TIME to Reach 90% TOF Ratio, Comparison between Clinical and Objective Means In Monitoring Neuromuscular Recovery

Dr. Myan Ihsan M. Tahir¹, Dr. Iyad Abbas Salman², Dr. Muthanna Abduldhim Saad Al-Juaifri³

¹Senior specialist anaesthetologist, Medical city complex, Baghdad, Iraq.
²Consultant anaesthetologist, Medical city complex, Baghdad, Iraq.
³Senior anaesthetologist, Medical city complex, Baghdad, Iraq.

Corresponding Author: Dr. Myan Ihsan M. Tahir

Abstract: Background Traditionally, in Iraq WE evaluated the degree of neuromuscular blockade during and after anesthesia using clinical criteria alone, which is inaccurate to assess recovery from neuromuscular block (NMB) which is imperative for the patient to have full control of pharyngeal and respiratory muscles. The train-of-4 (TOF) ratio should return to at least 0.90 to exclude potentially clinically significant postoperative residual block. The time gap between clinical recovery (subjective) by using a PNS until objective recovery i.e TOF ratio has returned to 0.90 can be considered "the potentially unsafe period of recovery. Aim To determine the time difference (from giving AD till reach 90% TOF readings at TOF watch monitor) between clinical (subjective) and objective monitors of muscle recovery, to provide a better monitoring efforts to control the potentially dangerous period of NM recovery. Patient And Methods A prospective, clinical trial study of one hundred ASA I or II females undergoing surgery of caesarean section. Muscle relaxation was monitored at the end of the operation by the quantitative nerve stimulator; TOF-Watch monitor (Organon, Inc., Dublin, Ireland). Patients were divided into two groups according to whether reversal of MR given based on clinical recovery (group c), or objective recovery at T3 twitch reading of the monitor (group T). Time to reach TOF Ratio reading of 90% was recorded. Results there were no statistically different results found regarding the time to reach 90% TOF ratio between the two groups (P value >0.05). Still there is statistically different values between the two groups in TOF readings at AD administration, and at Extubation (P value <0.05) which indicate early AD administration and early extubation with higher possibility of respiratory complication in clinical group due to incomplete NM recovery. Pulse rate, at TOF 90%, was significantly higher among patients in clinical group (107 ± 15) p/min rather than among patients in TOF group (97 ± 16) p/min, P value<0.05, which may be explained by better awareness and recovery state, probably more feeling of comfort at operative site, and more proper oxygenation and/or ventilation level in TOF group.

Conclusions:
1-pulse rate at the end of operation where significantly higher in clinical group than in TOF group.
2-there was no significant difference between the two study groups regarding Time from AD administration till TOF% recovery of 90%, Time from AD till Extubation, and Time from Extubation till TOF% recovery of 90%.
3-there was no significant difference between the two study groups in TOF readings at AD administration, and at Extubation.
4-the objective AMG measurement of TOF twitches and TOF % is more sensitive than clinical monitoring combined with simple nerve stimulator in detecting adequate recovery of neuromuscular function.

Key Words: TOF, PNS; Fade; NMBA; Extubation; Reversal

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I. Introduction

The use of muscle relaxants is essential part modern anesthetic practice. In 1942, Griffith and Jonson introduced the first muscle relaxant into clinical practice. Its chemical name was d-tubocurarine. Neuromuscular blocking agents are used to improve conditions for tracheal intubation, to provide immobility during surgery, and to facilitate mechanical ventilation. Since then many other muscle relaxants were developed: gallamine in 1947, succinylcholine in 1949. Since the discovery of curare nearly 50 neuromuscular blocking agents have been introduced, but many of these drugs have been abandoned because of the undesirable side effects.

The introduction of MR(muscle relaxant) into clinical practice revolutionized the Era of the new modern medicine as adjunct to anesthetic drugs providing muscle relaxation to facilitate tracheal intubation.

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Mechanical ventilation, provide immobility during surgery, positioning, and surgical manipulation e.g. cardiac, abdominal surgery, etc.

MR has no anesthetic, analgesic, or hypnotic effects. Neuromuscular blocking agents should be administered only to anesthetized individuals to provide relaxation of skeletal muscles. 130 MR are typed according to their mechanism of action into:

1-Nondepolarizing MR: that also divided according to their chemical structure into: [a] aminosteroids: vecuronium. [b] benzylisoquinolines: mivacurium.

2-Depolarizing MR: ex: succinylcholine.

Physiological Tips:
- The transmitter at the neuromuscular junction is acetylcholine, which is synthesized from acetyl-coenzyme A and choline, stored in vesicles and released in response to a nerve stimulus.
- The acetylcholine receptor is made of 5 subunits and acts as a cation channel causing depolarization at the motor end plate.
- The acetylcholine receptor acts as an amplifier and a switch.
- Acetylcholine is broken down to choline and acetate, catalyzed by acetylcholinesterase.
- The neuromuscular junction is so vital to life that everything is done to excess, excess transmitter release, and an excessive post-synaptic potential to ensure transmission of the stimulus and skeletal muscle contraction.

II. Pharmacology:

Neuromuscular blocking agents (NMBAs) or muscle relaxants are classified as depolarizing or nondepolarizing NMBA depending on their mechanism of action. Nondepolarizing NMBA is further subdivided into aminosteroids: (e.g. rocuronium, vecuronium, pancuronium, pipcuronium) and benzyisoquinolines (e.g. atracurium, cisatracurium, mivacurium, doxacurium) according to basic chemical structure.

Succinylcholine is the only depolarizing drug of clinical relevance. 130 None of the currently available nondepolarizing muscle relaxants equals succinylcholine’s rapid onset of action or short duration; however, the onset of nondepolarizing relaxants can be quickened by using either a larger dose or a priming dose. The ED₉₀ is the effective dose of a drug in 95% of individuals. One to two times the ED₉₀ is usually used for intubation. Although a larger intubating dose speeds onset, it exacerbates side effects and prolongs the duration of blockade. For example, a dose of 0.15 mg/kg of pancuronium.

1-Nondepolarizing nmba: [NMBA]

Mechanism of Action: These agents act as competitive antagonists at the post-synaptic acetylcholine receptors, inducing flaccid paralysis; they bind to the same receptor subunit as the physiological agonist acetylcholine; unlike acetylcholine they donot induce opening of the central ion channel of the receptor. It is sufficient for the nondepolarizing NMBA to block just one of these two subunits to prevent activation of ACH receptors, thus they only block the receptors and donot induce depolarization.

In addition to their action at the post-synaptic ACH receptor, they also inhibit presynaptic ACH receptors at the nerve terminals and thereby impair recruitment of ACH. By increasing the concentration of NMBA at the NMJ the amplitude of the end plate potential (EPP) decreases progressively.

Over 70—90% of ACH receptors at the motor end plate must be occupied by NMBA before initial signs of a neuromuscular blockade become evident (NEUROMuscular safety margin). Accordingly an initial dose of NMBA must be large enough.

At the end of the intervention, more than 70% of the receptors may still be occupied by NMBA. Without any signs of a neuromuscular (residual) blockade being detectable.

The nmba blockade is characterized by:
- Fade of the response after TOF, DBS, or titanic stimulations, which attributed to binding of the NMBA to the presynaptic ACH receptors resulting in inhibition of the recruitment of ACH from the reservoir pool.
  - POST-TETANIC potentiation: after titanic stimulation, a transient increase in the concentration of ACH occurs at the motor end plate.
  - NMBA that presently available:
    - Short acting: e.g. Mivacurium.
    - Intermediate acting: e.g. Atracurium, Cisatracurium, Vecuronium, Rocuronium.
    - Long acting: Doxacurium, Pancuronium, Pipcuronium.

Metabolism: Generally speaking the Benzylisoquinolins metabolized in blood by plasma esterases, and Aminosteroids metabolized in the liver.
2- depolarizingmmbas:
Depolarizing blocking agents (DBAs):

such as succinylcholine and decamethonium, initially depolarize the post-synaptic membrane by opening receptor channels, in a similar manner as Ach, acting as ACH receptor agonists. However, because they are not hydrolyzed by acetylcholinesterases at the NMJ, their action persists, resulting in prolonged end-plate depolarization. Because opening of the lower gate in the perijunctional sodium channels is time limited after initial excitation and opening these channels close and cannot reopen until the the end-plate repolarises, this is called phase I block. This brief period of consecutive excitations is manifested clinically by transient muscle fasciculations, followed shortly by neuromuscular transmission block and spastic paralysis. During both a depolarizing and a non-depolarizing block, the muscle continues to respond to direct electrical stimulation (e.g., electrocautery) despite the inactivation of the receptors. If the exposure to a depolarizing relaxant is prolonged (by administering relaxants in large or repeated doses or by infusion), the typical depolarizing (phase 1) block may assume the characteristics of a non-depolarizing (phase 2) block.

Desensitization is thought to be the primary mechanism responsible for phase 2 block. Desensitization may occur when the receptors are no longer responsive to the presence of agonists on both alpha subunits, thus inactivating the receptors.

Desensitization involves a conformational change in the structure of the receptor, preventing it from opening the channel normally. In addition, many agents that enhance neuromuscular block also promote desensitization of the nicotinic receptor and/or may cause an open channel receptor block (e.g., barbiturates, volatile anesthetics, local anesthetics, and cholinesterase inhibitors). The ratio of blocked receptors to unblocked receptors rendering the junction inactive varies between muscle fibers, which explains the sigmoid form of relaxation and recovery curves. The fibers are normally distributed in respect to this characteristic and the cumulative distribution curve is sigmoidal.

Reversal Of Neuromuscular Blockade:

Because depolarizing MRs are NOT metabolised by acetylcholinesterase, they diffuse away from the neuromuscular junction and hydrolysed in the plasma and liver by another enzyme pseudocholinesterase, which is rapid process. Fortunately because there is no specific reversal agent for depolarizing MRs available.

Reversal of the NNMBAs(except mivacurium): are reversed by:
- redistribution ; gradual metabolosim; excretion by the body and administration of specific reversal agent(eg:cholinesteraseinhibitors,andsugamadex{specific for aminosteroidsnnmba}).

ASSEMENT OF THE NEUROMUSCULAR BLOCKADE:

Agreat inter individual variation in the onset ,duration ,and recovery of action of any particular drug (we consider NNMBAs) depends on:
1-patient factors : gender,age,genetic predisposition ,temperature,PH, concomitant illness with its medications, and renal and/or hepatic function.
2- anesthetic technique planed: type ,duration, and other drugs to be administered per operatively.
3-surgical operation planed:extent,duration,site ,etc. We consider in our study the effect of NNMBAs.

The action of NNMBAs should be monitored as a routine course ;because it is easy to monitor and can be adjusted to meet the individuals need by subsequent injections ;any potential re-curarization NNMBAs may cause at the end of operation can be reversed.this permits the anesthesiologist to manage the pharmacodynamic action of NNMBAs ,despite their great variability, and to adapt their effects as needed to the specific situation.
monitoring is done for one or more of: during anesthesia induction (facilitate intubation), intraoperative level of relaxation (control subsequent injections of NMBAs), and neuromuscular recovery (end of effect and the need for reversal). In our study we consider monitoring of neuromuscular recovery. 

III. Methods of monitoring:

1-clinical criteria of recovery: eye opening, breathing efforts, sustained head lift for 5 seconds, hand grip, tongue protrusion, limb lift, tongue depressor test, tidal volume, maximal inspiratory pressure more than -25 cm H2O, etc. Clinical criteria lose its sensitivity at TOF ratio of 0.6 i.e. there is still risk of residual Nm blockade that may cause upper airway obstruction and respiratory insufficiency in the postoperative period.

2-simple qualitative nerve stimulation in which the muscle response to stimuli is detected by subjective means (visual and tactile). In most clinical settings, regardless of the pattern of neurostimulation or the current intensity delivered, there is no significant difference in the ability to detect fade between visual and tactile means. 

3-quantitative nerve stimulation: in which muscle response detected by objective means (can plotted graphically on screen, percentage, etc).

It is the most sensitive method at present where it can measure TOF recovery ratio of more than 0.9. Detecting quantitative muscle response to electrical stimulus can be done by one of several types of signal measurements:

a—MMG, mechanomyography, by directly measure the muscle force.

b—EMG, electromyography; measure electrical activity of the muscle in response to stimuli.

c—AMG, acceleromyography; depending on piezoelectric effect (acceleration transducer) application of the second Newton’s law; i.e. crystal that generate an electrical current via application of mechanical force (acceleration).

Second newton’s low state: FORCE = MASS * ACCELERATION.

AMG is the mode chosen in our study.

d—KMG, kinemyography: a mechanosensor is integrated into a piezoelectric crystal to generate electric current induced by M contraction applied on mechanosensor.

e—PMG, phonomyography; the force of M contraction generating asound by a condenser microphone applied on skin surface that sound is measured and is proportional to the force of contraction.

Principles of Nerve Stimulation

Ohm’s Law (U = I • R, where U = voltage, I = current, and R = electrical resistance) describes the factors involved in production of an action potential (AP). The nerve stimulator must provide constant current intensity, as opposed to constant voltage. 

The strength or total charge, in microCoulombs (μC), of the stimulus depends on its duration (pulse width in microseconds, μsec), and current amplitude (intensity in milliamperes, mA) that reaches the nerve fiber. One of the most important determinants of the evoked muscle response is the stimulation current amplitude, which depends on the impedance between the electrode and the skin. Using stainless steel needle electrodes, tissue impedance generally is between 500 and 2,000 ohms. Similar impedance is obtained when using silver/silver chloride surface electrodes if the skin is adequately prepared by wiping the skin with alcohol swabs to remove insulating natural skin oils. In neuromuscular research rubbing an electrolyte solution into the skin, abrading the skin, and/or applying a conducting paste may be necessary. When using disposable ECG-electrodes, it may be necessary to moisten the pads that have dried out during storage. Despite meticulous skin preparation, a constant current is
Another important determinant of the evoked muscle response is the current intensity. When pulse duration and skin-electrode resistance are constant, the 7 stimulating current required to depolarize all fibers of a nerve bundle is called the maximal current. Below this value, the relationship between the number of nerve fibers recruited and the intensity of stimulating current is sigmoidal. This reflects the distribution of individual nerve fiber sensitivities in response to various current intensities. To ensure consistent and maximal recruitment of fibers despite minor variations in skin resistance over time, a supramaximal current (i.e., 10-20% higher than the maximal current) is delivered.

In addition to skin impedance and current intensity, the duration of the stimulus (pulse width) is also important in determining the amplitude of the evoked muscle response. The relationship between pulse duration and the amplitude of evoked single twitch response is also sigmoidal; if the current intensity is kept constant, the amplitude of the evoked response shows little change when pulse duration exceeds 0.15-0.30 ms. In clinical practice, pulse widths of 0.2-0.3 ms are used. Durations longer than that may cause repetitive firing and therefore are not recommended. Some devices that deliver a pulse of only 0.1 ms duration may achieve less than maximal fiber recruitment, possibly influencing assessment.

The effect of muscle temperature must also be appreciated. Peripheral cooling decreases the evoked muscle twitch response and increases the electromyographic (EMG) response area, while local heating increases muscle force and decreases the compound EMG response.

The stimulus application rate to the nerve (stimulation frequency) also induces changes in muscle response. At the normal, unblocked NMJ, supraphysiological stimulation rates (e.g., above 70-200 Hz) cause muscle fatigue. Stimulation at physiologic rates (brief tetanus at 50 Hz) at the unblocked NMJ, in contrast, results in sustained contraction without fade. In the presence of a nondepolarizing block, a fade is noted at slower stimulation rates. In addition to inducing fatigue at the NMJ, high-frequency stimulation also increases local blood flow five- to six-fold, facilitating delivery of relaxant muscle. In the clinical setting, the stimulation frequency and the rate of block onset are directly proportional, such that an increase in stimulation frequency will result in a falsely elevated rate of onset.

Induction of fatigue and an increase in blood flow also reduce the apparent (but not actual) dose requirements for all muscle relaxants, to the stimulated.

During a relatively steady and slowly recovering neuromuscular block, the interstimulus interval should be no less than 10-20 seconds, since at shorter stimulation intervals, the evoked responses become artificially decreased. The explanation for this may be the same as for the train-of-four fade; the first stimulation causes a muscle twitch and redistribution of antagonists on the end plate so that smaller and smaller numbers of muscle fiber responses follow consecutive nerve stimulations.

Patterns of Nerve Stimulation

The majority of nerve stimulators deliver a wide range of stimulating patterns, allowing for the differentiation between depolarizing and non-depolarizing block. The patterns include single-twitch, train-of-four, double burst, and tetanic stimulation, as well as a post-tetanic twitch count (facilitation). The stimuli delivered should be square-wave, supramaximal, and most often 0.2 ms in duration. The modes of neurostimulation differ in the intervals and pattern of the delivered stimuli.

Single Twitch

If a single-twitch (ST) pattern is used, a baseline amplitude of the muscle response (Rref) must be established prior to the administration of muscle relaxant (Figure 4). The degree of block produced by the relaxant can be estimated by comparing a subsequent response to the baseline (R1/Rref x 100% = ST%). In the presence of non-depolarizing muscle relaxants, high frequency stimulation can induce “fade” of the single twitch response. For instance, the ED95 (effective dose for 95% response suppression of the thumb adduction) of d-tubocurarine is decreased by a factor of three when the stimulus frequency is increased from 0.1 Hz to 1.0 Hz.

A supramaximal, 0.2-msec duration stimulus with a frequency of 0.1 Hz (10 s intervals or 6/min) is the most common single stimulation mode in many handheld nerve stimulators. Other inter-stimulus intervals used in the clinical setting include a stimulus pattern every 12 seconds (0.08 Hz or 3/min), 15 seconds (1/15 ~ 0.066 Hz or 4/min), 20 seconds (0.05 Hz or 3/min), or 60 seconds (1/60 ~ 0.0166 Hz).

Figure 4

The motor response to ST is not reduced until 70-75% of the receptors are occupied, and disappears once 90-95% receptor occupancy occurs (Figure 7). Thus, the range of receptor block detected by ST stimulation (i.e., between 75% and 95% receptor occupancy) is narrow, limiting its clinical usefulness. Other factors that limit the clinical usefulness of ST stimulation include the great variability of evoked responses to alterations in current, skin and muscle temperature, and resting muscle tension (preload). Therefore, careful documentation of baseline response is mandatory for comparison with subsequent stimulation responses. When
the control height is evaluated by sight (visually) or by touch (tactile), as is the traditional clinical practice, the change in subsequent responses is difficult to assess and quantify accurately. Quantification of the evoked response by measuring force, AMG, acceleration, or movement greatly enhances the sensitivity of

**Train-of-Four**

In the train-of-four (TOF) pattern, four individual stimuli are separated by 0.5 sec (2 Hz). The “train” can be repeated by chosen intervals but the optimal frequency is every 15 or 20 seconds(21). At this rate, TOF itself does not cause artificial fade. In the absence of block, the pattern induces four clearly defined muscle responses (R). In the presence of non-depolarizing block, TOF will exhibit fade (Figure 5). The degree of fade is proportional to the extent of the neuromuscular block; the ratio of the amplitude of the fourth response (R4) to that of the first response (R1) estimates the extent of non-depolarizing block (i.e., the degree of receptor occupancy). This is known as the R4/R1 or TOF ratio.

Figure 5

At the unblocked NMJ, the R4/R1 approximates 1.0. During a partial depolarizing block, the response height is reduced to the same extent in all four responses (no fade), and the R4/R1 ratio is 1.0.

However, the ratio of R1 to the control, or baseline twitch (R1/Ref) will be less than 1.0. If a phase 2 block develops after succinylcholine administration, the TOF responses will show “fade.” During a non-depolarizing block, the R4 begins to decrease when 70–75% of the receptors are occupied (similar to when single twitch fade begins); the R1 declines when the R4/R1 ratio falls below 0.7. The R4 response is completely lost at approximately 80% receptor occupancy. The R3 and R2 responses are lost when approximately 85% and 85–90% of the receptors are occupied, respectively. When 90–95% of the receptors are blocked, R1 disappears. During recovery of neuromuscular block, the responses appear in reverse order, R1 first and R4 last.

The recovery of TOF ratio is also depicted. TOF stimulation has become the most popular method of assessing neuromuscular block in clinical practice. As long as all four responses are detectable, the TOF ratio remains consistent, regardless of the current intensity. This consistency is evident at current intensities that are at least 10 mA above threshold. TOF is less painful than tetanic stimulation, and thus is more comfortable for awakening patients at risk for residual paralysis, as pain is directly related to the intensity of the stimulating current.

Submaximal stimulation currents enable rather painless monitoring in intensive care patients requiring muscle relaxants as part of their therapy(21). TOF stimulation shows fade during a partial non-depolarizing block, but unlike tetanus, the TOF pattern does not induce changes in apparent onset or recovery. Unlike single twitch, TOF does not require a preblock control response, as the degree of block is proportional to R4/R1. A TOF ratio of 0.75 generally correlates with a sustained muscle response to 50 Hz for 5 seconds and with the first stimulation response having returned to baseline (see Figure 9). This degree of block also correlates with clinically adequate neuromuscular function, although a greater degree of recovery may be necessary for all cholinergic synapse.

It should be noted that the TOF ratio cannot be calculated before all four stimulations elicit a response, irrespective of the measurement method (if the R4 response is not present, the ratio would be zero). This means that the minimum R1% at the point where the ratio can be calculated is around 25–30 %.Double burst stimulation DBS; Tetanic stimulation TS; and Post tetanic count PTC are not comparable to TOF in objective evaluation of Nm recovery of nmba (tof ratio). (3)
Sites Of Nerve Stimulation For Monitoring: Accessiblety to a superficial nerve is the most important . (22)

An ideal stimulation site must be; easily accessible,and the corresponding neuromuscular response can be identified and unmistakably,a general rule that any direct muscle stimulation should be avoided and a nerve-muscle unit should be selected that best allows the twitch to be recorded. In clinical practice there are four nerve-muscle units in use; the ulnar nerve/adductor pollicis muscle, the posterior tibial nerve/flexor hallucis brevis muscle, the facial nerve/orbicularis oculi muscle, and the facial nerve/corrugator supercilii muscle. (6)

The ulnar nerve/adductor pollicis muscle are the nerve-muscle unit that is most frequently used in clinical practice because;
1-the monitoring not affect the surgical condition.
2-this N-M unit is easily accessible intraoperatively.
3-can evaluate tactile, visual and objective means concurrently.
4-the adductor pollicis M is located on the lateral side of the arm while the ulnar nerve runs along the medial side, i.e the risk of any direct muscle stimulation can be ruled out. To stimulate the ulnar nerve, one electrode is placed on the radial side of the volar forearm about 1 cm (0.4") proximal to the wrist. The other electrode may be placed 3–4 cm (1.2-1.6") proximal to the first electrode (Figure 12) or over the ulnar groove at the elbow. (5)

SENSETIVITY Of Various M Groups To Nmbas: Muscle groups differ in their sensitivity to muscle relaxants . (23) Therefore, the results obtained in monitoring one muscle group may not accurately reflect the state of relaxation at another muscle group. Proposed factors include differences in regional blood flow, muscle temperature, density, type of receptors and muscle fiber composition. After a bolus dose of relaxant, the diaphragm and upper airway muscles achieve onset and recovery of block quicker than peripheral muscles, possibly because of their higher blood flow and higher receptor density. When compared to the adductor pollicis muscle, the diaphragm requires 1.5-2 times more relaxant to achieve paralysis. Differences in sensitivity to relaxants and in the onset times have clinical implications when peripheral sites are monitored. When high doses of relaxants are used (more than twice the ED95), the faster onset time at the diaphragm predominates, and block is achieved here before it is seen at the adductor pollicis muscle. However, if lower doses of relaxant are used, the adductor pollicis twitch may be ablated before maximal diaphragmatic relaxation is achieved.

The response of the orbicularis oculi muscle to facial nerve stimulation may be more accurate than peripheral muscles because it more closely reflects the sensitivity and time course of the airway musculature. However, direct muscle stimulation must be avoided, as it may result in an enhanced response and underestimation of the degree of overall block . (24)
Acceleromyography (AMG)

The principle of accelerography is based on Newton’s Law which states that force equals mass times acceleration (F = m • a). As mass is held constant, the force of thumb adduction in response to ulnar nerve stimulation is directly proportional to acceleration. A thin transducer (piezoelectric wafer) is attached to near the tip of the thumb. Whenever the thumb moves, a voltage is generated which is proportional to the degree of angular acceleration. The signal is amplified and displayed on a monitor screen. The monitor can also display the percent change of the evoked response from baseline, the calculated TOF ratio, and the PTC. \(^{(25)}\)

Accelerography results are comparable to mechanomyographic TOF monitoring at varying current amplitudes. Accelerometers are less bulky and easier to use than force transducers, and because they measure isometric contraction, they do not require a muscle preload. However, any interference of free thumb movement will reduce the accuracy of measurement. \(^{(26)}\) Accuracy may also be affected by thumb movement, or by failure of the thumb to return to its baseline position after a contraction, resulting in a TOF ratio greater than 1.0 in the unblocked state.

A hand adapter is used to ensure:
1. that the thumb returns to its original position after each measurement. This improves the quality of the results.
2. the starting position of the thumb will no longer be affected by intraoperative repositioning of the patient. \(^{(6)}\)

Clinical Assessment of Neuromuscular Function

To estimate muscle strength and adequacy of reversal, a variety of clinical signs have been employed: the patients’ ability to open their eyes, protrude their tongue, swallow, lift their head or leg, sustain a hand grip, or clench their teeth. Although useful in the clinical setting, clinical assessment has been shown to be inadequate in detecting all cases of residual block. These studies have found that between 2% and 41% of postoperative
patients may have a TOF ratio less than 0.70, despite being able to meet clinical criteria of recovery. An initially strong muscle contraction that weakens with time is characteristic of residual paralysis. The patients’ movements may appear jerky due to their inability to sustain muscular activity. While clinical tests of neuromuscular integrity are useful in assessing the degree of block, they require the patients’ collaboration and cannot be performed with unconscious patients. The pattern of respiration and the adequacy of the tidal volume, vital capacity, and negative inspiratory pressure have been used as markers for neuromuscular integrity. In the presence of partial block, however, patients may have adequate ventilation, but their airway reflexes and ability to cough can be impaired. In addition, postoperative respiratory difficulties may be due to residual effects of anesthetic agents. High end-tidal CO2 may be a sign of inadequate respiratory capacity. Residual block should always be excluded as a cause of respiratory depression by using a quantitative NMT monitor. The combination of clinical evaluation along with neuromuscular monitoring should be used.

When the TOF ratio is greater than 0.6, most patients are able to sustain head lift for three seconds or more, but this does not ensure normal muscle strength.

When a TOF ratio exceeds 0.75, eye opening, cough and tongue protrusion may be clinically normal. Recently, it has been shown that the hypoxic breathing response is impaired at TOF ratios below 90%. Furthermore, even despite the use of ultra-short acting muscle relaxants (mivacurium) and full reversal with anticholinesterases, some volunteers did not feel “street ready” and had residual abnormal activities.

IV. Patient And Methods

A prospective randomized clinical trial study carried out in Baghdad teaching hospital in medical city complex during a period of four months from the first of September 2012 to the end of December 2012 and was conducted in 100 pregnant ladies aged 18-42 years all of ASA I and II scheduled for emergency and elective caesarian section surgeries.

Exclusion criteria:
1. presence of neuromuscular, hepatic, renal, or cardiac disease.
2. body mass index of more than 35.
3. expected procedure duration more than 75 minutes.
4. anticipated difficult ventilation or endotracheal intubation.
5. receiving drugs known to interfere with neuromuscular transmission.
6. the need for extra drugs or procedures indicated during operation and not scheduled in our thesis.

A detailed history was taken from each patient, information of the past medical and surgical history. A clinical examination was performed by general examination and vital signs. After obtaining intravenous (IV) access intravenous induction was done by thiopental 4-6 mg/kg slowly (anesthetising dose) followed by succinylcholine 1.5 mg-kg followed by tracheal intubation using endotracheal tube. Anesthesia was maintained using halothane in oxygen in 1% concentration at the beginning of operation and 5% concentration after the delivery of the baby till the end of the operation, and intermittent positive pressure ventilation. Muscle relaxation maintained by atracurium in dose of 0.3mg/kg, Monitoring was done using electrocardiogram,
SpO2 and blood pressure monitoring. Intraoperative analgesia was provided with intravenous fentanyl in dose of 50 microgram after the baby was delivered.

The TOF–watch (Organon, Inc., Dublin, Ireland) device connected to patient by stimulation of the ulnar nerve the electrodes are best applied at the volar side of the wrist, the distal electrode should be placed about 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon of carpiunlaris muscle. The proximal electrode preferably should placed 2 to 5 cm proximal to the distal electrode, the piezoelectric ceramic wafer An acceleration transducer was taped distal to the distal interphalangeal joint of the thumb, and the study arm immobilized with a splint. The study arm was positioned to allow free movement of the thumb.

When the surgical procedure was completed the patients are randomly divided into two groups depending on timing of giving the reversal each group with 50 patients:
1. In the first group we assess the patients for the signs of neuromuscular recovery from the action of MR, at least two signs are required, using the clinical signs recorded on questionniare paper (upper limb movement, lower limb movement, breathing effort, head movement, swallowing, spontaneous eye opening) to give reversal of MR (neostigmine 2.5 mg combined with atropine 1.2 mg).
2. A second group of patients already linked on TOF watch monitor and to be given reversal when T3 detected.

Then we assess the patients for the adequacy of neuromuscular recovery after reversal using standard clinical criteria for extubation (5-s head lift, eye opening on command, negative inspiratory force more than -20 cm H2O, vital capacity breath -15 cc/kg, hand grip, and tongue depressor test). When the anesthesia care providers determined that full recovery of neuromuscular function was present, and that tracheal extubation could be performed the peripheral nerve stimulation performed and measure the TOF ratio. The time of reversal, Time of extubation, and also Time from reversal till measurement of TOF of 90% where recorded.

### Data collection sheet

- **Group:**
- **casefile No.:**
- **Age:**
- **wt:**
- **ht:**
- **gender:**
- **Duration of surgery:**

**A: Reversal at clinical recovery:**
1) UL move.
2) LL move.
3) Diaphragm:
4) Breathing effort:
5) Tongue protrusion:
6) Head movement:
7) Swallowing:
8) Eye opening:

**B: Reversal at TOF(T3):**
- **Time Induction:**
- **AD:**
- **Extubation TOF ratio 90%:**

**Time:**

**Vital signs at TOF 90%:**
- **BP**
- **Temperature**
- **Pulse rate**
- **Spo2 value**

### V. Statistical analysis

Data of all patients in both study groups; TOF(T3) group and clinical group were entered into a computerized database management program. Microsoft excel was used for this purpose, checking of data was made by the candidate for any error or inconsistency, data then were coded and transformed into statistical form for analysis.

SPSS (statistical package for social sciences) software for windows was used for statistical analysis.

Descriptive statistics were presented as mean ± standard deviation (SD) and ranges for all variables under study.
TIME To Reach 90% TOF Ratio , Comparison Between Clinical And Objective Means In Monitoring

Students’ t test was used to compare means in between both groups and to find the significance of possible differences. Differences in means considered as significant if P.value \( \leq 0.05 \). Finally results were presented in tables and figures.

There were 95 patients enrolled in this clinical trial, they were aligned into two groups, namely, the T group which included 45 patients and the clinical group included 50 patients.

Baseline characteristics of patients:

The baseline characteristics of patients in both groups are shown in table 1. No statistical differences had been found in between both groups regarding the means of age, weight, height, BMI or the duration of operation, in all comparison P.value was >0.05.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of patients in study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Age (year)</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
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<td></td>
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<tr>
<td>BMI (kg/m2)</td>
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<tr>
<td></td>
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<tr>
<td>Duration of surgery (min)</td>
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<td></td>
</tr>
</tbody>
</table>

Comparison of vital signs and SPO2:

Comparison of means of vital signs and SPO2 in between study groups is summarized in table 2. Pulse rate, at TOF 90%, was significantly higher among patients in clinical group (107 ± 15) b/min rather than among patients in TOF group (97 ± 16) b/min, P.value<0.05, table 2, and figure 1. Other vital signs and SPO2, did not show a statistically significant difference amongst groups, P.value>0.05, table 2.

<table>
<thead>
<tr>
<th>Table 2. Comparison in vital signs and SPO2 in between study groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Pulse rate at TOF 90%</td>
</tr>
<tr>
<td>Temp at TOF 90%</td>
</tr>
<tr>
<td>Systolic pressure at TOF 90%</td>
</tr>
<tr>
<td>Diastolic at TOF 90%</td>
</tr>
<tr>
<td>SPO2 at 90 TOF</td>
</tr>
</tbody>
</table>

| Figure 1. Comparison of mean Pulse rate at TOF 90% |

Time distribution and TOF reading: (table 3 and figures 2-5)

The time period from the administration of antidote to extubation was relatively shorter in clinical group compared to TOF group; (3.5 ± 2.7) min vs.(4.1± 2) min respectively, figure 2.
The mean time duration between extubation and TOF 90% was relatively longer (9.2 ± 4.7) min in clinical group compared to (8.1 ± 4) in TOF group, figure 3.

Also an apparent slight difference in mean time from Antidote administration to TOF 90% had been observed, figure 4.

However, the differences in time parameters were not statically significant, P.value> 0.05, table 3.

The mean of TOF readings at antidote administration was lower in clinical group (1.8 ± 1.3) than TOF group (3), in fact all patients in the TOF group recorded readings of (3) twitches, the difference amongst groups was statistically significant, P<0.05, table 3.

On the other hand a statistically significant difference had been found in the mean of TOF readings at extubation, Clinical group patients showed lower readings (21.4 ± 18.5) vs. (32 ± 16) in TOF group, P.value <0.05, table 3 and figure 5.

Table 3. Comparison in the time and TOF readings parameters amongst study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Groups</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between AD and extubation</td>
<td>Clinical 3.52±2.7</td>
<td>TOF 4.13±2.0</td>
</tr>
<tr>
<td>Time between extubation and TOF 90%</td>
<td>9.2±4.7</td>
<td>8.1±4</td>
</tr>
<tr>
<td>Time from AD to TOF 90%</td>
<td>12.7±5</td>
<td>12.3±5</td>
</tr>
<tr>
<td>TOF reading at AD (twitches)</td>
<td>1.8±1.3</td>
<td>3.0±0.0</td>
</tr>
<tr>
<td>TOF reading at extubation(%)</td>
<td>21.4±18.5</td>
<td>32±16</td>
</tr>
</tbody>
</table>

Figure 2. Comparison of mean time (in minutes) from the administration of antidote to extubation

Figure 3. Comparison of the mean time from extubation to TOF 90%.

Figure 4. Comparison of the mean time from AD to TOF 90%.
TIME To Reach 90% TOF Ratio, Comparison Between Clinical And Objective Means In Monitoring

Figure 5. Comparison of TOF reading at AD administration.

Figure 6. Comparison of TOF reading at Extubation.

VI. Discussion

In our study we have 95 patients divided into 2 groups; first group of 45 patients given reversal when there is sufficient spontaneous recovery (third twitch recovered) detected objectively using AMG based TOF watch nerve stimulator monitor. A second group of 50 patients given reversal according to clinical bases when two or more criteria of muscle recovery are noticed clinically. In both groups we measure and compare duration of time from giving AD till recovery of TOF ratio have reached sufficient standardized value where residual paralyses and possible respiratory complication are excluded (TOF ratio ≥ 90%) measured by TOF watch monitor. In the TOF group the time from AD administration to recovery of TOF ratio to 90% was 12.3 ± 5 minutes while in the clinical group it was 12.7 ± 5 minutes, our study shows no statistically significant difference between the two results regarding means ± standard deviation, P value was > 0.05.

Kim et al. in his thesis; Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Administered neostigmine 0.07 mg/kg to surgical patients at a TOF count of 1, 2, 3, and 4 to determine the time required to achieve an MMG-derived TOF ratio of 0.7, 0.8, and 0.9. The median (range) times from neostigmine administration until a TOF ratio of 0.9 was reached in patients receiving sevoflurane anesthesia were 28.6 (8.8 – 75.8), 22.6 (8.3 – 57.4), 15.6 (7.3 – 43.9), and 9.7 (5.1 – 26.4) minutes in patients with TOF counts of 1, 2, 3, and 4, respectively. This clearly takes longer time regarding T3 than in our study (range 7-18 minutes) which may be due to the use of different agents for maintaining anesthesia.

Kopman et al.30. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? Antagonized cisatracurium and rocuronium-induced neuromuscular block at a tactile TOF count of 2. In the rocuronium group, TOF ratios 10 minutes after reversal were 0.76 (range, 0.47 – 0.95), and 5 of 30 patients did not reach a TOF ratio _0.9 30 minutes after neostigmine was administered. In the cisatracurium group, TOF ratios 10 minutes after reversal averaged 0.72 ± 0.10 (range, 0.38 – 0.94), and 2 of the 30 patients did not reach a TOF ratio _0.9 within 30 minutes of reversal.

The same investigators antagonized steady-state infusions of NMBD at a single twitch depression of 10% of control. Recovery times following droperidol and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions.

Twenty minutes after reversal with neostigmine, EMG TOF ratios of 0.89 _ 0.06 were observed in patients randomized to receive vecuronium. These studies illustrate an important limitation of anticholinesterase drugs: regardless of the TOF count at the time of reversal, it is not always possible to achieve a TOF ratio _0.9 in all patients within 30 minutes of anticholinesterase administration.31, which disagree with our study where all the patients reach TOF ratio of 90% within 20 minutes of giving reversal that may be explained sample size.

Thomas Fuchs-Buder et al.31 Antagonism of Low Degrees of Atracurium-induced Neuromuscular Blockade When given at a TOF ratio of either 0.4 or 0.6, time to 0.9 and
1.0 TOF ratio was significantly shorter with any dose of neostigmine than without. The probability of successful reversal after 20 ug/kg neostigmine was 100% when a TOF ratio of 0.9 was the target; for a TOF ratio of 1.0, the probability was 93% and 67%, dependent on whether the dose of neostigmine was given at TOF ratio of 0.6 or 0.4, respectively. With a dose of 30 ug/kg, a TOF ratio of 1.0 is expected to be reached within approximately 5 min. Low doses of neostigmine are required to reach a TOF ratio of 0.9 or to accept an interval of 10 min.

VII. Conclusion:

Reduced doses (10–30 g/kg) of neostigmine are effective in antagonizing shallow atracurium block. For successful reversal within 10 min, as little as 20 ug/kg neostigmine may be sufficient. These dose recommendations are specific for atracurium and an intravenous anesthetic background. This is true because in our research we gave AD neostigmine of 70 ug/kg to reverse NM blockade of ≤ 3 twitches and required average > 12 minutes to reach recovery of 90% TOF ratio, so it is agreed with our research regarding the need for more shallow block (guaranteed by TOF ratio reading) at time of AD administration to ensure complete NM recovery at proper time and to eliminate the unsafe period of recovery lying between complete clinical recovery and until reach TOF ratio reading of 90%.

Conclusion:

1-there where no significant difference between the two study groups regarding Time from AD administration till TOF% recovery of 90% , Time from AD till Extubation , and Time from Extubation till TOF recovery of 90%.

3-there where significant difference between the study groups in TOF readings at AD administration , and at Extubation.

4-the objective AMG measurement of TOF twitches and TOF % is more sensitive than clinical monitoring combined with simple nerve stimulator in detecting adequate recovery of neuromuscular function

Recommendation:

It is recommended to depend on objective AMG in the assessment of neuromuscular status.

References:

[7]. Peper K, Bradley R J, and Dreyer, F. The acetylcholine receptor at the neuromuscular junction. Physiol. Rev. 1982; 62: 1271-1340

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TIME To Reach 90% TOF Ratio , Comparison Between Clinical And Objective Means In Monitoring Neuromuscular Recovery


Abbreviations

Ach acetylcholine
AMG acceleromyography
ASA American Society of Anesthesia
cMAP compound muscle action potential
DBA depolarizing blocking agent
AP adductor pollicis
DBS double burst stimulation
EMG electromyography
KMG kinemyography
MAP muscle action potential
MEP motor end plate = post-synaptic membrane
MEPP miniature end-plate potential
MMG mechanomyography
NDBA non-depolarizing blocking agent
NM neuromuscular
NMBA neuromuscular blocking agent
NMI neuromuscular junction
NMT neuromuscular transmission
PTC post-tetanic count
PTF post-tetanic facilitation
PTP post-tetanic potentiation
ST single-twitch
TOF train-of-four
OR operation room