Performance Assessment of a New Electromyography-based Neuromuscular Monitor and Subjective Discomfort in Unmedicated Volunteers

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Abstract

Objective: The aim of this prospective, unblinded, randomized study was to provide performance data of the prototype of new electromyography-based neuromuscular monitor, the NEAT device (Acacia Designs BV, Amsterdam, the Netherlands) and assess the subjective discomfort associated with neurostimulation in unmedicated healthy volunteers.

Methods: The study enrolled ten male and ten female volunteers. Based on a priori randomization the ulnar nerve of the left or right arms was stimulated in 1 Hz single twitch and train-of-four modes. Stimulating current intensity was increased from 10 mA to 60 mA in 10 mA steps. Electromyography recordings were performed at the abductor digiti minimi and adductor pollicis muscles via surface electrodes. The volunteers were asked to rate the discomfort in association with neurostimulation on a 0-10 visual analogue scale.

Results: The overall train-of-four ratio was 1.02 (0.98-1.06) (median and (interquartile range)). The abductor digiti minimi muscle required lower stimulating current intensity to evoke maximal stimulation, than the adductor pollicis (30 vs. 50 mA, p<0.001). The overall intracurrent variability of compound muscle action potential amplitudes was 0.42 (0.21-0.87) mV, that was unaffected by the type of muscle or the stimulating current intensity. Women reported moderately higher visual analogue scale scores than men. The largest recorded difference was 5 (3.75-6) vs. 3 (3-4), p<0.05.

Conclusion: The Acacia Designs BV NEAT monitoring device was suitable to deliver neurostimulation, record and analyze the elicited muscle action potentials. The precision of stimulations was acceptable. The volunteers reported the discomfort in association with neurostimulation as tolerable.

Keywords: Neuromuscular monitoring; Electromyography; Visual analogue scoring scale; Abductor digiti minimi muscle; Adductor pollicis muscle

Introduction

Objective neuromuscular (NM) monitors help optimize the timing and dosing of neuromuscular blocking agents, the timing of safe tracheal extubation at the end of operations, and thus decrease the incidence of residual paralysis and its postoperative consequences [1-4]. Over the last few years, a strong educational effort has been observed, which urged the extended use of NM monitors to improve patient safety and outcomes [2,3,5-8]. In 2009 Kopman proposed that objective neuromuscular monitors be available in any modern anesthetizing location when neuromuscular blocking drugs are administered [9]. In 2016, the Association of Anaesthetists of Great Britain and Ireland prescribed the use of peripheral nerve stimulators whenever NM blocking agent is administered and recommended the use of quantitative monitors [10]. Despite its known limitations, the acceleromyography (AMG) based, portable TOF-Watch series was one of the most frequently used NM monitor in clinical practice and research. Most recommendations on safe management of NM blockade were based on AMG
EMG proved to be an excellent alternative. Electromyography is a physiologic and precise method of measuring the synaptic transmission, the compound muscle action potentials (CMAP). For this reason, EMG is less susceptible to interference from presynaptic or postsynaptic events, and is likely a better indicator of pure neuromuscular function [2]. Therefore, it is probably the most physiologic and precise method of measuring the synaptic transmission, and thus the degree of NM relaxation [3]. Other practical advantages of EMG over MMG and AMG are that EMG does not require the complete immobilization of the hand, the fixation of the arm in the supine position or the use of a muscle preload. Additionally, the staircase phenomenon does not affect EMG measurements [12], unlike MMG and AMG; therefore, the calibration of the device to determine the supramaximal stimulating current intensity is simpler and shorter. Yet, currently there is no freestanding, hand-held EMG-based NM monitor available in the market. To our knowledge, there are only a couple of anesthesia workstation integrated NM transmission modules that use electromyography or kinemyography (GE Healthcare, Waukesha, WI, USA) [3], or acceleromyography (IntelliVue NMT, Philips, Amsterdam, the Netherlands; Infinity Trident NMT SmartPod, Dräger, Lübeck, Germany) [3].

The Acacia Designs’ prototype monitor (NEAT device, Amsterdam, the Netherlands) is a dedicated electromyography-based NM monitor intended to deliver, record, and analyse CMAPs. The NEAT device is the first prototype of the TetraGraph™ neuromuscular monitor (Senzime BV, Uppsala, Sweden). The prototype was designed to conduct preclinical investigations. It is battery-powered, uses simple electrocardiography (ECG) electrodes both for stimulation and recording, and registers data on an integrated secure digital (SD) card. The stimulating parameters of the prototype match the parameters of the TetraGraph™. The aim of the current investigation was to test the prototype that uses the design and electronics intended for the final product, gain performance data and assess the discomfort evoked by neurostimulation in unmedicated, healthy volunteers.

**Materials and Methods**

This prospective, unblinded, randomized, single-center study was approved by the Hungarian Office for Health Authorization and Administrative Procedures (028605-010/2014/OTIG) and registered at clinicaltrials.gov (NCT02630576). Data presentation is in accordance with CONSORT 2010 guidelines.

**Volunteers**

The study population consisted of normal, healthy volunteers of age 18 years and older, American Society of Anesthesiology (ASA) physical status I. Ten male and ten female volunteers were enrolled in the study (Figure 1). All subjects were required to provide written informed consent prior to inclusion in the study. Exclusion criteria were presence of an underlying neuromuscular disease, use of medications known to interfere with neuromuscular transmission (e.g., antiepileptics, anticholinesterases and magnesium sulphate), presence of renal or hepatic disease, or presence of open sores at the skin sites needed for electrode application.

**Figure 1: CONSORT study flowchart.**

**Device specifications**

The NEAT device is the first prototype of a new electromyography-based, battery-powered, portable neuromuscular monitor, whose software was specially developed for research and clinical purposes. It can stimulate the peripheral nerves using parameters and settings currently in use by many peripheral nerve stimulators, and record the evoked muscle response (CMAP). Data is saved onto an SD-card for further analysis.
Subject preparation and neurostimulation

Neuromuscular testing was performed at two separate stimulation/recording sites: ulnar nerve stimulation and abductor digiti minimi muscle (mADM) recording; as well as ulnar nerve stimulation and adductor pollicis muscle (mAP) recording (Figure 2). The side of testing (right or left hand) was determined a priori via envelope randomization, to ensure that 10 volunteers (5 male and 5 female) each were tested on the right and 10 on the left hands.

![Figure 2: Stimulating and recording electrode placement. Stimulating electrodes are placed along the ulnar nerve. The positive electrode is placed proximally, the negative electrode distally. The recording electrodes are placed on the bellies of the abductor digiti minimi (hypothenar eminence) and adductor pollicis (thenar eminence) muscles. The reference electrodes are placed above the first interphalangeal joint of the little finger and the thumb (tendon insertion sites).](Image)

The stimulating ECG electrodes were placed on the lightly abraded, alcohol-cleansed skin over the ulnar nerve of the randomized volar forearm near the wrist. The negative (distal) electrode was placed on the ulnar side of the volar forearm, 2 cm-3 cm proximal to the flexor crease. The positive electrode was placed with its center 3 cm proximally to the negative electrode. The recording electrodes were placed (after proper skin cleaning with alcohol and abrasion) on the thenar and the hypothenar eminence (on the muscle belly of the mAP and mADM, respectively) and reference electrodes on the first interphalangeal joints (muscle insertion) of the thumb and the fifth finger, respectively (Figure 2).

The stimulation protocols (ST and TOF) were identical for the two muscles. The stimulating parameters of ST stimulation were 1 Hz frequency, 0.2 msec pulse width and 10-60 mA current intensity that was increased in 10 mA steps. The stimulating parameters of TOF stimulations were 0.2 msec pulse width, 20 sec interval time between TOF sequences, and 10-60 mA current intensity levels, increased in 10 mA steps. All ST and TOF stimulations were repeated three times at each current intensity level.

All measurements were saved to the built-in SD card of the device for off-line analysis

The lowest current intensity of any stimulation mode that elicited a repeatable visible muscle contraction (twitch) in the fingers was considered the clinical threshold current intensity (I\textsubscript{th, clinical}) and was recorded on the data sheet. This was compared to the lowest current intensity that could elicit a measurable CMAP (I\textsubscript{th, EMG}). The current intensities that elicited the highest CMAP amplitudes (I\textsubscript{max}) were noted.

The volunteers were asked to rate the discomfort of neurostimulation at every current intensity of each stimulation mode on a 0-10 visual analogue scoring (VAS) scale. Zero represented "no discomfort" and 10 represented "worst pain ever experienced" elicited by the stimulation. Whenever the VAS score exceeded 6 points, the volunteers were asked if they gave their consent to continue the measurement. No volunteer was asked to undergo neurostimulation if he/she felt it would be intolerable.

Study objectives and endpoints

The primary objective of the study was to provide performance data of the Acacia Designs BV NEAT prototype monitoring device in volunteers and assess the subjective discomfort associated with neurostimulation.

**Primary endpoint of the study:**

- Assessment of the ability of the prototype to deliver neurostimulation, and assessment of the ability to acquire muscle action potentials, analyze and record these evoked responses on the SD-card.

**Secondary endpoints included:**

- Confirmation that the prototype can independently stimulate and record repetitive patterns of neurostimulation, including 1 Hz ST and TOF stimulation protocols;
- Verification of the delivery of neurostimulation at varying current intensities, from the lowest current intensity that produces an evoked response (threshold current, I\textsubscript{th, EMG}) to the current intensity above which the evoked response no longer increases (maximal current, I\textsubscript{max}), at increasing current levels separated by steps of 10 mA;
- Examination of the intracurrent variability of CMAP amplitudes evoked by 10-60 mA ST stimulation (difference of highest and lowest CMAP amplitudes at the given intensity). Determine any difference in recording performance between the two hand muscles, two sexes, and dominant vs. non-dominant hand;
- Validation of the consistency of TOF stimulations and their deviation from the ideal 1.0 value in unmedicated volunteers. Determine any difference in recording performance between the two hand muscles (mAP and mADM), two sexes, and dominant or non-dominant hand;

- Establishment of discomfort, if any, associated with nerve stimulation in the awake, unmedicated volunteers. A visual analogue scoring scale, anchored with 0 (representing no distress) and 10 (representing the worst pain ever experienced) was used to rate the level of discomfort;

- Assessment of skin reactions to the stimulation or recording electrodes, if any.

**Data analysis**

All measurements were saved on the internal SD card of the device for post hoc analysis. MATLAB TetraAnalyzerViewer2014a64 software (MathWorks, Natick, MA, USA) was used to measure CMAPs and TOF ratios.

When the parametric assumptions of normality and equal variance were met, paired T-test was used to compare data pairs from the same volunteer and Student's T-test and one-way ANOVA to compare study groups. When the above assumptions were not met, paired Signed Rank test, Mann-Whitney U-test and One-way ANOVA on Ranks were used. For normally distributed variables, mean ± standard deviation (SD) and for non-normally distributed variables, median and the interquartile range (IQR) are presented. The predetermined level of significance was p<0.05. Sigma-Plot for Windows Version 11.0 (Systat Software Inc., San Jose, California, USA) was used for calculations.

**Results**

**Demographic data**

Demographic data of the volunteers are summarized in Table 1. There was no statistical difference in age (p=0.592), body mass index (p=0.231) and handedness (p=1.0) among the four groups. All volunteers were right-handed, therefore the terms dominant and non-dominant side refer to all volunteers. The female and male groups had similar body weight (p=0.145), height (p=0.684) and wrist circumference (p=0.247).

**Table 1**: Demographic data of the volunteers. Statistical comparison of age and BMI was performed for all study groups. Body weight, height and wrist circumference were statistically compared between the same sex groups. * represents the p value for the male groups, † represents the p value for the female volunteers.

|                      | Male Left hand | Male Right hand | Female Left hand | Female Right hand | p   |
|----------------------|----------------|-----------------|------------------|-------------------|-----|
| Age (years) median (IQR) | 23 (22.75-30.25) | 24 (23.75-33)  | 24 (22.75-44.25) | 23 (21.75-28)    | 0.59|
| BMI (kg/m²) mean (SD)      | 25.04 (3.43)       | 22.72 (3.19)   | 26.48 (6.89)     | 21.05 (1.95)     | 0.23|
| Body weight (kg) mean (SD) | 79.6 (9.81)*            | 71.6 (12.92)*     | 73.8 (16.86) †    | 60.4 (7.8) †     | *0.30† 0.15|
| Height (cm) mean (SD)      | 178.4 (4.39)*          | 177.2 (8.2)*      | 167.6 (4.83) †    | 169.2 (6.98) †   | *0.78† 0.68|
| Wrist circumference (mm) mean (SD) | 176.2 (6.18)*            | 171.2 (8.9)*      | 164.2 (12.38) †   | 156.2 (6.54) †   | *0.33† 0.25|
| Left:Right-handed         | 0.5             | 0.5             | 0.5              | 0.5              | 1.0 |

The threshold current intensity that could elicit visible muscle twitches ($I_{\text{Th-clinical}}$) and recordable CMAPs ($I_{\text{Th-EMG}}$) was found to be 20 (20-30) mA [median (IQR)]. The clinical examination ($I_{\text{Th-clinical}}$) and monitor ($I_{\text{Th-EMG}}$) recordings were congruent (p=0.854) in 64 out of 80 stimulation protocols (80%). Women needed significantly lower current intensity than men to elicit recordable CMAPs [20 (20-20) vs. 30 (20-30) mA, p=0.002]. The abductor digiti minimi muscle had lower $I_{\text{Th-EMG}}$ than the adductor pollicis [23.75 ± 7.0 vs. 25.3 ± 6.78 mA (mean ± SD), p=0.039]. There was a moderate correlation between wrist circumference and $I_{\text{Th-EMG}}$ (Pearson’s r=0.51, p=0.0217) and between BMI and $I_{\text{Th-EMG}}$ (Pearson’s r=0.505, p=0.023).

**Threshold stimulating current intensity**

Increasing current intensities resulted in the increase of elicited CMAP amplitudes (Figure 3). The current intensity that induced the highest CMAPs ($I_{\text{Max}}$) was significantly different between the two muscles. The mADM needed lower current intensity than mAP to reach maximal stimulation [30 (20-40) mA vs. 50 (50-60) mA, respectively, p<0.001]. During maximal stimulation, the highest elicited CMAP amplitudes were moderately lower in the mADM (10.40 ± 1.9 mV) than in the mAP (12.84 ± 5.1 mV), p=0.031.

**CMAP amplitude tendencies at increasing intensity ST stimulation**

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Female volunteers had higher CMAP amplitudes than men at the same stimulating current intensity, especially in the dominant mAP. Also, the female volunteers required lower stimulating current intensity to elicit maximal CMAP amplitudes than men (40 (20-50) vs. 45 (30-60) mA, respectively, p=0.042).

**Consistency of CMAP amplitudes (intragroup differences) in ST protocol at increasing stimulation current**

The consistency of CMAP amplitudes was examined in 240 ST stimulation protocols (20 volunteers × 2 muscles × 6 current intensities). Of these, 59 stimulation protocols were excluded from the analysis because the current was under the threshold to evoke measurable CMAP. Another 4 protocols were missed because two female volunteers wished to discontinue the testing at higher (50-60 mA) current intensity. Altogether, CMAP amplitude consistency was examined in 177 cases (73.75%). The overall intracurrent difference, when the results of all stimulating intensities were pooled, was 0.42 (0.21-0.87) mV. In 145/177 (81.92%) of cases, the intracurrent difference was <1.0 mV (Figure 4). There was no statistical difference in the consistency of CMAP amplitudes between sexes [men: 0.37 (0.18-0.84) mV vs. women: 0.47 (0.25-0.87 mV, p=0.285) or between the two muscles [mADM: 0.42 (0.24-0.90) mV vs. mAP: 0.44 (0.19-0.87) mV, respectively, p=0.511]. The stimulating current intensity (20, 30, 40, 50, 60 mA) did not influence the level of intracurrent CMAP amplitude variability during ST stimulation [0.36 (0.24-1.13), 0.28 (0.20-1.01), 0.33 (0.17-0.61), 0.67 (0.21-0.89), 0.30 (0.15-0.83), respectively, p=0.688], if it was high enough to evoke reproducible CMAPs.

**Consistency of TOF measurements**

Seven hundred-twenty TOF measurements were performed in the study (20 volunteers × 2 muscles × 6 current intensities × 3 stimulations at each current intensity). TOF analysis could be performed in 532 (74%) cases, those in which the stimulating current intensity was sufficient to elicit CMAPs and produce TOF ratios. Two
female volunteers declined TOF stimulation at 50 mA and 60 mA. In 4 cases, false detection was experienced, as only a TOF count was determined instead of TOF ratio. The overall consistency of elicited TOF ratios was 1.02 (0.98-1.06). In 445/532 (83.64%) of cases, the TOF ratios were in the range of 0.9-1.1 (Figure 5). The TOF ratios were closer to the expected 1.0 in men than in women (1.01 (0.97-1.06) vs. 1.02 (0.99-1.05), respectively, p=0.029) and in mADM than in mAP (1.01 (0.98-1.05) vs. 1.02 (0.99-1.06), respectively, p=0.031). The stimulating current intensity (20, 30, 40, 50, 60 mA) did not influence the precision of TOF ratio measurement (1.03 (0.99-1.06), 1.02 (0.99-1.07), 1.01 (0.97-1.05), 1.01 (0.98-1.06), 1.02 (0.99-1.05), respectively, p=0.256).

Skin irritation

Two volunteers presented mild, painless hyperemia at the stimulation site after removing the ECG electrodes. The hyperemia disappeared in a few minutes and no further irritation or adverse events were reported.
We aimed to obtain performance data in various subjects; therefore, the demographic characteristics of the volunteers were not standardized. The male and female volunteers showed a difference regarding threshold current \((I_{th})\), but the sex of volunteers did not influence the reproducibility (consistency) of ST stimulations. In this cohort, women required lower stimulating currents to elicit recordable CMAPs, and similar intensity stimulation produced higher muscle responses (Figure 3). It is presumed that female volunteers had lower skin impedance. This could have resulted in higher total stimulus charges delivered to the ulnar nerve and higher muscle action potentials. This is consistent with the slightly higher VAS scores reported by female volunteers compared with their male counterparts. However, there was only moderate correlation between BMI or wrist circumference and the threshold current to evoke CMAP as it was previously described by Kopman [14].

Phillips et al. previously studied the evoked electromyographic responses to supramaximal TOF stimulation at the mAP and mADM during recovery from non-depolarizing neuromuscular blockade [18]. They found that the mADM was more resistant to NM blockade and recovered faster than mAP. They also concluded that EMG recordings from mADM were more precise. The repeatability coefficient was lower for mADM than for mAP (4.4% vs. 5.9%, respectively) [18]. In this study, the mADM required 20 mA lower stimulating current intensity to reach maximal stimulation \((I_{max})\). This resulted in a 1.86-point lower VAS scores on the average, hence less discomfort at clinically required maximal stimulation. Additionally, the TOF ratios recorded from mADM were closer to the expected value of 1.0. This greater consistency of evoked responses and lower stimulating energy (charge) requirement may make the mADM preferable for monitoring awake patients in the postoperative setting without needing to employ submaximal currents, but this needs further investigation.

Helbo-Hansen et al. studied the repeatability of TOF ratios at varying stimulating currents in anesthetized patients [19]. They found that the accuracy of TOF monitoring was poor at low stimulating currents close to \(I_{th}\). Good repeatability was achieved only above 45 mA stimulating current intensity or \(I_{th}+25\) mA.

There is a controversy in the literature about the ideal stimulating current for awake patients. Involuntary movement in response to a painful stimulus (withdrawal, contractions) might alter measurements. At the same time, low currents might not deliver equal charges to each stimulus in the TOF sequence. It was previously speculated that submaximal (20-30 mA) stimulation should be used in an awake patient as the best compromise of patient discomfort and repeatability [16,20]. However, another study revealed only moderate agreement between two AMG measurements with 30 mA in the postoperative care unit [21]. In general, our volunteers found the discomfort associated with increasing current intensity acceptable. Our VAS scores were comparable to those in previous reports [16,17,22]. In this setting, the stimulating current did not influence the repeatability of TOF measurements; however, the study was underpowered for this purpose.

In conclusion, the performance of the electromyography based Acacia Designs BV NEAT device, the prototype of future TetraGraphTM neuromuscular monitor, was acceptable. The present electronics and design would be compatible with the surgical environment. The interface of the device is user-friendly and intuitive. Following further development, the future TetraGraphTM monitor may prove to be an easy to use, reliable and portable NM monitor that fits well in the surgical environment and anesthesia practice.

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Hungarian Office for Health Authorization and Administrative Procedures on December 30th, 2014. Identifier: 028605-010/2014/OTIG. Written informed consent was obtained from all individual volunteers prior to inclusion in the study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Author Réka Nemes has received financial support from Acacia Designs BV (Amsterdam, the Netherlands) to attend the congress of Euroanaesthesia 2015. The other authors declare that they have no conflict of interest.

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