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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Detecting Residual Weakness: an Update on Quantitative Neuromuscular Monitoring

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Abstract

Purpose of Review The purpose of this review is to summarize the newest generation of quantitative neuromuscular monitors and the different modalities that can be used to minimize the risk of postoperative residual weakness.

Recent Findings New guidelines and consensus statements are emerging that emphasize the importance of using quantitative monitors whenever neuromuscular blocking agents (NMBAs) are administered. Additionally, there are new technologies emerging in this area.

Summary Residual neuromuscular blockade remains a common occurrence in the postoperative period. Even small degrees of residual muscle weakness can produce significant postoperative complications. Qualitative (subjective) assessment is an unacceptable technique to exclude residual neuromuscular blockade because fade is difficult to detect when train-of-four ratios are between 0.4 and 0.9. For that reason, using objective quantitative monitors is essential to confirm adequate recovery in all patients receiving NMBAs and ensure patient safety.

Keywords Neuromuscular blockade · Residual neuromuscular blockade · Quantitative neuromuscular monitoring · Quantitative neuromuscular monitors · Objective neuromuscular monitoring

Introduction

Neuromuscular blocking agents (NMBAs) are a class of medications routinely used during anesthesia to facilitate endotracheal intubation [1] and improve conditions for optimal surgery [2]. Since its introduction by Griffith and Johnson in 1942 [3], NMBAs have become an integral part of anesthesia practice. In addition to improving tracheal intubation conditions, this class of medications has been shown to reduce laryngeal trauma and hoarseness [4], as well as optimizing surgical conditions during abdominal surgery [5, 6]. However, these medications are also associated with respiratory complications (as well as delays in recovery times and unpleasant symptoms of muscle weakness) in the early postoperative period due to residual neuromuscular blockade (RNMB) [7–9]. Adequate recovery is defined as a train-of-four ratio (TOFR) ≥ 0.9 as measured at the adductor pollicis after ulnar nerve stimulation. Even shallow levels of residual paralysis are associated with impaired function of respiratory and pharyngeal muscles [10], upper airway obstruction [11], and hypoxemia [12].

Recently, an international panel of experts released a consensus statement specifying that quantitative (objective) monitoring should be used whenever NMBAs are administered in order to ensure adequate recovery of neuromuscular function [13••]. Likewise, the Association of Anesthetists of Great Britain and Ireland have submitted a guideline mandating at least the use of a peripheral nerve stimulator during all stages of anesthesia in patients receiving neuromuscular blockade agents, although this statement notes that quantitative monitoring device is the only means to accurately measure the TOFR and confirm recovery [14••].

Many anesthesiologists utilize qualitative monitors (peripheral nerve stimulators) or subjective methods to assess the level of neuromuscular blockade. These methods are far from optimal as even experienced anesthesiologists cannot detect fade when the TOFR is > 0.4 [15]. Many studies have shown that subjective evaluation may provide inaccurate information regarding the degree of recovery compared with

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objective evaluation [16, 17]. Furthermore, utilizing a peripheral nerve stimulator with various patterns of stimulation such as train-of-four (TOF) stimulation, double-burst stimulation, 50 Hz tetanus, and 100 Hz tetanus was still less accurate in detecting residual paralysis than objective monitoring [18].

In this article, we will review newer quantitative neuromuscular monitoring devices that can be used to accurately determine the level of blockade, ensure adequate recovery, and enhance patient safety by minimizing the risk of postoperative complications due to residual neuromuscular blockade.

Quantitative Neuromuscular Monitoring

Quantitative neuromuscular monitoring devices objectively measure muscle responses to nerve stimulation and allow for quantification of the degree of neuromuscular blockade. Responses to train-of-four count (TOFC) and TOFR are displayed numerically in real time. These monitors can be categorized based on the modality utilized to obtain such measurements, as well as whether the monitor is a portable, handheld unit, or incorporated into an anesthesia workstation. Mechanomyography (MMG) has served as the historical gold standard for quantitative monitoring as it directly measures the isometric force of muscle contraction after nerve stimulation. This modality requires a complex setup, and these devices are no longer commercially manufactured. As such, advances in monitoring have led to the utilization of other, more user-friendly modalities.

Acceleromyography

Acceleromyography (AMG) is the modality most frequently used for the objective evaluation of neuromuscular function in the clinical setting. This technique is based on Newton's second law of motion (Force = Mass × Acceleration) and measures the acceleration of muscle contraction. Traditionally, AMG has been applied to the thumb to measure the response of the adductor pollicis to ulnar nerve stimulation. Surgical positioning may limit its use because AMG requires unobstructed movement of the hand and thumb. Additionally, patient movement upon emergence from anesthesia can prove to be a significant obstacle to obtaining AMG-derived TOFR. One of the most widely available AMG-based stand-alone quantitative monitor was the TOF-Watch (Schering-Plough Corp., Kenilworth, NJ, USA). Over time, this device became the most widely utilized objective monitor and became the standard monitor for clinical use and research [19]. However, this monitor was discontinued and has not been manufactured since 2016. Currently, there are two AMG devices incorporated into the anesthesia workstation: Infinity Trident NMT SmartPod (Drager Medical AG & Co. KGaA, Lubeck, Germany) and IntelliVue NMT module (Philips, Amsterdam, Netherlands). Both of these monitors have the advantage of synching the measurements into the electronic medical record but are less portable and may not be compatible with equipment in the recovery room. Infinity Trident NMT SmartPod offers TOFC, TOFR, single twitch (ST), and post-tetanic count (PTC). Settings can be adjusted and include auto or manual (5 to 60 mA in increments of 5 mA), as well as varying measurement intervals (none, 1, 10, 20 s, 1, 5, 15, 30 min) [20]. IntelliVue NMT (Fig. 1) was designed to be integrated exclusively into the Philips anesthesia station. It has a single peripheral cable to provide stimulation to the ulnar nerve through two electrodes, as well as a piezoelectric sensor to measure the thumb movements in every direction. It delivers TOFC, TOFR, ST, double burst (DB), and PTC. The module allows the clinician to configure the stimulation patterns and display the current results and trends [21]. Two years ago, the manufacturer introduced a dedicated accelerometer hand adapter and calibration function. This update improved the precision and provided results more similar to those derived from the TOF-Watch SX [22].

There are two stand-alone, portable AMG-based monitors: TOF-Scan (Drager Technologies, Mississauga, ON, Canada) and Stimpod NMS 410/450X (Xavant Technology, South Africa). These monitors have modified the traditional measurement of the thumb motion in one vector plane to measure the acceleration in all directions. TOF-Scan is a new acceleromyography monitor with a 3-dimensional accelerometer sensor to measure contraction of the adductor pollicis in multiple planes. The piezoelectric sensor attaches to the thumb and uses an integrated hand adapter that provides a consistent preload (Fig. 2), a feature that can provide more precise readings [23]. Such hand adaptors can also decrease TOFR variability associated with AMG-based monitoring and minimize the effect of reverse fade phenomenon, in which repetitive stimulation causes an exaggerated response in subsequent stimulations that can result in TOFR > 100%. According to the manufacturer, no sensor calibration is required before first measurement [24]; however, normalization of values can be useful with AMG devices as baseline TOFR have been reported to be as high as 141%. [23]. The electrical stimulation is monophasic, with duration of impulse of 200 μs, and it has adjustable intensity (0 to 60 mA) with a default output of 50 mA. TOF-Scan delivers TOF count, TOFR, ST (0.1 Hz and 1 Hz), DB, and PTC. However, to calculate the TOFR, this device uses the fourth twitch/second twitch (T4/T2) rather than the accepted standard fourth twitch/first twitch (T4/T1) when the T2 is greater than T1. Later models of the TOF-Watch utilized a similar algorithm, despite its validation in the literature [25]. In addition, the TOF-Scan will not display TOFR numbers greater than 100%, a feature that can preclude normalization. Nonetheless, this device requires minimal setup and can operate on batteries that maintain power for about a

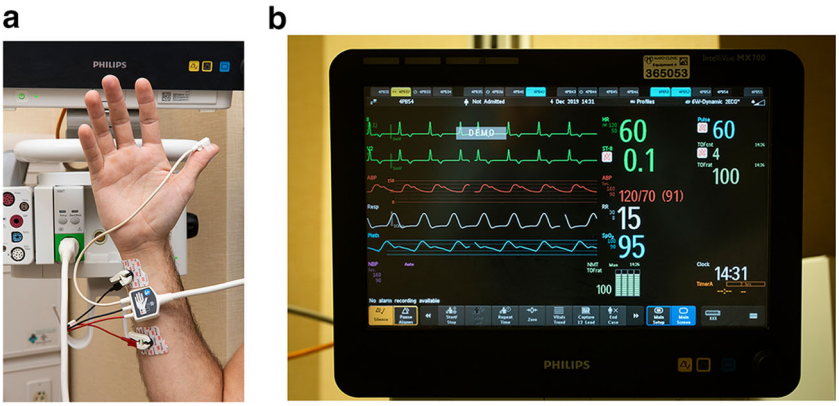

Fig. 1 **a** Philips IntelliVue NMT module. **b** Display with Philips IntelliVue NMT module incorporated into anesthesia workstation

month with typical use. TOF-Scan is commercially available and approved by the US Food and Drug Administration (FDA).

A recent observational study compared the neuromuscular function recovery between the well-accepted TOF-Watch SX and the new monitor TOF-Scan [26]. There was good agreement between the two quantitative monitoring devices during neuromuscular recovery. However, the previous study showed poor agreement between the two devices for onset and early recovery at deep block level of neuromuscular blockade, but better agreement at recovery from shallow levels of blockade [27]. Future studies are needed to determine if TOF-Scan could be the new standard AMG-based monitoring device in the clinical setting and research, as the TOF-Watch is no longer commercially manufactured.

The Stimpod NMS 410/450X is another AMG-based monitor commercially available and FDA approved. This device also has a 3-dimensional accelerometer like TOF-Scan to more accurately measure acceleration in multiple planes [28]. The electrical stimulation is monophasic square wave, with current ranges from 0 to 80 mA and a pulse width of 0.2 ms. It can be used to measure TOFR, single twitch, DB, and PTC. Additionally, Stimpod can also be used in regional anesthesia for nerve mapping and a precise nerve location during procedures. The mapping mode allows the clinician to map out a particular superficial nerve by percutaneous neurostimulation utilizing a nerve mapping probe [29].

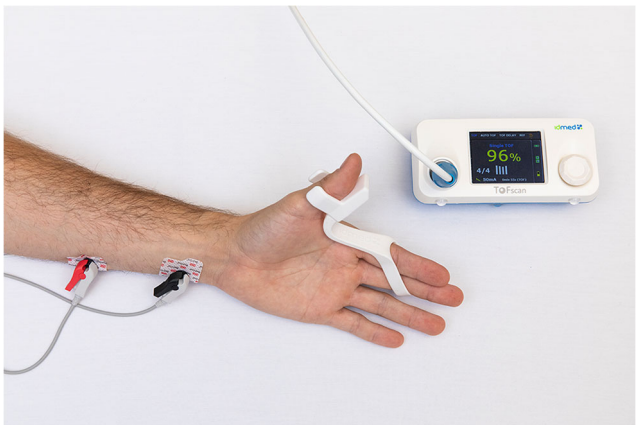

Fig. 2 TOF-Scan device

Electromyography

Electromyography (EMG) is the oldest method used and the most physiologic method of measuring neuromuscular blockade [30]. EMG measures the compound muscle action potential resulting from nerve stimulation. The sensing electrodes are usually placed at the adductor pollicis, abductor digiti minimi, or first dorsal interosseous muscle after ulnar nerve stimulation. In contrast with AMG, it does not require free movement of the thumb for accurate measurement. Currently, the TetraGraph (Senzime AB, Uppsala, Sweden) and TwitchView (Blink Device Company, Seattle, WA) are two stand-alone EMG-based devices available for clinical use. In addition, GE Healthcare is the only manufacturer of a commercially available EMG device incorporated into anesthesia workstation, Datex-Ohmeda E-NMT neuromuscular transmission module.

The TetraGraph is a portable EMG-based device that recently received FDA approval. This device uses disposable electrodes (TetraSens) that are applied over either forearm. TetraSens electrodes consist of two stimulating electrodes proximal to the connector and two recording electrodes distal. The round distal recording electrodes can be placed over the adductor pollicis, first dorsal interosseous, or the abductor digiti minimi muscles (Fig. 3). The electrical stimulation is monophasic square wave, with pulse width of 200 μs or 300 μs and adjustable intensity (0–60 mA). The operating modes are TOFC, TOFR, ST, and PTC [31].

TwitchView is also an EMG-based stand-alone monitoring device commercially available in the USA and approved by the FDA. The device also measures the degree of neuromuscular blockade by stimulating the ulnar nerve. The monitor connects to a single-use electrode array, which consists of five independent electrodes, two for stimulation and three for

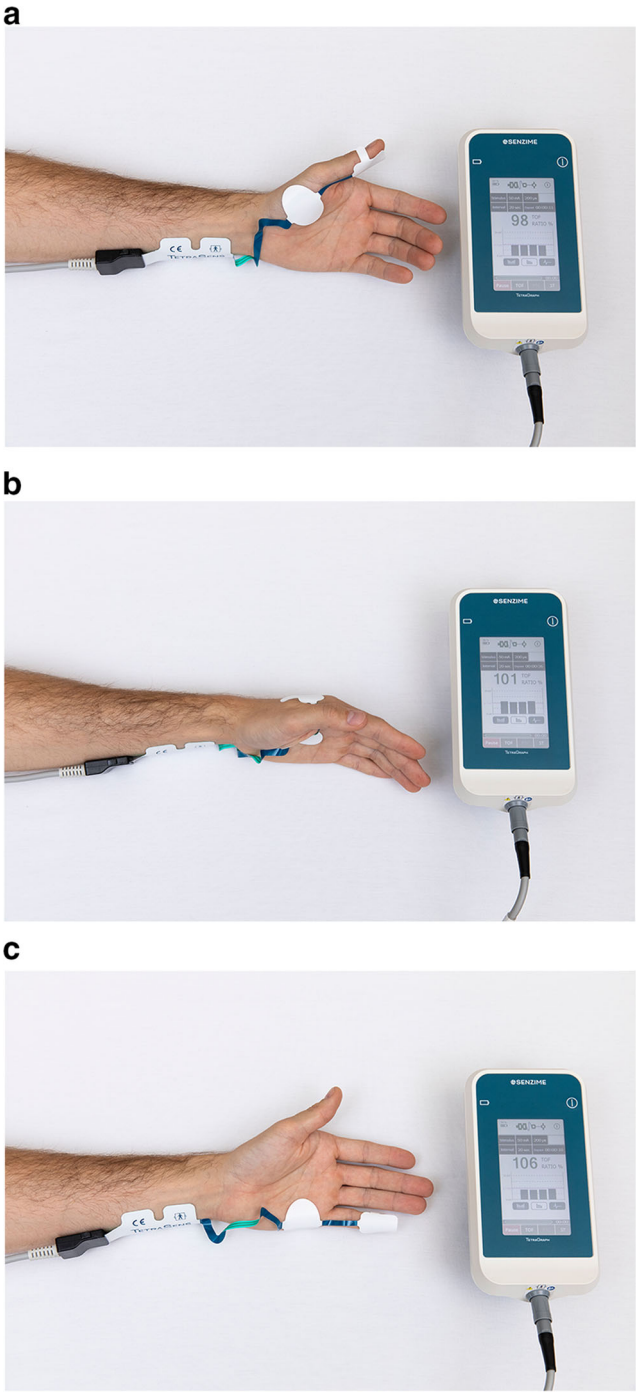

Fig. 3 **a** TetraGraph monitoring adductor pollicis muscle. **b** TetraGraph monitoring first dorsal interosseous muscle. **c** TetraGraph monitoring adductor digiti minimi

recording responses. The device delivers TOFR, ST, and PTC [32]. A recent study comparing TwitchView, Stimpod NMS450, and a newly constructed mechanomyography [33] revealed several interesting caveats to comparing monitoring modalities. Over various levels of neuromuscular blockade, the TwitchView-derived TOFR had better agreement with mechanomyography-derived TOFR than values obtained from Stimpod NMS450. Additionally, the AMG-derived TOFRs often exceeded 100%.

GE (Datex-Ohmeda) neuromuscular transmission E-NMT module has interchangeable electromyography and kinemyography sensors and allows for automatic cycling at a user-defined time interval each time, providing three parameters: TOFC, TOFR, and PTC [34].

Kinemyography

Kinemyography (KMG) measures the degree of bending of a piezoelectric motion sensor placed at the base of the thumb and index finger. This technique is similar to AMG, but the accuracy is not superior and has the same limitation of requiring a freely moving thumb. GE Healthcare manufactures a KMG-based monitor that is incorporated into the anesthesia workstation and is available in both adult and pediatric sizes. A comparative study of EMG and KMG using Datex-Ohmeda neuromuscular transmission monitor showed that KMG-derived TOF ratios were consistently higher than with EMG-derived TOF ratios. The authors ultimately concluded that values from these two modalities could not be used interchangeably [35]. Despite the limitations, KMG monitoring requires minimal setup time and can be a useful technique to objectively determine level of blockade [36].

Cuff Pressure Modality

The TOF-Cuff (RGB Medical Devices, S.A., Madrid, Spain) is a device that allows monitoring of the blood pressure and the neuromuscular blockade at the same time. This is a method based on the stimulation of the brachial plexus (most likely, the ulnar and median nerve) through a modified noninvasive blood pressure cuff that incorporates stimulating electrodes on the inner surface [37]. The neuromuscular activity is measured by the changes in pressure generated in the cuff after the stimulus. According to the manufacturer, the device tracks the last 75 stimulations and shows the T4/T1 ratio over time [38]. The device delivers TOF, ST, and PTC, with duration of impulse of 100, 200, or 300 μs and an adjustable intensity (1–60 mA). The first pilot study using TOF-Cuff compared this method with MMG. According to the bias and limits of agreement between the two methods, TOF-Cuff was found to be useful to monitor neuromuscular blockade. Likewise, they found the new method easy and simple to use, although more studies are needed to further validate this device and modality [39]. A recent clinical trial demonstrated that this device had poor correlation with MMG when TOFR is > 0.9, but good agreement with a TOF ratio > 0.7 [40]. Similarly, Kazuma et al. found that the TOF-Cuff underestimated TOFR in comparison with the TOF-Watch device in the later recovery period. These

authors ultimately concluded that the TOF-Cuff may not be sufficient to evaluate significant residual neuromuscular blockade in all patients [41]. This notion was also recently supported as Krijtenburg and colleagues determined that TOF-Cuff measurements cannot be used interchangeably with measurements obtained at the adductor pollicis using EMG or AMG [42].

Conclusions

Residual neuromuscular blockade continues to be a common problem among patients receiving NMBAs during the perioperative period. While not every patient with residual weakness develops a postoperative complication, many can experience avoidable critical respiratory events. Quantitative monitors have been demonstrated to reduce the incidence of postoperative residual weakness. However, several barriers exist that have prevented the widespread application of these devices, such as costs and additional training. Nonetheless, it is imperative that anesthesiologists take action and familiarize themselves with the nuances of quantitative neuromuscular monitoring. Subjective evaluation with a peripheral nerve stimulator may be a common practice; however, this method is inadequate to confirm recovery of neuromuscular function. Residual neuromuscular blockade is an important patient safety issue that affects postoperative outcomes, and proper monitoring is crucial to improving neuromuscular management, enhancing safety, and improving patient care.

Compliance with Ethical Standards

Conflict of Interest Vivian Hernandez-Torres declares that he has no conflict of interest. J. Ross Renew has received research support through a grant from Merck (with funds to Mayo Clinic).

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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