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Qualitative Neuromuscular Monitoring: How to Optimize the Use of a Peripheral Nerve Stimulator to Reduce the Risk of Residual Neuromuscular Blockade

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Abstract This review provides recommendations for anesthesia providers who may not yet have quantitative monitoring and sugammadex available and thus are providing care within the limitations of a conventional peripheral nerve stimulator (PNS) and neostigmine. In order to achieve best results, the provider needs to understand the limitations of the PNS. The PNS should be applied properly and early. All overdosing of neuromuscular blocking drugs should be avoided and the intraoperative neuromuscular blockade should be maintained only as deep as necessary. The adductor pollicis is the gold standard site and must be used for the pre-reversal assessment, also when the ulnar nerve and thumb were not accessible intraoperatively. Spontaneous recovery should be maximized and neostigmine should be administered after a TOF count of 4 has been confirmed at the adductor pollicis. Extubation should not occur within 10 min after administration of an appropriate dose of neostigmine.

Keywords Residual neuromuscular blockade · Residual paralysis · Neuromuscular monitoring · Qualitative neuromuscular monitoring · Neuromuscular block reversal · Neuromuscular block antagonism

This article is part of the Topical Collection on *Neuromuscular Blockade*.

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Introduction

Historically, anesthesia providers have had substantial difficulty using conventional peripheral nerve stimulators (PNS) to achieve a low incidence of residual neuromuscular blockade (NMB). In a meta-analysis which aimed to examine the effect of intraoperative neuromuscular monitoring on the incidence of postoperative residual NMB, the authors "could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of postoperative residual neuromuscular blockade" [1]. Multiple studies that have reported on the use of conventional PNS and intermediate-acting neuromuscular blocking drugs (NMBDs) have documented a high incidence of residual NMB [2–4]. A more recent and well-conducted multicenter observational study reported a 63.5 % incidence of residual paralysis at the time of extubation [5••]. Taken together, these results indicate that reducing the incidence of residual NMB is a great challenge when working with conventional PNS and cholinesterase inhibitors. This review provides recommendations for anesthesia providers who may not yet have quantitative neuromuscular monitoring and rely on monitoring with conventional qualitative peripheral nerve stimulators (PNS). The authors summarize what they believe is the best practice with a qualitative standard PNS monitor and neostigmine. In order to highlight the differences between qualitative and quantitative monitors, we briefly discuss also the latter. It is assumed that the reader is somewhat familiar with TOF monitoring and the TOF ratio and that long-acting muscle relaxants such as pancuronium are no longer preferred due to their significant association with residual neuromuscular blockade.

Limitations of Conventional Peripheral Nerve Stimulators

Conventional nerve stimulators may also be referred to as subjective, simple, or qualitative. A major limitation of a qualitative PNS monitor is that it cannot confirm that reversal is successful [6], i.e., the absence of residual paralysis, which is currently defined as a train-of-four (TOF) ratio (the ratio of the amplitudes of the fourth twitch to the first twitch, T4:T1) < 0.9 at the ulnar nerve/adductor pollicis [7]. Qualitative PNS do not provide an objective, quantitative assessment of the amplitudes of the twitch heights, but rather rely on subjective visual or tactile assessment of the relative strength of the twitches.

Despite this limitation, anesthesia providers who carefully apply and thoroughly understand the limitations of a qualitative PNS can improve management of NMBDs. Most importantly, by using the qualitative PNS monitor to guide the timing for pharmacological reversal, the incidence and severity of residual paralysis can be reduced. This was shown by Kopman et al. in 2004 when they reported the results of using a protocol for muscle relaxant and subsequent neostigmine administration (0.05 mg/kg) that included reversal at a TOF count of 2 [8]. Patients received cisatracurium or rocuronium and only 2 of 60 patients had TOF ratios <0.70, 15 min after reversal. To further improve on these results with the aim of reaching the updated threshold TOF ratio of 0.9, while still working within the limitations of PNS and neostigmine, it is necessary to confirm a higher level of spontaneous recovery prior to reversal.

Start Monitoring Early

The PNS should be applied early after anesthetic induction and before muscle relaxants have been administered. The electrodes should be placed over the ulnar nerve near the wrist. The distal black (negative) electrode should be placed near the wrist crease and the proximal red (positive) electrode should be placed 3–6 cm proximal to the black electrode along the path of the ulnar nerve. The PNS should be able to display the stimulating current, which should be at least 50–60 mA [9]. The hand and fingers should be immobilized while the thumb should be able to move freely. We recommend tactile assessment which is performed by holding the thumb in full abduction and the evoked twitch response is evaluated at the distal thumb phalanx in the direction of the adductor pollicis contraction (the trajectory of this contraction may vary from patient to patient) [10]. Early use of the qualitative PNS monitor immediately after induction of anesthesia and prior to administration of neuromuscular blockade allows confirmation of proper placement of electrodes and functioning of the PNS and helps to prevent the situation where the anesthesia provider finds no twitch response at the end of the surgical procedure and may be in doubt whether the monitor works properly.

An additional important benefit of early monitoring is early identification of so-called outliers. There is great inter-patient variation in response to NMBDs, and we refer to the patients who have a substantially prolonged effect from usual doses of NMBDs as outliers. These patients are at increased risk of residual paralysis. They can be identified by a slower than expected reappearance of twitches after the initial intubating dose of NMBD [11]. When such patients are identified, it is important to monitor them closely and to reduce each incremental dose in order to avoid accumulation and a prolonged duration of the block. When an outlier has been identified and anesthesia is maintained with a potent inhalational agent, it may be reasonable to consider conversion to total intravenous anesthesia (TIVA) as reversal with neostigmine under TIVA is more predictable compared to reversal in the context of inhalational anesthesia [12]. This is consistent with volatile anesthetics potentiating the effects (prolong duration of action and recovery) of nondepolarizing muscle relaxants. Outlier patients may also make good candidates for sugammadex, if this drug is available.

Site of Monitoring

After baseline TOF has been established over the ulnar nerve as described previously, a more accessible site for qualitative PNS monitoring may need to be chosen depending on the procedure and positioning of the arms. When the adductor pollicis is unavailable bilaterally, the next best site for the evaluation is the great toe twitch with stimulation of the posterior tibial nerve, if it can be easily and safely accessed and monitored. Several studies have compared posterior tibial and ulnar nerve stimulation and have found a more rapid recovery of the TOF response at the great toe [13–17]. Monitoring of the great toe may, therefore, result in a relative underestimation of the neuromuscular blockade and it is important to move monitoring to the adductor pollicis for the pre-reversal assessment when the arms become accessible again at the end of the surgical procedure. Facial nerve stimulation and evaluation of eye muscle twitches have been shown to be unreliable and associated with a five-fold increase in the incidence and severity of residual paralysis [18•]. Muscles surrounding the eye, which are stimulated in facial nerve monitoring, are relatively resistant to NMBDs compared to the adductor pollicis and studies have consistently documented an earlier recovery of twitches at this site [19–27]. It is possible that direct muscle

stimulation, circumventing the neuromuscular block, plays a role in some cases. Importantly, if an alternate site other than the ulnar nerve/adductor pollicis is used, expert researchers have suggested to move monitoring to the ulnar nerve/adductor pollicis at the end of the procedure and prior to administration of neostigmine to properly assess the degree of neuromuscular blockade [28•].

Depth of Neuromuscular Blockade

The primary purpose of intraoperative administration of NMBDs is to provide optimal surgical conditions. The appropriate depth of intraoperative neuromuscular block is highly variable and depends on many factors including the type and phase of the surgical procedure, individual patient and surgeon, and also on the anesthetic technique. The block should not be deeper than what is required, and for many procedures a TOF count of 1–2 is appropriate. For lower abdominal surgeries, there is rarely a need to maintain a deep block [29]. The required depth of block is a clinical judgment based on several factors. Optimal adjustment of the depth of the block requires effective communication with the surgeon regarding his/her requirement for intraoperative muscle relaxation. If the block is too deep for TOF monitoring, i.e., there are no twitches in the TOF response, then post-tetanic count (PTC) should be used for monitoring. This is a mode that takes advantage of post-tetanic facilitation and is performed as follows: a 50 Hz tetanic stimulus is given for 5 s, this is followed by a 3-s pause after which single twitch stimulation at 1 Hz (one twitch per second) is started. The PTC is equal to the number of twitches counted. A PTC of 1 or 2 reflects a very deep block and virtually guarantees patient immobility in cases where this is important, e.g., in certain neurosurgical and open eye surgical procedures. There is no convincing evidence that a deep block is of benefit in laparoscopic surgery [30], and although a period of PTC = 0 may occur after the intubating dose has been administered, there is rarely a need to maintain a block that is deeper than PTC = 1. When rocuronium is used, the first twitch in the TOF can be expected to appear when the PTC reaches approximately 10 (range 6–16).

Use of the PNS at Time of Reversal

When anesthesia providers subjectively assess the twitch response of the adductor pollicis to ulnar nerve stimulation, they are not reliably able to identify fade when the TOF ratio exceeds 0.4 [6]. This means that even when the amplitude of the 4th twitch is only half of the amplitude of the first twitch, and the TOF ratio is 0.50, we perceive this as four equal twitches and fail to detect the fade. When using a qualitative PNS monitor, the TOF ratio ranging from 0.40 to 0.90 has therefore been referred to as *"the zone of blind paralysis"* [31]. The main benefit of a quantitative nerve stimulator is that it can reliably and quantitatively measure TOF ratios throughout this entire range. Although the method of delivering tetanic stimulation for 5 s at 100 Hz with the qualitative PNS monitor has been demonstrated to detect fade at TOF ratios of 0.8–0.89, its reliability is significantly less than that of a quantitative PNS monitor to detect residual paralysis, and it can cause a mild degree of fade itself [32]. Additionally, the high stimulation frequency used for this method is also painful for an awake or nearly awake patient, making its use restricted to deeper levels of anesthesia.

When a quantitative PNS monitor is not available and we use a qualitative PNS monitor, it is critical to maximize the chances of a successful reversal. This is most reliably accomplished by confirming an adequate level of spontaneous recovery prior to administration of neostigmine. This may be considered the most critical aspect of management when aiming to prevent residual paralysis while using a qualitative PNS monitor and neostigmine.

Reversal at a TOF Count of 4 At the Adductor Pollicis

Many providers were taught in training to administer neostigmine with only one or two twitches present. However, several studies have led to the updated recommendations to administer neostigmine only after the 4th twitch has reappeared [12, 28•, 31, 33–35]). In fact, a successful reversal to TOF ratio of ≥0.9 is not guaranteed even when neostigmine is administered at a TOF count of 4; but, the odds of a successful reversal are significantly improved with this approach compared to when neostigmine is administered at a lower degree of spontaneous recovery. Kirkegaard et al. reported on the likely outcome from reversal at the various TOF counts [33]. When giving neostigmine with only the first twitch present, the odds of achieving a TOF ratio of 0.9 in 10 min was zero and the odds of getting a TOF ratio of at least 0.8 was 0.07. The odds of achieving a TOF ratio of 0.8 in 10 min increased to 2.0 when neostigmine administration was delayed until the fourth twitch had reappeared. This means that relative to a patient who received neostigmine with a TOF count of 1, a patient who receives neostigmine with a TOF count of 4 is 30 times more likely to achieve a TOF ratio of ≥0.8 in 10 min. Kim et al. also reported data strongly supporting the advantage of reversing from TOF count of 4 (Fig. 1) [12]. If spontaneous recovery is allowed to progress until qualitative visual or tactile assessment of fade in the TOF

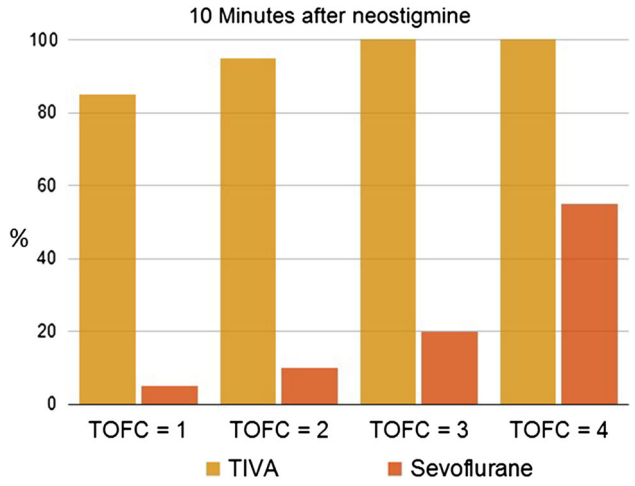

Fig. 1 Percent of patients with recovery greater than train-of-four (TOF) Ratio of 0.9 at 10 min after neostigmine (70 mcg/kg) administration during propofol- or sevoflurane-based anesthesia. *Bar graphs* are based on data reported by [12]

disappears before neostigmine is administered (i.e., the TOF ratio is expected to be at least 0.4), the odds of a successful reversal become excellent as long as the neostigmine dose is appropriately adjusted [36, 37]. The dose of neostigmine should be reduced and not exceed 20–25 mcg/kg when no fade is observed with qualitative TOF monitoring.

If the TOF count is 3 or less, the patient should be kept anesthetized or deeply sedated until the 4th twitch is clearly present [31, 35]. It is understandable that delaying reversal (and thereby also delaying the subsequent emergence and extubation), while first awaiting the return of the 4th twitch, will often be considered inconvenient. Of course, avoiding all overdosing will help ensure that the blockade is not unnecessarily deep at the end of the surgical procedure. This includes careful dose adjustment of NMBDs for age, gender, obesity, as well as only judicious administration of incremental doses towards the end of the surgical procedure [38, 39•, 40–42]. It may also be helpful to educate all members of the surgical and perioperative teams about fundamentals of safe management of NMBDs to increase acceptance of this critical step of awaiting adequate spontaneous recovery. Return of spontaneous ventilation and normal tidal volumes should not be used for timing of pharmacologic reversal as intubated patients often have adequate ventilation despite low TOF counts. An earlier reversal, such as at TOF counts of 1 to 3, will routinely yield a TOF response with no fade at 10 min after reversal, however without a quantitative monitor there is no way of confirming that the reversal was successful. Patients who are reversed at lower TOF counts while receiving volatile anesthetics are more likely to end up in *the zone of blind paralysis* (i.e., TOF ratio 0.4–0.9) than to achieve a TOF ratio of ≥0.9 at 10 min after neostigmine [12, 43••]. Thus, reversal at low TOF counts often leads to low TOF ratios which are not adequate for a safe extubation. Increasing number of TOF twitches prior to reversal correlates with a decreasing incidence and severity of residual paralysis, and a decreased incidence of postoperative pulmonary complications such as atelectasis and pneumonia [7]. Every attempt to maximize reversal should be used in patients with known or anticipated airway or pulmonary impairment.

After administering neostigmine, it is important to allow a sufficient amount of time prior to extubation. It may take as much as 10 min for neostigmine's peak effect to occur [44, 45]. Patients who are successfully reversed should have no fade with double burst stimulation or tetanic stimulation at 50 Hz [46].

However, the use of tetanic stimulation is not the most sensitive approach to detecting residual paralysis. Clinical tests (head lift, hand grip, etc.) are not adequate to rule out residual paralysis, either [47].

Anesthesiologists who use a quantitative monitor can take a different approach from the one recommended for use with a PNS. In this case, neostigmine can be administered at a lower TOF count of 1 or 2. While it would be expected that reversal to a TOF ratio of 0.9 often takes 20 min or even longer, the quantitative monitor eliminates the problem of *the zone of blind paralysis* and the patient can be accurately monitored throughout. In some cases, reversal will occur more quickly, and when this is confirmed with the quantitative monitor, extubation can be safely performed without delay. Quantitative monitoring has proved to be not only efficacious but also effective [48–51]. Currently, the most widely available monitor is the TOF-Watch® which is based on acceleromyography. Calibration of this monitor is easily performed in less than 30 s and improves its accuracy. It is performed after induction of general anesthesia but before administration of NMBDs. Measurements often show some variability and it is therefore customary to perform several measurements until two consecutive measurements are within 10 % and then to average these. The monitor works best when applied to a freely moving thumb, and devices have been developed to protect the thumb from external disturbances during surgery. If a freely moving thumb is not available intraoperatively, the monitor can be used at alternate sites but should be moved to the ulnar nerve/adductor pollicis when this site becomes available at the end of the case. As mentioned, reversal can be administered at lower TOF counts with the quantitative PNS monitors as the TOF ratio can be assessed continuously to ensure a TOF ratio equal to or greater than 0.9 prior to extubation. When all operating rooms in an anesthesia department were equipped with these monitors, the incidence of residual paralysis declined continuously over a 9-year period from 62 % to just 3 % [48]. This

improvement was accomplished while the only reversal agent available was neostigmine.

Conclusions

While optimal management of NMBDs requires a quantitative monitor, this review provides recommendations also for anesthesia providers who have access only to conventional qualitative monitoring.

The PNS should be used throughout the case to help the anesthesia provider to titrate and monitor the required intraoperative relaxation but most importantly to confirm adequate spontaneous recovery prior to reversal with neostigmine. The best location for monitoring is the ulnar nerve/adductor pollicis and if a different site has been used intraoperatively, monitoring should be moved to the ulnar nerve/adductor pollicis prior to reversal. The return of 4 twitches at the adductor pollicis should be confirmed prior to administering neostigmine. When fade is absent in the TOF, the neostigmine dose should be adjusted and not exceed 25 mcg/kg. While following the recommendations in this article will reduce the incidence and severity of residual paralysis, only a quantitative monitor allows for definitive confirmation of full recovery from the effects of muscle relaxants prior to extubation.

Compliance with Ethics Guidelines

Conflict of Interest Stephan R. Thilen and Sanjay M. Bhananker declare that they have no conflict of interest.

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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