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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Should Neuromuscular Blockade Be Routinely Reversed?

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Abstract

Purpose of review The purpose of this article is to present the consequences and incidence of residual paralysis and define solutions to reduce the risk of its occurrence.

Recent findings Small degrees of residual paralysis, defined as a train-of-four (TOF) ratio < 0.9, may increase the risk of postoperative respiratory complications and influence outcomes following surgery. Routine monitoring of neuromuscular block can allow the detection of incomplete neuromuscular recovery and is an important factor in the prevention of residual paralysis. Administration of neostigmine or sugammadex to reverse residual paralysis should be based on the degree of spontaneous recovery. Sugammadex acts much faster than neostigmine and can even reverse deep levels of neuromuscular blockade.

Summary Meticulous management of neuromuscular blockade, including routine reversal of the effects of muscle relaxants, is essential in avoiding residual block and associated complications.

Keywords Residual paralysis · Neuromuscular blocking agents · Neuromuscular monitoring · Postoperative respiratory complications · Anticholinesterase agents · Neostigmine · Sugammadex

Introduction

Despite important advances in knowledge relating to dosing, monitoring, and reversal of neuromuscular blockade, the routine use of reversal agents remains debated. Meanwhile, the incidence and the occurrence of respiratory complications during residual paralysis remain highly underestimated. In 2010, most respondents from the USA (64.1%) and Europe (52.2%) considered the incidence of clinically significant postoperative residual neuromuscular weakness to be < 1% [1]. However, the clinician should be aware that the lingering effects of neuromuscular blockade may last well beyond surgery and can have significant clinical consequences.

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Does Residual Paralysis Exist?

Every physician should understand that neuromuscular blocking agents (NMBAs) do not have the same effect on all muscles of the body. The diaphragm and the abdominal wall muscles are among the more resistant muscles to NMBA; thus, recovery from neuromuscular block is significantly faster at these respiratory muscles than at the adductor pollicis. Studies have demonstrated that tidal volume can be preserved even at a train-of-four count of 0. Initially, a train-of-four (TOF) ratio of 0.7 at the adductor pollicis was considered a safe threshold assuring recovery from neuromuscular block because ventilation had returned to control values obtained before administration of a NMBA. This belief was supported by a study from Berg et al. who were able to demonstrate that during pancuronium-induced neuromuscular blockade, patients with a TOF ratio less than 0.7 had milder or even severe episodes of desaturation in the PACU and were more likely to develop postoperative pulmonary complications [2]. As a consequence, some clinicians still consider that routine reversal from neuromuscular block, before extubation of the patient, is unnecessary when tidal volume and minute ventilation have recovered to normal values.

Nevertheless, respiratory function depends on more than adequate recovery of the diaphragm.

The muscles of the upper airway are particularly sensitive to the effects of muscle relaxants. The masseter muscle is approximately 15% more sensitive to non-depolarizing muscle relaxants than the adductor pollicis. Weakness of the upper airway muscles may exist even when peripheral muscles such as the adductor pollicis have almost completely recovered from neuromuscular block (Table 1). A TOF ratio less than 0.9 at the adductor pollicis is associated with impaired pharyngeal function, a reduced resting tone in the upper esophageal sphincter muscle and airway protection, which may cause misdirected swallowing [3]. Patients may still be clinically weak, although able to breathe adequately as long as their airway is secured with a tracheal tube. These findings also explain why patients with a TOF less than 0.9 in the PACU are more likely to develop respiratory events than those whose TOF ratio exceeded this value. An indirect demonstration of this effect was illustrated by Arbous et al., by studying the morbidity and mortality rate in more than 850,000 patients in Holland. These authors were able to document that the use of reversal agents at the end of the case could induce a very significant decrease in morbidity and mortality (odds ratio 0.10; 95% confidence interval 0.032–0.314) [5].

What Is the True Incidence of Residual Paralysis?

The initial studies in the late 1970s have reported an incidence of residual paralysis of 10–15% when intermediate-acting NMBAs were used because the threshold chosen at that time was a TOF ratio of 0.7 [6]. The duration of action of an intermediate-acting NMBA has been underestimated for many years. Many clinicians still consider that following the recommended intubating dose, i.e., twice the ED_{95} at the adductor pollicis, complete spontaneous recovery from intermediate duration of action NMBA and a TOF ratio above 0.9 will occur in less than 60–90 min after drug administration. Recent studies on a large number of young and healthy ASA I and II patients have clearly demonstrated that even 2 h after drug administration, around 30–40% of the patients receiving intermediate duration of action NMBA still have a TOF ratio less than 0.9 [7].

When using a TOF ratio threshold of 0.9, studies have highlighted that the prevalence of residual paralysis ranges between 20 and 50% [8]. Such a wide range can be explained by discrepancies in the routine use of monitoring or administration of reversal agents. Although some clinicians believe that muscle weakness is a rare event with few consequences, multiple studies have confirmed that many patients are admitted to the postanesthetic care unit (PACU) with a TOF ratio less than the desired threshold of 0.9. In a multicenter study, Fortier et al. studied ASA I–III patients undergoing abdominal surgery lasting less than 4 h. Residual blockade (TOF ratio < 0.9) was present in 63.5% of patients at tracheal extubation and in 56.5% on arrival at the PACU [9].

Table 1 Consequence of residual paralysis at TOF ratio < 0.9

Upper airway obstruction [3]
Impaired ability to swallow [3]
Impaired coordination of pharyngeal muscles [3]
Reduced upper esophageal muscle tone [3]
Increased risk of aspiration [3]
Postoperative hypoxemia [4•]
Inability to breathe deeply when required [4•]
Unpleasant symptoms of muscle weakness [4•]

Complications Due To Residual Paralysis

Recent studies have clearly demonstrated that even when long-acting NMBAs were avoided, the risk of postoperative pulmonary complications in the PACU may be increased when the TOF ratio was less than 0.9. Murphy studied 7459 patients arriving in the PACU. The patients who developed critical respiratory events such as severe hypoxemia or/and upper airway obstruction had a mean TOF ratio of 0.62. In contrast, in the control group, the mean TOF ratio was 0.98 and no control patients had a TOF ratio less than 0.7 [4•, 10]. When objective monitoring is used instead of a conventional peripheral nerve stimulator, there is a significant reduction in the incidence of residual blockade [11] and associated unpleasant symptoms of muscle weakness in the PACU such as blurred vision or facial weakness or subjective difficulty speaking. Similar findings were observed in another large prospective study including more than 18,000 patients receiving an intermediate-acting NMBA. Their use was associated with respiratory complications such as desaturation after extubation, postoperative reintubation, or unplanned admission to an intensive care unit [12].

Bulka et al. recently investigated the risk of postoperative pneumonia in patients receiving NMBAs and reversal agents. Their results confirmed previous finding by demonstrating an association between the use of an intermediate-acting NMBA, reversal agents and the risk of postoperative pneumonia (incidence rate ratio (IRR) 1.79). The most important finding was that among patients who received NMBA, those who were not reversed with an acetylcholinesterase inhibitor were more than twice as likely to develop pneumonia after surgery (IRR, 2.26) [13••].

Preventive Strategies to Avoid Residual Paralysis

Given the myriad potential negative sequelae of residual paralysis, clinicians should routinely utilize strategies to reduce the risk of residual block, including routine use of monitoring and administration of reversal agents.

Routine Use of Neuromuscular Monitoring

The routine use of neuromuscular monitoring does not prevent the occurrence of residual paralysis but facilitates management of residual paralysis when correctly interpreted. Clinical signs cannot assess accurately the presence of residual paralysis. The head lift test cannot detect residual paralysis unless TOF ratio of less than 0.5 is present. The tongue depressor test is considered more sensitive but it requires cooperation of the patient in the PACU and does not detect lower levels of residual paralysis [14, 15•].

Visual or tactile evaluation of the TOF at the adductor pollicis can be used reliably to count preoperatively the number of responses but fails to detect residual paralysis when the TOF ratio is above 0.4 even for experienced anesthesiologists and may provide reassuring but misleading information [15•]. When using DBS at the adductor pollicis, fade can only be detected at degrees of neuromuscular blockade corresponding to a TOF ratio of no more than 0.6 [16]. The primary role of simple nerve stimulators remains to improve timing of dosing of NMBAs and proper use of the reversal agents at the end of the case. Shorten and colleagues found a significant reduction in the incidence of incomplete neuromuscular recovery in the PACU when patients had a standard TOF intraoperative monitoring [17]. Unfortunately, despite ready availability of peripheral nerve stimulators, 10–20% of clinicians still never use them and it is estimated that more than half of clinicians cannot identify accurately signs of residual paralysis when using them [18•].

Every clinician should be aware that detection of residual paralysis could be greatly improved by the use of objective monitoring such as acceleromyography or electromyography, which displays the results numerically in real time. Todd et al. were able to show that the introduction of an EMG-based quantitative monitoring in combination with extensive educational efforts could result in a significant reduction in the number of inadequately reversed patients arriving in the PACU [19••].

Strategies for Reversal of Neuromuscular Blockade

Although there are now enough scientific data demonstrating that reversal of NMBA should be routine, many physicians are still questioning this routine use of reversal agents. As previously discussed, a vast majority of anesthesiologists still consider that they had never observed patients with residual paralysis in the PACU. It is likely that the lack of routine use of quantitative monitoring causes an underestimation of the number patients arriving in the PACU with a TOF ratio less than 0.9. The debate should be more focused on an understanding of information provided by routine use of neuromuscular monitoring leading to correct use of reversal agents. The understanding of data provided by neuromuscular monitoring in association with the knowledge of the pharmacology of reversal agents could reduce the risk of residual paralysis. Baillard et al. have clearly demonstrated that the rate of residual paralysis in the recovery room had significantly decreased over 10 years by routine monitoring of neuromuscular block in association with administration of neostigmine when residual paralysis was detected [20]. The rate of residual blockade as defined as a TOF ratio < 0.9 decreased from 62 to 3%, confirming the benefit of reversal in routine anesthetic practice.

For many years, anticholinesterase agents were the only drugs that could be used in clinical practice to reverse residual paralysis. Neostigmine is effective against all non-depolarizing NMBAs but presents several slight limitations that must be considered in balance with the important benefits of reversing neuromuscular block. There is the absolute need to use it in association with atropine to avoid muscarinic effects such as bradycardia or hypotension. The concomitant use of atropine may induce its own side effects such as tachycardia, dry mouth, or blurred vision. Timing based on careful assessment of neuromuscular recovery is important in the proper use of neostigmine. Neostigmine is more effective when given to antagonize moderate-to-light levels of block. Time to full recovery (TOF > 0.9) is dependent upon the extent of spontaneous recovery when the block is reversed. The time is shortened when at least two responses at the TOF are observed and reduced further when four responses are detected (Fig. 1). However, it should be remembered that neostigmine is effective when properly given and is a slow acting drug; 10–15 min being usually needed to reach a TOF ratio greater than 0.9 even when administered at a TOF count of 4. There are no advantages in giving neostigmine earlier even in larger doses because the major drawback of neostigmine is the presence of a ceiling effect. Doses above 70 μg/kg are not recommended and a maximum effect is reached at 40–50 μg/kg [21]. Moreover, it has been shown that systematic use of high doses neostigmine may lead to collapse of upper airway muscles, especially if the drug is given with little or no muscle relaxant. These findings are compatible with data published by Grosse-Sundrup et al. and Sasaki et al. In both studies, neostigmine administration was associated with an increased risk of postoperative pulmonary complications such as desaturation or atelectasis [12, 22•].

There are no convincing evidence that neostigmine, when properly given with the help of a nerve stimulator, increases

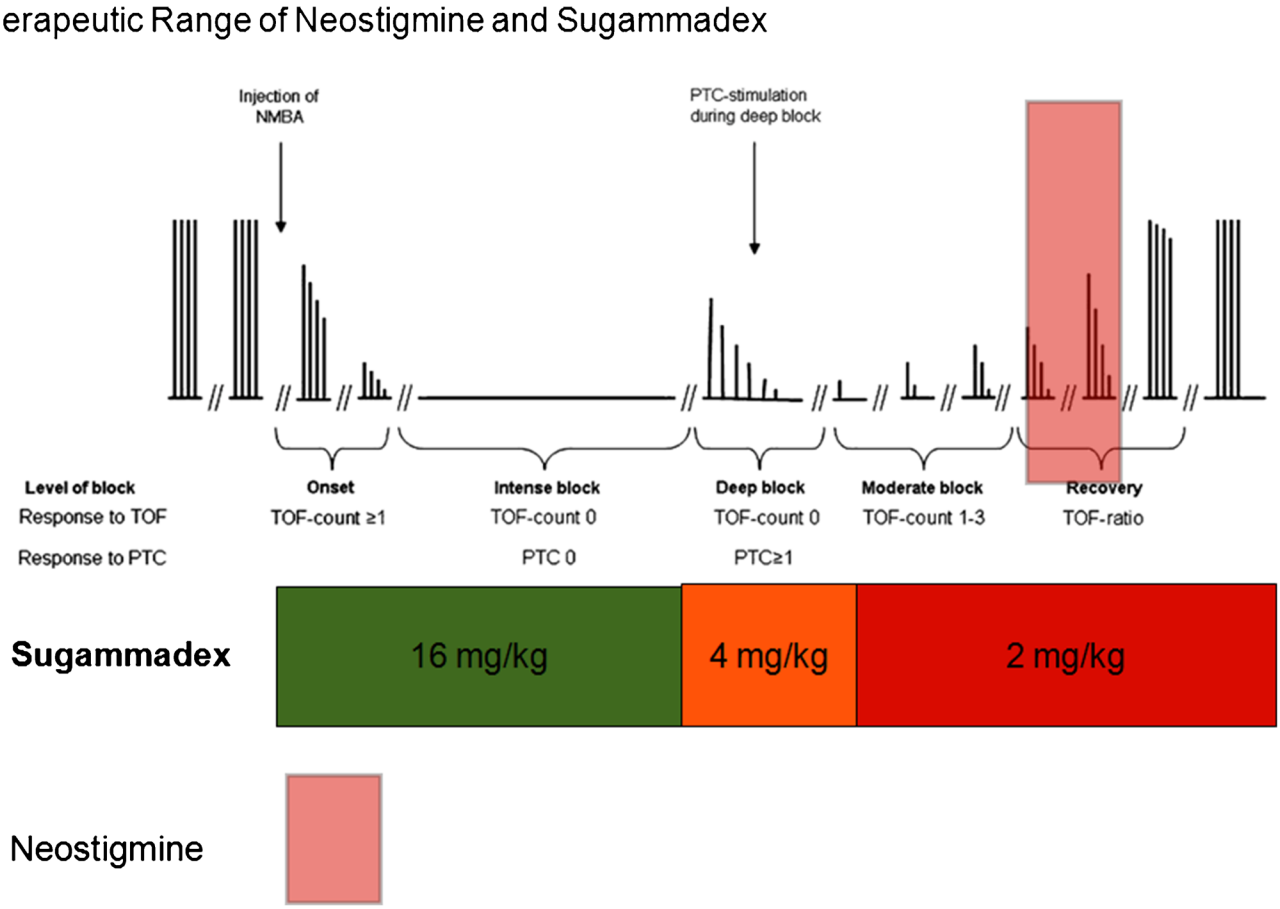

Fig. 1 Compared therapeutic window for sugammadex and neostigmine during rocuronium-induced neuromuscular block. Reproduced from Meistelman C., Fuchs-Buder T., Raft J. "Sugammadex Development and Use in Clinical Practice." *Curr Anesthesiol Rep*. 2013; 3(2):122–129, with permission from Springer Nature

the risk of postoperative pulmonary complications. Bronsert et al. have assessed the adverse outcomes in patients who had received NMBA with and without neostigmine. In their institution where nerve stimulators were used to titrate NMBAs and neostigmine reversal, patients without neostigmine reversal compared with neostigmine had an increased risk of respiratory complications (1.75 [95% CI, 1.23–2.50]) [23]. It is likely that the lack of monitoring, improper management of data provided by neuromuscular monitoring or incorrect neostigmine dosing might contribute to residual paralysis and respiratory complications observed in some studies. In the study published by Sasaki et al. [22•], one out of five patients receiving NMBA did not have a single TOF count recorded contrary to expert recommendations. In an observational analysis including 48,499 cases, McLean et al. recently confirmed this hypothesis. Neostigmine was associated with a dose-dependent increase in the risk of postoperative pulmonary complications (respiratory failure, pulmonary edema, pneumonia) within the 3 days following extubation. However, the most important finding was that doses of neostigmine greater than 60 μg/kg were associated with an increased risk of postoperative pulmonary complication and that proper use of neostigmine guided by neuromuscular monitoring could help eliminate postoperative pulmonary complications associated with the use of an intermediate-acting NMBA [24].

To summarize when neostigmine is administered "blind" without information provided by monitoring, there is a risk for the anesthetist to feel overconfident and to extubate the patient before a 0.9 TOF ration has been yet reached. Therefore, it is strongly recommended to use routinely objective monitoring to assess complete recovery from neuromuscular blockade [25]. The reversal of mild degrees of residual paralysis, for example, four responses at the TOF at the adductor pollicis but fade at the DBS, remained until recently discussed, because of the fear of negative respiratory consequences due to collapsibility of upper airway muscles [26, 27]. Several studies have even demonstrated that 20 μg/kg neostigmine was as effective as 40 μg/kg when TOF visual or tactile fade is no longer detectable, justifying the practice of giving a half-dose if complete recovery cannot be ascertained [28, 29]. More recently, Murphy et al. have shown that administration 40 μg/kg neostigmine to patients with TOF ratio 0.9 to 1.0 did not adversely affect respiratory function or induce postoperative muscle weakness or airway obstruction [30].

Sugammadex

Until recently, the action of NDMR could only be reversed by anticholinesterase drugs. However, as previously discussed, their use has several pitfalls due to their muscarinic effects, their relatively slow onset, or the inability to reverse deep levels of neuromuscular block [25]. The release of sugammadex in 2009 provides a new approach in the management of neuromuscular blockade during surgery and the prevention of residual paralysis at the end of the case.

Sugammadex binds tightly to steroid-based NMBA such as rocuronium or vecuronium allowing rapid removal of these drugs from the neuromuscular junction but is ineffective when blockade is produced by mivacurium, atracurium, or cisatracurium. Because sugammadex does not act as neostigmine by inhibition of acetylcholinesterase and indirect action on receptors, but by encapsulation in the plasma, it is not expected to have such side effects than anticholinesterase agents. Dahl et al. have confirmed the lack of cardiovascular effects of both 2 and 4 mg/kg sugammadex in patients with cardiovascular disease undergoing non-cardiac surgery [31].

The main advantage of sugammadex is its speed of action when compared with neostigmine. When given for reversal of shallow neuromuscular block at reappearance of two TOF responses, it has been shown that a 0.90 TOF ratio can be obtained in approximately 2 min with sugammadex compared 17 min using neostigmine [32]. In addition to its speed of action, predictability of response is greater with sugammadex than with neostigmine. For example, 98% of sugammadex patients reached a TOF ratio above 0.9 within 5 min when given at a dose of 2 mg/kg at two responses at the TOF.

As previously discussed, the major limitation of neostigmine is that it is effective in reversing neuromuscular block only after spontaneous recovery as started and four responses at the TOF are obtained. Because neostigmine binds to rocuronium or vecuronium in a 1:1 ratio, complete restoration from residual paralysis is possible at any depth of neuromuscular block. However, a larger dose of sugammadex is required when neuromuscular block is more intense. Jones et al. compared the efficacy of sugammadex versus neostigmine for reversal of deep level of rocuronium-induced paralysis. Sugammadex or neostigmine was given at reappearance of 1 to 2 responses at the PTC when no responses at the TOF at the adductor pollicis could be detected. A 0.9 TOF ratio was attained in 2.9 min with sugammadex versus 50.4 min in patients receiving neostigmine—glycopyrrolate. The most important finding was the reproducibility and the small range of recovery times when sugammadex is given, with 97% of patients receiving sugammadex acheiving a TOF ratio above 0.9 within 5 min of administration, whereas a large number of patients receiving neostigmine did not recover until 30–60 min and 23% did not recover to a 0.9 TOF ratio until more than 60 min [33]. There has always been an unsatisfied need for a reversal agent that can rapidly reverse neuromuscular block regardless of its depth. This ability of sugammadex to reverse intense neuromuscular block very rapidly and reliably provides the opportunity to maintain deep neuromuscular block until the complete end of the procedure. There are clinical situations where the surgeon would require complete relaxation of the patient until the end of the case (major abdominal or thoracic surgery, laparoscopic surgery). Before the introduction of sugammadex in clinical practice, anesthesiologists were reluctant to provide full paralysis [34•] because it was impossible to reverse it with neostigmine and it could delay recovery and turnover of patients in the operating room. Now, it is possible to maintain paralysis of the diaphragm and the abdominal wall muscles until the very-end of the procedure. The need for monitoring remains important since it is the only objective manner to follow evolution of deep neuromuscular block and decide of the dose of sugammadex that need to be administered (2 or 4 mg/kg) at the end of the case (Fig. 1).

It could be tempting for some clinicians to use sugammadex without taking into account the information provided by neuromuscular monitoring although proper dosing depends on the depth of neuromuscular block and information provided by monitoring. Because of the 1:1 M ratio, it is mandatory to give the correct dose because sufficient sugammadex molecules are needed to encapsulate all of the free molecules of steroidal NMBA. In a multicenter study in which subjective or objective neuromuscular monitoring was not used, 117 patients received an average dose of 2.7 mg/kg sugammadex. The incidence of TOF ratio < 0.9 after tracheal extubation was 4.3% (95% CI, 1.7 to 9.4) highlighting the use of at least a peripheral nerve stimulator to adapt the dose of sugammadex to the depth of neuromuscular block. On the other hand, due to its mechanism of action, it would be tempting to use lower doses of sugammadex to decrease costs, particularly when there are already four responses at the TOF with a measurable TOF ratio; however, using low doses could lead to reappearance of neuromuscular block after an initial and successful recovery. Such a risk was confirmed by Eleveld et al. who described reappearance of neuromuscular block following initial recovery, when using too low doses [35].

Although limited, a few studies have documented the incidence of postoperative residual paralysis following sugammadex administration. Brueckmann et al. have shown that the use of sugammadex at the end of surgery could eliminate the risk of residual paralysis at PACU admission. Timing of administration of either neostigmine or sugammadex was based on the provider's clinical judgment. Of 154 patients included, 0 out of 74 sugammadex patients and 33 out of 76 (43.4%) receiving neostigmine had a TOF ratio < 0.9 when arriving in the PACU. For Carron et al., sugammadex, through a rapid and predictable reversal of rocuronium-induced neuromuscular block, could minimize the risk of postoperative

residual complications and induce potential economic benefits in avoiding respiratory-related ICU admission [36].

Conclusion

Prevention of residual paralysis depends first on appropriate use of NMBA and careful management of neuromuscular block in the OR. Whenever a NMBA is administered, neuromuscular function must be monitored by observing the evoked muscular response to peripheral nerve stimulation. Systematic use of at least a peripheral nerve stimulator or ideally an objective monitor is essential to determine the timing of tracheal extubation. There are now enough objective data to support the routine use of reversal agents [37•]. The benefits of routine reversal based on monitoring decrease the risk of residual paralysis or unpleasant symptoms in the PACU and outweigh the theoretical risk of paradoxical muscle weakness. Although sugammadex acts much faster than neostigmine, neostigmine should not be withdrawn from our clinical use, because it is the only reversal agent acting against residual paralysis induced by benzylisoquinoline NMBA. Moreover, its use can still be discussed for the low levels of residual paralysis such as a TOF ratio above 0.4. Now that anesthesiologists have available many drugs with a short offset times (desflurane, sevoflurane, propofol, remifentanil), it will also be possible to have a very precise control of neuromuscular block when NMBAs are used to maintain relaxation, to obtain a rapid and reliable recovery from neuromuscular block, and to decrease the rate of postoperative critical respiratory events due to residual paralysis.

Compliance with Ethical Standards

Conflict of Interest Julien Raft declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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