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THE IMPORTANCE OF SUGAMMADEX AT POSTOPERATIVE RESIDUAL NEUROMUSCULAR BLOCK

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ABSTRACT

Introduction*: postoperative residual neuromuscular blockade is the postoperative muscle paralysis caused by incomplete or null antagonism of neuromuscular blocking agents. Post-surgical residual paralysis (PORP) has a high incidence and may cause adverse effects, increasing postoperative morbidity and mortality. The gold standard for complete reversal of neuromuscular blockade is a T4/T1 ratio of 0.9. Small degrees of paralysis are associated with an increased risk of postoperative pulmonary complications. Recent research indicates that residual neuromuscular blockade is a significant risk factor for patient safety.*

Objective: to detail the current information related to postoperative residual paralysis, in addition to explaining the use and characteristics of sugammadex in its reversal.

Methodology*: a total of 45 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 35 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: postoperative residual neuromuscular block, postoperative muscle weakness, sugammadex, anticholinesterase inhibitors.*

Results*: Neuromuscular block occurs due to muscle fragility in the postoperative period due to antagonism, which produces a decrease in the musculature of the upper and lower airways. When this phase is properly managed, extubation delays are reduced, and postoperative pulmonary complications are reduced. Sugammadex is a relaxant that decreases the possibility of persistent neuromuscular paralysis; as neuromuscular blockade increases, contraction decreases. Therefore, when this drug is used, the risk of adverse effects, mostly respiratory, is avoided. This drug inactivates rocuronium, and the adverse effects it presents (although very infrequent) are dysgeusia, cough, grimacing or increased secretion through the endotracheal tube.*

Conclusions*: sugammadex is suggested to be used before neostigmine, although it should be used in patients with high risk of postoperative complications, such as patients over 80 years of age or with post cardiothoracic surgery. However, sugammadex reverses neuromuscular blockade more rapidly, with a decrease in the frequency of residual neuromuscular blockade and postoperative pulmonary complications such as pneumonias. A point to consider is that sugammadex is more expensive and is usually accompanied by higher presentations of adverse effects.*

KEY WORDS: *sugammadex, paralysis, residual, postoperative, antagonism, neuromuscular.*

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INTRODUCTION

Postoperative muscle paralysis or frailty resulting from incomplete or no antagonism of adespolarizing neuromuscular blocking agents (NMBs) is called postoperative residual neuromuscular blockade, also known as postoperative residual paralysis (PORP). The gold standard for complete reversal of neuromuscular blockade is a T4/T1 ratio of 0.9 across the four-stimulus sequence (SQE) (1,2).

PORP shows a high incidence and may cause adverse effects, increasing postoperative morbimortality. In some clinical studies, monitoring of neuromuscular blockade through quantitative tests such as acceleromyography is recommended. The use of anticholinesterase agents for pharmacological reversal of neuromuscular blockade is not free of side effects(1).

Some authors have presented studies in which small degrees of residual paralysis (train-of-four ratio of 0.7 to 0.9) have been shown to be associated with altered pharyngeal function and increased risk of aspiration, upper airway muscle weakness and airway block, change in hypoxic ventilatory response, and bothersome symptoms of muscle weakness. Both observational studies and randomized clinical trials have shown that lack of neuromuscular recovery in the early postoperative period can lead to unpleasant symptoms of muscle weakness, prolonged stays in the postanesthesia care unit, delays in tracheal extubation, and an increased risk of postoperative pulmonary complications. These complications include hypoxemia and airway obstruction. Recent research indicates that neuromuscular management has an impact on postoperative outcomes and that residual neuromuscular blockade is a significant risk factor for patient safety(2).

METHODOLOGY

A total of 40 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 35 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: postoperative residual neuromuscular block, postoperative muscle weakness, sugammadex, anticholinesterase inhibitors. The choice of the bibliography exposes elements related to postoperative residual paralysis; in addition to this factor, the use and characteristics of sugammadex in its reversion are presented.

DEVELOPMENT

The possibility of postoperative residual neuromuscular blockade has long been recognized and still is today. When neuromuscular blockade is severe and profound, traditional pharmacological antagonists (anticholinesterases) are unable to reverse it; however, at the other end of the recovery curve, when recovery is nearly complete, anticholinesterases can cause paradoxical muscle weakness. Sugammadex, a novel selective relaxant-binding agent, can reverse any degree of blockade caused by aminosteroid relaxants (but not benzylisoquinolinium); however, the appropriate dose must be determined based on an objective assessment of the degree of neuromuscular blockade(3).

The non-depolarizing steroid neuromuscular blockers rocuronium and vecuronium are reversed using a modified gamma-cyclodextrin called sugammadex. After surgery, residual neuromuscular blockade is typical; an estimated 30 to 60 percent of patients experience it in the recovery area. Hypoxia, weakness of the supralaryngeal muscles that increases the risk of upper airway obstruction, difficulty swallowing and an elevated risk of aspiration have been associated with low-level neuromuscular blockade, which is less than what can be seen with the naked eye. Sugammadex significantly reduces the likelihood of developing persistent neuromuscular paralysis and accelerates the rate at which neuromuscular blockade reverses.

It does not inhibit conventional acetylcholinesterase-like reversal drugs such as neostigmine, so there is no need to use an antimuscarinic drug such as glycopyrrolate(4).

Assessment of neuromuscular function with a peripheral nerve stimulator is necessary to direct appropriate postoperative care. Despite the fact that subjective (visual and tactile) assessment of muscle responses is used in many settings, this assessment has had only modest success in preventing persistent paralysis. Like respiratory parameters (tidal volume and vital capacity), clinical assessments of muscle force return (head lift and grip strength) are insensitive for detecting neuromuscular weakness. Only objective measurement (a train-of-four ratio greater than 0.90) can establish adequate tracheal extubation time, ensure normal muscle function and ensure patient safety(3).

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Table 1.Suggested Definitions of Depth of Neuromuscular Block Based on Subjective and Measured (Objective) Criteria.

Depth of Block	Posttetanic Count	Train-of-Four Count	Subjective Train-of-Four Ratio	Measured Train-of-Four Ratio
Intense (profound) block	0	0	0	0
Deep block	≥ 1	0	0	0
Moderate block	NA	1–3	0	0
Light (shallow) block	NA	4	Fade present	0.1–0.4
Minimal block (near recovery)	NA	4	No fade	> 0.4 but < 0.90
Full recovery (normal function)	NA	4	No fade	≥ 0.90–1.0

NA = not applicable

Source: Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS. Postanesthesia Care Unit Recovery Times and Neuromuscular Blocking Drugs(5).

According to several studies, the incidence of PORP (postoperative residual paralysis) after the end of anesthesia ranges from 5% to 88.0%. PORP is defined as the T4/T1 ratio 0.9(6-8).

The train-of-four (TOF) method is most commonly used to monitor neuromuscular function during anesthesia. The distal forearm is generally used to stimulate the ulnar nerve with TOF peripheral nerve monitors (such as the TOF-Watch TM monitor). The adductor pollicis muscle of the thumb will contract (spasm) in response to four successive supramaximal electrical stimuli, or TOF. The amplitudes of the four motor responses will be equal under normal circumstances. Fading is the process by which the amplitude of subsequent contractions decreases relative to previous contractions as the degree of BNM (neuromuscular blockade) caused by non-depolarizing NMBA (neuromuscular blocking agents) increases.

All contractions will eventually stop as the NMBA increases. The intensity of BNM is determined by the amount of perceptible thumb movements and the level of fading. The amount of fading can also be expressed as a ratio by dividing the motor response at the fourth and first movement (T4 and T1), which is known as the train-of-four (TOF) ratio. According to currently available evidence, the BNM must recover to a TOF ratio of 0.9 or greater before the patient can be safely extubated(9-12).

BNM measurement of the ulnar nerve will not show thumb spasm when high doses of NMBA are administered (TOF = 0). A 50 Hz tetanic stimulus is applied to the ulnar nerve for five seconds to assess the level of BNM in this situation. Acetylcholine is released in large amounts at the neuromuscular junction in response to the tetanic stimulation. Then 15 individual electrical stimuli are delivered at one-second intervals after this tetanic facilitation. The post-tetanic count (PTC) is the total number of thumb movements recorded. For example, PTC equals six when six thumb movements are observed after tetanic facilitation. TOF and PTC measurements can be used to classify the depth of BNM into the following categories: (a) moderate BNM: TOF 1 to 3 of 4 spasms; (b) deep BNM: TOF zero contractions and PTC more than zero contractions; and (c) intense BNM: zero TOF and zero PTC contractions. In reality, the presence of intense BNM is limited to the time immediately following the induction dose of BNM when anesthesia is felt. Depending on the type of surgery, BNM is allowed to recover to deep or moderate BNM, which can be maintained to preserve adequate surgical working conditions(9,13).

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Table 2. Quantitative Monitoring Technologies Used in Research and Clinical Care.

Modality	Principle	Advantages	Disadvantages	Monitoring Site	Clinical Availability
Mechanomyography	Directly measures isometric muscle contraction force.	- Measures muscle force directly. - The "reference" modality.	Cumbersome and time-consuming setup. Not suitable for clinical practice.	- Ulnar nerve - adductor pollicis muscle; - posterior tibial nerve - flexor hallucis brevis muscle	Commercially not available
EMG	Measures compound muscle action potentials evoked by neurostimulation.	- Many different muscles can be examined. - Does not require freely moving limbs. - Easy and fast set up and short calibration.	Possible interference from other electrical equipment (electrocautery).	- Ulnar nerve - adductor pollicis, abductor digiti minimi and first dorsal interosseous muscles; - posterior tibial nerve - flexor hallucis brevis muscle; - phrenic nerve - diaphragm	-E-NMT (GE DATEX-Ohmeda NMT; USA); https://www.gehealthcare.com -TetraGraph (Senzime Inc.; USA); https://www.senzime.com -TwitchView (Blink Device Company; USA); https://www.blinkdc.com -StimPod (Xavant Technology; South Africa; awaiting Food and Drug Administration clearance as of September 1, 2021); https://www.xavant.com
Acceleromyography	Measures the acceleration of the thumb or any freely moving muscle. The acceleration is directly proportional to the force according to Newton's second law.	- Current neuromuscular blockade management guidelines are based on acceleromyography measurements. - Most widely used technique.	Requires use of hand adapter (increases precision), fixation of arm and fingers, free movement of thumb, normalization of recovery train-of-four ratios.	- Ulnar nerve - adductor pollicis muscle; - facial nerve - orbicularis oculi, corrugator supercilii muscles; - posterior tibial nerve - flexor hallucis brevis muscle	-Infinity Trident NMT SmartPod (Dräger; Germany); https://www.draeger.com -IntelliVue NMT (Philips; The Netherlands); https://www.usa.philips.com -TOF-Scan (IDMed; France); https://www.idmed.fr -StimPod (Xavant Technology; South Africa); https://www.xavant.com
Kinemyography	Measures the distortion of a piezoelectric film sensor. The level of distortion is proportional to the force of thumb contraction.	- Easy to apply.	Available only in modular form. Validation *vs.* mechanomyography and electromyography questionable.	- Ulnar nerve - adductor pollicis muscle	M-NMT (GE DATEX-Ohmeda NMT; USA); https://www.gehealthcare.com
Cuff pressure modality	Measures the pressure change in a modified non-invasive blood pressure cuff due to upper arm muscles' contraction in response to brachial plexus neurostimulation.	- Easy to apply.	Needs further validation, overestimates the train-of-four ratio at the adductor pollicis by mechanomyography and acceleromyography.	- Brachial plexus - muscles of upper arm	TOF-Cuff (RGB Medical Devices; Spain); https://www.rgb-medical.com

EMG, electromyography.

Source: Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS. Postanesthesia Care Unit Recovery Times and Neuromuscular Blocking Drugs(5).

The return of adequate breathing and upper airway muscle function depends on full recovery of BNM after anesthesia. By definition, PORP is present when BNM (TOF ratio 0.9) persists at some level after extubation since most NMBAs have much slower recovery times than the hypnotics and opioids that are frequently used during general anesthesia, this is a situation that is readily possible. Furthermore, because of the wide interindividual variability in recovery times, it is impossible to predict NMBA recovery by pharmacologic reasoning (PKPD) (9,14). The upper respiratory tract and the ability of pulmonary muscles to function are adversely affected by postoperative residual paralysis (PORP). The upper airway collapses and ventilation is compromised. This is important because dysfunction in the upper esophageal and pharyngeal sphincter muscle; and increased upper airway collapsibility are associated with even a mild degree of residual paralysis (e.g., a TOF ratio between 0.6 and 0.9). As a result of blockade of nicotinergic acetylcholine receptors in the carotid bodies, NMBAs also directly reduce the hypoxic ventilatory response. The risk of hypoxia in patients increases when the hypoxic ventilatory response is inhibited. PORP has a strong correlation with postoperative respiratory complications as a result of these effects. Unfortunately, there is a significant incidence of PORP among patients in the postanesthesia care unit (PACU), with rates ranging from 20 to 60 percent. The use of a neuromuscular monitor and appropriate BNM reversal are crucial tactics to reduce the prevalence of PORP(2,9,15-19).

Sugammadex was found to have a lower incidence of respiratory events and residual paralysis in several meta-analyses performed for multiple randomized controlled studies comparing neostigmine and sugammadex(20-23).

Sugammadex has a linear, dose-dependent pharmacokinetic profile after administration at doses ranging from 2 mg/kg to 16 mg/kg, with renal clearance close to 100% and an elimination half-life of 100 to 150 minutes. Sugammadex acts in a 1:1 ratio; therefore, a higher dose of the drug is needed to disarm a deeper

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level of neuromuscular blockade, requiring 2 mg/kg to disarm mild neuromuscular blockade (two spasms in response to stimulation), 4 mg/kg for deep blockade (one or two post-tetanus counts after a 5-second 50-hertz tetany), and 16 mg/kg for immediate reversal after an intubating dose of rocuronium (1. 2 mg/kg) are all acceptable doses. A train-of-four ratio > 0.9 can be achieved within an average of 3 minutes after a sugammadex dose of 2 or 4 mg/kg because there is significantly less antagonism than with neostigmine(4,24,25).

Sugammadex is a modified γ-cyclodextrin and relatively free of adverse effects and well tolerated. As for its mechanism of action it inactivates rocuronium by encapsulating (chelating) the free molecule to develop a stable complex. In terms of chemical architecture it presents a hydrophobic cavity and a hydrophilic exterior due to the arrangement of polar hydroxyl groups. Hydrophobic interactions envelop the drug in the cyclodextrin cavity, forming a water-soluble host-guest complex(10,26).

Among the adverse reactions reported in some of the clinical studies are dysgeusia (metallic or bitter taste) usually observed after doses of 32 mg/kg or more, limb or body movement or coughing during anesthesia, coughing, grimacing or suctioning of the endotracheal tube, recurrent block and hypotension during surgery(26,27). A variable amount of residual BNM often remains after taking neostigmine and other acetylcholinesterase inhibitors. Therefore, it is not surprising that the impact of BNM reversal with neostigmine on postoperative respiratory complications and outcome is, at best, ambiguous. Reversal with neostigmine (without the use of a TOF watch) of BNM does not appear to increase postoperative respiratory safety and may even increase the risk of atelectasis, hypoxemia and subsequent reintubation.(9,28,29). The anticholinesterase drug neostigmine has a ceiling effect and is associated with adverse effects such as autonomic disturbances, including bradycardia, which tentatively leads to a number of problems during extubation in cardiothoracic surgery patients, nausea and vomiting; these adverse effects are not noted with sugammadex(26,30).

Table 3. Sugammadex vs neostigmine.

TIEMPO DE RECUPERACIÓN			
Sugammadex 2 mg/kg	Neostigmina 0,05 mg/kg	Sugammadex 4 mg/kg	Neostigmina 0,07 mg/kg
1.96 minutos	12.87 minutos	2.9 minutos	48.8 minutos
6.6 VECES MAS RAPIDO		**16.8 VECES MAS RAPIDO**	

Source: Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults(31).

Table 4. Adverse events: Sugammadex vs neostigmine at any dose

EFECTOS ADVERSOS (CUALQUIER DOSIS)		
	Sugammadex	Neostigmina
BRADICARDIA	13/1000	84/1000
NAUSEA Y VOMITO	68/1000	131/1000
SIGNOS GENERALES PRPO	52/1000	131/1000
RIESGO DE EFECTOS ADVERSOS GRAVES	6/1000	10/1000

Source: Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults(31)

These findings can be explained in several ways. Successful reversal of moderate BNM depends on timely management and exclusive reversal. Clearly, this requires adequate neuromuscular monitoring. In addition, the duration of complete reversal after neostigmine therapy varies greatly among patients and is unpredictably long. Sugammadex may perform better in both respects, allowing for rapid, complete and predictable reversal of moderate and profound BNM. According to recently available data, sugammadex is more effective than neostigmine in reversing BNM because it reduces the rate of postoperative residual curarization. According to a recent study, patients who received sugammadex for reversal experienced a 0% PORP rate, compared with 46% of those who received neostigmine. These results are encouraging, but in an unmonitored setting, PORP after sugammadex reversal still occurred in 4% of patients. This emphasizes the importance of complete neuromuscular control in any situation involving the use of NMBA, regardless of the type of reversal agent(9,32-35).

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CONCLUSIONS

Sugammadex is a gamma cyclodextrin characterized by encapsulating neuromuscular blockers, with higher affinity for rocuronium. It`s antagonistic effect restores normal transmission and neuromuscular function, with a faster effect than neostigmine. The dose varies according to the degree of blockade, since if it is a profound blockade, the dose is 4 mg/kg; if it is a moderate blockade, the dose is 2 mg/kg. When intubation and ventilation are very difficult, the dose of sugammadex is 16 mg/kg, which reverses the blockade in 3 minutes. Elimination is renal, so it is not suitable for patients with renal insufficiency; contraceptive inhibition occurs if used concomitantly with sugammadex. Unfortunately, this drug has been associated with perioperative anaphylaxis reactions, which usually occur within minutes; bradycardia and asystole may also occur, although present in 1%.

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Conflict of Interest Statement

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