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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Clinical Practice Guideline for the Management of Neuromuscular Blockade: What Are the Recommendations in the USA and Other Countries?

Réka Nemes[1] · J. Ross Renew[2]

Abstract

Purpose of Review This review addresses various societal guidelines, standards, and consensus statements regarding optimal neuromuscular blockade management. We discuss the historical evolution of neuromuscular management as a means of identifying possible future trends.

Recent Findings While a recent international panel of experts has called for abandoning clinical assessment and subjective evaluation using a peripheral nerve stimulator in favor of adopting quantitative monitoring, few anesthesia societies mandate similar practices at the moment.

Summary The current status of neuromuscular monitoring in the world is still variable and unsatisfactory. Nevertheless, a positive trend can be observed in the anesthesia community to adopt and learn this neglected technique. The development of user-friendly monitoring devices should also help this process, but anesthesia national societies still need to do a lot to replace outdated and substandard practices.

Keywords Residual neuromuscular blockade · Neuromuscular monitoring · Patient safety · Guidelines · Consensus statement

Introduction

Seventy years after the introduction of neuromuscular blocking agents (NMBA) into anesthesia practice, anesthesiologists still face challenges with correct management of neuromuscular blockade (NMB). Recovery from NMB, whether spontaneous or pharmacologic, occurs with significant interindividual variability, and can lead to incomplete recovery in many patients [1–3]. In 1979, Viby-Mogensen reported the incidence of postoperative residual neuromuscular blockade (RNMB) to be 42% [4]. Forty years later, the incidence persists between 40 and 60% [5–7, 8••] as an unacceptably high number of patients leave the operating theater with residual paralysis and carry the potential risk for associated postoperative pulmonary and other complications. Neuromuscular blockade could and should be tailored to each patient and surgical scenario. However, anesthesiologists must be willing to master fundamentals of NMB and utilize best practices to avoid the iatrogenic complications associated with RNMB.

Curare was introduced into anesthesia practice in the 1942 by Griffith and Johnson [9] in Canada. Subsequently, Gray and the Liverpool anesthetic technique had a major contribution to its general adoption [10–12]. These pioneers began the process of gathering experience and data with neuromuscular blocking agents, as much remained undiscovered about the neuromuscular junction and relevant pharmacology. It comes as no surprise that Beecher and Todd reported a six-fold increase in the mortality of those patients who received curare in these early days of NMB [13].

The next few decades brought significant discoveries and developments in the field of NMB, their reversal agents, and monitoring techniques. However, there were several detours and even dead ends on the journey to safe management of

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neuromuscular blockade. Numerous pharmacological and monitoring practices emerged that were ultimately found to be inadequate, yet such practices had already become entrenched into routine clinical practice and remain in use today.

Advances in Neuromuscular Blockade Pharmacology

Until the beginning of the 2000s, the administration of cholinesterase inhibitors, especially neostigmine, was the only way to enhance recovery from neuromuscular blockade. However, the indirect antagonism of non-depolarizing NMBAs has always been unpredictable [3]. Fearing the muscarinic side effects, anesthesiologists were likely to administer lower doses than necessary, or forego its use altogether. If administered too early (train-of-four count < 4), the ceiling effect of these drugs presented an obstacle to hastening recovery [14]. Conversely, there was also a fear that if administered too late, neostigmine itself might cause muscle weakness [15, 16]. Even if administered in appropriate doses at appropriate levels of NMB, an average of 15 min is required to achieve adequate recovery defined as a train-of-four ratio > 0.9 [3]. Due to these difficulties, it is no surprise that neostigmine reversal in the absence of objective monitoring has been shown to not significantly affect the incidence of RNMB [6, 17, 18].

The introduction of sugammadex into clinical practice represented a significant breakthrough in not only the arena of NMB but also anesthesia in general. This drug has a well-defined dosing scale that provides a fast and reliable reversal for aminosteroidal NMBAs from any depth of blockade [19]. To define the optimal dose, anesthesiologists should determine the level of the neuromuscular blockade at the time of sugammadex administration. After the introduction of sugammadex into clinical practice, there was a period in which anesthesiologists hoped that sugammadex reversal would eliminate the need for rigorous monitoring. However, several investigations have demonstrated that sugammadex is not foolproof, and empiric administration that is not based of the degree of block does not eradicate residual neuromuscular block. Kotake et al. reported an incidence of RNMB of 4.3% in patients receiving sugammadex without monitoring [20]. Additionally, several other cases have been documented in which sugammadex proved ineffective [21], had a prolonged onset of action [22–24], or resulted in recurrence of NMB when sugammadex was used without objective monitoring [25, 26].

Peripheral Nerve Stimulators—a Step in the Right Direction

The first peripheral nerve stimulator (PNS) was developed in 1958 by Christie and Churchill-Davidson [27]. However, in the beginning, only a handful of people had the access to this new technology. Most anesthesiologists had to rely on clinical tests, such as the 5-s head lift, leg and arm lift tests, and the tongue protrusion test to exclude RNMB. Additionally, measuring the tidal volume and relying upon the expected pharmacokinetics (duration of action, reversal time) of NMBAs were also common practices. These early, unreliable practices were the result of both unfamiliarity with the novel PNS technology and the limited availability. However, this time period also spawned important work in the field as anesthesiologists started to compare patients' ability to perform clinical tests to objective electrophysiological measurements of NMB. It became evident that patients could "pass" clinical tests even in the presence of significant RNMB. Most patients are able to maintain a 5-s head lift test at a train-of-four ratio < 0.5 [4, 28]. No single clinical test or a combination of tests has a useful sensitivity (0.18–0.35) or positive predictive value (0.47–0.52) [29].

With these emerging data, the anesthesia community started to endorse the use of peripheral nerve stimulators. Indeed, these simple hand-held devices were cost-effective, were very easy to use, and gained wide popularity over the years. In two clinical investigations from the 1990s, the clinical use of PNSs decreased the occurrence of RNMB compared with the use of simple clinical examination [30, 31]. However, PNSs possess the inherent limitation, in that the clinician has to rely on subjective (visual or tactile) means to determine the level of NMB. This shortcoming was confirmed since the 1980s, as several investigations demonstrated that human observers are not able to reliably identify the degree of fade (train-of-four ratio > 0.4–0.6), regardless of the pattern of neurostimulation [30, 32–34]. As a consequence of this subjectivity, PNSs proved inferior to objective monitoring devices in preventing RNMB and associated airway complications in two clinical outcome studies [35, 36]. The RECITE and RECITE-US multicenter studies also proved that the common practice of subjective monitoring-guided neostigmine reversal leads to RNMB rates higher than 60% [6, 8••]. To guarantee adequate recovery, measurement of fade (objective monitoring) is an absolute requirement [37••].

The Introduction of Objective Monitoring

Objective neuromuscular monitoring (NMM) became widely available after the development of acceleromyography (AMG) in the 1980s [38, 39]. Compared with the predecessors, the bulky and sophisticated mechanomyography- and electromyography-based devices, the AMG-based monitors proved portable and relatively easy to use. However, clinical tests and peripheral nerve stimulators had already gained wide acceptance, as the older objective monitoring techniques were only available in dedicated centers. In addition,

anesthesiologists would have to take several additional steps to obtain reliable measurements when using AMG [19]. Without immobilization of the arm and fingers, the use of preload to the thumb, and calibration of the device, AMG measurements can be highly variable [40], which deprives the technique of its credibility in the eyes of clinicians. In a recent Danish survey, 75% of respondents reported regularly having difficulties with objective monitoring devices (mostly referring to acceleromyography-based devices). The most frequent problems were the fluctuating and unreliable train-of-four values as well as error messages from the monitor [41]. Nevertheless, objective NMM has been shown to decrease the incidence of RNMB and postoperative respiratory complications [35, 36]. In addition, it has been reported that an institutional leader who is dedicated to a comprehensive education and implementation plan of objective monitoring can dramatically decrease the number of RNMB and critical respiratory events [42–46].

For two decades, experts' editorials have advocated the application of objective NMM and universal reversal techniques whenever NMBAs are administered [47–49]. In 2003, Eriksson sent a short and clear message to anesthesiologists calling for objective monitoring whenever NMBA is administered [49]. In 2009, El-Orbany also opined that objective NMM should become standard of care [50]. Unfortunately, the anesthesia community has still not heeded this experts' advice. National surveys from around the world showed that anesthesiologists still rely on the imprecise and antiquated practices of clinical evaluation and subjective assessment [51–54]. In 2010, Naguib et al. conducted a large international survey to measure the knowledge of European and American anesthesiologists in NMB management and survey their clinical practice [55]. The survey clearly showed that inappropriate NMB management still dominates clinical practice worldwide, as 9.4% of American and 19.3% of European anesthesiologists claimed never to use NMMs. Europeans were more likely to use objective monitors, while twice as many Americans routinely administered reversal agents at the end of the case (18 vs. 34.2%) [55]. This survey also revealed that 64.1% of American and 52.2% European anesthesiologists believed the incidence of RNMB is < 1% yet multiple large-scale, contemporary studies have demonstrated the incidence to be between 40 and 60% [5–7, 8••]). Perhaps as a result of extensive educational efforts [19, 56–58], more recent surveys [41, 59] have shown an improvement in general knowledge about neuromuscular blockade management and larger willingness to monitor and administer reversal agents properly. However, such important practice updates have been gradual and slow.

Experts presume several factors have served as obstacles and slowed the progression to widespread utilization of evidence-based NMB management. There has been a paucity of reliable, user-friendly objective neuromuscular monitors [37••]. In the last several years, various medical device manufacturers have developed their own modular or stand-alone objective monitors, suggesting this issue eventually may be addressed. Fortunately, many of these emerging technologies have emphasized the ease of use to increase the acceptance and popularity of the devices. While validation studies are still in progress, early reports investigating new monitors have been very promising [60–67]. It appears that the anesthesia community will have multiple options to select from when adopting quantitative monitoring. Nevertheless, anesthesiologists will need to be aware of the strength and limitations of the monitoring modalities to select the one that is best tailored to their needs.

Clinicians' (over) confidence in their current clinical practice might be another large obstacle to change [68]. Therefore, experts are encouraging national societies to mandate the use of monitoring devices as a first step [37••]. In 2010, Kopman wrote that "It is time for anesthesia's professional organizations to finally draft evidence-based guidelines detailing how best to monitor and manage the perioperative administration of neuromuscular blocking drugs" [48].

Specialty Society Guidelines and International Panels

To help and guide national specialty societies and provide clarity in terms and definitions of NMB management, a consensus statement authored by an international panel of experts was published in 2017 [37••]. This statement provided definitions of NMM modalities and standardized descriptor for levels of NMB. The statement proposes that quantitative (objective) NMB monitoring should be used whenever non-depolarizing NMBAs are administered. It also recommended that subjective monitoring and clinical evaluation of muscle strength be abandoned in favor of objective monitoring. However, the panel recognized that replacing conventional PNS devices with quantitative monitoring equipment would take time and education. During this interim period, the use of a PNS in any patient receiving a NMBA should be mandatory [37••].

In spite of such efforts, anesthesia leadership has been slow to develop guidelines outlining optimal NMB management. Large anesthesia societies like the European Society of Anaesthesiology (ESA) and the American Society of Anesthesiology (ASA) have abstained from making statements on the subject so far. Interestingly, ESA has recently organized a task force on publishing their first NMB management guideline (personal communication). The 2015 American Standards for Basic Anesthesia Monitoring document authored by the ASA does not mention neuromuscular monitoring as part of the minimum monitoring standards [69]. The ASA Practice Guideline for Postanesthetic Care from

2013 is also insufficient in addressing optimal NMB care as it states that "assessment of neuromuscular function primarily includes physical examination and, on occasion, may include neuromuscular blockade monitoring." [70]. It is hoped that the alarming numbers of patients with significant RNMB in the recently published RECITE-US study [8••] will underscore the existing problem and provide the impetus for the American Society of Anesthesiologists to recommend positive changes in the near future. Other large societies also fail to call for quantitative monitoring. Constrained by the resource limitations of low- and middle-income countries, the 2010 World Federation of Societies of Anaesthesiologists (WFSA) International Standards for Safe Practice of Anesthesia recommend the use of PNSs when neuromuscular blocking agents are administered [71].

Nevertheless, smaller national societies have slowly started to take steps forward and include neuromuscular blockade management in their basic anesthesia standards or even develop national guidelines. The specifics of these standards and guidelines are highly variable. This review is not intended to present all available worldwide documents, guidelines, statements, or recommendations, and does not include countries where recommendations are missing. Rather, this review was intended to illustrate the wide spectrum of solutions in the way that various national anesthesia societies handle this important patient safety problem.

National Practice Parameters

The 2016 Norwegian and 2018 Japanese standards simply advocate the monitoring of neuromuscular function when NMBAs and reversal agents are used [72, 73]. The 2014 Swiss anesthesia standards mandate neuromuscular monitoring when NMBAs are administered without specifying the type of the monitor [74]. The 2019 Dutch anesthesia practice parameters list PNSs as part of minimal monitoring standards and mandate PNS use "for controlling neuromuscular function" whenever NMBAs are administered [75].

The Danish general anesthesia guideline from 2017 states that a nerve stimulator should be used whenever a non-depolarizing muscle relaxant is administered [76]. Despite not calling for quantitative monitoring, Denmark has an advanced monitoring practice that involves quantitative monitoring [41, 51, 77]. A survey in 2017 showed that 58% of the 653 responding anesthesiologists always use objective monitoring and 86% in at least three quarter of their patients. Nearly all (97%) of the respondents reported having access to objective monitors [41].

The 2017 Australian and New Zealand College of Anaesthetists (ANZCA) Guidelines on Monitoring During Anaesthesia supports objective monitoring by stating that "Neuromuscular function monitoring, preferably quantitative, must be available for every patient in whom neuromuscular blockade has been induced and should be used whenever the anaesthetist is considering extubation following the use of non-depolarising neuromuscular blockade" [78]. The background paper for this guideline also describes the debate on whether to mandate the use of quantitative monitors. Consideration of current cost implications vs. patient benefit has kept ANZCA from taking this step [79]. Nevertheless, it would be interesting to see the impact of this guideline on Australian clinical practice. A survey conducted in 2013 among the anesthesiologists of Australia and New Zealand revealed similar gaps in knowledge and underutilization of objective monitors as in other parts of the world [53]. Over 35% of respondents never or almost never monitored NM function at that time, and 40% had no access to quantitative devices [53].

The Association of Anaesthetists of Great Britain and Ireland also used a strict tone in their Recommendations for Standards of Monitoring during Anaesthesia and Recovery in 2015 [80]. The document states that "a peripheral nerve stimulator is mandatory for all patients receiving neuromuscular blockade drugs. Peripheral nerve stimulator monitors should be applied and used from induction (to confirm adequate muscle relaxation before endotracheal intubation) until recovery from blockade and return of consciousness … A quantitative peripheral nerve stimulator is required to accurately assess the train of four ratio, but other stimulation modalities (e.g. double burst or post tetanic count) can also be used for assessment. Anaesthetic departments are encouraged to replace existing qualitative nerve stimulators with quantitative devices" [80].

It would be reasonable to suppose that these guidelines contributed to the change in monitoring practices in Great Britain. In 2007, a survey by Grayling showed that 62% of British anesthesiologists never used monitors, and only 9.4% used them routinely [52]. In 2016, a similar survey by Chaco et al. showed a positive change: only 8.9% of the responding anesthesiologists said that they never monitored, while 31.7% did it routinely [59].

The 2017 Perioperative Monitoring Guidelines of the Chilean Anesthesiology Society also recommends that every patient who receives NMBA should be monitored until tracheal extubation and also recommends the use of objective monitoring as it is more reliable to guarantee the recovery to TOF ratio 0.9 and the exclusion of RNMB [81].

According to the 2018 South African Practice Guidelines, "a peripheral nerve stimulator to monitor neuromuscular function with double burst stimulation, train-of-four and post tetanic count facilities is an essential item (therefore the use is mandatory) and considered a minimum requirement for the safe conduct of anesthesia" [82]. An interesting appendix of the guideline (which is somewhat inconsistent with the earlier statement) emphasizes that, "the use and dose of sugammadex should be guided by quantitative neuromuscular transmission (NMT) monitoring as a minimum for all patients (as for all

patients who receive neuromuscular blocking agents). Such monitoring should be made available in all facilities where neuromuscular blocking agents are used" [82].

The 2016 anesthesia monitoring guideline of the Finnish Society of Anaesthesiologists was meant to serve as guidance for more detailed local practice standards. It promotes the use of quantitative train-of-four monitoring to ensure adequate surgical relaxation and safe extubation [83]. The 2016 Finnish guideline abandoned clinical testing which had been part of the previous (1999) guidelines [84].

There are countries which proscribe the healthcare institutions to provide neuromuscular monitors for clinicians but do not mandate their use. The Greek minimal monitoring standards list PNSs as those devices that must be immediately available when they are needed [85]. The German Minimal standards from 2012 also state that a "relaxometer" should be available (without significant delay) when NMBAs are administered [86]. The 2018 Hungarian Patient Safety Guideline states that quantitative neuromuscular monitors must be accessible [87]. In Belgium, a "monitor of neuromuscular function" (type not specified) has been part of minimal monitoring standards for every anesthesia workstation since 2002 [88]. In Morocco, a monitor of neuromuscular function (type not specified) is prescribed for every surgical unit [89].

In 2016, Canada was in a similar situation as the above countries where the use of a peripheral nerve stimulator was not mandated when patient safety advocates called on the Canadian Anesthesiologists' Society (CAS) to mandate PNS use when NMBAs are administered [90]. At that time, Canadian Guidelines stated that a nerve stimulator only needed to be "exclusively available for each patient" [91]. The Canadian Society's reply was rather surprising "… it may reasonably be considered not essential that a nerve stimulator be applied to every patient for every moment of every procedure during which NMBDs have been used, such as is now 'required' for electrocardiography or pulse oximeter use" [92]. While the 2017 guidelines did not provide an update on this controversy [93], the 2018 guideline took one step forward, stating that, "Cautious dosing, vigilant monitoring, and the appropriate reversal of neuromuscular blocking drugs are all essential for patient safety. Neuromuscular monitoring should be utilized when non-depolarizing neuromuscular blocking agents are administered … The following monitoring equipment shall be exclusively available for each patient: Peripheral nerve stimulator, when neuromuscular blocking drugs are used" [94]. The 2019 guidelines made no changes [95], but the 2020 revision will take another step forward. The 2020 CAS guideline will make neuromuscular monitoring mandatory when NMBAs are used and will also list PNSs as "required" for each patient, meaning that these monitors must be in continuous use throughout the administration of all anesthetics [96•]. In their special announcement, the authors of the 2020 guidelines also describe that they feel objective monitoring is superior to subjective monitoring. The reason for not currently mandating the use of objective monitoring is that it is not universally available [97].

National Guidelines on Neuromuscular Blockade Management

Another approach by national societies to NMB management is to publish detailed evidence-based guidelines that not only address monitoring but also indications of NMB and pharmacological reversal. In 2010, the Czech Society of Anesthesiology published a consensus-based practice parameter that provided a description of clinical assessment, subjective and objective monitoring, and recommended the use of objective monitoring, although did not make it obligatory [98]. In 2017, the Czech Society also published a recommendation encouraging Czech institutions to obtain quantitative neuromuscular monitoring devices as soon as possible, and to achieve this, it was proposed that monitoring devices should be included in anesthesia development tenders [99]. The Romanian Guidelines published in 2012 also summarized the then-available evidence on NMB management and concluded that "objective monitoring of the blockade will improve the patient outcome" [100].

The Spanish Society of Anesthesiology and Reanimation (SEDAR) also posted a detailed practical expert guideline on NMB management that unfortunately does not contain a date of publication [101]. It recommended that subjective monitoring should be performed in every patient when NMBAs are administered, but confusingly also recommended the use of objective monitoring, especially if repeated doses or continuous infusion of NMBAs were used, or when the patients have any neuromuscular disease. The level of recommendation at the time of these experts writing of the guideline was described as "good" [101].

The 2018 Good Clinical Practice Guideline of the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Care (SIAARTI) includes principles similar to the Spanish guidelines [102]. It uses the term "desirable" for objective monitoring when repeated doses or continuous infusion of NMBAs are used. However, objective monitoring is "mandatory" only in case of neuromuscular disease, severe renal and hepatic insufficiency, body mass index > 30, and when deep block is required [102].

The French Society of Anesthesiology (SFAR) first published recommendation on neuromuscular blockade management in 2000. The short text recommended "instrumental monitoring of train-of-four stimulation" with a good level of evidence [103]. However, the wording of the recommendations was somewhat confusing regarding the differentiation between "instrumental subjective" and "instrumental objective" monitoring [103]. Contrary to the recommendations from 2000, the updated 2018 SFAR evidence-based

guidelines on NMB management provide a detailed description of advantages and disadvantages of each monitoring modality, monitoring sites, and many aspects of NMB and reversal strategies [104•]. Specifically, the 2018 expert guidelines recommend monitoring of neuromuscular blockade in the perioperative period with the highest evidence level (G1+) and states that it is probably recommended to use TOF monitoring of the thumb to assess neuromuscular blockade in the perioperative period (G2+) [104•].

In 2018, the Portuguese Anesthesiology Society also published a very detailed and advanced consensus guideline on the proper use of neuromuscular blocking and reversal agents [105•]. The guideline mandates instrumental monitoring of NMB whenever NMBAs are administered, and also recommends the use of objective monitoring with the highest evidence level 1A, as it is considered the only method to exclude RNMB [105•].

Conclusion

The introduction of NMBA to anesthesia practice represents a significant pharmacologic advancement that has at the same time also introduced iatrogenic complications related to RNMB. Advances in reversal agents such as sugammadex have improved patient safety; however, monitoring remains a cornerstone of optimal NMB management.

Significant gaps in knowledge within the anesthesia community regarding optimal, evidence-based NMB management have served as a significant obstacle to improving patient safety. Many anesthesiologists drastically underappreciate the scope of this issue and think RNMB happens very infrequently. While the use of quantitative monitoring can minimize the risk of RNMB and its associated complications, there has been a paucity of intuitive objective monitors. As newer devices emerge, hopefully such quantitative monitoring can serve as an important feature in optimal NMB management strategies widely utilized by the anesthesia community.

While an international panel of experts has recently developed a consensus statement strongly recommending quantitative monitoring, anesthesia societies have been slow to adopt similar guidelines. The expansion of such anesthesia specialty guidelines may represent the next step in the right direction to correct this pervasive patient safety threat.

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- •• Of major importance

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