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Monitoring of Neuromuscular Block

Conor D McGrath, Jennifer M Hunter*
*Correspondence Email: jennie@liv.ac.uk

Summary

Postoperative residual curarization occurs even after administration of intermediate-acting non- depolarizing neuromuscular blocking drugs, for example, atracurium or vecuronium.

Satisfactory recovery from neuromuscular block has not occured until the train-of-four ratio is >0.9.

Quantitative methods of measuring evoked responses, for the example, acceleromyography or mechanomyography, are necessary to ensure adequate recovery from block.

There is increasing evidence that residual neuromuscular block is common, and also that it may adversely affect patient outcome. A study by Debaene and colleagues[1] found that 45% of patients had residual curarization (train-of- four [TOF] ratio<0.9) in the postoperative recovery room after a single intubating dose of the intermediate-acting drugs atracurium, vecuronium or rocuronium. Another study found residual curarization (TOF ratio<0.7) in 42% of patients in the postoperative recovery room after vecuronium.[2] Neuromuscular block was not antagonized in either study and the use of neuromuscular monitoring was not recorded, as anaesthetists were encouraged to carry out their practice routinely during these investigations. Although there is no evidence that residual neuromuscular block leads to increased mortality, significant pulmonary morbidity has been demonstrated after using longer-acting agents such as pancuronium.[3] As well as interfering with pulmonary mechanics, residual neuromuscular block impairs the ventilatory response to hypoxia.[4] At low doses, these drugs significantly impair pharyngeal function and lead to an increased risk of tracheal aspiration and airway obstruction.[5]

When neuromuscular monitoring is used, visual or tactile evaluation of the degree of neuromuscular block is unreliable. Even experienced anaesthetists are unable to detect fade when the TOF ratio is >0.4.[6] It is now thought that significant residual curarization is still present if the TOF ratio is <0.9[7] (not 0.7 as previously suggested[8]). It is clear that as well as monitoring neuromuscular block clinically, we should be using quantitative techniques to assess the degree of recovery.

MONITORING NEUROMUSCULAR FUNCTION

On recovery, the anaesthetist can assess muscle power by a variety of clinical tests, such as the ability to sustain head lift for 5 seconds,[8] or the ability to hold a tongue depressor between the teeth. These are a crude assessment of neuromuscular function, and can be influenced by many factors, for example, residual sedation or inability to follow instructions. In 1958, Christie and Churchill-Davidson described the use of a nerve stimulator to monitor neuromuscular block. However, it was not until the TOF pattern of stimulation was described in 1970, that such equipment came into routine clinical use.[9]

STIMULATING THE MOTOR NERVE

The degree of neuromuscular block can be assessed by applying a supramaximal stimulus to a peripheral nerve, and then measuring the associated muscular response. (The motor unit consists of a motor neurone and a muscle, which are separated by the neuromuscular junction. Typically, one nerve fibre will innervate between 5 and 2000 muscle fibres). The nerve chosen to be stimulated must fulfil a number of criteria. First, it must have a motor element; second, it must be close to the skin; and third, contraction in the muscle or muscle group which the nerve supplies must be visible or accessible to evoked response monitoring.

In order to stimulate a nerve, an electrical current will need to be applied. The current is usually applied transcutaneously, using ECG electrodes. The chosen nerve will contain many motor nerve fibres. All of these fibres will need to be stimulated in order to produce a maximal muscle contraction. Generating an action potential in all of the nerve fibres in a motor nerve will require a current of sufficient magnitude and duration. Most nerve stimulators will apply a current for 0.1–0.3ms, which is more than adequate. The current which generates a response through all nerve fibres and hence a maximal muscle contraction is termed a maximal stimulus. Traditionally, a current of 25% above the maximal stimulus is applied when stimulating a peripheral nerve: this is termed a supramaximal stimulus.

IDEAL NERVE STIMULATOR

The ideal nerve stimulator would possess certain basic properties: it should be battery operated and able to deliver a *constant current*, up to a maximum of 80mA. This is preferable to a nerve stimulator that can only deliver a constant voltage.

Current magnitude is the factor that determines whether a nerve depolarizes or not. At a constant voltage, current will vary depending on the resistance of the skin. The two are related by Ohm's Law which is given by the equation V = IR, (V = voltage, I = current and R = resistance). Skin resistance will range from 0 Ω

Conor D McGrath
Honorary Lecturer

Jennifer M Hunter
Professor of Anaesthesia
University Department of Anaesthesia
Duncan Building
Daulby Street
Liverpool L69 3GA
UK

to 5kΩ, and is affected by such factors as skin temperature, adequacy of electrode application, and disease state, for example, diabetes mellitus or chronic renal failure. Adequacy of electrical contact should be displayed on the monitor screen.

The pulse stimulus should last no longer than 0.3ms and be of a monophasic, square wave type. This will ensure that a constant current is maintained throughout the stimulus. The polarity of the electrode leads should be indicated; it is recommended that the negative electrode be placed directly over the most superficial part of the nerve. The positive electrode can then be placed in a position along the course of the nerve, usually proximally to avoid direct muscle stimulation. The nerve stimulator should be capable of delivering a variety of patterns of stimulation including: single twitch (at 1Hz); TOF twitch stimulation (usually 2Hz with at least a 10s interval between trains); tetanic stimulation at 50Hz for up to 5s; and double-burst stimulation (DBS). Good electrical contact with the skin can be established using ECG electrodes of the silver/silver chloride variety. The skin should always be cleansed adequately before applying the electrodes. The ideal stimulator would also enable monitoring of the evoked responses. The pattern of the evoked response generated by nerve stimulation will depend on the type of drug used to produce neuromuscular block, and the pattern of stimulation.

PATTERN OF NERVE STIMULATION

Single twitch stimulation

A single square wave supramaximal stimulus is applied to a peripheral nerve for a period of about 0.2ms, at regular intervals, and the evoked response is observed. The twitch response will only be depressed when a neuromuscular blocking agent occupies 75% of the post-synaptic nicotinic receptors. Twitch depression will need to be more than 90% in order to provide good conditions for abdominal surgery.

The most useful time to apply the single twitch pattern of nerve stimulation is at the onset of neuromuscular block. Using a single twitch at 1Hz (1 twitch every second), it is possible to establish the level at which a supramaximal stimulus is obtained. The onset of neuromuscular block can then be observed, using a single twitch at 0.1Hz (1 twitch every 10s). The onset and recovery from depolarizing and non-depolarizing block monitored using single twitches have a similar pattern, differing only in timescale — Figures 1A and B.

The major limitation to this technique is the need to measure a control twitch before administering the neuromuscular blocking agent. Single twitches are also used in the post-tetanic count, but in this instance a control twitch height is not required.

Train-of-four stimulation

The TOF pattern of twitch stimulation was developed in 1970 by Ali and colleagues,[9] in an attempt to provide a clinical tool to assess neuromuscular block in the anaesthetized patient. The principle was to produce a pattern of stimulation that did not require the comparison of evoked responses to a control response obtained before administration of a neuromuscular blocking drug. The pattern involved stimulating the ulnar nerve with a TOF supramaximal twitch stimuli, with a frequency of 2Hz, that is, four stimuli each separated by 0.5s. The TOF was then repeated every 10s (train frequency of 0.1Hz). As well as enabling the observer to compare T1 (first twitch of the TOF) to T0 (control), it also enables comparison of T4 (fourth twitch of the TOF) to T1. This is known as the *TOF ratio*.

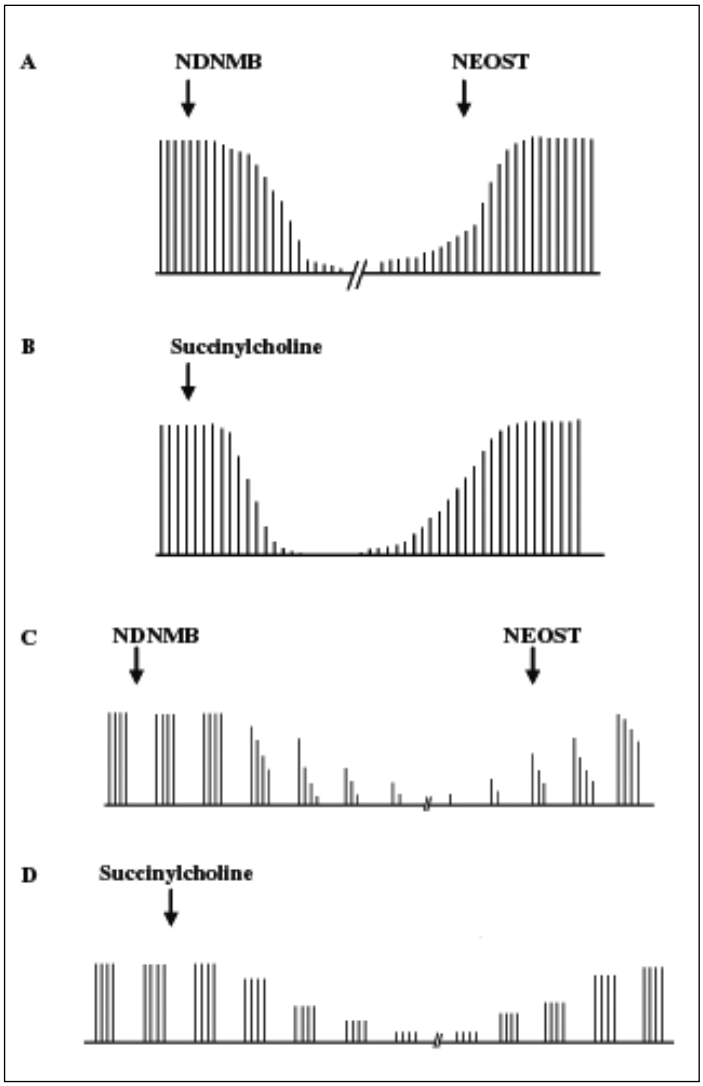

Figure 1. *(A) Pattern of evoked muscle responses to twitch stimulation after administration of a non-depolarizing neuromuscular blocking drug (NDNMB), followed by antagonism with neostigmine (NEOST). NEOST hastened the rate of recovery, if the twitch has already started to increase. (B) Pattern of evoked muscle responses to twitch stimulation after administration of succinylcholine. (C) TOF monitoring of onset of neuromuscular block produced by a NDNMB, followed by antagonism with NEOST, given when three twitches of the TOF are detectable. (D) TOF monitoring of onset of, and recovery from, neuromuscular block produced by succinylcholine.*

When a non-depolarizing agent is given, a typical pattern is observed. There is a reduction in the amplitude of the evoked responses, with T4 affected first, then T3, followed by T2, and finally T1 (Figure 1C). This decrement in twitch height is known as *fade*. As the non-depolarizing block becomes more intense, T4 disappears followed by T3, T2, and finally T_1. The reverse is true during recovery from non-depolarizing block: T1 reappears first followed by T2, T3, and finally T4 (Figure 1C).

During onset of non-depolarizing block, T4 disappears at about 75% depression of T1, T3 at 80–85% depression of T1, and T2 at 90% depression. During partial non-depolarizing block, the number of twitches *(TOF count)* correlates with the degree of neuromuscular block. Twitch suppression of 90% would equate to a TOF count of 1 or less. Reversal of residual neuromuscular block can safely be achieved when the TOF count is 3 or greater.[7]

The T4/T1 ratio is important as it is thought to be closely related to T1/T0. One of the most useful clinical applications of the TOF ratio is in monitoring recovery from neuromuscular block. Traditionally, it had been accepted that a TOF ratio of 0.7 or greater was an indication of adequate reversal.[9] However, this has been challenged recently and it is now thought that a TOF ratio of 0.9 should be achieved before tracheal extubation.

The TOF pattern is less useful in monitoring depolarizing neuromuscular block. During onset of depolarizing block, each of the four twitches is decreased equally in size, that is, there is no fade (Figure 1D). This is also observed during recovery. However, if larger doses of depolarizing agent are given, for example in techniques that require repeated bolus doses or infusions of succinylcholine, then a *Phase 2 block* may develop. This is a block produced by a depolarizing drug which develops some of the characteristics of a non-depolarizing block. With TOF monitoring, fade is observed.

Tetanic stimulation

Tetanic stimulation uses a high frequency (50–200Hz) 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 a non-depolarizing neuromuscular blocking drug, the muscle, depending on the degree of block, will show signs of fade, that is, the stimulated muscle will be unable to sustain a muscular contraction. At higher frequencies (100–200Hz) muscular fatigue may develop, but at a stimulation frequency of 50Hz this should not occur, and 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 tetanic stimulation is extremely painful.

Tetanic stimulation has complex effects on the neuromuscular junction especially in the presence of a neuromuscular blocking drug. Fade is thought to be an effect of a non-depolarizing agent on the presynaptic nerve membrane. Acetylcholine released during a tetanic stimulus into the synaptic cleft has a positive feedback effect through its actions on presynaptic receptors. These actions ensure that the amount of acetylcholine released from the nerve terminal is far greater than that which is required to generate an adequate end-plate potential and sustain a tetanic contraction. In the presence of a non-depolarizing neuromuscular blocking agent, this margin of safety is greatly reduced. The competitive block at the presynaptic receptors decreases the amount of acetylcholine mobilized and released, contributing to the fade seen during tetanic stimulation.

During partial depolarizing block, fade is not observed in response to tetanic stimulation. The amplitude of the evoked response will be lower but the tetanic contraction will be maintained.

Post-tetanic count

During profound non-depolarizing neuromuscular block, there may be no response to TOF or single twitch stimulation. In such circumstances, a post-tetanic count (PTC) may be useful. If a 5 second tetanic stimulus at 50Hz is administered, after no twitch response has been elicited, followed 3 seconds later by further single twitches at 1 Hz, there may be a response to single twitch stimulation. Although this pattern will not be seen during very profound block, a response will be seen in the early stages of recovery, before the TOF reappears. This is known as *post-tetanic facilitation*. 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. The number of post-tetanic twitches is an indication of when the first twitch of the TOF will reappear. For instance, the first twitch of the TOF generally returns with a PTC of 9 when using atracurium or vecuronium.

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. It should be remembered that a tetanic stimulus, by mobilizing acetylcholine, might affect the neuromuscular junction of a stimulated nerve for a significant time. 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 minutes.[10]

Double-burst stimulation

DBS was developed to enable the anaesthetist to detect even small degrees of neuromuscular block clinically. Significant residual neuromuscular block can be assessed using the TOF response. However, small degrees of residual block may be easier to appreciate with DBS.

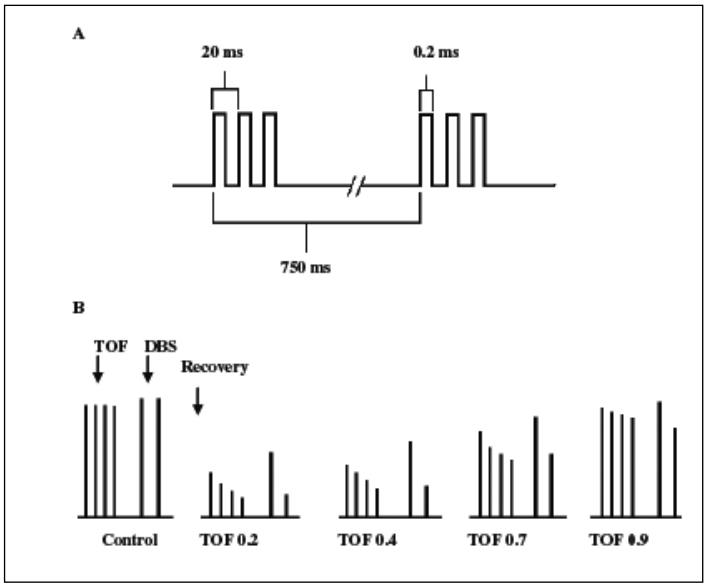

Figure 2. *(A) Double-burst Stimulation. Three impulses in each burst lasting 0.2ms, and separated by 20ms. The two bursts are separated by 750ms. (B) Comparison of evoked muscle responses with DBS and TOF stimulation, after administration of a NDNMB. Fade with DBS is easier to appreciate clinically than fade with TOF stimulation.*[11]

In DBS, two short bursts of tetanus at 50Hz at a supramaximal current are applied to a nerve. Typically, each burst will have three impulses lasting 0.2ms. Each impulse is delivered every 20ms and the two bursts are separated by 750ms (Figure 2A). In unparalysed muscle, two separate muscle contractions of equal intensity will occur. In muscle partially paralysed with a non-depolarizing agent, the response to the second burst is reduced. This is the phenomenon of fade. The ratio of the magnitude of the second stimulus to the first is known as the DBS ratio. The DBS ratio has very similar properties to the TOF ratio (Figure 2B). However, tactile evaluation of the DBS ratio has been shown to be more accurate than tactile evaluation of the TOF ratio.[11]

MEASURING EVOKED MUSCLE RESPONSES

Assessing muscle responses by visual or tactile means is difficult. There are a number of mechanical (mechanomyography [MMG] and acceleromyography) and electrical (electromyography [EMG]) methods for detecting and measuring these evoked responses more accurately.

Mechanomyography

MMG is the measurement of evoked muscle tension. The most commonly studied muscle is adductor pollicis in the thumb. When the ulnar nerve is stimulated at the wrist, the adductor pollicis contracts and causes the thumb to move. If the thumb is stabilized and placed under a fixed amount of tension (preload), then evoked responses can be measured as a change in tension develops.

This is achieved using a strain gauge transducer and recorder. Note that the thumb will not move in this situation; the muscular contraction is said to be isometric. The evoked change in tension is detected by the strain gauge and transduced into an electrical signal, which can then be displayed. In order to ensure accurate readings, the arm and hand must be fixed and movement of the thumb must be along the length of the transducer. This technique can be used for assessment of any pattern of nerve stimulation and is the gold standard. It has the disadvantage of being cumbersome and impractical for use in the operating theatre. There some commercially available mechanomyographs, for example, Myograph 2000 (Biometer Int A/S).

Electromyography

EMG is the recording of a compound action potential that occurs during muscular contraction, whether voluntary or evoked. Again, the adductor pollicis and ulnar nerve are the most commonly used, although other sites in the hand have been advocated, for example, the hypothenar eminence or first dorsal interosseous muscles. Evoked action potentials are a measurement of electrical changes that occur in muscle during stimulation; it is assumed that these are equivalent to the muscular contraction that occurs after excitation–contraction coupling.

The stimulating electrodes are placed over the ulnar nerve. The recording electrodes must be placed carefully: one over the muscle belly; a second, over the tendinous insertion of the muscle; and a third, in a neutral site distant to the muscle. On stimulation, a number of low voltage motor action potentials will be generated. These can be summated into a compound action potential which, because of the very low voltages measured, must be amplified. Recording of EMG potentials has several advantages over MMG. The equipment needed is not as bulky and is easier to assemble. The arm and hand do not need to be fixed as rigidly. The EMG does, however, have a number of disadvantages. It is particularly prone to interference, especially from diathermy. Hand temperature and movement will adversely affect the readings to a greater degree than with MMG. Another potential source of inaccuracy is direct muscle stimulation. Some of these devices are particularly prone to drift. Despite the availability of the Datex Relaxograph, the limitations of EMG mean that it is unlikely to gain widespread clinical use.

Acceleromyography

Acceleromyography was developed as a more convenient method of monitoring evoked responses in the operating theatre. The principle is similar to MMG; however, instead of measuring force of contraction directly, acceleration of the contracting muscle is measured. Force can then be calculated using Newton's second law of motion: force = mass x acceleration. Acceleration is measured by a piezoelectric ceramic wafer that is strapped to the thumb. When the adductor pollicis is stimulated, the thumb will move and the attached transducer will produce a voltage, which is proportional to its acceleration. The voltage can then be converted into an electrical signal and displayed as a twitch response. For accurate measurement, the accelerating digit must be free to move.

It has been established that acceleromyography is comparable to MMG.[12] Acceleromyography is particularly suited to TOF measurement and most of the commercially available machines will enable TOF ratio monitoring, for example, TOF Watch (Organon). Although neither tetanus nor DBS can be monitored by this method, PTC can be.

WHICH NERVE TO STIMULATE AND WHEN?

It must be remembered that onset and offset of block is faster in central muscles with a good blood supply, for example, diaphragm and larynx. Conversely peripheral muscles, with a relatively poor blood supply, will have a slower onset of block and a longer recovery time, for example, adductor pollicis. The muscles of the upper airway and pharynx behave as central muscles at onset; however, they are sensitive to neuromuscular blocking drugs and recovery is slow, mirroring the peripheral muscles.

Table 1. *Conditions where neuromuscular monitoring is essential*[10]

After prolonged infusions of neuromuscular blocking drugs or when long-acting drugs are used
When surgery or anaesthesia is prolonged
When inadequate reversal may have devastating effects, for example, severe respiratory disease, morbid obesity
In conditions where administration of a reversal agent may cause harm, for example, tachyarrhythmias, cardiac failure
Liver or renal dysfunction, when pharmacokinetics of muscular relaxants may be altered

Induction of anaesthesia

During induction of anaesthesia and tracheal intubation, the muscles of the larynx and jaw must be paralysed as well as the diaphragm. The orbicularis oculi is probably the ideal muscle to monitor at this time as it is more similar to a central muscle: onset of block will be similar to the laryngeal muscles and diaphragm.[13] Single twitch or TOF stimulation is the most valuable stimulation pattern at induction. Single twitch stimulation will allow the maximal stimulation level to be obtained. Disappearance of the TOF will correspond to optimal intubating conditions.

Maintenance of anaesthesia

As the diaphragm is relatively resistant to neuromuscular block, a more sensitive peripheral muscle such as the adductor pollicis may not adequately reflect the degree of block required at this stage of anaesthesia. A central muscle which is resistant to neuromuscular block, for example, orbicularis oculi, will reflect the diaphragm more closely and should be monitored at this time. PTC and TOF monitoring are most useful during profound neuromuscular block.

Reversal and recovery

Before administering a neuromuscular antagonist, the TOF count should be at least 3.[7] At this time, monitoring a peripheral muscle such as adductor pollicis is the best option. The respiratory muscles are likely to have recovered to a greater degree, and monitoring a peripheral muscle provides a larger margin of safety. Neuromuscular monitoring should be used routinely when a neuromuscular blocking drug is given; however, there are certain conditions when monitoring neuromuscular block is essential and these are given in Table 1.

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