IAPA advisory for Neuromuscular monitoring in Pediatric patients.

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Summary

Neuromuscular blocking agents (NMBA) are widely used in pediatric population including neonates for securing the airway and for providing muscle relaxation during surgery. These agents need to be used cautiously especially in young children, with immature physiology of neuromuscular junction. Intraoperative monitoring of neuromuscular junction is essential for documentation of baseline and adequate return of neuromuscular function after usage of NMBAs. Although monitoring devices are available, the neuromuscular monitoring (NMM) in pediatric patients is not widely practiced leading to potential morbidities and mortalities. This advisory by the Indian Association of Paediatric Anaesthesiologists briefly reviews the literature available, emphasizes upon the need for perioperative neuromuscular monitoring (specific indications) and describes anatomical and physiological changes in the new born, infant and child neuromuscular (NM) receptors. This advisory will also focus on the monitoring techniques available, their limitations, modifications and finally recommendations for use of NMM in pediatric patients.

Introduction

The quantitative NM monitoring in children and neonates increases the margin of safety when using neuromuscular agents during general anaesthesia. The technique assesses the onset of neuromuscular blockade, determines the level of muscle relaxation achieved during the surgery and evaluates patients' recovery from NM blockade thus minimizing the risk of residual paralysis (1,2).

Residual blockade results in impairment of pharyngeal and upper esophageal muscle activity. There is reduced ability to maintain a patent airway and increasedrisk of aspiration of gastric contents. There is reduction in chemoreceptor sensitivity to hypoxia and decreased forced vital capacity leading to patient discomfort. Increased risk of postoperative pulmonary complications can prolong post-operative care unit (PACU) and hospital stay. (3-6).

Is routine neuromuscular monitoring required? - Literature review

There is a scarcity of literature pertaining to the usage of neuromuscular monitoring in children and only few studies highlight the role of neuromuscular monitoring in pediatric age group. The reported incidence of residual neuromuscular blockade following use of muscle relaxants is 28% in pediatric patients (train of four (TOF) ratio <0.9), with 6.5% having a severe (TOF ratio <0.7) residual NM blockade. (7-9). De Souza et al (2011) reported inadequate reversal in 71% of children aged 3 months to 12 years, with 10% of them having TOF ratio <0.9 at the time of endotracheal tube removal (10). The incidence of residual neuromuscular blockade as assessed by accelerogram was 48.2% just before

extubation and 26.9%. in PACU in a prospective observational study in 291 patients with age ranging from 29 weeks to 19 years (11). Thus, without quantitative monitoring residual blockade cannot be excluded in pediatric patients.

The risk factors responsible for the residual nerve blockade in operation theatres include age of the patient (with every year of increasing age, there was 8% risk reduction in the incidence of residual block), type of NMBAs used, and time interval between the administration of neuromuscular blocking agent and measurement of TOF (with every 10 minutes since administration of neuromuscular blocker there was 19% risk reduction in the residual blockade) (11).

The recommendations of the Association of Anaesthetists of Great Britain and Ireland for standards of monitoring during anaesthesia and recovery include quantitative neuromuscular monitoring whenever neuromuscular blocking agents are used (12). Similarly, the Guidelines for the management of tracheal extubation by the All India Difficult Airway Association emphasize upon the importance of the reversal of neuromuscular blockade in order to reduce the incidence of postoperative airway complications (13). The consensus guidelines by Paediatric Intensive Care Society, United Kingdom, mentions about daily TOF monitoring during continuous administration of neuromuscular blocking agents in critically ill children (14). Hence, NM blocking agents need to be used cautiously especially in young children with immature physiology of neuromuscular junction, and NMM should be done to improve functional outcome and minimize the incidence of adverse events.

Table 1. Indications for neuromuscular monitoring in children (1)	
1	General anaesthesia especially for procedures requiring deep neuromuscular blockade (neurosurgery/vascular surgery/ophthalmic surgery).
2	Children with neuromuscular disorders.
3	Children with history of sensitivity to muscle relaxants
4	Children with severe hepatic and renal dysfunction.
5	Children undergoing renal or hepatic transplant.
6	Use of muscle relaxants infusions in pediatric intensive care units

How do neuromuscular junction and receptors differ in children from adults: anatomical and physiological aspects

There are some peculiarities of neuromuscular junction in new born and infants which differentiate it from those of adults (15,16).

- The junction continues to grow in the first 4-12 months of life, with increased metabolic activity of receptors. The post-junctional acetylcholine receptors in adults are made up of five subunits (2 α, β, ε and δ). The ε subunit is replaced with γ subunit in neonates, which makes it metabolically unstable and leads to prolonged opening of ionic channels. Immature receptors depolarize easily, have increased affinity for depolarising agents and decreased affinity for non-depolarising agents. Neonates and infants have a narrow margin of safety, with easy tendency for neuromuscular fatigue, which gets augmented under anaesthesia. Synaptic transmission is slow at birth. Also, the rate of acetyl choline released during repeated nerve stimulation is limited in neonates and infants particularly in preterm neonates. Due to immaturity of neuromuscular junction in neonates it shows an abnormal evoked response to a stimulus even in absence of neuromuscular blocking agent.

- The musculature in neonates and infants also differs from that in adults. There are two types of muscle fibres, type I or slow twitch which are more sensitive to non-depolarising muscle relaxants, and type II or fast twitch fibres which are less sensitive to non-depolarising muscle relaxants. Adult diaphragm has 55% of slow fibres, whereas the diaphragm of a full term and a preterm neonate has only 26% and 14% of slow fibres respectively. Hence neonates are more prone to early fatigue. Thus, while recoveringfrom muscle paralysis, the diaphragmatic movements start appearing at deeper levels of neuromuscular blockade in neonates than older children and adults (17).

- Another age-related effect is alteration in the degree of neuromuscular blockade with change in body composition and distribution of drugs. Non-depolarising blockers are relatively more distributed in extracellular fluid. As neonates and infants have increased extracellular fluids and increased volume of distribution, they require higher dosage of neuromuscular blocking agents (18,19).

- Adequacy of NM transmission is an important anaesthetic consideration in children since a slight reduction in NM function can diminish respiratory capacity (6). Some of the factors affecting patients' response to NM blockers are enumerated in Table 2.

- Future studies are required to provide more insight into physiology of neuromuscular junction, response of new born or infantile acetylcholine receptors to NMBAs and monitoring of neuromuscular function in children.

Table 2: Patient factors affecting the clinical response to neuromuscular blockade (18,19)
Changing volume of distribution

Increased muscle mass
Transition of muscle fibers
Maturation of elimination processes
Maturation of the NM junction

Monitoring techniques of neuromuscular junction: equipment and technical aspects

Equipment required for NM monitoring

The equipment required for NMT monitoring includes a nerve stimulator, and silver/silver chloride stimulating electrodes 20-40 mm in size. The limitation in children is the availability of appropriate size of electrodes. *Caution*: Use of needle electrodes should be avoided in children as they can damage nerves.

Sites of monitoring

The sensitivity of central (diaphragmatic and airway muscles) and peripheral muscles (adductor pollicis) to NMBAs is different. Hence the onset, speed and recovery from neuromuscular block depends on the muscle being monitored. As compared to peripheral muscles, the muscles of diaphragm, larynx, and facial muscles are more resistant to NMBA. Therefore, the onset of neuromuscular blockade is fast, , it lasts for a shorter time and recovers fast in these muscles. Amongst facial muscles, corrugator supercilli muscle follows the course of laryngeal adductor muscles whereas, orbicularis oculi follow time course of peripheral muscles.

Table 3. Choice of nerve muscle units for monitoring

Nerve	Muscle	Response
Ulnar	Adductor pollicis	Thumb abduction
Facial	Orbicularis oculi	Eyelid twitching
Posterior tibial	Flexor hallucis brevis	Plantar flexion of big toe

It would be more appropriate to use the facial nerve (corrugator supercilli muscle) for monitoring the earliest time for optimal intubation (for rapid sequence induction) or blockade of the diaphragm and the abdominal wall muscles. The adductor pollicis muscle and ulnar nerve unit, correlates best with pharyngeal muscle recovery and used as a best guide for extubation (Figure 1). In children complete block occurs earlier in orbicularis oculi than adductor pollicis. Also, the onset and recovery are slower at flexor hallucis brevis than at the adductor pollicis during inhalational anaesthesia.

Peripheral nerve stimulation: technological insights

Patterns of nerve stimulation

Although different patterns of stimulation may be applied, response to each pattern is age dependent.

1. Single twitch stimulation (Figure 2 (a), (b))

   A single supra-maximal electrical signal at 1.0 to 0.1 Hz is applied to a peripheral motor nerve. The response depends on the frequency at which individual stimuli are applied. It has limited clinical use.

2. Train of four stimulation (figure 3 (a), (b), (c))

   Four supramaximal stimuli are given every 0.5 secs (2 Hz). Stimuli are repeated every 10 or 20 seconds. Each stimulus causes the muscle to contract and fade, this fade is depicted by a decrease in twitch height, and this fade forms the basis of evaluation. It is the most widely used pattern of stimulus that can be applied since birth. The ratio of fourth to first response is referred to as TOF ratio. In absence of neuromuscular blockade, the TOF ratio equals one, i.e., all responses are equal. During partial non-depolarising neuromuscular block, fade occurs and TOF ratio decreases. The TOF ratio is inversely proportional to the degree of blockade. During partial depolarising blocker, there occurs no fade and TOF ratio remains one. TOF stimulation is less painful than tetanic stimulation. A TOF ratio less than 0.4 cannot be detected subjectively. In premature neonates (<32 weeks) TOF values are lower 83±2%. Similarly, in infants less than one month old, the 4^{th} evoked response is smaller. It is only once the child is more than 2 months old all the 4 evoked responses are equal in size.

   NMBA should be titrated to maintain at least one response to TOF stimulation in children under anaesthesia. The administration of anticholinesterase for reversal of neuromuscular blockade should be based on the response to nerve muscle stimulation (TOF: 0.4-0.9 and TOF count 4). Patients with no response should not receive anticholinesterase. Whereas, patients with a TOF count of 2 and TOF ratio> 0.9 reversal should not be given.[20]

3. Tetanic stimulation

   It is one of the most sensitive methods, and consists of rapid delivery of electrical stimuli at 30, 50 or 100 Hz, the most commonly used being 50 Hz for 5 secs. The response of a normal muscle to tetanic stimuli is a sustained response whereas after a non-depolarising muscle relaxant, the response is a fade. It is very painful, is used only under anaesthesia and has limited clinical utility. In infants less than 12 weeks of age, the use of tetanic stimulus is difficult to decipher due to fade and post-tetanic exhaustion even without using NMBA. On prolonged stimulation there results higher degree of fade in small infants, with more marked decrement in premature infants.

   The fade of the response to a high-frequency (tetanic or TOF) stimulation is considered a presynaptic event. At the start of tetanic stimulation large amounts of acetylcholine are released from the immediately available stores in the nerve terminal. As these stores become depleted, the rate of

acetylcholine decreases until equilibrium between mobilization and synthesis of the neurotransmitter is achieved. The muscle response to tetanic stimulation is maintained as long as acetylcholine release is greater than the amount necessary to evoke the response. When the margin of safety at the postsynaptic part of the neuromuscular junction (i.e., the number of free cholinergic receptors) is reduced by a nondepolarizing neuromuscular blocking agent, the decrease in the amount of acetylcholine release during tetanic stimulation produces fade of the neuromuscular response. Another mechanism which contributes to fade in response to the tetanic or TOF stimulation is blockade of the prejunctional cholinergic receptors at the nerve ending.

4. Post-tetanic count stimulation

   Use of neuromuscular blocking agents in doses sufficient to produce intense blockade to assist a smooth tracheal intubation usually does not show any response to TOF or single twitch, hence these cannot be used to determine the degree of blockade. This intense blockade can be quantified by applying tetanic stimulus (50 Hz for 5 secs) followed by post-tetanic response to a single twitch (1 Hz for 3 secs) at the end of tetanic stimulus. In case of intense block there occurs no response to either tetanic stimulus or to post-tetanic stimulus. As the blockade dissipates response to post-tetanic stimulus appears. It is used in surgeries which debar sudden movements in children and used to predict recovery from deep neuromuscular blockade in children. Some of the infants demonstrate post-tetanic exhaustion, with more marked fade and post-tetanic exhaustion in premature neonates due to fatigue.

5. Double burst stimulation (figure 4 (a), (b), (c))

   Herein, two short bursts of 50 Hz tetanic stimulus are applied parted by 750 msec with each impulse lasting for 0.2 msec. Most frequentlyused pattern is three impulses in each two tetanic bursts (DBS 3,3). DBS was developed with a explicit aim to allow manual (tactile) detection of residual block. In case of a partial block, second response is weak than the first response. Tactile evaluation of DBS is better than TOF, but a TOF ratio >0.6 cannot be detected subjectively. In children DBS is more sensitive as compared to TOF when manually detecting residual neuromuscular block.

Assessment of response (21)

a. Mechanomyography: This basically involves measurement of evoked mechanical response of the muscle. Most commonly used nerve muscle unit is stimulation of ulnar nerve which leads to adduction response by adductor pollicis which acts on force displacement transducer.
b. Electromyography: It evaluates and records compound action potentials of skeletal muscles. The most commonly used muscles are thenar/ hypothenar and first intraosseous muscle innervated via median and ulnar nerves. The hypothenar muscles are best avoided in infants and small children, as onset latency between stimulus and compound action potential is shorter than 3 msecs leading to artifacts. The initial calibration sequence is painful and should be done under anaesthesia in children. The other two sites for electromyography are larynx and diaphragm.

c. Accelerography: It measures the force of a muscle and is based on the formula F=ma. Accelerography uses piezoelectric electrodes, where exposure of the electrode to force generates an electrical voltage proportional to acceleration of the electrode. Commonly used nerve muscle unit is ulnar nerve and adductor pollicis muscle. On stimulation of ulnar nerve an electrical signal is produced on thumb movement. It is an effective method of NM monitoring in children. Very small acceleration transducers (0.5cm×1 cm) weighing 20 gm, are available which can be placed on infants' thumb or big toe (22).

d. Piezoelectric: The principle behind the technique is that stretching or bending a piezoelectric film in response to nerve stimulation leads to generation of a voltage proportional to the amount of stretching or bending. It is available in both adult and pediatric sizes. Most commonly used nerve muscle unit is ulnar nerve and adductor pollicis muscle. A piezoelectric film is positioned between the base of thumb and base of index finger, 2 electrodes are applied on the dorsal surface along the course of ulnar nerve, the negative electrode is placed near the proximal crease and the positive electrode is positioned 4-5 cm proximal to it. In response to ulnar nerve stimulation, thumb adducts and causes bending of the strip (figure 1).

e. Phonomyography: Also referred to as acoustic myography, it is based on the principle that muscle contraction leads to generation of lower frequency sounds which can be recorded through small microphones. It demonstrates a good concordance with recovery from NMB and can be applied to almost all muscle nerve units with special interest in corrugator supercilli muscle.

Factors influencing NM blockade and monitoring in children

1. Hypothermia limits the interpretation of responses. Central body temperature is the primary determinant of adductor pollicis temperature (>32 $^{\circ}$C), with hypothermia interfering with mechanomyography and accelerography. For each degree below 35 $^{\circ}$C, adductor pollicis peak twitch height is reduced by 15% (23).

2. Certain antibiotics, acidosis and hypocalcemia can prolong or potentiate neuromuscular blockade by NDMRs

3. Inhalational agents such as sevoflurane can have potentiating effects on pre- and post-synaptic neuromuscular junction, and also enhances fade of the neuromuscular response to high frequency stimulation. Discontinuation of sevoflurane leads to accelerated return of NM function (24).

4. Validation of NMT monitoring parameters with clinical parameters in children is sometimes difficult.

    a. NM response may appear normal despite persistence of receptor occupancy (40-50%) by neuromuscular blockade in children

b. Children may have weakness even at TOF ratio as high as 0.8-0.9.

c. Adequate recovery does not guarantee adequate ventilatory function or airway protection.

5. Lack of quality evidence available in literature regarding use of NMT in children.

Figure 1. Application of Electrodes and Neuromuscular Monitoring device for stimulation of ulnar nerve

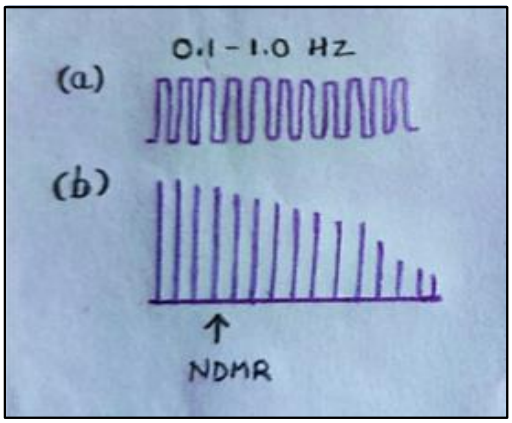

Figure 2. (a) Single twitch stimulus (b) response to Non depolarising muscle relaxant

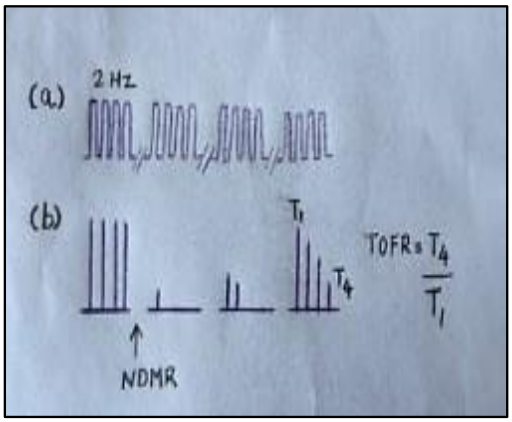

Figure 3.(a) Stimulus to train of four (b)response to non depolarising muscle relaxant

(c) Multichannel monitor showing Train of Four (TOF)response.

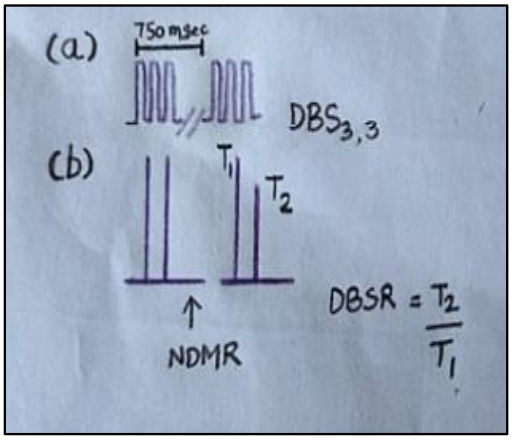

Figure 4. (a) Stimulus of DBS (b) response to non depolarising muscle relaxant

(c) Monitor showing DBS (Double Burst Stimulation) response.

Recommendations
1. Quantitative neuromuscular monitoring should be considered when neuromuscular blocking agents are used.
2. Age-appropriate equipment and electrodes are required for accurate NM monitoring when repeated doses of NMBAs are used.
3. TOF count 1 or 2 is adequate for surgical manipulation under anaesthesia.
4. To reverse a block in children, TOF count should be at least 1.
5. TOF ratio >0.9 indicates adequate return of pharyngeal function to prevent aspiration.
6. Caution: Below three months of age NMT gives erratic readings. TOF ratio in neonates is never one.
7. Search for accurate tools for small children is going on. Keep updating your knowledge about newer modalities of NMM.

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