

# Feasibility of intraoperative quantitative neuromuscular blockade monitoring in children using electromyography

## ABSTRACT

**Background:** Quantitative train-of-four (TOF) monitoring remains essential in optimizing anesthetic outcomes by assessing the depth and recovery from neuromuscular blockade. Despite this, residual neuromuscular blockade, defined as a TOF ratio  $<0.90$ , remains a concern in both adult and pediatric patients. Quantitative TOF monitoring has seen limited use in infants and children primarily due to a lack of effective equipment. This study evaluates a new electromyography (EMG)-based TOF monitor in pediatric patients undergoing inpatient surgical procedures including laparoscopic (restricted arm access) surgery.

**Methods:** Pediatric patients undergoing inpatient surgery requiring the administration of neuromuscular blocking agents (NMBAs) were enrolled. The EMG electrodes were placed along the ulnar nerve on the volar aspect of the arm to provide neurostimulation. The muscle action potentials from the abductor digiti minimi muscle were recorded. Neuromuscular responses were recorded by the device throughout surgery at 20-s intervals until after tracheal extubation. Data recorded on the monitor's built-in memory card were later retrieved and analyzed.

**Results:** The study cohort included 100 pediatric patients (62% male). The average age was 11 years (IQR: 8, 13) and the average weight was 39.6 kg (30, 48.7). Automatic detection of supramaximal stimulus was obtained in 95% of patients. The muscle action potential mean baseline amplitude (in mV) was 7.5 mV (6, 9.2). The baseline TOF ratio was 100% (100, 104). After administration of a neuromuscular blocking agent, monitoring of the TOF ratio was successful in 93% of the patients. After antagonism of neuromuscular blockade, monitoring was possible in 94% of patients when using an upgraded algorithm. The baseline amplitude recovered to 6.5 mV (5, 7.8), and the TOF ratio recovered to a mean of 90.1% (90,97) before tracheal extubation.

**Conclusion:** Our results indicate that neuromuscular monitoring can be performed intraoperatively in pediatric patients weighing between 20 and 60 kg using the new commercially available EMG-based monitor. Automatic detection of neuromuscular stimulating parameters (supramaximal current intensity level and baseline amplitude of the muscle action potential) by an adult neuromuscular monitor is feasible in pediatric patients receiving nondepolarizing neuromuscular blocking agents.

**Key words:** Laparoscopic surgery, neuromuscular blockade, neuromuscular blocking agents, train-of-four monitoring

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<b>DOI:</b> 10.4103/sja.sja_326_22	

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**How to cite this article:** Owusu-Bediako K, Munch R, Mathias J, Tobias JD. Feasibility of intraoperative quantitative neuromuscular blockade monitoring in children using electromyography. Saudi J Anaesth 2022;16:412-8.

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**Submitted:** 19-Apr-2022, **Accepted:** 21-Apr-2022, **Published:** 03-Sep-2022

## Introduction

Neuromuscular blocking agents (NMBAs) may be indicated intraoperatively to provide skeletal muscle relaxation and facilitate endotracheal intubation, provide surgical relaxation for specific operative procedures, and supplement general anesthesia and provide a motionless patient during anesthetic care. Inadequate reversal of neuromuscular blockade may result in postoperative respiratory complications, including respiratory insufficiency, respiratory failure, the need for unplanned tracheal reintubation, pulmonary edema, more frequent intensive care unit admissions, and prolonged hospital stay.<sup>[1-3]</sup> Developed in the early 1970s to assess the depth and recovery from neuromuscular blockade in the anesthetized patient, the train-of-four (TOF) pattern of neurostimulation is critical for anesthetic care and the selection of appropriate doses of NMBAs and antagonists.<sup>[4-6]</sup> Responses to TOF stimulation can be evaluated subjectively (qualitatively) using visual observation of muscle twitches in response to a peripheral nerve stimulator (PNS) or objectively using quantitative technologies such as mechanomyography, acceleromyography, or electromyography (EMG). While the visual observation of the TOF response is used most commonly in clinical practice in the United States, outcome data have shown that objective quantitative monitoring of muscle response to TOF stimulation is superior to subjective assessment using a PNS.<sup>[4-6]</sup> The positive predicted value (precision) of most clinical tests to identify residual neuromuscular block (rNMB) is no better than 50%, while detection of fade to TOF stimulation by subjective assessment fails when the TOF ratio is  $>0.4$ .<sup>[7]</sup>

Despite the abundance of evidence that rNMB, defined as a TOF ratio  $<0.9$ , results in postoperative respiratory complications, there are limited data regarding the optimal means of quantitative monitoring of TOF in children, the incidence of rNMB in this vulnerable patient population, and its impact on pediatric postoperative outcome.<sup>[8,9]</sup> Data from adult studies suggest that only 40% of practitioners regularly assess the degree of neuromuscular blockade, and practitioners who use sugammadex for antagonism of neuromuscular block do so even less frequently.<sup>[10]</sup> In the pediatric population, only a minority (15.3%) of clinicians routinely use quantitative monitoring of NMB.<sup>[9]</sup> The incidence of rNMB in pediatric patients may be as high as 48.2%, regardless of the agent used for antagonism.<sup>[11,12]</sup>

Commonly cited reasons for the lack of using quantitative TOF monitoring include lack of reliable monitors, particularly those applicable to the pediatric patient; time (clinical productivity) pressure; challenges with calibration of

existing acceleromyographic monitors; limited clinical exposure to newer technologies such as EMG; lack of standards and guidelines; and departmental culture.<sup>[12]</sup> Another common limitation of quantitative monitors that are based on the measurement of muscle movement (such as acceleromyography and kinemyography) is their inability to function reliably when the target muscle (typically, the adductor pollicis muscle of the thumb) is unable to move freely or is inaccessible as it is under the surgical drapes.<sup>[13]</sup> EMG-based neuromuscular monitors do not have such limitations, as they measure the evoked muscle action potentials as a function of the degree of receptor occupancy without the need for measurement of muscle movement.<sup>[14]</sup>

To date, there are limited data regarding the use of EMG-based TOF monitors in pediatric patients. The primary aim of this study was to prospectively assess the feasibility of using the commercially available adult EMG-based monitor (TetraGraph™, Senzime BV, Uppsala, Sweden) and adult electrode array (TetraSens™) in pediatric patients undergoing routine inpatient surgical procedures. The secondary aim was to determine whether EMG-based neuromuscular monitoring was possible in laparoscopic surgeries in which the patients' arms were placed under surgical drapes (restricted arm movement settings). We limited the neuromuscular testing to pediatric patients with a minimum weight of 20 kg due to the size limitations of the adult-developed electrode array (TetraSens™), which is too large to be used in patients less than 20 kg. Determination of neurostimulation characteristics, such as the lowest current necessary to induce muscle contraction, the maximal (and supramaximal) current necessary for ulnar nerve stimulation, the baseline amplitude (in mV) of the evoked muscle response, and the lack of fade in the TOF ratio (TOF ratio = 100%) in the unblocked neuromuscular junction are important parameters to characterize in the pediatric patient. We, therefore, hypothesized that monitoring of neuromuscular function during onset and recovery of the nondepolarizing neuromuscular block using an adult neuromuscular monitor and electrode array would be feasible in pediatric patients, weighing 20 to 60 kg.

## Methods

**Study design and study population:** This study was approved by the Institutional Review Board of Nationwide Children's Hospital, Columbus, Ohio (IRB#: STUDY00001075, date of approval: July 24, 2020) and written informed consent was obtained from a parent or legal guardian. The study was registered before patient enrollment at clinicaltrials.gov (NCT04475250, date of registration: July 13, 2020).

We enrolled pediatric patients weighing between 20 and 60 kg who were scheduled for surgical procedures requiring the administration of a nondepolarizing NMBA. Exclusion criteria included patients with a history of a peripheral neurologic, myopathic, or neuropathic disease, peripheral edema, or in whom the upper extremity could not be used for TOF monitoring, such as a surgical procedure involving that limb, and patients for whom the adult-sized electrode array was too large. Intraoperative anesthesia management, including the choice of anesthetic agents, and the dose of NMBA and antagonist, was at the discretion of the attending pediatric anesthesiologist. Anesthesiologists were not blinded to the reading of the TOF ratio and count displayed on the TetraGraph™ EMG monitor but were encouraged to follow their usual practice, such as using the PNS and visual determination of responses to guide the dose and timing of NMBA administration and antagonist. Based on local institutional routine clinical practices, rocuronium and sugammadex were the choices for NMBA and antagonist, respectively.

The EMG-based TetraGraph™ is a commercially available device that provides electrical stimulation to a peripheral nerve and directly measures the amplitude of the evoked responses of the innervated muscle (muscle action potential), thereby providing a quantitative and automatic measurement of the muscle response to a stimulus. In addition to eliminating the need for visual observation of the twitch response, the TetraGraph™ allows a more sensitive measure of the evoked EMG, thus providing information regarding neuromuscular recovery, which is not feasible when using subjective evaluation with a PNS.<sup>[15,16]</sup> The device is United States Food & Drug Administration approved for use in adults and was considered a non-significant risk by our institutional IRB for pediatric use. The skin was prepped with an alcohol swab to ensure a clean and dry surface before the placement of the sensors. The recording electrodes (TetraSens™) were placed on the palmar surface of the abductor digiti minimi muscle and its insertion on the fifth digit. The stimulating electrodes were placed along the ulnar nerve on the volar surface of the forearm [Figure 1]. The electrodes were then connected to the TetraCord cable before the induction of anesthesia. The TetraGraph™ device automatically determines the stimulating current necessary for maximal muscle contraction to ensure consistent recruitment of all muscle fibers. After the first 50 patients were enrolled, the TetraGraph™ software was upgraded to enhance the clinical utility of the TOF monitoring of the next 50 patients. The upgrade consisted of a change in the software algorithm that improved the ability to identify and select the optimal EMG responses (the peaks and troughs of the muscle action potentials).



**Figure 1: The TetraGraph™ electromyograph monitor with attached electrodes**

**Outcomes and statistical analysis:** The primary endpoint evaluated the efficacy and feasibility of using the TetraGraph™ EMG monitor in pediatric patients weighing 20 to 60 kg. The device recorded the TOF ratio, the TOF counts, post-tetanic count (PTC), and responses during maintenance of block and block recovery with sugammadex throughout surgery at 20-s intervals until after tracheal extubation. Data from the built-in secure digital memory card from the TetraGraph™ were retrieved and analyzed. As a secondary aim, we also evaluated the feasibility of EMG monitoring with the TetraGraph™ in laparoscopic surgical settings (e.g., we tested the ability of the device to record and display TOF data throughout the surgical procedure in which the patient's arms were tucked under surgical drapes) by measuring the number of failures of reporting neuromuscular data among the cohort.

Continuous variables were summarized as mean (IQR) and categorical variables as percentages. We used descriptive statistics to compare the characteristics of neuromuscular monitoring with the TetraGraph™ between the first 50 patients and the second cohort of 50 patients after an upgrade of the device software. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software for Windows, version 26.0 (IBM Corp., Armonk, NY).

## Results

The study cohort included 100 pediatric patients (62% male). The first 50 patients were monitored using the original TetraGraph™ algorithm, while the second 50 were monitored with an updated algorithm, which was developed to improve the ability of the TetraGraph™ device to better filter environmental interference from the elicited EMG response and display TOF ratios, counts, and PTCs on the monitor. The data are listed in Tables 1-3.

For the entire cohort, the mean (SD) age was 11 (2.9) years, and the mean (SD) weight was 39.6 (10.8) kg. Table 2 summarizes the characteristics of neuromuscular monitoring using the TetraGraph™ EMG for the entire cohort of 100 patients. Automatic detection of supramaximal stimulus (SMS; current amplitude required to initiate a maximal single muscle twitch plus 30%) was obtained in 95% of patients. SMS current intensity (mA) at a pulse width of 200  $\mu$ s was 30 mA in 3%; 40 mA in 42%; 50 mA in 28%; and 60 mA in 22% of the patients [Figure 2]. The muscle action potential mean (SD) baseline amplitude was 7.5 mV (2.4). The average baseline TOF ratio was 100% (8.4), and after administration of an NMBA, fade in the TOF from baseline could be recorded in 93% of the patients. After antagonism of neuromuscular blockade, the baseline amplitude recovered to a mean (SD) of 6.5 mV (2.0), and the TOF ratio recovered to a mean of 90.1% (13.1). Table 3 summarizes the differences in the characteristics of neuromuscular monitoring between the first 50 patients and the next 50 patients following a software upgrade. The mean baseline TOF ratio was 98.5% (IQR: 100, 102) and recovered to a mean of 91.6% (IQR: 92, 100) for the first 50 patients, whereas the mean baseline TOF ratio for the next 50 patients was 101.4% (IQR: 100, 106) and recovered to a mean of 90% (IQR: 90, 94). The average baseline amplitude before NMBA for the first 50 patients was 7.9 mV, recovering to a mean of 7.1 mV compared to the average baseline amplitude of 7.2 mV which recovered to a mean of 6.1 mV for the next cohort of 50 patients. With the algorithm upgrade, there was an improvement in the number of patients in whom the EMG was effectively read, and the data displayed on the monitor from 23 of 50 patients (46%) to 47 of 50 patients (94%).

We also separately analyzed TOF responses of a subset of 88 pediatric patients from the entire study cohort, who underwent laparoscopic (restricted arm settings) surgical procedures, with arms tucked under surgical drapes [Figure 1]. Patients ranged in age from 4 to 17 years (38.6% female) with an average weight of 40 kg (11.1) and height of 144 cm (15.6).

Train-of-four ratio (TOFr) was accurately obtained in 71 out of the 88 patients. Among this cohort (analyzed with a combination of both the old and new software), the average baseline muscle action potential amplitude before NMBA administration was 7.4 mV (2.3) and the baseline TOF ratio was 100.1%. Supramaximal current amplitude (pulse width of

**Table 1: Patient demographics of study cohort**

Patients (number)	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )	Gender (M/F)
100	11 $\pm$ 3.0	39.5 $\pm$ 10.8	145 $\pm$ 16	18.7 $\pm$ 3.3	62/38
First 50	11 $\pm$ 2.8	39.8 $\pm$ 10.3	146 $\pm$ 15	18.6 $\pm$ 3.3	29/21
Second 50	10 $\pm$ 3.0	39.2 $\pm$ 11.5	143 $\pm$ 17	18.8 $\pm$ 3.2	33/17

Data are listed as the mean $\pm$ standard deviation or absolute values. BMI=body mass index; kg=kilograms; cm=centimeters

**Table 2: Neuromuscular monitoring in 100 pediatric patients using TetraGraph™ EMG**

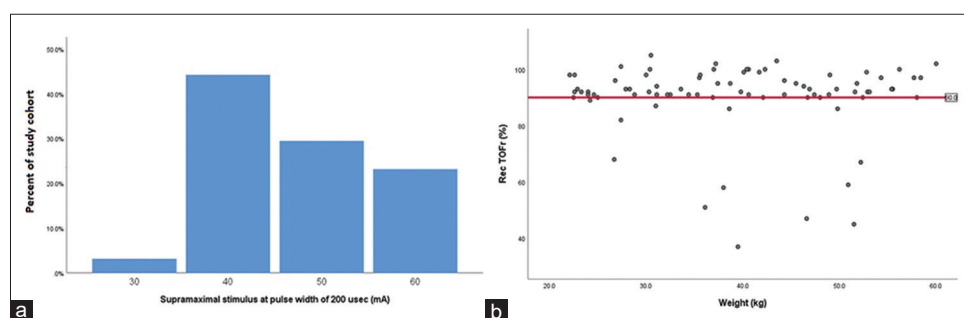
Characteristic	Mean $\pm$ SD	IQR
Baseline TOFr (%)	100.1 $\pm$ 8.4	(100, 104)
Recovered TOFr (%)	90.1 $\pm$ 13.1	(90, 97)
Baseline amplitude (mV)	7.5 $\pm$ 2.4	(6.0, 9.1)
Recovered amplitude (mV)	6.5 $\pm$ 2.0	(5.0, 7.8)
Rate of muscle recovery (minutes)	2.6 $\pm$ 1.4	(2.0, 3.8)

TOFr=train-of-four ratio; SD=standard deviation; IQR=interquartile range; mV=millivolts

**Table 3: Differences between first 50 and second 50 patients following software upgrade**

Characteristic	First 50 patients		Second 50 patients	
	Mean (SD)	IQR	Mean (SD)	IQR
Baseline TOFr (%)	98.5 (8.6)	100, 102	101.4 (8.1)	100, 106
Recovered TOFr (%)	91.6 (15.3)	92, 100	90.0 (11.1)	90, 94
Baseline amplitude (mV)	7.9 (2.6)	5.9, 9.6	7.2 (2.1)	6.1, 8.7
Recovered amplitude (mV)	7.1 (2.2)	5.9, 8.6	6.1 (1.9)	5.0, 7.7
Rate of muscle recovery (min)	2.8 (1.4)	2, 4	2.5 (1.3)	1.8, 3.0
Display of data on monitor (%)	54 (27/50)		94 (47/50)	

TOFr=train-of-four ratio; SD=standard deviation; IQR=interquartile range; mV=millivolts



**Figure 2: Bar graph showing the different supramaximal stimulus current intensity (electrical stimulation sufficient to cause all muscle fibers to contract) of the entire study cohort at a pulse rate of 200  $\mu$ s (left). Simple dot plots of weight (kg) with recovered TOFr showing 88% of patients in the study cohort with a recovered TOFr  $\geq$ 90% (red line) (right). TOFr = train-of-four ratio**



200  $\mu$ sec) was achieved in 95% of patients at currents ranging between 40 and 60 mA [Table 4].

## Discussion

The current prospective study assesses neuromuscular monitoring using TOF with the EMG-based TetraGraph™ in pediatric patients undergoing inpatient surgical procedures in a large tertiary care children's hospital. Consistent with studies in adults, our preliminary results demonstrate that intraoperative neuromuscular monitoring in pediatric patients ranging in weight from 20 to 60 kg is feasible using the commercially available EMG-based TetraGraph™ monitor even with adult-sized sensors.<sup>[15,16]</sup> Adequate TOF monitoring was obtained using the adult-sized sensing electrode and during restricted access surgical procedures including laparoscopy. Although there was limited improvement in the TOF parameters between the first 50 patients and the subsequent 50 patients after the software upgrade, there was a significant difference between the two groups regarding the clinical utility and accessibility of the TOF data. In the first 50 patients, data from 27 (54%) of 50 patients displayed on the monitor as the measured TOF ratio, compared to 47 (94%) of 50 patients after the algorithm upgrade. The upgraded algorithm resulted in the improved interpretation of the data so that it was displayed on the monitor for clinical use.

TOF monitoring can be achieved objectively with a quantitative monitor or qualitatively with visual observation of the TOF with a PNS. Recent evidence supports the routine use of quantitative TOF monitoring as best practice, since the clinical assessment of recovery from neuromuscular blockade including extremity movement/strength, sustained head-lift, hand grip, or spontaneous respiration have been shown to be inaccurate with sensitivities ranging from 10% to 30%.<sup>[6,17]</sup>

Recent recommendations for standards of monitoring during anesthesia by the Association of Anesthetists from Great Britain and Ireland (AAGBI) suggest that quantitative neuromuscular monitoring should be used whenever a neuromuscular blocking drug is administered, throughout

all the phases of anesthesia from before initiation of neuromuscular blockade until after recovery from the TOFr to  $>0.9$  had been confirmed.<sup>[18]</sup> A quantitative monitor can also detect fade and therefore does not result in a "monitoring gap" associated with qualitative monitoring. In this study, the patient's trachea was extubated after a subjective clinical evaluation of recovery from NMBA. In confirming the TOFr with the TetraGraph™, the TOF ratio had recovered to a mean of 90.1% (0.9) after reversal with sugammadex at the time of tracheal extubation. This compared favorably to the mean baseline TOFr of 100% (1.0), indicating that a significant proportion (88%) of the study cohort had adequate recovery from NMB before tracheal extubation [Figure 2]. However, the addition of clinical use of the TetraGraph™ could add clinical utility to the remaining cohort of 12% in whom the TOF ratio was less than 90% at the time of tracheal extubation. As it was not part of this study, residual neuromuscular blockade was not assessed in the post-anesthesia care unit (PACU). However, none of the patients in this study cohort had postoperative respiratory complications or the need to escalate the level of postoperative care.

With the expansion of minimally invasive and laparoscopic surgical techniques, including robotic surgery, there has been an increased use of NMBAs to achieve deep neuromuscular block (defined as subjective/measured TOF ratio of 0, TOF count of 0, and PTC  $\geq 1$ ) to provide the required intraoperative conditions for these procedures. This increased need for deep neuromuscular blockade has increased the need for quantitative TOF monitoring to assess the onset, maintenance, and recovery from neuromuscular blockade. EMG and acceleromyography are the two most commonly used quantitative techniques for TOF monitoring.<sup>[18]</sup> However, a major limitation of acceleromyography is that it requires that the target muscle (usually the thumb) move freely or be seen, limiting its use in procedures where the patient's arms are restricted by surgical drapes, as occurs in laparoscopic or robotic surgeries. The TetraGraph™ TOF monitor has no such limitations as it measures the evoked muscle action potential without the need for visual observation or free motion of the involved muscle groups (adductor pollicis).<sup>[14,15]</sup> In our secondary analysis, we explored the feasibility of TOF monitoring using the TetraGraph™ EMG in pediatric patients undergoing laparoscopic surgeries where the anesthesiologist has no access to the target muscle (the abductor digiti minimi), as the arms are tucked under surgical drapes [Figure 1]. We obtained TOF ratios from all 88 patients enrolled, with an average baseline TOF ratio of 100% (1.0), which recovered to a mean of 90% (0.9) after reversal with sugammadex and before tracheal extubation. SMS, defined as the electrical stimulation sufficient to cause all muscle

**Table 4: Characteristics of neuromuscular monitoring during laparoscopic surgery**

Characteristic	Mean (SD)	IQR
Baseline TOFr (%)	100.1 (8.6)	(100, 104)
Recovered TOFr (%)	90.0 (13.7)	(90, 97)
Baseline Amplitude (mV)	7.4 (2.3)	(5.9, 9.2)
Recovered Amplitude (mV)	6.3 (1.8)	(5.0, 7.7)
Rate of muscle recovery (minutes)	2.7 (1.3)	(2.0, 3.0)
Stimulation level/200 $\mu$ s (mA)	47.8 (8.6)	(40, 60)

TOFr=train-of-four ratio; SD=standard deviation; IQR=interquartile range; mV=millivolts

fibers to contract, was detected in 95% of patients and ranged between 40 and 60 mA.

Additional challenges have been reported with both PNS and acceleromyography monitoring. The risk of postoperative residual NMB has been shown to be 5-fold higher when PNS is used for monitoring the TOF ratio and the supramaximal current was not determined.<sup>[19]</sup> Acceleromyography has another peculiar characteristic where the baseline TOF ratio is often >1.0 (>100%), and in some cases may be as high as 1.6.<sup>[20,21]</sup> The exact mechanism responsible for this phenomenon is unknown, but it could be due to the target muscle not returning to the initial starting position during a TOF stimulation. This falsely elevated baseline requires that the recovering TOF ratio be normalized to the starting baseline ratio to avoid inaccuracy in measuring rNMB. If the baseline TOF ratio with acceleromyography were 150%, a recovery TOF ratio of 90% (0.9) would represent a TOF ratio of only 60% (90% of 150% baseline). This level of recovery indicates significant residual neuromuscular weakness. EMG technology does not result in this idiosyncrasy in the baseline measurement. In our study cohort, the highest baseline TOF ratio measured with the TetraGraph™ was 116%.

In conclusion, although developed primarily for use in adults with an adult-sized sensor, our preliminary data suggest that the TetraGraph™ EMG monitor can be used in pediatric patients as small as 20 kg. This preliminary study suggests the potential to use quantitative monitoring with the EMG-based technology in pediatric patients. With the updated algorithm, the nerve stimulation parameters and clinical display were consistent with those reported in adults. As EMG-based technology does not require visual observation or free motion of the stimulate muscle group, these results demonstrate that this technology can be used in surgical procedures with restricted arm positions such as laparoscopic and robotic procedures. Since alternative sites for intraoperative monitoring such as the facial nerve can lead to overestimation of recovery and an increased incidence of residual neuromuscular blockade, monitoring responses at the abductor digiti minimi muscle using the EMG-based TetraGraph™ monitor is preferable. Automatic detection of neuromuscular stimulating parameters (supramaximal current intensity level and baseline amplitude of the muscle action potential) by the adult neuromuscular monitor is feasible in pediatric patients, weighing 20 to 60 kg, during the administration of receiving nondepolarizing NMBAs. The feasibility of using this monitoring in pediatric patients allows prospective clinical studies to compare EMG-based monitoring to other quantitative monitors or qualitative monitoring with a PNS.

## Acknowledgements

The monitor and disposable sensors for the study were provided without charge by TetraGraph™, Senzime BV, Uppsala, Sweden. No other funding was provided.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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