Neuromuscular Monitoring : A Review

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ABSTRACT

Residual neuromuscular blockade in the postoperative period contributes to significant morbidity and possibly mortality. The incidence of residual neuromuscular blockade has been shown to decrease with the use of neuromuscular monitoring and short acting neuromuscular blocking drugs. Because of marked variation in patient's sensitivity to neuromuscular blockade, the neuromuscular function of the patient receiving intermediate or long action muscle relaxant should be monitored. This article reviews the basic principles of peripheral nerve stimulation, pattern of nerve stimulation and methods used to evaluate evoked neuromuscular responses.

KEYWORDS : Neuromuscular blocking agents, Train of four, Double burst stimulation

Neuromuscular blocking agents (NMBA) are being used in clinical anesthesia for more than half a century now. Under anesthesia and during recovery from anesthesia, assessment of neuromuscular function can be done either by clinical tests or by the response of muscle to nerve stimulation. Clinical tests for assessment of neuromuscular function are muscle tone, head lift, eye opening, tongue protrusion, handgrip, tidal volume, peak inspiratory pressure etc.

In perioperative period, a variety of factors can influence response of a patient to NMBA. Because of marked variation in patient sensitivity to NMBA, problem of postoperative residual NM paralysis is increasing. Therefore, the response of the muscle to nerve stimulation should be assessed to titrate use of NMBA to desired clinical effect in an anesthetized patient. The use of peripheral nerve stimulation allows the clinician to assess the intensity of neuromuscular blockade (NMB). Profound muscle relaxation (to permit tracheal intubation and ensure immobility), moderate muscle relaxation (to facilitate surgical procedure) and recovery of neuromuscular function can be evaluated by monitoring evoked muscle response to nerve stimulation. This article reviews an overview of anatomy and physiology of neuromuscular transmission, fundamental principles of neurostimulation, patterns of nerve stimulation, equipment used for neuromuscular monitoring and evaluation of recorded evoked responses.

Neuromuscular junction

The region of approximation between motor nerve fiber and a muscle cell is the neuromuscular junction (NMJ) (Figure-1).1 The membrane of the nerve terminal and muscle fiber are separated by a narrow gap of 20-50 nm called synaptic cleft. Adult NMJ is formed by three cells that constitute the synapse- the Schwann cell, the motor nerve and the muscle fiber (Figure-1). The motor neuron from the ventral horn of the spinal cord innervates the muscle. Each muscle fiber receives only one synapse. The motor neuron losses its myelin sheath to terminate on the muscle fiber and forms a spray of terminal branches against the muscle surface and is covered by Schwann cell. The terminal Schwann cell extends to the muscle fiber enclosing NMJ and separating it from extra cellular fluid.1 The nerve terminal has vesicles clustered around the membrane thickening, which are the active zone. The muscle surface (muscle end plate) is corrugated with deep invaginations of the...
junctional cleft- the primary and secondary clefts. The shoulders of the folds are densely populated with acetylcholine (Ach) receptors.  

**Neuromuscular transmission : An overview**

Ach is synthesized and stored in small vesicles in axonal terminal of motor nerves. Each vesicle contains approximately 5,000 to 10,000 molecules. Ach in the nerve terminal is available in two fractions: a small, immediately available, active pool stored in vesicles and a larger reserve pool found both free in cytoplasm and in vesicles. When a nerve is stimulated, action potential is generated and reaches the nerve terminal, the voltage gated ion channels open and calcium influx occurs. This leads to fusion of 200-400 vesicles from the active pool with the axonal membrane and release Ach into the synaptic cleft. Released Ach gets attached to the receptors on the muscle end plate and depolarizes it by opening ion channels. This produces an end plate potential and triggers adjacent muscle membrane into initiating a contraction.

**Fundamental principles of neurostimulation :**

Neuromuscular function is monitored by evaluating the response of the muscle to supramaximal stimulation of a peripheral motor nerve. Stimulation of a single muscle fiber follows all-or-none principle. However, when the whole muscle is stimulated, the response depends upon the number of muscle fibers stimulated. If the nerve is stimulated with sufficient intensity, all the muscle fibers supplied by the nerve contract and a maximal response is triggered. After administration of a neuromuscular blocking drug, the response of muscle decreases in parallel to number of nerve fibers blocked. The degree of reduction in response to continuous stimulation reflects the extent of neuromuscular blockade.

**Current**

For the above principle to be effective, the stimulus must be truly maximal throughout the period of monitoring. The amount of current required to elicit a detectable muscle response is the threshold current (15mA). The current needed to induce depolarization in all the fibers in a nerve bundle is the maximal current. For clinical monitoring, a supramaximal current is usually applied, which is 10%-20% greater than the maximal current and 2-3 times higher than the threshold current. A 50-60mA current across surface electrode is required to produce a supramaximal response which may be painful in an awake patient. Though this is not a concern during anesthesia, it may become uncomfortable during recovery. Although several investigators have indicated the use of submaximal current to assess NM function postoperatively, the accuracy in monitoring is unacceptable at low current. Therefore; supramaximal current should always be used whenever possible.

**Character of waveform and pulse duration**

The impulse should be monophasic and rectangular (i.e. it should be a square wave) so that constant current is maintained over the entire impulse. A biphasic pulse may cause burst of action potential in nerve (repetitive firing), thus increasing the response to the stimulation. The optimal pulse duration is of 0.2 to 0.3 ms. A pulse exceeding 0.5ms may stimulate the muscle directly or cause repetitive firing.

**Resistance**

The force opposing the flow of energy to the peripheral nerve is the resistance. Current is equal to voltage divided by the resistance. Any increase in resistance (cooling of skin) will require a proportionate increase in voltage to maintain a constant current. Most
Peripheral nerve stimulators deliver a constant current over a range of changing resistance by varying the internal voltage. Resistance between the surface electrodes and the skin can be reduced by removing hair, decornifying and degreasing the skin and cleaning the area beneath the electrodes with alcohol.  

Patterns of nerve stimulation (Figure 2)  

Five patterns of nerve stimulation are commonly used in clinical practice:

- Single twitch stimulation.
- Train-of-four stimulation.
- Tetanic stimulation.
- Post-tetanic count stimulation.
- Double burst stimulation.

Single twitch stimulation:

Single supramaximal stimuli are applied at frequency of 0.1 Hz (once every 10 seconds) to 1.0 Hz (once every second). 0.1Hz is generally used. If the frequency is >0.15 Hz, the evoked response gradually decreases and settles at lower levels. A frequency of 1.0 Hz shortens the time for detection of supramaximal stimulation, hence this frequency is sometimes used during the induction of anesthesia for evaluating baseline response. The twitch height will remain normal until 75% of Ach receptors are blocked and will completely disappear when 90% to 95% of Ach receptors are occupied. There are few limitations associated with this pattern of stimulation. A controlled twitch height must be obtained before muscle relaxant is administered and specialized recording equipment is required to compare subsequent responses. The response of stimulation is frequency dependent. At 0.1Hz, there is no impact on NM transmission. When frequency is increased to 1.0 Hz, fade will be observed and a faster onset of NMB can develop in the stimulated muscle.

Train-of-Four Stimulation (TOF)

This is the most widely used mode of nerve stimulation. Four supramaximal stimuli of 2Hz (four stimuli every 0.5 sec) are applied over 2 second interval which are repeated every 10-12 second. The response is observed as TOF count or TOF ratio.

The TOF count is an assessment of number of twitches (0-4) after TOF stimulation. It is commonly used in operation room and intensive care unit because it can be quantified without recording devices. In the absence of NMB, all four responses of equal height are present. Absent 4th response represents 75-80% receptor blockade. When 85%, 85-90% and 90-98% of Ach receptors are blocked, T3, T2, T1 responses are abolished respectively. The fade in response to TOF stimulation provides the basis for evaluation.

TOF ratio is measured by dividing the amplitude of fourth to the amplitude of first response. Its accurate determination requires specialized recording devices. In the absence of NMB, TOF ratio is 1. In partial non-depolarizing block, the ratio decreases and is inversely proportional to the degree of block. In partial depolarizing block, the amplitude of all the four responses

Figure-2

Patterns of stimulation
decreases but TOF remains 1.0. If fade appears in depolarizing block, it indicates phase II block.\textsuperscript{5}

TOF monitoring has many advantages. Unlike single twitch pattern, it does not require the recording of control value. During non-depolarizing block, the degree of block can be read directly from TOF responses even if control value is lacking.\textsuperscript{15,16} TOF ratio is more sensitive in detecting subtle degree of NMB than single twitch stimulation. TOF monitoring is less painful than tetanic stimulation, therefore, it can be used to detect residual block in awake patients. TOF monitoring can be performed more frequently (once every 10-12 seconds) without influencing the twitch height. This is in contrast to tetanic stimulation which, if repeated within less than 2 minutes, may show exaggerated response because of posttetanic potentiation.\textsuperscript{12}

**Mechanism of fade and post tetanic potentiation**

High frequency stimulation of motor nerve produces large release of immediately available stores of Ach in the nerve terminal. As the stores become depleted, the rate of Ach release decreases until equilibrium between mobilization and synthesis is achieved. Normal muscular contraction occurs with high frequency nerve stimulation because far more Ach is released than is required to produce a full muscular response (a wide margin of safety). In the presence of partial non-depolarizing block, the number of free Ach receptors on the postsynaptic membrane is reduced. This reduces the margin of safety of neuromuscular transmission and leads to reduced force of muscle contraction (fade).\textsuperscript{17} Fade can be observed with TOF, tetanic or double burst stimulation modes. Muscle relaxants can also produce fade by blocking presynaptic cholinergic receptors which play a role in the mobilization of Ach in motor neurons.\textsuperscript{18} High frequency stimulation of motor nerve also facilitates the mobilization of Ach from the reserve pools to the immediate stores and increases the synthesis of Ach. This enhanced synthesis and mobilization of Ach explains the phenomenon of posttetanic potentiation.\textsuperscript{5}

Tetanic stimulation has many disadvantages. It is extremely painful and should not be used in awake patients. In late phases of recovery, it may produce a lasting antagonism of NMB, the muscle used can't assess the recovery of NMB.\textsuperscript{19,20} It is not very useful in every day clinical practice except for post-tetanic count stimulation.

**Post-tetanic count (PTC) stimulation**

PTC can be used to evaluate intense NMB when no response to single twitch or TOF can be measured. PTC involves application of 50Hz tetanic stimulation for 5 seconds followed 3 seconds later by 1 Hz single supramaximal stimulus. This modality is used when profound muscle relaxation is required (to ensure smooth tracheal intubation) and complete immobility of the patients is essential (during surgery on an open globe or in cases of elevated intracranial pressure). During these times, the PTC should be 0.\textsuperscript{21} PTC is also used to estimate the time to recover from intense NMB. When PTC of 1 is recorded in patients who had received pancuronium, approximately 30-40 minutes will elapse.
before T1 in TOF is observed. During vecuronium or atracurium NMB, PTC of 1 will predict return of T1 within 7-8 minutes.

Double burst stimulation (DBS)

DBS allows manual (tactile) detection of subtle degree of NMB without the use of recording devices. It involves application of two short bursts of 50Hz which are separated 750 ms. It consists of a series of 3 and 2 impulses (DBS 3, 2) or 3 and 3 impulses (DBS 3, 3). Good correlation between the ratio of second burst to first burst (D2/D1) and TOF ratio has been reported. Fade is more easily detected manually with DBS than with TOF. Fade can only be detected reliably on manual evaluation of TOF response, when TOF ratio is <0.4. However, manual assessment of DBS response allows detection of fade up to TOF ratio of 0.6.

Figure-4

Electrode placement for stimulation of ulnar nerve and for recording of compound action potential from three sites of hand (Electromyography). A) Abductor digiti minimi muscle in the hypothenar eminence B) Adductor pollicis muscle in the thenar eminence C) First dorsal interosseous muscle

Equipment used for NM monitoring

- The nerve stimulator,
- The stimulating electrodes, and
- The recording equipment.

The nerve stimulator

It delivers the stimulus to the electrodes. Although many nerve stimulators are commercially available, not all meet the basic requirement for clinical use. The real nerve stimulator should have the following properties.

- It should deliver monophasic and rectangular waveform pulse of constant current.
- It should deliver a current up to 60-70 mA but not >80mA.
- It should be battery operated and should have a battery check.
- It should have either built in warning system or current level display that alerts the user when the current selected is not delivered to the nerve (in case of increased skin resistance)
- It should have polarity indicators for electrodes.
- It should deliver different modes of stimulation.

The Stimulation Electrodes

Electrical impulses are transmitted from the stimulator to the nerve by means of surface or needle electrodes. Surface electrodes are commonly used in clinical anaesthesia. These are pregelled silver/silver chloride electrodes having approximately 7-8 mm diameter of the conducting area.

If tissue resistance prevents the stimulating current from reaching the nerve (i.e. in the morbidly obese patients), needle electrodes can be used. A Current = 10mA will usually produce supramaximal stimulation when subcutaneous needle electrodes are used. Although specially coated needle electrodes are commercially available, ordinary steel injection needles can be used.

Sites of nerve stimulation

In clinical anesthesia, the ulnar nerve at the wrist
is the most popular site for nerve stimulation, and the response at the adductor pollicis is observed or recorded. During many surgical procedures, the patient's arm may not be accessible due to positioning. In these situations, facial nerve is often used for stimulation and the contraction of the muscles around the eye is evaluated. Median nerve, posterior tibial nerve and common peroneal nerves are sometimes used.

Optimal nerve stimulation occurs when the negative electrode is placed directly over the nerve. The positive electrode is placed proximal to the negative electrode to avoid depolarizing a different nerve. For ulnar nerve stimulation, the electrodes are best applied on the volar side of wrist. The distal electrode should be placed 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon of flexor carpi ulnaris muscle (Figure-3). The proximal electrode should preferably be placed 2-3 cm proximal to the distal electrode or at the ulnar groove of the elbow.

While interpreting the motor response to the peripheral nerve stimulation, it is important to remember that different muscles have different onset times, offset times and sensitivities to muscle relaxants. The results obtained from one muscle cannot be extrapolated automatically to other muscles. The diaphragm is the most resistant of all the muscles to NMBA. In general, diaphragm requires 1.4-2.0 times as much muscle relaxant as the adductor pollicis muscle for the same degree of block. However, the onset and offset times are relatively rapid as a result of high regional blood flow. The muscles of larynx and face are less resistant.

Assessment of responses to nerve stimulation (Recording devices)

Visual and tactile assessment

It is the most common method used to monitor evoked responses. Unfortunately significant residual muscle weakness might not be detected when this method is used. Use of DBS pattern of stimulation could improve detection of residual paresis in the perioperative period.

Electromyography (EMG)

EMG was the first method used for recording NMB. It was introduced by Davidson and Chirstie in 1959. It records the electric activity (compound action potential) of the stimulated muscle. Electrical activity in muscle precedes the mechanical contraction. The two active electrodes are placed over the body and the tendinous insertion of the muscle to be monitored and a
third neutral electrode is placed at a remote site. After ulnar nerve stimulation, EMG responses are typically measured from thenar eminence, the hypothenar eminence or the first dorsal interosseous muscle of the hand (Figure-4). EMG unit calculates the amplitude of the signal, which represents either the sum of the individual compound muscle action potentials or area under the EMG curve. Good correlation between EMG and mechanomyography (MMG) has been reported, but the two cannot be interchangeably used. Advantages of EMG are that it is less bulky and easy to set up and it can be recorded from muscles that are not accessible to mechanical recording. It can also be used to investigate spontaneous muscle activity such as breathing. However, it is an expensive device and the quality of EMG can be adversely affected by an electrical interference, improper electrode placement, direct muscle stimulation and hypothermia. It does not return to baseline value. It is mainly used for research purposes.

**Mechanomyography (MMG)**

MMG measures the isometric contraction of adductor pollicis muscle response to ulnar nerve stimulation. A force transducer is used for this purpose. When ulnar nerve is stimulated, the thumb (the adductor pollicis muscle) acts on a force displacement transducer (Figure-5). The force of contraction is then converted into an electrical signal, which is amplified, displayed and recorded. As it measures isometric contraction, preload of 200-300 gm must be attached to the thumb. For accurate measurements, the hand must be immobilized and the force transducer must be aligned with the direction of movement of the thumb. It is an economical device and is used for research purposes.

**Acceleromyography**

Acceleromyography measures the isotonic acceleration of the stimulated muscle. It is based on Newton’s second law which states force equals mass into acceleration. If mass is constant, muscle contraction can be calculated if acceleration is measured. It uses a small piezoelectric transducer, which is attached to the stimulated muscle (Figure-6). The movement of muscle generates voltage in the piezoelectric crystal, which is proportionate to the acceleration of that muscle. The signals are analysed in a specially designed analyzer and results displayed. It was introduced primarily for clinical use. The devices are small, portable and easy to use. Because isotonic contraction is measured, no preload is required. It can be used at the sites where MMG cannot be used such as orbicularis oculi muscle. Good correlation has been reported with MMG.

**Evaluation of Recorded evoked responses**

**Intense NM blockade**

Intense NMB is required for smooth tracheal intubation and in few surgeries when patient immobility is essential. During intense NMB, no response to TOF or single twitch is observed. PTC may determine the degree of intense blocked as mentioned previously.

**Moderate or surgical blockade**

During any surgical procedure, the smallest dose of NMBA that will provide optimal surgical condition should be used. Surgical blocked begins when first response to TOF reappears. Maintaining a TOF count of 1 or 2 is appropriate. However, patient’s movement is still possible at this level. Fade on TOF, DBS and posttetanic potentiation is present during partial non-depolarizing block or phase II block. During pure depolarizing block (phase I) no fade or posttetanic potentiation is observed with TOF stimulation. All responses are to TOF stimulation are decreased with
pure depolarizing block and TOF ratio remains 1 (Figure-7).

Recovery

The return of the 4th response in TOF heralds' recovery plan and antagonisms should be tried at this point. Most NDM non depolarising muscle relaxant can be fully reversed with in 10 minutes if T4 is present. Most NDM non depolarising muscle relaxant can be fully reversed with in 10 minutes if T4 is present.3

Good correlation exists between TOF ratio and clinical observation, but the relationship between TOF ratio and signs and symptoms of residual blocked varies greatly amongst patients.40

- When TOF ratio is 0.4 or less, the following are observed
  - Patient is unable to lift head or arm
  - Tidal volume may be normal
  - Vital capacity and inspiratory force will be reduced

- When TOF ratio is 0.6, the following are observed
  - Patient is able to lift head for 3 seconds
  - Open eyes widely
  - Stick out tongue
  - Vital capacity and inspiratory forces are still reduced

- When TOF ratio is 0.7 -0.75, the following are observed
  - Patient can normally cough sufficiently
  - Can lift head for at least for 5 seconds
  - Grip strength may be as low as about 60% of control

- When TOF ratio is 0.8 or more, the following are observed
  - Vital capacity and inspiratory forces are normal
  - Patient may still have diplopia or facial weakness.

Adequate recovery of NM function requires return of TOF ratio to 0.9, which cannot be guaranteed without the use of mechanomyography, electromyography or acceleromyography.51,42,43

To conclude, close neuromuscular monitoring should be applied to all patients receiving muscle relaxants because of marked variation in patient's sensitivity to neuromuscular blockade. Monitoring neuromuscular function during anaesthesia reduces the incidence of morbidity and mortality associated with residual paralyses.

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