ADDUCTOR POLLICIS, LEFT AND RIGHT PLANTAR FEXORS	2 HZ	10 SEC	15 MIN	40, 60, 80 MA	60 MA WAS FOUND MORE SUITABLE TO ACHIEVE SUPRAMAXIMAL TOF STIMULATION
SAITOH ET AL. (1995)	90	VECURONIUM	ULNAR NERVE OF FOREARM	2 HZ	0.2 MSEC	12 SEC	20, 30,40, 50, 60 MA	LONGER RETURN TIME AT 20 MA, 30 MA OPTIMAL CURRENT
WARDHANA ET AL. (2019)	72	ROCURONIUM	FOREARM, WRIST CREST	2 HZ	NOT SPECIFIED	12 SEC	50 MA	NO SUBJECTS HAD TOF RATIO <0.70, ADVERSE EVENT, MUSCLE WEAKNESS IN ONE GROUP

Table 4. Train of Four studies. Extra studies show different parameters for TOF and the stimulation site, frequency, interstimulus interval, and amount of stimulation (mA) used.

Figure 2. Risk of Bias Assessment. Analysis of RCT studies and their level of risk.

DISCUSSION

Figure 3 illustrates the recovery times for Sugammadex and Neostigmine across 11 studies (Figure 3). On average, Sugammadex showed a recovery time of 8.07 minutes, while neostigmine had an average recovery time of 18.45 minutes. Huang et al. reported a minimum recovery time where patients administered Sugammadex exhibited a recovery time of 0.5 minutes, whereas, in the same study, patients given Neostigmine had a recovery time of 5.3 minutes ([24]. A medium recovery was achieved by Tang et al.,

where the average recovery time for patients administered Sugammadex was 4.8 minutes [25]. However, Tsai et al. showed a recovery time of 14.7 minutes for patients administered neostigmine [26]. Lastly, in a study conducted by Togioka et al. 2020 (maximum recovery time), patients administered Sugammadex had a recovery time of 22.8 minutes [27], while interestingly, both Li et al. 2022 [22] and Deana et al. 2020 showed a recovery time of 34.6 minutes in patients that were administered Neostigmine [28]. These findings suggest that compared to Neostigmine, Sugammadex reverses neuromuscular blockade quicker. As it ensures a quicker reversal, Sugammadex also restores neuromuscular activity quicker [24] and facilitates an easier recovery from anesthesia [29].

A common element throughout some of these studies was that the TOF count was at two, and the ratio at reversal was ≥0.9, indicating that most of the functions had returned to normal, in addition to the reversal achieved with the administration of sugammadex. Additionally, the inclusion of TOF, when it comes to how anesthesia is managed, is crucial for patient recovery. By utilizing TOF, professionals can precisely assess the degree of neuromuscular blockade and reversal. Furthermore, attaining a ratio of 0.9 is ideal when it comes to the recovery of neuromuscular functions before extubating, as well as making sure there is minimal risk of paralysis and any adverse effects. We found that across all 11 studies we reviewed comparing Sugammadex and Neostigmine, with the TOF ratio less than 0.9, neostigmine showed more adverse complications than Sugammadex (table 3).

The previously known optimal TOF stimulation rate is 30mA. This was found to be true in a study conducted by Saitoh et al. (1995), finding that anything below 30mA led to a longer return time. TOF is found to be sufficient at levels below 40mA, but one study concluded that out of 72 subjects monitored at 50mA, none had a TOF ratio of <0.70 [30]. However, one adverse event was reported with muscle weakness in one group. Another study looking at the TOF ratio at 50mA did report that 28/95 subjects experienced a TOF of <0.70 (29%), with 31.6% reaching optimal levels above 0.95 [31]. As Wardhana et al. (2019) stated in a more recent study, recording technology may have improved over time to achieve more accurate ratio measurements [30]. Studies reporting higher stimulation between 60-80mA found no significant changes over 60mA to highlight increased stimulation advantages [32]. Due to no specific differences in stimulation higher than 60mA, this stimulation level was more suitable to achieve supramaximal TOF stimulation, a technique to improve responses for deeper neuromuscular blockades. Sugammadex is known to be able to reverse all levels of neuromuscular blockade. However, our gathered studies did not report specific NMB measurements (light, moderate, deep) or specifically applied stimulation mA. Tsai et al. (2023) reported using 70mA to achieve a TOF > 0.90 response, yet no mention of adverse effects was listed in the paper [26]. When comparing the recovery time of Sugammadex, the differences were negligible to the amount of dosage applied (2 mg/kg: 3.98 minutes v. 4mg/kg: 4.80 minutes) [25,26]. However, of all studies comparing Sugammadex using the optimal dosage of 2mg/kg, recovery times ranged from 0.5 to 22.8 minutes. This broad range brought us to look at the amount of muscle relaxants used during surgeries but was also met with mixed results and under-reported weight

per kg amounts. Future research should look for optimal muscle relaxant dosage compared to TOF and Sugammadex recovery to discover if dosage may help identify better parameters and reduce adverse events postoperatively.

Although Sugammadex has more apparent benefits than neostigmine, it still has some limiting factors. Some studies have indicated that the cost and resources of Sugammadex are uncertain as neostigmine has continued to be the drug most often utilized [34]. Kim et al. 2024, even mentioned in their studies that the cost of Sugammadex impacted their patient selection [11]. Future studies might focus on expanding the accessibility of Sugammadex, particularly given its evident efficiency over neostigmine in terms of a quick reversal, as well as including studies on its cost-effectiveness. Furthermore, when it comes to IONM, it is essential to have an IONM expert who has passed the CNM exam to ensure that IONM is being monitored constantly in the operating room.

CONCLUSION

In this systematic review, we were able to understand better-existing research and clinical studies on the efficacy of Sugammadex for neuromuscular blockade reversal and optimal TOF monitoring techniques. With a TOF of less than 0.9, we can conclude that Sugammadex is less likely to have adverse side effects than neostigmine. With emphasis on the safety advantage of Sugammadex, it is also more effective at reversing neuromuscular blockade.

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