Residual neuromuscular blockade: management and impact on postoperative pulmonary outcome

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Purpose of review
To revise the current literature on concepts for neuromuscular block management. Moreover, consequences of incomplete neuromuscular recovery on patients' postoperative pulmonary outcome are evaluated as well.

Recent findings
The incidence of residual paralysis may be as high as 70% and even small degrees of residual paralysis may have clinical consequences. Neostigmine should not be given before return of the fourth response of the train-of-four-stimulation and no more than 40–50 μg/kg should be given. Sugammadex acts more rapidly and more predictably than neostigmine. Finally, there is convincing evidence in the literature that incomplete neuromuscular recovery may lead to a poor postoperative pulmonary outcome.

Summary
New evidence has emerged about the pathophysiological implications of incomplete neuromuscular recovery. Not only are the pulmonary muscles functionally impaired, but respiratory control is also affected. Residual paralysis endangers the coordination of the pharyngeal muscles and the integrity of the upper airway. However, neuromuscular monitoring and whenever needed pharmacological reversal prevent residual paralysis.

Keywords
neostigmine, neuromuscular monitoring, postoperative pulmonary outcome, residual paralysis, sugammadex

INTRODUCTION

Even small degrees of residual paralysis [i.e. a train-of-four (TOF) ratio >0.6] may lead to clinical relevant consequences. Especially upper airway integrity and swallowing ability are still markedly impaired. Neuromuscular monitoring and pharmacological reversal are key elements for the prevention of residual paralysis.

DEFINITION OF RESIDUAL NEUROMUSCULAR BLOCKADE

For many decades, a TOF ratio of 0.7 has been considered to represent adequate neuromuscular recovery. This was mainly based on the observation that two parameters of pulmonary function, that is tidal volume and vital capacity, start to recover at a TOF ratio of 0.7 [1]. Although higher degrees of neuromuscular recovery are needed before they return to baseline, a TOF ratio of 0.7 was for a long time accepted as the minimum neuromuscular recovery required before starting extubation. However, our understanding of residual paralysis has continuously been improved over the last 15–20 years. The pathophysiological consequences and the incidence of residual paralysis are now better understood and any TOF ratio or less 0.9 must be considered as residual paralysis.

PATHOPHYSIOLOGIC CONSEQUENCES OF RESIDUAL PARALYSIS

Pulmonary muscles

In the 1970s, researchers investigated the effects of residual neuromuscular blockade on the respiratory muscle function in anesthetized patients [1]. They found that when the first response of the TOF (T1) at the adductor pollicis muscle is less than 10% of

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KEY POINTS

- Any train-of-four ratio (TOF ratio) or less 0.9 must be considered as residual paralysis.
- Even small degrees of residual paralysis may have clinical consequences. Pulmonary muscles are functionally impaired, respiratory control is affected, and coordination of the pharyngeal muscles and integrity of the upper airway is endangered.
- Neuromuscular monitoring and pharmacological reversal are key elements for successful management of neuromuscular blockade.
- Small degrees of residual paralysis may be treated with reduced doses of neostigmine.
- Neostigmine when used without neuromuscular monitoring and without bodyweight adjusted doses may not be efficient to prevent residual paralysis.

baseline, the patient has neuromuscular block-induced apnea. Moreover, tachypnea and a reduced respiratory volume are observed at a T1 response greater than 25% (corresponding to three responses to TOF stimulation). In addition, the investigators also found that the tidal volume of spontaneously breathing patients under anesthesia becomes adequate at a T1 response of at least 50% (corresponding to a TOF ratio of approximately 0.3). However, the impairment of forced vital capacity (FVC) from the effects of neuromuscular blockade still persists at these degrees of neuromuscular recovery. Return of the FVC to baseline values only occurs at a TOF ratio of at least 0.8 [2].

Upper airway

Inspiratory obstruction of the upper airway can occur in the presence of residual neuromuscular blockade [3]. At a TOF ratio of 0.5, there is marked impairment of inspiratory flow to around 50% of baseline and even at a TOF ratio of 0.8, upper airway dysfunction persists as manifest by decreased peak inspiratory flow, impaired ability to swallow, diminished upper airway volume, and impaired function of the genioglossus muscle.

Respiratory control

The hypoxia-related increase in ventilation is mediated by chemoreceptors in the carotid body. Residual paralysis weakens this increase in ventilation and baseline values are not reached until recovery of the TOF ratio to 0.9 [4].

Pharyngeal function

Eriksson *et al.* evaluated pharyngeal function during partial neuromuscular blockade using video radiography and computerized pharyngeal manometry. They could demonstrate that the pharyngeal muscles have a particular sensitivity to the effects of neuromuscular blockade leading to an increased risk of pulmonary inhalation [5]. The risk of pulmonary aspiration is increased even with minimal neuromuscular block.

INCIDENCE OF RESIDUAL PARALYSIS

The extent of neuromuscular recovery at the end of an intervention not only depends on the NMBA administered, the duration of the intervention, and the presence of concomitant disease, but also on the anesthetic technique. Indeed, at the same NMBA dose and the same duration of anesthesia, residual paralysis occurs more frequently after volatile inhalational anesthesia than after intravenous anesthesia. Moreover, the probability of residual blockade after administration of a single dose of a muscle relaxant is much greater, the shorter the surgical intervention [6]. Nevertheless, the incidence of residual paralysis varies from 10 to 70%, depending on study design and anesthesia technique. According to a meta-analysis published by Naguib *et al.* [7] the incidence of residual paralysis defined as a TOF ratio less than 0.7 was 12% when studies using intermediate-acting NMBAs were analyzed but it was as high as 41% with a TOF ratio less than 0.9 as benchmark.

MANAGEMENT OF NEUROMUSCULAR BLOCKADE

Both neuromuscular monitoring and pharmacological reversal are key elements for successful management of neuromuscular blockade. In a survey of neuromuscular management, Baillard *et al.* [8] report a reduction of the incidence of residual paralysis, defined as a TOF ratio less than 0.9, from initially 62% to finally 3%. To achieve this, they made neuromuscular transmission monitors available in any operating theater and promoted their use. As a consequence, measurement and reversal of neuromuscular blockade increased significantly and the incidence of residual neuromuscular block strongly decreased. Similar results were recently reported by Todd *et al.* [9] also. The implementation of quantitative neuromuscular monitoring, accompanied by an extensive educational effort, significantly increased the adherence to neuromuscular transmission monitoring and improved neuromuscular recovery. The incidence of moderate residual

paralysis decreased from 17 to 5% and deeper levels of residual paralysis were eliminated completely. Moreover, no major airway complication related to neuromuscular blockade management was observed after the implementation of neuromuscular monitoring.

NEUROMUSCULAR MONITORING

Clinical signs

Frequently in anesthetic practice only clinical signs are used to assess neuromuscular recovery. Although these tests do deliver useful information that may help the anesthetist make the decision to extubate, they do not provide accurate detail about the degree of neuromuscular recovery and cannot always be performed in anesthetized patients. They do not allow detection of residual paralysis. In addition, poor understanding of which clinical signs are reliable or unreliable limits their usefulness.

In 1961, Dam and Guldmann proposed that the head-lift test could be used as a reliable test for assessing neuromuscular recovery [10]. A head lift sustained for 5 s is considered equivalent to a TOF ratio of 0.5–0.7. But in clinical practice, the test is limited by the fact that it is rarely performed for 5 s. The shorter the test interval, the less powerful is the veracity of its findings.

The tongue-depressor test is currently regarded as the most sensitive clinical sign for assessing neuromuscular recovery [11]. A TOF ratio of greater than 0.8 is required to perform this test. This test is difficult to implement routinely as the often sleepy patient is asked to press a tongue depressor against the roof of their mouth while the anesthetist tries to retract it.

Asking the patient to open the eyes, protrude the tongue, or lift the arms are used in clinical practice, as are measurement of respiratory volume, vital capacity, and maximal inspiratory pressure. However, they are all unreliable in assessing neuromuscular recovery and should not be applied.

Neuromuscular transmission monitors

Depending on the evaluation of the response, nerve stimulators are classified into two types: simple nerve stimulators, which allow only subjective estimation of the muscular response; and quantitative nerve stimulators, which objectively measure the extent of the neuromuscular blockade.

Simple nerve stimulators

They are not equipped with a readout, and only allow stimulation of the target nerve. The ensuing response is assessed subjectively by the investigators' senses, be they tactile or visual. When applying TOF stimulation and evaluating the TOF count, these devices may deliver clinically useful information about the onset of neuromuscular block or the need for an incremental dose of relaxant and with the post-tetanic count deep levels of neuromuscular block can be assessed. Moreover, timing and dosing of reversal agents may be guided by them a well. It is the determination of complete neuromuscular recovery in which these devices are limited, when the need is to reliably detect residual neuromuscular block [12]. Thus, a simple nerve stimulator only acts as a guide and should not be considered as a diagnostic tool to exclude residual paralysis.

Quantitative nerve stimulators

These devices permit the anesthetist to objectively measure, that is to quantify, the muscular response, and hence to more reliably detect residual paralysis using the TOF mode [13,14]. Various methods can be employed to objectively measure the degree of neuromuscular block, acceleromyography is most often applied. It was developed for clinical use; the movement of the thumb generates a voltage in a piezioelectric element that correlates with the acceleration of the muscle: at constant mass, the force of muscle contraction can be evaluated by measuring the acceleration. It can only be performed on muscles whose movement after stimulation is easily measured. Usually, the ulnar nerve is stimulated and the acceleration is measured with a piezoelectric element fixed to the thumb. This allows assessment of the force developed in the adductor pollicis muscle. The latest device based on this technology is the TOF scan (Fig. 1).

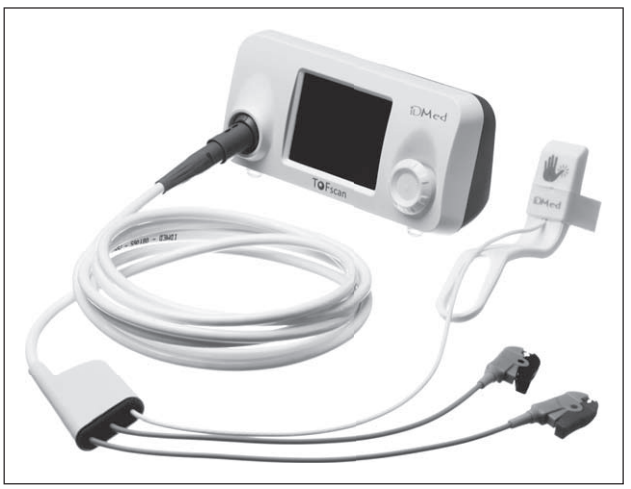

FIGURE 1. TOF scan.

PHARMACOLOGICAL REVERSAL OF NEUROMUSCULAR BLOCKADE

For several decades, the action of nondepolarizing neuromuscular blocking agents (NMBA) could only be antagonized by drugs which inhibited the acetylcholinesterase. Their use, however, has several pitfalls. Indeed, they are associated with muscarinic effects, may increase postoperative nausea and vomiting, have rather slow and unpredictable onset of action, and cannot antagonize deeper level of neuromuscular blockade. The release of sugammadex expands the arsenal of drugs that the anesthesiologists can use to antagonize steroidal neuromuscular blockade, it belongs to a new class of reversal drugs and is now approved for clinical use in more than 50 countries, including the USA.

Neostigmine

There are discrepancies in the literature concerning the role of neostigmine in the prevention of residual paralysis, questioning whether neostigmine really improves neuromuscular recovery or not. Sasaki *et al.*[15] reported a similar incidence of residual paralysis whether patients received neostigmine or not. Fortier *et al.* further conformed this findings [16▪]. This, however, raises the question about the therapeutic range of neostigmine. Especially, appropriate dosing and timing of neostigmine need to be determined. There are two milestone papers in this context: Kirkegaard *et al.* assessed the efficacy of neostigmine (70 μg/kg) when given at 1, 2, 3, or 4 TOF responses. Their conclusion was that it was not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration [17]. This limitation of neostigmine is best explained by a ceiling effect. Increasing the dose will not further increase the effect. Baurrain *et al.* [18] determined conditions to optimize the reversal action of neostigmine. According to their results no more than 40 μg/kg should be given at 25–50% recovery of twitch height. Surprisingly, higher doses of neostigmine were less efficient, leading more often to less complete recovery. Thus, rather than increasing the dose of neostigmine, increasing the degree of spontaneous prereversal recovery is the key to success. Fuchs-Buder *et al.* [19,20] reported that even reduced doses of neostigmine (20 μg/kg) may be sufficient to antagonize shallow degrees of residual paralysis, that is a TOF ratio of 0.4. A TOF ratio of 0.4 corresponds to the degree of neuromuscular recovery that can no longer be detected by tactile or visual evaluation of the TOF. Indeed, when no fade is detectable the TOF is at least 0.4 but may be as high as 1.0. However, even shallow degrees of residual neuromuscular block may be harmful and affect patients' outcome and thus, should be prevented. Routine administration of reduced doses of neostigmine (i.e. 10–20 μg/kg) even when no fade is felt after TOF could be a simple and well tolerated concept to prevent shallow, but potentially harmful, degrees of residual paralysis. Moreover, such a concept should further improve the role of simple nerve stimulators in the management of neuromuscular block.

Sugammadex

The underlying mechanism of action of sugammadex differs completely from that of ACh-inhibitors like neostigmine as it directly encapsulates free circulating steroidal NMBA and thus results in a decrease in the concentration of free NMBA. This creates a gradient between the neuromuscular junction and plasma with a movement of NMBA away from neuromuscular junction into plasma. Because of this new mechanism no minimum degree of spontaneous reversal is required, but any degree of neuromuscular block can be antagonized.

NEUROMUSCULAR BLOCKADE AND POSTOPERATIVE PULMONARY OUTCOME

Increasing evidence suggests that residual neuromuscular block is a risk factor for postoperative pulmonary complications and may affect the outcome. Impaired function of the upper airway with an increased risk for silent pulmonary inhalation and inspiratory upper airway obstruction may explain the link between incomplete neuromuscular recovery and poor postoperative pulmonary outcome. Berg *et al.* [21] showed a direct association between incomplete neuromuscular recovery, defined as a TOF ratio less than 0.7, and postoperative pulmonary complications, such as atelectasis and pneumonia. Postoperative pulmonary complications were four times more common in patients with residual block than in patients with a TOF ratio greater than 0.7. Murphy *et al.* [22] observed a high incidence of severe residual blockade in patients with critical respiratory events in the PACU, which was absent in patients without critical respiratory events. Thus, there is convincing evidence that residual neuromuscular blocks affect patients' outcome. However, it is still unclear whether the respiratory morbidity associated with neuomuscular blocking agents can be mitigated by better clinical management, chiefly neuromuscular monitoring and, if needed, reversal [23]. In a recently published large-scale cohort study including more than 35 000 patients, Grosse-Sundrup *et al.* [24] found no beneficial effect, but a rather harmful association of the use of neostigmine reversal with respiratory

complications. This may surprise providers, but it is in line with published data. Indeed, Blobner *et al.* [25] confirmed a limited predictability of neostigmine reversal for moderate neuromuscular block. Although 98% of the patients were sufficiently recovered within 5 min following sugammadex 2 mg/kg, it was 100 min after neostigmine 50 μg/kg. In an observational multicentre study, Esteves [26] recently confirmed a high incidence of postoperative residual paralysis (30.5%), despite neostigmine reversal. Moreover, Kopman *et al.* [27] antagonized rocuronium-induced and cisatracurium-induced neuromuscular block with 50 μg/kg neostigmine given at two fourth TOF responses; 30 min later, the incidence of residual paralysis, defined as a TOF ratio less than 0.9, was still 12%. Similar results were reported by Kirkegaard *et al.* [17]. The message is that, in current clinical practice, some of these patients run the risk of extubation before adequate recovery of the upper airway, especially when neostigmine is used without appropriate neuromuscular monitoring. The high incidence of slow responders after neostigmine may, at least partly, explain the findings of Grosse-Sundrup *et al.* and emphasize the necessity to redefine its therapeutic range. Of interest in this context, Brueckmann *et al.* [28▪] recently reported that none out of 74 patients antagonized with sugammadex but 33 of 76 (43.4%) antagonized with neostigmine had residual neuromuscular blockade at PACU admission. Ledowski *et al.* [29] identified both, the American Society of Anesthesiologists' (ASA) status at least three and elderly patients as independent risk factors for postoperative pulmonary complications after use of NMBAs. Moreover, according to their findings, reversal with sugammadex, but not with neostigmine, or no-reversal led to a significant risk reduction for pulmonary complications in these fragile patients. These findings suggest that sugammadex may improve postoperative pulmonary outcome in a population at risk, most probably by a more efficient reversal of neuromuscular block with less residual paralysis. However, the design of their study as a retrospective data analysis with a rather heterogeneous cohort limits the informative value. Thus, these findings should be confirmed by a properly designed and powered prospective randomized controlled trial.

CONCLUSION

Residual paralysis is a risk factor for postoperative pulmonary complication and sugammadex-based reversal led to a significant reduction of this risk. Proper timing and dosing is crucial when using neostig to antagonize residual paralysis; its therapeutic range must be revised.

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