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REVIEW PAPER

Muscle relaxant use during intraoperative neurophysiologic monitoring

Tod B. Sloan

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Abstract Neuromuscular blocking agents have generally been avoided during intraoperative neurophysiological monitoring (IOM) where muscle responses to nerve stimulation or transcranial stimulation are monitored. However, a variety of studies and clinical experience indicate partial neuromuscular blockade is compatible with monitoring in some patients. This review presents these experiences after reviewing the currently used agents and the methods used to assess the blockade. A review was conducted of the published literature regarding neuromuscular blockade during IOM. A variety of articles have been published that give insight into the use of partial pharmacological paralysis during monitoring. Responses have been recorded from facial muscles, vocalis muscles, and peripheral nerve muscles from transcranial or neural stimulation with neuromuscular blockade measured in the muscle tested or in the thenar muscles from ulnar nerve stimulation. Preconditioning of the nervous system with tetanic or sensory stimulation has been used. In patients without neuromuscular pathology intraoperative monitoring using peripheral muscle responses from neural stimulation is possible with partial neuromuscular blockade. Monitoring of muscle responses from cranial nerve stimulation may require a higher degree of stimulation and less neuromuscular blockade. The role of tetanic or sensory conditioning of the nervous system is not fully characterized. The impact of neuromuscular pathology or the effect of partial blockade on monitoring muscle responses from spontaneous neural activity or mechanical nerve stimulation has not been described.

Keywords Anesthesiology · Muscle relaxants · Neuromuscular blockade · Electromyography · Motor evoked potentials

1 Introduction

Neuromuscular blocking agents (NMBA) are commonly used in anesthesiology to improve conditions for placement of an endotracheal tube, facilitate mechanical ventilation, and for relaxation of muscles necessary for the conduct of the surgical procedure. However, their use during intraoperative electrophysiological monitoring (IOM) using muscle derived responses [e.g. spontaneous and stimulated electromyography (EMG) and muscle responses to transcranial motor evoked potentials (MEP)] are controversial because they can reduce the amplitude of the responses and simulate loss of neural function; many individuals recommend their avoidance during the monitoring portion of procedures [1, 2]. After a brief review of the commonly used NMBAs and clinical monitoring of blockade, this review will summarize the state of knowledge and experience of the use of partial NMB with IOM.

2 Physiology of NMBA and the neuromuscular junction

Normal transmission across the neuromuscular junction (NMJ) is accomplished by the release of acetylcholine (ACh) from the presynaptic terminal in response to the depolarization of the peripheral nerve. The ACh exists in two

T. B. Sloan (✉)
Department of Anesthesiology, University of Colorado School of Medicine, Academic Office West (AO1), MS 8202, 12631 E 17th Avenue, Aurora, CO 80045, USA
e-mail: tod.sloan@ucdenver.edu

Table 1 Drug doses and effects of commonly used neuromuscular blocking agents

Drug	Intubating dose (mg/Kg)	Onset (min)[1]	Duration (min)[2]
Succinylcholine	1	1	10
Cis-atracurium	0.1	2.5	45
Rocuronium	0.6	1.3	33
Vecuronium	0.1	3	33
	1. Time to 95 % depression T1		
	2. Time to 25 % recovery T1		

basic pools, one in vesicles ready for release with the remainder available to move to the readily available pool when needed. The released ACh diffuses across the synaptic cleft and activates the post junctional acetylcholine receptor (AChR) which results in a depolarization of the muscle and contraction [3, 4]. The ACh is very rapidly metabolized by acetylcholinesterase in the cleft terminating the effect.

Neuromuscular blocking agents (NMBA) act by blocking the effect of Ach on the postjunctional receptors and by acting at the presynaptic terminal to alter the amount of readily available Ach. Currently the commonly used NMBAs include succinylcholine (Anectine®), vecuronium (Norcuron®), rocuronium (Zemuron®), and cisatracurium (Nimbex®). (Table 1) Each of these has the capability of blocking acetylcholine (ACh) transmission through the neuromuscular junction (NMJ) resulting in pharmacologic paralysis.

Commonly used NMBA are of three general chemical structures. Succinycholine (SUX) is essentially two ACh molecules attached together. When given intravenously it diffuses to the NMJ and binds at the post junctional AChR causing an initial depolarization with muscle contraction (hence it is referred to as "depolarizing"). It occupies the NMJ desensitizing the receptor and blocking transmission until the concentration falls by diffusion into the blood stream where it is metabolized by butyrycholinesterase (also known as plasma cholinesterase or pseudocholinesterase). Its onset of action is reasonably quick (1–1.5 min) and duration is short (10–12 min) unless inherited abnormalities in the butyrycholinesterase slow metabolism (in which the paralysis may last up to 4–6 h) [5].

For many practitioners SUX remains the choice of NMBA in circumstances where the airway needs to be acquired rapidly (e.g. a patient at risk for regurgitation of gastric contents). In addition, the short duration of action allows the patient to begin breathing if the rare circumstance occurs where the anesthesiologist in unable to intubate and unable to ventilate the patient. However, the depolarizing aspect leads to some undesirable qualities including hyperkalemia (life threatening in some circumstances such as recent spinal cord injury, burns and crush injuries), increases in intraocular and intracranial pressure, and triggering of malignant hyperthermia in susceptible patients. In addition, when large doses are given, or when given to patients without adequate butyrycholinesterase function, a prolonged block can occur which is referred to as a "phase II block." If its use is not contraindicated, this is an excellent drug for IOM applications where the induction of anesthesia and intubation is accomplished with minimal time to acquisition of baseline evoked responses post intubation and before positioning.

The second class of drugs is the non-depolarizing NMBAs which do not result in a muscle contraction when they act. When given intravenously, these medications diffuse into the synaptic cleft and reversibly bind to the AChR also desensitizing the receptor and competing for binding with ACh producing neuromuscular blockade (NMB). Like SUX, these medications terminate their action by diffusing away from the NMJ and undergoing metabolism and elimination. These NMBAs can also be used by infusion to maintain partial NMB (pNMB).

In general, these NMBAs have an onset of action that is slower than SUX and duration of action that is longer than SUX. They are referred to as "intermediate duration of action." Agents with a longer duration of action are also available but less commonly used. In addition to acting at the postjunctional AChR they act at prejunctional receptors which regulate the amount of ACh available for release when a nerve impulse occurs [6, 7].

Two of the commonly used agents are aminosteroids. Vecuronium (VEC) was the first to be released into common practice. Rocuronium (ROC) has subsequently been released and is more frequently used in many centers. The onset of ROC is shorter and approaches SUX; however it has a duration that exceeds SUX. This duration is usually reasonable for intubation for most IOM circumstances where evoked muscle baselines need to be acquired after induction and intubation.

The third commonly used non-depolarizing agent is cisatracurium (CIS) which is a benzylisoquinolinium structure similar to its predecessor atracurium (ATR). This NMBA is unusual in that its chemical structure undergoes spontaneous decomposition (Hofmann elimination) which does not require the hepatic or renal function which is required for VEC and ROC [8]. As such it is frequently used when hepatic and renal function is compromised.

3 Interactions with NMBA action and duration

In addition to the uncommon genetic variant of SUX metabolism (about 1:2,000 patients), several circumstances

can change the potency or duration of the pharmacological NMB. For example, the potent inhalational agents have effects at the NMJ which result in more profound NMB after they have equilibrated at anesthetic doses (after about 30 min) [9–11]. This effect is such that NMB can be accomplished by about one-half the NMBA dose that would otherwise be required. Similarly, hypothermia, some antibiotics (e.g. clindamycin), magnesium, local anesthetics, furosemide, and acidosis (respiratory or metabolic) can increase the block [12–21]. The presence of anti-epileptic medications has varying effects. Acute administration of phenytoin augments the NMB whereas chronic use (phenytoin and carbamazepine) decreases the NMB duration due to increased metabolism, and possibly up regulation of the AChR [22–26].

4 Reversal of NMBA action

When desired, the NMB can sometimes be reversed to allow clinical NMJ transmission. This is often done at the conclusion of a procedure where the patient was pharmacologically paralyzed for the procedure. At present, there is no effective method to reverse the action of SUX. Fortunately, since the non-depolarizing agents competitively block the AChR, increasing the ACh concentration in the cleft can tip the balance of competition to allow physiological transmission. This is accomplished by giving anticholinesterase agents such as neostigmine (Prostigmin®) which block the metabolism of ACh so that its concentration builds up in the synaptic cleft and can compete with the residual NMBA [27]. Since this is a competitive effect, reversal can only occur if the NMBA is already sufficiently metabolized (i.e. this method will not reverse a "deep" block). Of note, these agents also block the metabolism of SUX and can prolong a SUX block if it is still present.

A second method of reversal has been developed for the reversal of ROC and VEC. In this case a cyclodextran molecule [sugammadex (Bridion®)] has been designed so that the center of the six sugar "doughnut" has a central pocket for these steroid NMBAs that binds them removing their action at the NMJ [28, 29]. At this writing sugammadex is unavailable in the USA.

5 Monitoring neuromuscular blockade

Several reviews have been published about monitoring NMB [4, 30–32]. The degree of NMB at the NMJ is typically measured by anesthesiologists in three ways. These all involve measuring the muscle response following supramaximal stimulation of a peripheral nerve similar to the stimulation used for the somatosensory evoked potential

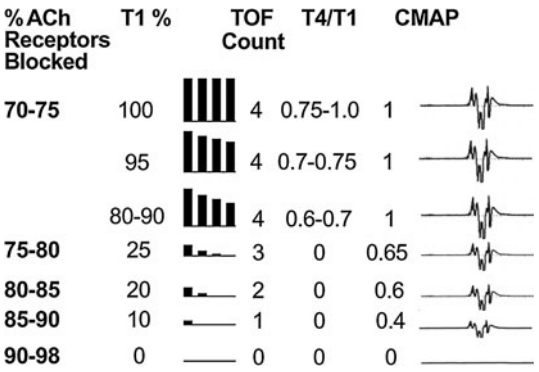

Fig. 1 Relationship of receptors blocked, single twitch response (T1), Train of four and MEP amplitude. Shown in the *left* column is the approximate percentage of acetylcholine receptors (AChR) blocked by neuromuscular blocking agents. To the *right* is the approximate height (%) of the T1 response at these levels compared to *baseline*. Next is a depiction of the train of four (TOF) response, the count of the 4 possible responses that are present, and the ratio of the fourth response to the first (T4/T1). Finally, the approximate peak amplitude of the compound muscle action potential (CMAP) of the MEP is shown using the data in Fig. 2. Data taken from various sources (see text)

(SSEP). Responses can be measured by electromyography as well as by mechanical measurements (e.g. accelerometry or visual inspection).

The muscle response (M response) to a single stimulus is used as a standard and referred to as T1; monitoring of the blockade using T1 is done by comparing the amplitude to a baseline response before any drug is administered. Problems with obtaining a reliable baseline response make it more difficult to use for monitoring, but it is a standard for most studies of NMBA. The T1 amplitude correlates with occupancy of the AChR by NMBAs. NMB occurs over a narrow range of receptor occupancy between 75 and 95 % of the post-junctional AChR (Fig. 1) [33]. Clinically useful NMB occurs when the receptors are 95 % blocked [34]. The dose to attain this is referred to as the ED_{95} (where 50 % of patients have 95 % receptor blockade) [35]. The duration of NMBA action is defined by the return of T1 to 25 % of baseline because this is a degree of blockade that is rapidly reversed by anticholinesterase agents.

A more practical method of monitoring NMB which does not require a baseline is monitoring of four supramaximal stimuli given every 0.5 s (2 Hz). This "train of four" technique (TOF) takes advantage of the presynaptic effect of the nondepolarizing NMBAs which limits the amount of readily releasable Ach so that the amount of Ach released with each of the four stimuli declines when the stimulation rate exceeds the nerve terminal's ability to synthesize ACh. This produces a progressive reduction of muscle responses ("fade") that is related to the degree of blockade. [36] Hence the nondepolarizing NMBAs have

two effects seen in the TOF: 1) a general reduction in the response quantified by reductions in T1 due to competitive inhibition at the post junctional AChR, and 2) a progressive decline in subsequent responses due to the presynaptic effect (fade). This is different from the depolarizing agents (SUX) which produce an equal decrease in all four responses with NMB (i.e. no fade).

Thus, as NMB from non-depolarizing agents increases, there is a progressive decline in the amplitude of T1 and increasing fade in the TOF [37–40] (Fig. 1). Thus the fourth twitch (T4) gets smaller compared to the first twitch (TOF ratio: T4/T1) until T4 is lost. At higher NMB doses the third response is lost, then the second and finally the first twitch. Therefore the TOF ratio (T4/T1) and the "count" of the number of twitches are used to estimate the degree of blockade.

When no twitches in the TOF are present (often referred to as a "deep" block) the degree of NMB can sometimes be assessed using a tetanic stimulus (50 Hertz supramaximal stimulus for 5 s) [40]. For the 1–2 min following this stimulus the level of ACh in the synaptic cleft is elevated such that subsequent ACh release from additional stimuli may produce a response [41]. Typically the number of "post tetanic responses" seen with stimulation at 1 s intervals starting 3 s after the tetanic stimulus inversely correlates with the time until T1 reappears (T1 reappears in approximately 15–20 min with intermediate acting NMBAs when one post tetanic response is present). As with T1 and TOF testing, a pause of 12–15 s between post tetanic testing is needed to allow the presynaptic terminal to restore ACh reserves before subsequent post-tetanic testing is conducted.

The muscle-nerve pair used for testing of NMB is extremely important; testing in one muscle may not reflect the degree of blockade in other muscles; different muscles have different onset times, maximum degree of NMB, and duration of NMB. The centrally located muscles (diaphragm, larynx) are less sensitive to NMBA whereas the abdominal muscles, orbicularis oculi, and peripheral muscles of the limbs are most sensitive [42–52]. Diaphragm and laryngeal muscles also have a faster onset. Some of these differences relate to differences in AChR density, number of NMJ per volume of muscle (receptor density), blood flow, muscle temperature, ACh release with stimulation, and acetylcholinesterase activity [53].

The most frequently monitored muscle by anesthesiologists is the response of the relatively sensitive thenar hand muscles following ulnar stimulation at the wrist. This is because this response gives reliable insight into the degree of relaxation in the upper airway muscles needed for intubation of the trachea and the muscles commonly relaxed for surgical procedures (e.g. the abdominal musculature). Other commonly monitored responses include the response of the facial muscles to facial nerve stimulation and the response to posterior tibial nerve stimulation [46].

6 The use of NMB during intraoperative monitoring

During procedures where IOM is conducted, pharmacologic paralysis is typically utilized with the induction of anesthesia to facilitate intubation (typical dose is twice the ED_{95}). This improves the intubating conditions and reduces the risk of laryngospasm when the endotracheal tube is placed. Intubation without NMB is occasionally done for patients with an unstable neck or known difficult intubation (e.g. awake fiberoptic intubation). In these cases the intubation is usually done with the patient lightly sedated and local anesthesia placed topically to anesthetize the airway. Intubation can also be done with the patient asleep using only an induction sedative (e.g. propofol). As with the awake intubation, local anesthesia is usually used and this may prevent the use of the vocalis muscle to monitor the vagal and recurrent laryngeal nerves. Finally, in the absence of an intravenous line (such as with children), intubation can be done after mask induction using inhalational agents (e.g. sevoflurane). This "inhalational induction" will make recording of some responses (e.g. MEP) difficult until the inhalational agent level subsides.

After induction, the NMB is usually allowed to spontaneously recover. Hence the subsequent acquisition of post intubation baselines will require the recovery time appropriate to the medication given (Table 1). TOF testing can be used as a guide during recovery. In addition, the presence of the motor activity from stimulation of peripheral mixed motor and sensory nerves for SSEP monitoring can also signify reduction in NMB.

Subsequent NMBA doses may be used as a part of the anesthetic if requested by the surgeon or proceduralist. For example, some operative teams request full muscle relaxation during certain procedures, such as the trans-abdominal approach to the anterior lumbar spine and the initial portions of a posterior thoracic spinal procedure where muscle activity is pronounced as it is dissected from the vertebra.

In those circumstances, complete muscle relaxation may prevent monitoring of MEP and EMG responses. However, monitoring with the SSEP and the MEP in the spinal canal (D wave) will be possible. Muscle relaxants are generally thought to have no effect on the sensory evoked responses [54]. SSEP's may actually improve with muscle relaxation because EMG interference is reduced in electrodes near muscle groups, such as with the subcortical SSEP responses recorded over the posterior cervical spine. This benefit to recording is also seen in epidural recording of the D

wave from transcranial stimulation. Here paraspinous muscle activity can obscure the response and complete or near complete neuromuscular blockade may be necessary for recording [55–58].

Partial neuromuscular blockade (pNMB) has been used to reduce the movement of the patient during MEP testing such as when a surgeon is operating through a microscope. One report of intracranial aneurysm clipping without pNMB indicated that the movement from transcranial stimulation at C1 and C2 (international 10–20 system) interferred with the microsurgical procedures in 10 % of their cases [59]. The authors indicate that in these cases direct cortical stimulation is associated with less movement and has been used in cortical surgery [60]. With respect to movement during surgery, it is important to note that movement can also often be moderated by judicious choice of the MEP scalp stimulus location and by timing the stimulation with a surgical pause (i.e. coordinating with the surgeon). pNMB may also be requested in the interventional suites to minimize movement between radiographs so that one image can be subtracted from the next to enhance a desired study ("mask" techniques).

pNMB has also been used in an occasional patient where tolerance to the components of total intravenous anesthesia (TIVA) results in continued patient movement. In these patients high doses of TIVA agents may not be hemodynamically tolerated or the anesthetic effect (e.g. propofol) may prevent MEP monitoring. As such inhalational agents or partial NMB may become necessary.

7 Studies of neuromuscular blockade and monitored muscle responses

Two studies in ketamine anesthetized monkeys with VEC and atracurium demonstrated the primary effect of pNMB is a reduction in the MEP amplitude of the muscle response [61, 62]. In these studies MEP was produced using transcranial magnetic stimulation and the response was measured in the thenar muscles where NMB was quantified by T1 and mechanical TOF to ulnar nerve stimulation. As shown in Fig. 2, minimal MEP amplitude reduction was seen when the T1 was 0.5–1.0. Similar reductions were seen when the TOF T4/T1 ratio was 0.3–1.0. The MEP amplitude reduction did not reach statistical significance until the TOF T4/T1 ratio reached 0.2 or the T1 response reached 10–20 % of baseline. In these animals, the MEP amplitude was 30–60 % of the unblocked response at a T1 of 10–20 % and 55–65 % when the mechanical TOF ratio was 0.1. The onset latency of the MEP was not increased until the T1 single response was reduced to 10 % and the TOF T4/T1 ratio was 0.1. The average values shown in

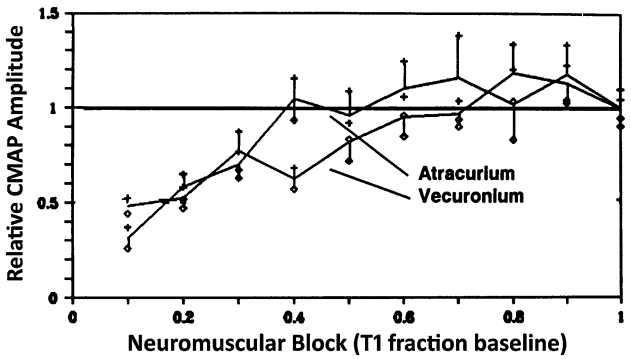

Fig. 2 Relationship of the M response and muscle response of the MEP during different levels of neuromuscular blockade. Shown are the combined data from two studies in monkeys which depict the amplitude (±SEM) of the compound muscle action potential (CMAP) of the MEP at various levels of neuromuscular blockade by vecuronium or atracurium as measured by the fraction of EMG remaining in the M response (T1). Redrawn from Sloan with permission [61, 62]

Fig. 2 were used to estimate the MEP amplitude shown in Fig. 1 at varying degrees of NMB.

Kalkman studied MEP during pNMB with VEC in 11 patients during sufentanil infusion with 60 % nitrous oxide [63]. The MEP was recorded in the Tibialis Anterior (TA) following transcranial electrical stimulation. pNMB was assessed by T1 and TOF using an accelerometer of the thenar muscles after ulnar nerve stimulation. The M response of the TA to peroneal stimulation was also assessed and was larger than the MEP (9.6 vs 1.21 mV). Despite loss of T1 in the hand following a bolus of VEC, the MEP and the M response could still be recorded in the TA. The responses in the TA were recorded when an infusion of VEC maintained 1 or 2 twitches in the hand. At this level of blockade the MEP amplitude in the TA was 59 % when the M response was 53 % of the unblocked state. At varying pNMB levels, the ratio of the MEP to the M response amplitude was similar (0.13) suggesting the M response might be used to calibrate the anticipated degree of MEP depression from NMB. Latency changes in the MEP were not observed at these levels of pNMB. The authors state that if the MEP amplitude is greater than 150 μV then MEP monitoring should be possible. This corresponded with a T1 at 5–15 % of baseline.

Kalkman also observed that an EMG response to stimulation could be recorded when the mechanical response was markedly reduced or absent; this also has been seen in other studies including several animal studies [35, 61–65]. This supports the concept that visible patient movement can be markedly reduced while electrical activity can still be recorded. The human and animal studies also demonstrate that the M response from peripheral nerve stimulation is reduced more than the CMAP response to transcranial motor cortex stimulation (for example the

MEP amplitude seen in these studies was 50–60 % of the unblocked value when M response was reduced to 20 % [61–63]). These non-linearities may be the result of the differences in muscle activation due to repetitive activation of spinal motor neurons which occurs with centrally applied stimulation due to spatial and temporal summation [66].

8 Clinical experience with partial neuromuscular blockade and cranial nerve monitoring

A variety of human studies have been conducted examining muscle responses from central or peripheral nerve stimulation [67]. Studies have been conducted examining the effect of pNMB on facial nerve monitoring when stimulation is used to identify the location of the nerve in the operative field and monitor its integrity. Cai studied facial nerve monitoring by recording EMG responses in the orbicularis oris and oculi during tympanoplasty in 40 patients. [68] pNMB with ROC was adjusted using stimulation of the ulnar nerve and recording of the T1 thenar response at 0, 25, 50, 75, 90 and 100 % of the baseline. All patients had recordable facial nerve EMG activity when the ulnar T1 was 50 % or more of the baseline. Four of 40 patients had no response to facial nerve stimulation of 1 mA (100 microsecond square wave constant current pulses) when T1 was 25 % or less. This degree of pNMB was also associated with a facial nerve EMG amplitude reduction and the need for a higher stimulation threshold. The impact of the higher stimulation threshold in identifying the nerve or inadvertently stimulating nearby nerves was not studied.

This study is consistent with similar studies where an infusion of atracurium was used to reduce the T1 to 50 % when measured in the hypothenar muscles following ulnar nerve stimulation [69, 70]. In 10 patients undergoing acoustic neuroma resection by the retrosigmoid approach, facial nerve function was assessed by EMG recordings from the orbicularis oculi, orbicularis oris and mentalis. All patients had normal clinical preoperative facial nerve function, but intraoperative testing revealed mild to moderate neuropathy in six. All patients had successful monitoring when stimulation of the nerve was done proximal and distal to the tumor bed. Of note, despite a 50 % decrement in the hypothenar muscle response, the maximal decrement in the facial nerve response was only 6 %.

This is consistent with other studies which have noted that the impact of pNMB on responses to stimulation of the facial nerve is consistently less than responses to stimulation of the ulnar nerve [52]. This ability to record facial EMG despite complete loss of electrical or mechanical response to ulnar stimulation has also been seen by Bauer [71]. It is suggested the differential sensitivity to NMB may be attributed to the motor unit size or an increased number of neuromuscular junctions [72–74].

Blair studied pNMB in 8 patients with cerebello-pontine angle tumor resection [75]. Monitoring of facial nerve function was done using EMG measurements in the orbicularis oculi and orbicularis oris following stimulation in the operative field. pNMB was assessed as reduction of T1 or of the TOF T4/T1 ratio in the thenar muscles following ulnar nerve stimulation. The authors observed a linear amplitude decrease of the facial muscle EMG to about 53 % as the T1 was reduced to 25 % of baseline. The change in T1 was a better predictor of amplitude decrease than the TOF T4/T1 ratio. A study conducted in rabbits by the same authors demonstrated that a linear relationship was also seen comparing facial nerve amplitude and T1 from sciatic nerve stimulation [75]. When the sciatic nerve was completely blocked the facial nerve was still recordable. In the rabbits, nerve traction injury was produced and train activity was seen in the EMG. In these injured neurons the effect of pNMB appeared greater than with normal nerves.

The effect of pNMB on monitoring of the recurrent laryngeal nerve during thyroid surgery was studied with pNMB quantified by accelerometry of the thumb following stimulation of the ulnar nerve. In this prospective study of 200 patients, ROC was used with an isoflurane-nitrous oxide anesthetic [76]. The EMG response from the vocalis was assessed following bipolar stimulation of the vagus and recurrent laryngeal nerve. Responses were reliably recorded when the accelerometry response was 10 % or better of baseline; at this level of pNMB the mean EMG response of the vocalis was approximately 32 % of the response with no relaxation. All postoperative vocal cord paresis was predicted by changes in intraoperative responses. The impact of preexisting clinical vocal cord dysfunction was not studied. Chu also noted that the effect of NMB was greater on the thenar muscles than on the vocalis [77].

9 Clinical experience with partial neuromuscular blockade and motor evoked potentials

A large number of clinical studies have been published examining MEP during pNMB. Successful monitoring of MEP has been reported with a T1 response at 5–15 % [78, 79], 10 % [80, 81], 15 % [82], 10–25 % [83–85], 20 % [86–90], 25 % [91], 30–50 % [79, 92–94] and 80–90 % [63, 83, 90, 93, 95] of the unblocked baseline. When neuromuscular blockade is assessed by TOF count, acceptable MEP monitoring has been conducted with only 1 [63, 96] or 2 of 4 [97–99] responses remaining.

The interaction of pNMB and inhalational agents was studied in 35 patients who were given either halothane, isoflurane, or sevoflurane at 0.5 or 1.0 minimal alveolar concentration (MAC) [96]. pNMB was studied at the APB and MEP was recorded at the APB and TA. After 20 min of the addition of the sevoflurane or isoflurane the TOF T4/T1 ratio and MEP amplitude was deceased. This suggested that the inhalational agents had two mechanisms of action on the MEP; reduction as a consequence of anesthetic depression of the MEP and as a consequence of amplitude reduction due to increasing the degree of pNMB.

The effect of two levels of pNMB on the variability of MEP responses was studied in 10 patients scheduled for aortic surgery [79]. pNMB was studied with T1 reduced to 5–15 % or 45–55 % of baseline as measured by the response of the thenar muscles to median nerve stimulation at the wrist. The variability of responses in the leg (TA) was greater than responses in the arm (extensor digitorum communis). The authors noted that the variability of the MEP within patients was less when a 6 pulse stimulation paradigm was used compared to a 2 pulse paradigm.

As a consequence of amplitude reduction, the ability to record with pNMB will be dependent on other factors which reduce the myogenic response such as anesthesia or neurologic disease. Hence, if neurologic pathology results in initially small responses, a reduction in amplitude by pNMB may make it difficult to distinguish from background. Similarly, anesthetic choices which reduce amplitude or increase the threshold for stimulation may compound this problem, particularly if pathology in the nervous system increases the anesthetic or NMBA effects. Hence a steady anesthetic management of all agents is important since non-muscle relaxant agents may impact the muscle responses directly or by changing the effect of the NMBA. Of note, this anesthetic effect may also be more profound in young children with incompletely developed nervous systems and the elderly with neural degeneration. Finally, NMB is known to alter the muscle components of frontal EEG monitors which have a component of EMG in their algorithm (e.g. entropy® and BIS®) such that the apparent effect of other anesthetic agents may be misrepresented if this effect is not recognized [100].

Fortunately the MEP amplitude is usually quite large which suggests pNMB can be used in some patients as noted in the studies above. Hence when it is used the anesthetic plan should include the possibility of eliminating the blockade similar to eliminating low dose inhalational agents when they are used. It is also important to recognize that the use of amplitude criteria for warning of impending neurological injury may not be possible as inevitable fluctuations in the degree of blockade may obscure the application of strict criteria. Alternatively amplitude criteria may be more useful by "calibrating" the MEP amplitude based on the size of the M wave response as noted above by Kalkman [63].

Finally, the effects of NMBA may not be consistent in all muscles in a given patient. For example, it has been reported that one patient with 2 of 4 recordable ulnar nerve TOF twitches and a recordable upper extremity MEP did not have a recordable lower extremity response [101]. In other patients a differential sensitivity has been noted between different muscle groups in the same patient such as differences between the left sided and right sided muscles [101].

In addition to amplitude effects, pNMB may require a higher stimulation voltage or current to acquire MEP responses from transcranial stimulation. In this case it is possible that the higher level of stimulation may prevent a recordable response, or that the stimulation may occur deep to the cortex rendering the monitoring less effective in detecting cortical pathology [102].

This higher level of required stimulation was also seen with nerve root stimulation when testing pedicle screw placement. [103] Minahan noticed that a pNMB of T1 of 20–25 % baseline in the APB from ulnar nerve stimulation falsely elevated stimulation thresholds when the L4-S1 nerve roots were directly stimulated. He noticed that with a T1 of >20 % baseline the average stimulation threshold was 1.62 MA (7.5 V) and with a greater degree of NMB 2.9 mA (11.2 V). The authors noted variability between different roots when T1 is <20 % baseline such that direct testing of only one root may be insufficient to predict the effects at other roots. Hence the authors do not recommend using criteria such as 2 visible twitches as been proposed by other authors [104, 105]. This effect may be more profound with chronically compressed nerves which are known to be more sensitive to NMBA [75, 106, 107]. The authors did not, however, study abnormal nerve roots so their behavior during pNMB is not clearly known.

Insufficient data are available for determining the expected impact of NMBA when IOM is used for evaluating EMG responses from mechanical irritation or spontaneous activity (such as with facial nerve monitoring or monitoring during cauda equina or spinal nerve root procedures). Although it would be logical to assume the amplitude of these responses is reduced, it is unknown if the stimulation threshold for mechanical stimulation is increased. These effects could make small responses difficult to identify or prevent mechanical irritation from producing a response that would otherwise be seen without pNMB. Further, given the more profound reduction in muscle movement with NMB, visible monitoring of muscle activity from nerve root irritation during pNMB may not be reliable.

10 MEP enhancement techniques

Since the muscle response of MEP is reduced by pNMB, methods to increase the MEP amplitude would be desirable when pNMB is used. Hayashi studied the effect of tetanic stimulation just prior to the MEP stimulation in patients given VEC titrated to a T1 amplitude of 2–5 mV (a T1 of 5–10 % of baseline) in the APB following median nerve stimulation [108]. In this study a 50 mA, 5 s tetanic conditioning stimulus was presented 1 s prior to the transcranial stimulation. They found that the amplitudes are increased similar to post tetanic assessment of NMB and 97 % of patients had MEP responses while only 80 % had responses without the tetanic conditioning. They also demonstrated that stimulation of the left posterior tibial nerve enhanced responses in hand and leg muscles (APB, anterior hallicus, TA, and soleus). This enhancement in other muscles was also seen by Kakimoto. [109].

Another study was conducted in 15 patients during propofol-fentanyl anesthesia with pNMB of T1 of 10 % in the APB following median nerve stimulation. They found responses in all patients who had no preexisting motor dysfunction (average amplitude 327 μV) where only 73 % had responses after unpotentiated transcranial stimulation (average amplitude 65 μV) [110]. In these studies the T1 response in the APB from ulnar stimulation was 1 mV which the authors suggest may be a sufficient marker for monitoring the NMB obviating the need for a baseline T1 value. The authors found that these levels of NMB reduced patient movement during spinal surgery such that operations with microscopic assistance were possible during MEP testing.

The enhancing effect from tetanic stimulation may be mediated by two different mechanisms. One mechanism is the tetanic stimulation at the neuromuscular junction enhances the muscles innervated by the nerve receiving the tetanus. The second mechanism, central conditioning, is proposed to explain the enhancement in muscles not innervated by the nerve receiving the tetanus. This central enhancement does not occur in the presence of sensory deficits or motor dysfunction.

This second mechanism may be similar to the central conditioning effect seen by applying a peripheral sensory stimulus such as when a train of stimuli is placed in the receptive field of the withdrawal reflex of the anterior tibialis muscle [111]. Studies show that lorazepam (Ativan®), a benzodiazepine which enhances GABA inhibition, reduces this enhancing effect suggesting an inhibition at the cortical level [112], and that enhancement will be effected by the choice of the anesthetic technique. The impact of sensory conditioning on muscles innervated by other nerves or mechanically stimulated EMG responses has not been reported.

11 Discussion

In general, when pNMB is used with IOM, the goal is to minimize patient movement so that it is not distracting or hazardous and still allow reliable MEP or EMG recording. The studies presented above suggest that in patients with normal neurological function and baseline responses with sufficient amplitude, a pNMB with T1 reduced to 10–20 % of baseline or a TOF with 2 of 4 responses is often acceptable. This also presupposes a supportive anesthetic technique such as TIVA since anesthetic agents may further hamper MEP monitoring. The role of routine tetanic conditioning in pNMB has not been fully explored but may be a method to facilitate IOM when pNMB is required.

Authors who advocate pNMB state that pNMB (1) facilitates surgical exposure, (2) eliminates the need for the surgeon to interrupt the procedure periodically to allow MEP testing, (3) reduces the risk of unexpected movement (especially in patients tolerant to opioid anesthetics), and (4) reduces the excessive EMG noise which may improve the signal to noise ratio and reduce acquisition time for subcortical SSEP or epidural D wave recordings.

However, with pNMB some patients may not have adequate responses for IOM. This may be a particular problem in patients with neurological disease or low amplitude responses. Further, when recorded the variability of the MEP response may be greater making alarm criteria based on a percentage reduction in amplitude more difficult to use. Further, anesthetic choices and the variety of other factors mentioned above may result in a variable or more profound pNMB than expected (including unexpected MEP loss mimicking neurological injury) or masking neurotonic discharges in their EMG. Hence, when pNMB is used, tight control of the drug effect by the anesthesiologist is critical. For this reason, most clinicians use drug infusions similar to the steady management of the other anesthetic agents. Some use closed loop systems to control the NMBA infusion by monitoring the drug effect. Ideally, similar to management of other anesthetic agents, if pNMB is planned, a pre-pNMB baseline should be obtained to assess the presence or absence of responses prior to instituting the pNMB. Because of the variability of the effects of NMBA on different muscles, assessment of the TOF by the IOM team is recommended in the actual muscles monitored.

12 Conclusion

In patients without neuromuscular pathology intraoperative monitoring using peripheral muscle responses from neural stimulation (EMG and MEP) is possible with partial neuromuscular blockade with T1 of 10–20 % or TOF with 2

responses out of four as measured at the ulnar nerve. Monitoring of muscle responses from cranial nerve stimulation may require a higher degree of stimulation and less neuromuscular blockade. The role of tetanic or sensory conditioning of the nervous system in monitoring and its impact on monitoring spontaneous muscle responses or those from mechanical nerve stimulation is not fully characterized.

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