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Review Article

Monitoring the Neuromuscular Blockade: Recent Developments and Recommendation for its Routine Implementations

Radmilo J Jankovic[1,2]* and Danica Markovic[2]

[1]*Department for Anesthesiology and Intensive care, School of Medicine, University in Nis, Serbia*

[2]*Center for Anesthesiology, Reanimatology and Intensive care, Clinical center in Nis, Serbia*

***Corresponding Author:** Radmilo J Jankovic, Department for Anesthesiology and Intensive care, School of Medicine, University in Nis, Serbia.

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Abstract

Although neuromuscular blocking agents (NMBAs) provide optimal surgical conditions and a reduced incidence of laryngopharyngeal lesions during tracheal intubation, there are evidence of delayed paralysis and higher morbidity and mortality after their use. To date many anesthesiologists do not routinely use objective method to monitor neuromuscular function due to the fact that there are no ideal monitoring devices yet. New devices and techniques, like kinemyography, phonomyography and the cuff method, are introduced in this field in addition to those which are being routinely used. New research point out the great importance of neuromuscular monitoring in everyday practice since it provides enhanced security for the patient. Nowadays objective monitors of neuromuscular function are relatively inexpensive, reliable and easy to use and they should be available whenever neuromuscular blocking drugs are administered.

Keywords: *Neuromuscular Blockade Monitoring; Train-of-Four Monitoring; Neuromuscular Block*

Abbreviations: NMBA: Neuromuscular blocking agent; TOF: Train of four; AP: Adductor pollicis; OO: Orbicularis oculi; CS: Corrugators supercilii; NMB: Neuromuscular blockade; PTC: Post-tetanic count; DBS: Double-burst stimulation; MIP: Maximum inspiratory pressure; HL: Head-lift; MMG: Mechanomyography; EMG: Electromyography; AMG: Acceleromyography; PMG: Phonomyography; PORC: Postoperative residual curarization.

Introduction

Neuromuscular management is important in clinical anesthesia and emergency medicine. Neuromuscular blocking agents (NMBAs) provide significant contributions such as optimal surgical conditions and a reduced incidence of laryngopharyngeal lesions due to tracheal intubation [1]. In contrast, numerous reports in the literature illustrate the increasing incidence of delayed paralysis and higher morbidity and mortality with the use of NMBAs compared with techniques that avoid NMBAs [2-5]. Recently published study by Debaene., et al. found 45% of the patients arrived in the recovery room with a residual neuromuscular block, defined as an adductor pollicis train of four (TOF) ratio of less than 0.9. Furthermore, sixteen percent had a TOF ratio of less than 0.7 [6]. Despite these upsetting observations, objective NMB monitoring techniques are still not widely used, with most anesthesiologists relying on visual or tactile assessment of the TOF ratio, or, in many cases, no neuromuscular monitoring at all. In addition, published data support the use of objective rather than subjective monitoring techniques in the sight that this may improve patient outcome [3,7]. Recently published nationwide surveys from Germany and United Kingdom revealed that neuromuscular monitoring was routinely used in only 10-18% of the anesthesia departments [8,9]. Similar unacceptable results also came from Denmark and Mexico [10,11]. Based on those disappointing findings, it is time to replace our old subjective methods with new objective measurements.

To date, the absence of an ideal monitoring device has been one of the most important reasons why many anesthesiologists do not routinely apply an objective method to monitor neuromuscular function. This highlights a need for easily used and reliable equipment for this purpose. In 1958, Christie and Churchill-Davidson described the use of a nerve stimulator to monitor neuromuscular block [12] but it wasn't introduced into everyday clinical practice until TOF stimulation pattern was initially described in 1970 [13,14]. Stimulating a peripheral motor nerve with an electric impulse results in a muscular response represents the basic principle of neuromuscular monitoring. A nerve stimulator should generate an impulse that is less than 0.5 milliseconds (typically 0.2-0.3 milliseconds) in duration to avoid direct muscle or repetitive nerve stimulation (by extending beyond the refractory period of the nerve), monophasic and rectangular (i.e, square-wave pattern) because a biphasic pulse might cause a burst of action potentials, and with a constant current to provide consistent stimulation (i.e, once the rheostat is set for delivery of a given current, the stimulator should be able to maintain this current by changing its voltage in response to varying resistances up to at least 5,000 Ω). The stimulating current required for effective depolarization of all fibers of a nerve bundle is called the maximal current. When monitoring absolute twitch height, the stimulus intensity should be supramaximal (i.e, 10%-20% higher than maximal current) to ensure consistent recruitment of all fibers even with minor variations of skin resistance over time. The most common nerve-muscle unit used for neuromuscular monitoring is the ulnar nerve-adductor pollicis (AP) muscle. The use of tibialis posterior and flexor hallucis brevis nerve-muscle unit might be a suitable alternative in cases when surgical procedures do not allow easy access to the patients' arms [15]. An additional option is to use the stimulation of the facial nerve for neuromuscular monitoring by the recording of the contraction of orbicularis occuli (OO) or corrugator supercili (CS) muscle [16]. Before administration of the muscle relaxant, calibration of the device is a prerequisite. Calibration requires that the gain is adjusted to obtain a twitch height of 100% using a single twitch mode of stimulation, or of T1 when using a TOF mode of stimulation [17]. The preparation and placement of the stimulating electrodes can have an influence on neuromuscular monitoring. Before placing the electrodes, the skin should be cleaned using an alcoholic solution and then rubbed. The electrodes should be positioned properly at the site to ensure that the current stimulates the target nerve appropriately. The distance between the two electrodes should be < 6 cm. In addition, it is recommended that the negative electrode be placed at the distal site. Skin temperature should be maintained ≥ 32ºC to avoid hypothermia-related increases in skin impedance [18].

Stimulation patterns

Single-twitch stimulation

Single-twitch stimulation consists of a square wave stimulus lasting at least 0.2m sec. delivered by a nerve stimulator every 10 seconds (0.1 Hz) or either each second (1 Hz). Although stimulation at 1.0 Hz may provide a quicker assessment of rapidly changing levels of block, such a relatively fast rate of stimulation may be associated with significant fade and increased blood flow to the stimulated neuromuscular junction and hence increased delivery of relaxant. On the other hand, single twitch at 0.1 Hz is relatively nondisturbing to the neuromuscular junction and it is preferable pattern in determination of onset time [19-21]. Recently Bogicevic and coauthors reported that monitoring the onset of rocuronium induced neuromuscular blockade using 0.1 Hz single twitch enables irreproachable intubating conditions but it was associated with considerable delay of intubation time in comparison to either TOF stimulation or clinical assessment of onset time [22]. Major limitation of monitoring single twitch is that baseline amplitude of the muscle response must be established before the administration of muscle relaxant. Single-twitch stimulation can be accurately used in a research set-up so long as control amplitude returns to control values. However, since most clinicians still use tactile or visual evaluation of the degree of neuromuscular blockade (NMB), TOF-stimulation is the preferred pattern of stimulation.

Train-of-four (TOF) stimulation

The TOF pattern of twitch stimulation was developed in 1970 by Ali and colleagues [13], in an attempt to produce a pattern of stimulation that did not require the comparison of evoked responses to a control response obtained prior to administration of a neuromuscular blocking drug. The pattern involved stimulating the nerve with a supramaximal twitch stimuli, with a frequency of 2 Hz, that is, four stimuli each separated by 0.5s and repeated every 10s. In the absence of a neuromuscular blocking agent, the four muscle contractions (twitches) are of equal height. In the presence of a depolarizing neuromuscular blocker, all four twitches are depressed equally with increasing block. In the presence of NMBAs, fade appears within the response where the fourth twitch becomes depressed before any of the others. A comparison of the amplitudes of the fourth and first twitches then gives the TOF ratio which can be used as a reliable indicator of the degree of neuromuscular block. Disappearance of the TOF will correspond to optimal intubating conditions. Sufficient neuromuscular blockade for most surgical procedures can be assumed until the reappearance of the two responses. On the other hand, it is now recommended that a TOF ratio of 0.9 should be achieved before tracheal extubation [18].

Tetanic stimulation

Tetanic stimulation uses a high frequency (50–200 Hz) with a supramaximal stimulus for a set time: normally 5s. In healthy skeletal muscle during normal movement, the response is maintained as a tetanic contraction. However, on administration of NMBAs, the muscle, depending on the degree of block, will show signs of fade. At stimulation frequency of 50 Hz the degree of fade will correspond more closely to the degree of neuromuscular block. This pattern of stimulation is very sensitive and can elicit minor degrees of neuromuscular block, which is potentially useful in the postoperative recovery room. However, its use is limited by the fact that titanic stimulation is extremely painful [23].

Post-tetanic count (PTC)

On completion of a tetanic stimulus, acetylcholine synthesis and mobilization continue for a short period. As a result there is an increased, immediately available store of acetylcholine which causes an enhanced response to subsequent single twitch stimulation. In such circumstances, if a 5s tetanic stimulus at 50 Hz is administered, after no twitch response has been elicited, followed 3s later by further single twitches at 1 Hz, there may be a response to single twitch stimulation. This phenomenon is known as post-tetanic facilitation. The number of post-tetanic twitches is known as PTC, and is indicates early recovery of profound non-depolarizing neuromuscular block, when there may be no response to TOF or single twitch stimulation. For instance, the first twitch of the TOF generally returns with a PTC of 9-11. The main use of PTC is when profound neuromuscular block is required, for example, during retinal surgery, when movement or coughing could have devastating effects. If two PTCs are administered in quick succession, the degree of neuromuscular block will be underestimated. It is recommended that tetanic stimulation should not be repeated for a period of 6 min [24].

Double-burst stimulation (DBS)

Double-burst stimulation (DBS) was introduced in the late 1980s as an alternative method of monitoring neuromuscular block. It entails 2 mini tetanic bursts (at 50 Hz) that are separated by 750 milliseconds. When DBS is applied in a patient with a partial nondepolarizing block, it induces a weaker second response, analogous to the fade induced by TOF. Furthermore, several studies suggested that DBS is preferable to TOF because DBS fade may be more readily detected than TOF fade by visual or tactile means [13,25-27]. Although initially thought to improve the detection of fade, DBS might give the clinician a false sense of security in its ability to manually detect fade, and DBS should not be considered a substitute for an objective quantitative method.

Techniques to monitor neuromuscular function

Clinical assessment

Subjective monitoring of NMB is still the most widely used method of neuromuscular monitoring. Clinical assessment of NMB consists of the clinical evaluation of the degree of relaxation based on the patient's ability to perform certain tests (tidal volume, vital capacity, maximum inspiratory pressure (MIP), sustained head-lift (HL), leg-lift or hand-grip sustained for more than five seconds) from which some tests can be quite reliable [28,29]. MIP is a measure of the pressure generated by deep inspiration in a closed system and is typically expressed as -cm H_2O. In the absence of neuromuscular weakness, MIP may exceed-100 cm H_2O. MIP is more sensitive to neuromuscular block than other ventilatory parameters, being compromised at significantly less than 70% receptor occupancy. Some authors suggested an MIP of at least -50 cm H_2O as predictor of airway competence [30]. Ability to maintain head lift for 5 seconds has long been recommended as an important indicator of readiness for tracheal extubation and it was also associated with TOFr > 0.8 and MIP > 50% of control. Nonetheless, it should be noted that despite a successful HL considerable weakness might still present [31,32]. Hand grip also may be very sensitive but quantification requires the use of a hand dynamometer [33,34]. Clinical tests of NMB recovery depend on the degree of consciousness and cooperation of the patient after general anesthesia and with optimal patient cooperation, failure to adequately perform these simple tests should lead the clinician to suspect residual NMB and initiate more objective testing including countering the number of TOF responses or more precisely using the DBS.

Equipment

Equipment for the monitoring of neuromuscular blockade can be divided into two groups, nerve stimulators that allow a quantitative monitoring of the blockade and devices that do not. The use of nerve stimulators without an option for quantitative measurement does not allow for the reliable detection of minor levels of neuromuscular block, i.e. a TOF ratio between 0.7 and 1.0. Therefore, the use of objective monitoring is now generally recommended [35].

Mechanomyography (MMG)

If neuromuscular monitoring should reflect the degree of relaxation of a given muscle, then measuring the actual force is the best method to monitor NMB. Of all the monitoring methods, MMG requires the most stringent preparations and precautions: ideally the muscle should be fixed in a specially molded cast to prevent changes of position, and a constant pre-load should be applied according to the muscle site monitored and the size of the muscle. MMG devices are awkward and bulky to prepare, require meticulous control of hand positioning, and can only be used to measure the response at the AP muscle. Other modalities exist which are MMG-alike, such as the balloon pressure method for monitoring either the larynx or the CS. These methods measure the actual force by indirect methods, such as the change of pressure exerted onto a balloon compressed by movement of the thumb or contraction of the CS muscle [35]. Again, these methods are not easy to apply in the clinical setting, and are reserved primarily for research purposes as a gold standard or reference against which other methods can be tested [36].

Electromyography (EMG)

Electromyography is the oldest method used for the assessment of neuromuscular blockade and has been mostly used for research purpose. The equipment is not as bulky as for mechanomyography recordings. Additionally, it can be used not only for the limbs but also at other sites of interest, e.g. the diaphragm or the larynx. Regarding the fact that the force of muscular contraction is proportional to the compound action potential of the muscle, the device records the electric activity of the stimulated muscle following the stimulation of the corresponding nerve [18].

Acceleromygraphy (AMG)

Acceleromyography measures the isotonic acceleration of the stimulated muscle. The basis for the method is Newton's second law (force = mass x acceleration). If mass is constant, the force of muscle contraction can be calculated if acceleration is measured? After placement of the stimulating electrodes on the target nerve a piezo-electric element is placed over the muscle innervated by that nerve. The movement of the end-organ, e.g. the thumb, generates a voltage in the piezo-electric element that correlates with the acceleration of the muscle. Accleromyography is one of the most popular quantitative monitoring techniques in daily clinical use because it is comparatively cheap, practical and easy to use. Currently, acceleromyography is increasingly used for research purposes. Details about the use of acceleromyography for research purposes are summarized in the last update of the guidelines for good clinical research practice in pharmacodynamic studies of NMBAs [36,37].

Introducing the new devices and techniques

Kinemyography is a relatively new technique based on measuring movement of the thumb. It employs a piezo-electric transducer and consists of a molded plastic device which mirrors the contour of the outstretched thumb and index finger. Kinemyography based neuromuscular monitoring device integrated in certain anesthetic machine has been recently introduced into clinical practice. Although is practical in the clinical setting, its accuracy is not superior to that of acceleromyography, and careful hand positioning is necessary to avoid artifacts. The response, especially during recovery of neuromuscular function, can be misleading [38].

Phonomyography (PMG) is the most recently introduced technique based on the fact that contracting muscles evoke sounds of low frequencies which can be detected using special microphones. The most frequently used transducers are microphones or capacitance accelerometers. The sound waves can be recorded at the surface of the skin and it is important to record low frequencies below 50 Hz, which represent approximately 90% of the signal power spectrum [39,40]. Published studies considering agreement between PMG and MMG showed controversies [40,41]. Good to very good agreement with MMG has been shown for the adducting laryngeal muscles [42] the corrugators supercilii muscle [43] and the adductor pollicis muscle [44]. The advantage of PMG lies in the fact that it can be applied to every muscle site of interest and that it is an easy-to-apply, non-invasive method. Phonomyography has been evaluated in several centers, but is not yet commercially available.

The cuff method a new and simple method for routine monitoring of neuromuscular function based on the stimulation of the peripheral nerve in the arm (brachial plexus, ulnar and median nerves principally). The active electrode is placed on the inner part of a standard blood pressure cuff and the reference electrode on the chest or shoulder. The evoked neuromuscular activity is recorded through the changes in pressure generated in the inner part of the cuff by the muscular activity after the stimulus (the same as the technique and hardware for non-invasive reading of blood pressure). Based on primarily promising results published by the Rodiera., *et al*. the cuff method may become a new useful monitoring system for evaluating neuromuscular blockade in clinical anesthesia [45].

Influence of monitoring site on the clinical response

Muscles differ in terms of onset, offset and peak effect of NMBAs. Monitoring solely muscles of the hand provides only a partial image of neuromuscular function of other major muscle groups. Several studies show that muscles around the eye, the CS and the OO, reflect accurately the response of laryngeal muscles or the diaphragm and recover faster from NMB than the AP [39]. Neuromuscular monitoring of the CS might be problematic because of the limited capability of the conventional acceleromyographic probe to detect acceleration created by this small muscle. However, recent study designed to measure the actual force created by the CS using an air-filled balloon as a pressure transducer found good agreement between PMG and this MMG-like method [35].

Peripheral muscles include AP, the great toe or the vastus medialis muscle need to be monitored in order to determine timely recovery of NMB [46]. Probably because of higher blood flow to the hand, most studies have found significantly longer onset times and shorter recovery of NMB at the great toe in comparison to the hand muscles. The pharmacodynamic differences between the great toe and the hand muscles limit the usefulness of the great toe as a replacement for monitoring NMB of the hand muscles in surgeries where access to the hand is impossible or movement of the hand is impaired. The vastus medialis muscle should be considered as an alternative monitoring site for those surgeries where there is no access to hand or foot muscles but more recent study using PMG, confirmed the shorter onset time, a less pronounced maximum effect, and a more rapid recovery of NMB at the vastus medialis muscle than at the AP [47,48].

A monitoring method based on MMG, EMG or PMG has been applied to the larynx by the stimulation of the recurrent laryngeal nerve. In comparison to stimulation of the phrenic nerve, concomitant stimulation of the brachial plexus or the vagus nerve is rare. In comparison to NMB at the AP, most studies confirm that onset and recovery of NMB at the larynx is faster [49-51,41].

Some studies have used EMG and MMG for monitoring the diaphragm. Transdiaphragmatic pressure technique, however, is more invasive, more difficult to apply because it has to be recorded during resting end-expiration and it requires bilateral phrenic nerve stimulation. Another disadvantage is that it cannot be used with an open abdominal cavity. In general, pharmacodynamic responses of NMBDs at the diaphragm have shown a similar time course and degree of NMB as responses at the larynx. The most difficult aspect of neuromuscular monitoring at the diaphragm is stimulation of the phrenic nerve [52-54].

Recently Saitoh and co-workers assess the degree of neuromuscular block acceleromyographically at the sternocleidomastoid muscle. They announced that onset of neuromuscular block at the sternocleidomastoid muscle did not significantly differ from that at the adductor pollicis muscle. Finally they concluded that sternocleidomastoid muscle is more resistant to vecuronium than the adductor pollicis muscle. Recovery from neuromuscular block is faster at the sternocleidomastoid muscle than at the adductor pollicis muscle [55].

Recommendations for optimal implementation

Monitoring the onset time

It must be remembered that onset of NMB is faster in central muscles with a superior blood supply, for example, diaphragm and larynx. The muscles of the upper airway and pharynx behave as central muscles at onset of NMB. Current best evidence suggests that monitoring of the CS or OO should be used to establish the earliest time for optimal conditions for tracheal intubation as they reflect laryngeal relaxation better than monitoring of the AP [46]. 0.1 Hz single twitch or TOF stimulation is the most priceless stimulation pattern at induction. Single twitch stimulation will allow the maximal stimulation level to be obtained. Disappearance of all TOF responses will also correspond to optimal intubating conditions [22,36].

Monitoring optimal surgical relaxation

Although clinical judgment of surgical conditions can be subjective, recent studies have revealed that NMBAs can improve surgical conditions, most specifically in abdominal surgery [56,57]. Neuromuscular blockade can be used to maintain a lighter plane of anesthesia. Otherwise, profound NMB can be useful for procedures such as intracranial surgery or complex eye surgery where even slight movement could result in critical events. PTC may be particularly helpful during surgery when every muscle movement is undesirable. Since the diaphragm and laryngeal adductor muscles are less responsive to NMBAs than the adductor pollicis muscle, ablation of the single twitch at the adductor pollicis does not necessarily assurance absence of coughing or cord movement. To more reliably ensure absence of all movement, the PTC should be zero [58]. Since muscles react differently with respect to onset, recovery, and the degree of NMB, an important means of providing 'optimal' relaxation for the surgical site should consider monitoring muscles of the surgical site, or alternatively, muscles which adequately reflect NMB at the surgical site. From those reasons, today, the following concept is proposed: for surgery of the upper or lower extremities, monitoring of the AP – or any other hand muscle - should be preferable. For surgery within the chest or abdomen where relaxation of the diaphragm is necessary, monitoring of the CS could be used [46].

Monitoring of neuromuscular blockade during reversal

Routine reversal of the residual effects of NMBAs is not standard of care in many departments of anesthesia. In contrast, according to recent guiding principles residual neuromuscular block should always be reversed unless there is objective evidence that the TOF ratio has recovered to acceptable levels [28]. Objective monitoring of NMB is also recommended when reversing neuromuscular block. As a general rule, if the TOF count is < 2, prompt recovery of neuromuscular function cannot be assured by anticholinesterase administration. Thus before administering a neuromuscular antagonist, the TOF count should be at least 3. It is clear that reversal of competitive neuromuscular block by cholinesterase inhibitors has its limitations. If concentrations of blocking drug at the neuromuscular nicotinic receptors are high enough, recovery will be incomplete. Recently published results of reversal of profound rocuronium induced block by sugammadex are very promising [59,60] but rationale administration of sugammadex necessitates some information of the extent of neuromuscular block [61,62].

Monitoring the recovery of neuromuscular blockade at the end of surgery

Probably, the most critical time to monitor neuromuscular function is at the end of surgery, prior to emergence from anesthesia. Recovery of neuromuscular transmission is best monitored at the AP since; in general, this is the last muscle group to recover from NMB. The respiratory muscles are likely to have recovered to a greater degree, and monitoring a peripheral muscle provides a larger margin of safety. It has been shown that a TOF ratio > 0.9 at the AP is necessary to achieve adequate airway protection in order to avoid postoperative respiratory complications [63].

Monitoring of NMB to detect the postoperative residual curarization

Three decades ago, Viby-Mogensen and coworkers measured the prevalence of significant residual curarization in the recovery rooms in patients received long-acting NMBAs. All of Viby-Mogensen's patients received neostigmine, 2.5 mg intravenously, at the end of anesthesia. They found a significant incidence of postoperative residual curarization (PORC) [64]. Recent studies report that the incidence of PORC may actually be greater than the value reported by Viby-Mogensen [65-67]. Despite the high incidence of residual paresis found in most PACUs, there is still remarkably little outcome information to suggest that this represents a frequent cause of major morbidity, but based on available evidence; return to a TOF ratio of 0.70 can no longer be considered optimal or even adequate neuromuscular recovery. The modern standard of recovery is now considered to be a TOF ratio of at least 0.90.

Now it is time to change old habits

Results from number of published studies highlighted that the use of objective neuromuscular monitors can decrease the incidence of PORC. Unexpectedly, a recent meta-analysis failed to demonstrate that the use of an intraoperative neuromuscular function monitoring decreased the incidence of PORC [68]. Unfortunately, in Naguib's meta-analysis, most of the studies cited that failed to demonstrate that monitoring had a favorable effect in reducing PORC were poorly designed to do so.

Objective neuromuscular monitoring should be used whenever a neuromuscular blocking agent is administered. Although is clear that in the real world of day-to-day practice, these suggestions have been widely ignored, it is now time to move from discussion to action and introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers and aficionados of muscle relaxants.

Conclusion

Today objective monitors of neuromuscular function can be purchased that are relatively inexpensive, reliable, and easy to use. They should be available in any modern anesthetizing location where neuromuscular blocking drugs are administered [69].

Conflict of interest

The authors of the article "Monitoring the Neuromuscular Blockade: Recent Developments and Recommendation for its Routine Implementations" declare that there is no conflict of interests regarding the publication of this paper.

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