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Postoperative Residual Paralysis

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Summary: Mathias LAST, Bernardis RCG – Postoperative Residual Paralysis.

DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

Multiple searches were carried out in the PubMed database to identify articles with better methodological design, followed by critical evaluation of their contents and classification according to the strength of evidence. According to the recommendations of the *Oxford Centre for Evidence Based Medicine*, literature systematic reviews and randomized clinical trials were preferred. Searches were carried out between January 2009 and July 2010. For the search in PubMed, different keywords combinations were used (*random**; *neuromuscular*; *postanesthesia*; *care*; *residual*; *paralysis*; *complications*; *blockade*; *curarization*) as well as controlled vocabulary terms (*Anesthesia*, *Perioperative Complications* [MeSH]; *Residual Neuromuscular Blockade* [MeSH]; *Postanesthesia Care Unit* [MeSH]; *Monitoring Neuromuscular blockade* [MeSH]; and *Randomized Controlled Trial*, *Guidelines*, *Task force* [*Publication Type*]). Were selected studies that evaluated the incidence, diagnostic tests, complications and prevention of postoperative residual paralysis in animals, conscious volunteers and patients submitted to surgical procedures, without distinction.

RECOMMENDANTIO DEGREE AND STRENGTH OF EVIDENCE

A: Experimental or observational studies of best consistency.
B: Experimental or observational studies of least consistency.
C: Case Reports (non-controlled studies).
D: Opinion without critical evaluation, based on consensuses, physiological studies or animal models.

OBJECTIVE

To evaluate incidence, diagnostic tests, complications and prevention of postoperative residual paralysis (PORP).

INTRODUCTION

Definition

Postoperative residual paralysis (PORP), also known as residual postoperative neuromuscular blockade, is defined as postoperative paralysis or muscle weakness due to incomplete or absent antagonism of nondepolarizing neuromuscular blockers (NMB) [1](D). The T4/T1 ratio of 0.9 was assessed using the "train-of-four" stimuli (TOF). It is currently considered the gold standard of complete reversal of neuromuscular blockade [1](D).

Incidence

PORP after the end of anesthesia has been reported in several studies, with an incidence ranging from 5% to 88%, considering PORP as T4/T1 ratio < 0.9 [2](B), [3](A), [4](B), [5](A).

What are the factors that alter the incidence of postoperative residual paralysis?

The great variability is due to different methods: use of T4/T1 ratio of 0.7, 0.8 or 0.9 as PORP criterion [6,7](B); use of different NMB of short, intermediate and long-term duration [3](A), [6,7](B); use of single or repeated doses, or continuous infusion of NMB [3](A), [6,7,8](B); assessment method of the residual NMB [1](D), [9](A); with or without reversal of neuromuscular blockade at the end of anesthesia with anticholinesterase drugs, with dose and interval between the anticholinesterase

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drugs and degree assessment of neuromuscular blockade [3](A), [4,6-8](B); age [10](B); presence of kidney, cardiac or neuromuscular dysfunction [11](D); drug use that can alter the pharmacodynamics and/or pharmacokinetics of NMB (calcium channel blockers, magnesium, lithium, antibiotics, local anesthetics, inhaled anesthetics, opioids, benzodiazepines) [11](D); and electrolyte abnormalities, metabolic or respiratory acidosis and hypothermia [1,11,12](D).

The comparison of the PORP incidence and duration after multiple doses of cisatracurium and rocuronium showed that, at the end of surgery, the PORP incidence is significantly lower with rocuronium (44%) than with cisatracurium (57%). However, the time to achieve a T4/T1 ratio < 0.9 after the last dose of NMB is significantly higher with rocuronium [2](B). The T4/T1 ratio measured 5 minutes after the end of the surgical procedure is significantly higher in the rocuronium group in comparison to cisatracurium, but at the end of 10 minutes there is no further significant difference between the T4/T1 ratio values for the two NMBs [5](A).

When long-term NMB is used, the PORP incidence is significantly lower in patients being monitored, while there is no significant difference for those using short and mid-term NMB [13](A).

The incidence of PORP upon entering the post-anesthetic care unit (PACU) also shows great variability [4,14-16](B). The relationship between PORP and time in the PACU using mid-term NMB shows that age and T4/T1 ratio < 0.9 are independent variables associated to the length of stay in the PACU, but not to the type of NMB (vecuronium and cisatracurium) [15](B).

Recommendation: As PORP can occur after any general anesthesia that used NMB, neuromuscular blockade monitoring is recommended during and after general anesthesia and throughout post-anesthesia recovery.

Diagnostic tests

What are the diagnostic tests of Postoperative Residual Paralysis?

The diagnostic tests are clinical, qualitative and quantitative.

Clinical tests

Several clinical tests have been recommended to assess the reversal of neuromuscular blockade, such as: capacity to hold up the head for 5 seconds or to elevate an arm or a leg; eye opening when requested; protrusion or capacity to remove the tongue when held manually; maintenance of hand grip strength (measured with a dynamometer); maximal inspiratory pressure > 25 cm H_2O, and vital capacity > 15 mL.kg^{-1} - all of them in conscious and cooperative patients [2,6,8](B), [17](D).

Qualitative or subjective tests

They consist in visual and/or tactile observation of the response evoked by electrical stimulation of the peripheral motor nerve. The number of responses and fatigue are assessed after TOF, or double burst stimulation (DB) of the ulnar nerve adductor pollicis muscle, or the presence of fatigue after tetanic stimulation (TS) at 50 Hz or 100 Hz, or post-tetanic count (PTC) that consists in the use of a continuous standard single stimulation 1 to 3 seconds after tetanic stimulation, counting the number of muscle contractions [17-19](D).

Quantitative or objective tests

These are tests in which a quantitative evaluation of TOF (T4/T1 ratio) is carried out using as standard the assessment of the ulnar nerve adductor pollicis muscle through acceleromyography, electromyography, kinemyography, phonomyography and mechanomyography.

The TOF and PTC monitoring allows the classification of neuromuscular blockade according to its depth: intense blockade is the period with no response of PTC (PTC = 0) and T4/T1 (0); deep blockade is the period with PTC ≥ 1 and no response of the T4/T1 ratio (0); and moderate blockade occurs when the T4/T1 ratio is between T1 and T3. From T4 return to the normal pattern of T4/T1 ratio (> 0.9), the period is called recovery (Chart 1) [20](D).

Recommendation: Quantitative analysis is always better than the qualitative one for the PORP diagnosis.

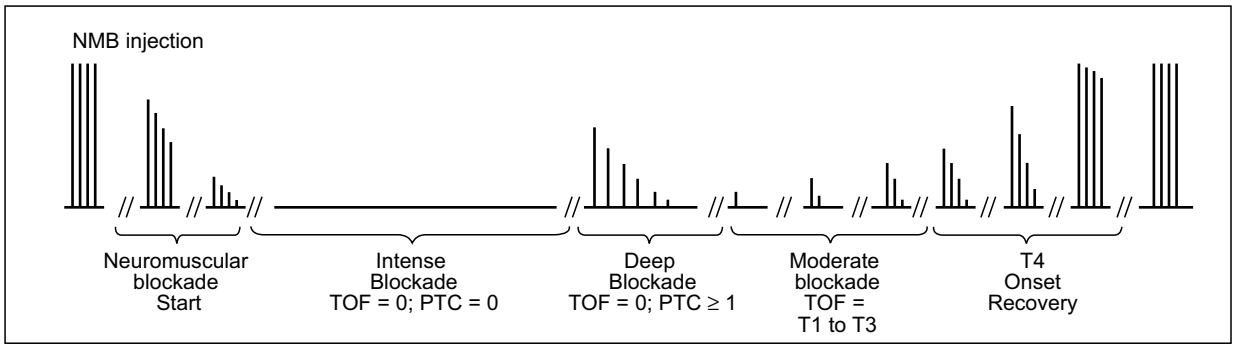
What is the validity and correlation between the different PORP diagnostic tests?

Clinical tests have shown the following values of sensitivity, specificity, positive and negative predictive values [19](D):

- Capacity to keep the head up for 5 seconds: 0.19; 0.88; 0.51; 0.64;
- Capacity to hold up the arm or the leg for 5 seconds: 0.25; 0.84; 0.50; 0.64;
- Protrusion or capacity to remove the tongue: 0.22; 0.88; 0.52; 0.64;
- Maintenance of hand grip strength: 0.18; 0.89; 0.51; 0.63.

None of the available clinical trials showed a positive correlation with the T4/T1 ≥ 0.9, or ruled out the possibility of PORP [7,8,19](B) [21](C).

Chart 1 – Levels of Neuromuscular Blockade After Administration of Non-Depolarizing NMB at a Single Intubation Dose [20](D).
NMB: neuromuscular blockade, TOF: T4/T1 ratio; PTC: post-tetanic counting



Qualitative tests were not superior to clinical trials [19](D), [22](A) and the use of DB did not eliminate the possibility of PC [19](D), [23](B).

There is no significant correlation between subjective and objective evaluation of the evoked response, considering T4/T1 ≥ 0.9 as the standard for PORP absence [24](B), [25](C).

There is no consensus that quantitative tests of neuromuscular function are superior to qualitative ones. Regarding neuromuscular monitoring and PORP, there is also no consensus that the use of quantitative tests of neuromuscular function promote a reduction in PORP incidence [9,13](A), [17](D).

Regarding the clinical and scientific use of acceleromyography compared to signals and/or symptoms of PORP and to pulmonary function, clinical or qualitative tests of neuromuscular function, one can concluded that accelerometry is the best test to diagnose PORP (Table I) [26](B) and intraoperative monitoring with acceleromyography improves PORP detection, being as sensitive as mechanomyography. There is not sufficient evidence that when accelerometry is used uncorrected (without normalization), the value of the T4/T1 ratio should be increased above 0.9 to exclude clinically significant PORP [9](A).

Recommendation: Acceleromyography is recommended for monitoring the NMB degree in intraoperative and post-anesthetic periods.

Table I – Comparison of Sensitivity, Specificity, Positive and Negative Predictive Value of Tests with Double Burst Stimulation of the Adductor Pollicis Muscle of the Ulnar Nerve, Tetanic stimulation at 100 Hz and Acceleromyography to Detect Postoperative Residual Paralysis [26](B)

	DB	Acceleromyography	TS
Sensitivity	29 (13-45)	70 (54-86)	74 (59-89)
Specificity	100 (100-100)	88 (67-100)	54 (23-88)
NPV	29 (13-45)	47 (23-71)	38 (12- 64)
PPV	100 (100-100)	95 (86-100)	85 (72-99)

Values shown in percentage and 95% confidence interval. DB: double burst stimulation; TS: tetanic stimulation with 100 Hz; NPV: Negative Predictive Value; PPV: Positive Predictive Value.

PORP Complications

PORP can lead to several complications.

There is association between T4/T1 ratio < 0.9 and the following complications:

- Impaired coordination between the lower pharyngeal constrictor muscle contraction and relaxation of the upper esophageal sphincter; difficulty in swallowing and delay on the start of swallowing reflex [27,28](B); decreased tonus of the upper esophageal sphincter [27,28](B); and increased risk of passive regurgitation [27,29](B);
- Decreased volume of the upper airways; muscle dilating function impairment of the upper airways; decreased retropalatal and retroglossal inspiratory volume of upper airways; attenuation of the normal increase of posterior airway diameter during forced inspiration; and decreased activity of the genioglossus muscle during maximum voluntary tongue protrusion [30](B);
- Decreased ventilator response to hypoxia in hypocapnia [31-33](B);
- Decrease in forced inspiratory volume in one second and of the inspiratory flow, upper airway obstruction, and incapacity to keep the patent airways [28](B);
- muscle weakness symptoms such as diplopia, difficulty to speak and drink, facial muscle weakness, incapacity to hold up the head for 5 seconds and generalized weakness [2](B);

At the end of the anesthesia, either at the PACU or the Intensive Care Unit (ICU), it is known that:

- There is increased risk of postoperative hypoxemia [3](A), [34](B);
- There is an incidence increase of upper airway obstruction during transportation to PACU [35](B);
- There are symptoms and signs of deep muscle weakness [3](A);
- There is an incidence increase of critical respiratory events in the PACU [34,35](B);

- There is delay in PACU discharge [3](B);
- There is an increase in ventilator weaning and intubation time in patients undergoing cardiac surgical procedures [36] (A);
- There is an increased incidence of postoperative pulmonary complications (atelectasis and pneumonia) [10](B).

PORP prevention

How can PORP be prevented?

The prevention of PORP is based on the complete reversal of the nondepolarizing NMB effects. It can be attained by waiting for the spontaneous termination of NMB effect, which is not predictable [6](B) or by pharmacological reversal, ensuring the safety of the effect end [11,37](D). The quantitative monitoring of neuromuscular blockade is the only sure way to evaluate its complete reversal [28,38,39](B). Reversal may be accomplished through the use of anticholinesterase agents (ACAs), or a specific reversal agent for vecuronium and rocuronium [11,37](D).

The ACAs used in anesthesia are neostigmine and edrophonium, administered intravenously at doses of 0.04 mg.kg^{-1} and 1.0 mg.kg^{-1}, with peak action occurring at 7-11 minutes and 1-2 minutes, respectively [11,37](D). Both have very variable latency to complete reversal of neuromuscular blockade [11,37](D), reaching up to 80 minutes [37](D), depending on the blockade degree.

ACAs have several limitations: they depend on the degree of neuromuscular blockade [40](B); they have adverse effects on different organs and systems due to the antimuscarinic action; they have a ceiling effect [41](D); they can lead to unpredictable reversal of neuromuscular blockade when used in patients with other comorbidities, or in situations such as hypothermia, or when using certain drugs such as calcium-channel blockers, aminoglycosides and magnesium sulphate [37](D); and they can promote blockade by desensitization, with increased muscle weakness when used at high doses, or when used after complete recovery of neuromuscular blockade or without previous use of NMB [43](C), [42,44](D). They can also decrease the activity of the upper airway dilating muscles, if used after recovery of neuromuscular blockade induced by rocuronium [45](B). When administered, ACAs should be associated with anticholinergic agents to reduce secondary muscarinic effects, with atropine being the most frequently used [37](D), [40](B).

The uncertainty regarding anticholinesterase drugs effectiveness in the neuromuscular blockade reversal, in addition to the incidence of their adverse effects has resulted in the use of sugammadex [37](D). Due to its selectivity, sugammadex reverses the neuromuscular block induced by vecuronium and rocuronium and does not inhibit the effects of NMB belonging to the class of benzylisoquinoline alkaloids [46](A), [47,48](B), [49](A).

The sugammadex-rocuronium complex is eliminated by the kidney [50](B). However, the comparative use between patients with chronic renal failure and with normal renal function, associated with rocuronium, shows that the time to reach T4/T1 of 0.9 is similar in both groups and there is absence of recurarization or of adverse effects [50](B).

Sugammadex has a higher reversal rate of rocuronium-induced neuromuscular blockade when compared with neostigmine in situations of moderate or deep blockade [51-54,56](A) [55](B). The same situation occurs in the reversal of neuromuscular blockade induced by vecuronium [57](A).

After rocuronium or vecuronium use, sugammadex at a dose of 2 mg.kg^{-1} completely reverses (T4/T1 ratio $\geq$ 0.9) the moderate neuromuscular blockade and at a dose of 4 mg.kg^{-1} it reverses deep neuromuscular blockade [58](A), [59,60](B). The use of sugammadex at doses < 2 mg.kg^{-1} is related to transient return of the neuromuscular blockade [61](D).

In "no ventilation, no intubation" situations, which often occur shortly after anesthetic induction and failed tracheal intubation attempt, sugammadex at a dose of 16 mg.kg^{-1} promotes immediate reversal of the neuromuscular blockade induced by rocuronium at a dose 1.0 to 1.2 mg.kg^{-1} [58](A), [60](B). In this situation, the reversal time of neuromuscular blockade with the association rocuronium 1.2 mg.kg^{-1} and sugammadex 16 mg.kg^{-1} (3 minutes after the NMB) is lower than of succinylcholine 1 mg.kg^{-1} [62](A).

Sugammadex was successfully used in children between 2 and 11 years old at a dose of 2 mg.kg^{-1}, without adverse events [63](A), as well as in patients with heart disease (coronary ischemic disease, arrhythmia and congestive heart failure) to be submitted to noncardiac procedures [64](A), in patients with history of pulmonary disease [11,37](D), in pregnant women who underwent a C-section [65](C), and in obese patients with body mass index (BMI) > 30 kg.m^{-2} [37](D). In elderly patients (age > 64 years), the use of sugammadex at a dose of 2 mg.kg^{-1} results in reversion of the neuromuscular blockade within a shorter time than in young adult individuals (difference of 42 seconds) [66,67](B).

The sugammadex interaction has been experimentally demonstrated with *flucoxacillin*, fusidic acid and toremifene, with a delay in the reversal time of neuromuscular blockade. However, the interaction with flucoxacillin has not been proven clinically and no drug has been shown to promote recurarization or reversal of neuromuscular blockade [68](C).

Adverse events due to sugammadex use are rare, including nausea, vomiting, headache, neck pain, back pain, coughing, dysgeusia, constipation, and pyrexia, most likely related to drugs used during anesthesia [46] (A). Movements can also be observed before the end of the anesthesia, due to superficial anesthesia [11](D), [49](A). The onset of spontaneous evolution of allergic reaction following the use of sugammadex has been reported in only six patients [37,11](D), [46](A).

Recommendation: PORP prevention after nondepolarizing NMB can be attained by using anticholinesterase agents associated with anticholinergics, or sugammadex if vecuronium or rocuronium are administered. Sugammadex is recommended whenever rocuronium or vecuronium is used, as it is the only specific reverser.

FINAL RECOMMENDATIONS

The PORP shows high incidence and may lead to adverse events with increased postoperative morbidity and mortality. Monitoring of the neuromuscular blockade is recommended by quantitative tests such as acceleromyography. The use of cholinesterase inhibitors for pharmacological reversal of neuromuscular blockade is not free of adverse effects. Therefore, we recommend the use of sugammadex for reversal of neuromuscular blockade induced by rocuronium or vecuronium.

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