Train-of-four Monitoring Using the Tetragraph Neuromuscular Transmission Monitor and Comparison to Standard (Visual) Train-of-four Assessment With a Peripheral Nerve Stimulator

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PROTOCOL TITLE: Train-of-four monitoring using the TetraGraph™ Neuromuscular Transmission Monitor and comparison to standard (visual) train-of-four assessment with a peripheral nerve stimulator

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2	1/21/2022	Increasing the number of subjects to 200, removing the weight stratification and lower weight limit, changing the time that identifying info will be kept to 6 years to meet NCH guidelines.	Yes
3	11/7/2022	Correcting spelling of device name. Adding recent FDA approval in children. Adding an additional cohort of 50 subjects that will have TetraGraph™ sensor applied to the arm and foot simultaneously. Total sample size of 200 unchanged.	Yes

1.0 Study Summary

Study Title	Train-of-four monitoring using the Tetragraph Neuromuscular Transmission Monitor and comparison to standard (visual) train-of-four assessment with a peripheral nerve stimulator
Study Design	Prospective, non-blinded comparative study
Primary Objective	The primary objective of this study is to evaluate the use of the Tetragraph Neuromuscular Transmission Monitor in pediatric-sized patients (≤60 kilograms) and to evaluate its utility determining sugammadex dosing
Secondary Objective(s)	To compare the difference in sensitivity between the arm placement and foot placement.
Research Intervention(s)/ Investigational Agent(s)	There will be no change in anesthetic management or use of investigational pharmacological agents.
IND/IDE #	Not applicable
Study population	Patients who are scheduled for elective, urgent or emergent surgery
Sample size	200
Study duration for individual participants	Duration of the surgical procedure (2-10 hours)
Study Specific Abbreviations/ Definitions	TOF = train-of-four NMBA = neuromuscular blocking agent MAP = muscle action potential EMG = electromyograpy

2.0 Objectives

2.1 The primary objective of this study is to evaluate the efficacy of TOF monitoring using the Tetragraph Neuromuscular Transmission Monitor in pediatric sized patients and to determine its utility in determining sugammadex dosing.

2.2 The secondary objective it to evaluate any difference between placing the TetraGraph™ sensor on the arm and hand versus placing it on the ankle and foot.

3.0 Background

3.1 The neuromuscular junction consists of the nerve terminal, the postsynaptic muscle end plate (sarcolemma), and the intervening gap. An action potential reaching the end of the neuron triggers the release of acetylcholine from synaptic vesicles. Acetylcholine then diffuses across the gap to the postsynaptic end plate, where nicotinic acetylcholine receptors are clustered. These receptors convert the chemical signal into an electrical impulse, causing depolarization in the postsynaptic membrane, release of calcium from the sarcoplasmic reticulum, and

muscle contraction. The action of acetylcholine is terminated by its passive dissociation from receptors, diffusion away from the end plate, and enzymatic degradation by acetylcholinesterase.

Neuromuscular blocking agents are commonly used during anesthetic care to facilitate endotracheal intubation or provide muscle relaxation during surgical procedures. These agents (non-depolarizing NMBAs) competitively inhibit the binding of acetylcholine to the sarcolemma thereby inhibiting skeletal muscle function. During clinical care, when neuromuscular blockade is no longer required, these agents are reversed, most commonly with a medication known as sugammadex which encapsulates the NMBA, resulting in cessation of its pharmacological effects.

The dosing of these medications is guided by monitoring neuromuscular transmission by use a peripheral nerve stimulator. This monitor stimulates the nerve (two impulses per second for two seconds) generating what is known as a TOF response. This monitor is routinely used during anesthetic care when NMBAs are in use. The electrodes are placed over a peripheral nerve and the number of twitches in the distal innervated muscle groups (hand) are noted when the device is activated. The number of twitches (0-4) is based on the receptor occupancy ratio of the NMBA. The response (number of twitches of the TOF) is used to judge the need for redosing of NMBAs as well as efficacy of reversal when sugammadex is administered. In clinical practice, the TOF is viewed by visual observation thereby leading to concerns that its use may be relatively inaccurate. Additionally, since up to 70-80% of receptors must be occupied before any change in the TOF is noted, the device is relatively insensitive. Although easy to use and part of our current clinical care, it has been shown that newer devices may be more accurate and useful in clinical care.

3.2 The TetraGraph™ provides an electrical stimulation of the peripheral nerve in the same way as a standard peripheral nerve stimulator, but instead of relying on visual observation of the twitch response, it directly measures the amplitude of the evoked response of the muscles (Muscle Action Potential or MAP), thereby providing a quantitative and automatic measurement of muscle response to a stimulus using electromyography (EMG). This avoids the visual observation of the twitch response and its potential inaccuracy. The device also allows a more sensitive measure of the EMG thereby providing information with less receptor occupancy than is needed to result in changes in the standard TOF. The device has been tested, validated, and approved for use in adults and children greater than 1 month of age

3.3 Most of the research that has been documented using the TetraGraph™ has been done by stimulating the nerves and the muscles in the hand. New anecdotal evidence has shown that it may be feasible to placement the monitor on the foot and generate an EMG. This may provide better EMG readings than using the arm in smaller children.

- Murphy GS. Neuromuscular monitoring in the perioperative period. Anesth Analg. 2018;126:464-468.

- Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. Anaesthesia 2017;72(Suppl. 1):16-37.
- Brull SJ, Eriksson L. The French Guidelines on muscle relaxants and reversal in anaesthesia: The chain is finally broken and the soul is freed. Anaesth Crit Care Pain Med 2020;39:31-33.
- Biro P, Paul G, Dahan A, Brull SJ. Proposal for a revised classification of the depth of neuromuscular block and suggestions for further development in neuromuscular monitoring. Anesth Analg 2019;128:1361-1363

4.0 Study Endpoints

4.1 The primary study endpoint is to evaluate the efficacy and feasibility of using the TetraGraph™ monitor in pediatric-sized patients (≤60 kilograms). The study will evaluate the ability of the monitor to generate, record, and evaluate the EMG. We will compare the new device with standard visual TOF monitoring using a peripheral nerve stimulator.

5.0 Study Intervention/Investigational Agent

5.1 The only novel intervention is the use of the TetraGraph™ device to monitor neuromuscular blockade. No change in the anesthetic technique will be required during the study. When NMBAs are administered, standard practice includes the use of a peripheral nerve stimulator with visual TOF monitoring. The study will include only patients scheduled for a surgical procedure that requires uses of NMBAs. The TetraGraph™ will be placed on one extremity and the standard peripheral nerve stimulator will be placed on a different extremity.

5.2 In a cohort of 50 subjects, the TetraGraph™ sensor will be placed on both an upper and lower extremity and simultaneous measurements will be recorded using two monitors.

6.0 Procedures Involved*

6.1 This is a prospective study that will evaluate the feasibility of using the TetraGraph™ in smaller pediatric patients (≤60 kilograms).

6.2 The study cohorts will include patients requiring anesthetic care and use of neuromuscular blockade. The device, which is FDA-approved for use in adults and children, will be attached to an extremity and data recorded by the device as it stimulates the nerve and generates the

EMG from the muscle. Data is recorded every 20 seconds by the TetraGraph™ based on its normal functioning parameters.

6.3 We will also compare data from the standard peripheral nerve stimulator and the TetraGraph™. Specifically, we will compare the visual TOF ratio obtained from the peripheral nerve stimulator and the one recorded from the Tetragraph at 5-15 minute intervals and at the time that reversal of neuromuscular blockade is required (administration of sugammadex).

6.4 The additional cohort of 50 subjects will allow placement of two TetraGraph™ sensors so that the efficacy can be compared between these two monitoring sites.

6.5 Exclusion criteria:

- Patients with history of a peripheral neurologic or neuropathic disorder
- Patients in whom the upper extremity cannot be used for TOF monitoring
- Patients undergoing a surgical procedure in which neuromuscular blockade is not required
- Edematous patients

6.6 There are no foreseeable risks associated with the use of TetraGraph™ device.

6.7 The data (EMG readings) will be downloaded from the TetraGraph™ device in the operating room. This is standard for this monitor and does not require additional software or any change in standard practice when using this device. The research team will transmit the data to the password-secured server and store it as an MP4 file and JPEG file. The data will then be deleted from the TetraGraph™ device.

7.0 Data and Specimen Banking*

N/A

8.0 Sharing of Results with Subjects*

8.1 Results will not be shared with subjects.

9.0 Study Timelines*

9.1 An individual study subject's participation in the study should last 2-8 hours depending on the duration of the surgical procedure.

9.2 All study subjects should be enrolled within 18 months of the start of the study.

9.3 The study data will be analyzed, a manuscript written, and the study completed within 24 months of the start of the study.

10.0 Inclusion and Exclusion Criteria*

10.1 Potential subjects will be identified by reviewing the surgery schedule in Epic and will be recruited from the main OR pre-operative area the day of their surgery.

10.2 Inclusion criteria: ASA 1-4 patients, weighing ≤60 kg undergoing a surgical procedure with general anesthesia and requiring the administration of a NMBA.

10.3 Exclusion criteria:

- Patients with history of a peripheral neurologic or neuropathic disorder
- Patients in whom the upper extremity cannot be used for TOF monitoring
- Patients undergoing a surgical procedure in which neuromuscular blockade is not required
- Edematous patients

11.0 Vulnerable Populations*

11.1 We will include children, and will not include pregnant women, and prisoners as they are not part of our usual patient population.

11.2 This study presents no more than minimal risk as it only requires use of a novel device for monitoring the TOF (TetraGraph™) which is non-invasive and poses no foreseeable risks and certainly none greater than standard TOF monitoring with a peripheral nerve stimulator

11.3 Study staff will discuss the study with the parents and children together, review the consent form with them, answer any questions, and obtain parental permission and assent from those children able to provide it.

12.0 Local Number of Subjects

12.1 200

13.0 Recruitment Methods

13.1 Potential subjects will be recruited in the surgical preoperative area on the day of the surgery. The research team will contact the adult patient or guardian/parents and obtain written consent/parental permission. Assent will also be obtained from age appropriate patients.

13.2 The patients to be recruited are those who are scheduled for surgery under general anesthesia in the NCH operating rooms.

13.3 Using Epic, the research team will check the patients scheduled for planned surgery in the NCH operating rooms.

14.0 Withdrawal of Subjects*

14.1 Patients may withdraw from the study at any time.

14.2 There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent.

15.0 Risks to Subjects*

15.1 Although not likely, there may be a potential risk for breach of patient health information. There is no study related physical risk to study subjects associated with this study. All study related procedures are non-invasive. All patients will receive our current standard of care with visual assessment of the TOF using a standard peripheral nerve stimulator. The only change in standard clinical practice is that additional placement of the TetraGraph™ device.

15.2 Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study. Subject PHI will be stored in a locked cabinet, and will be stored and maintained in password protected computer files.

16.0 Potential Benefits to Subjects*

16.1 There are no specific immediate benefits to the patient.

16.2 We hope what we learn from this study will benefit other pediatric surgical patients requiring train-of-four monitoring in the future.

17.0 Data Management* and Confidentiality

17.1 Statistical analysis and data presentation will be a descriptive analysis of the feasibility of using the device in patients of various

weight ranges. Feasibility, for the purpose of using this monitor intraoperatively, will defined as the generation of appropriate EMG for monitoring with ≥ 75% of the nerve stimulations. This will depend on the ability of the device to stimulate a peripheral nerve and generate the EMG of the muscle. We will compare the TOF from the TetraGraph™ with that from the standard peripheral nerve stimulator.

17.2 De-identified data will be shared with the manufacturer of the monitor, Senzime. They will be assisting with data analysis, as well as, using the data for approval in pediatrics.

17.3 Research records will be stored in a locked cabinet and password protected computer. Only certified research personnel will be given access to identifiable subject information

17.4 Following publication of study results, research records will be stored for a period of 6 years and then will be destroyed by placing in a secure shredding bin.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

18.1 The study will only be monitored by the study investigators.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study.

20.0 Compensation for Research-Related Injury

20.1 Not applicable

21.0 Economic Burden to Subjects

21.1 None

22.0 Consent Process

22.1 The consent process will begin in the preoperative surgery unit on the day of surgery, by PI, Sub-Investigators, Study Coordinators, and/or trained research staff.

22.2 The study will be thoroughly explained to the patient and their family. There will be ample time allotted for questions and answers. An explanation of voluntary participation will take place, and the family will be asked if they are interested in participating in the study. If the patient and their parent(s), or legal guardian agrees to participate they will be asked to sign consent and assent form. The patient will then be enrolled in the study with the understanding that they can elect to stop the study and be withdrawn from the study at any time.

23.0 Process to Document Consent in Writing

23.1 We will be following "SOP: Written Documentation of Consent (HRP-091)."

24.0 Setting

24.1 Research procedures will be performed in the operating room during anesthetic care.

25.0 Resources Available

25.1 We will need approximately 20 minutes per patient to explain the research protocol, obtain consent, and enroll patients. The Department of Anesthesiology & Pain Medicine has 2 research coordinators/RNs and 4 research associates who will be enrolling subjects for this study. All study staff will be trained regarding the study procedures. Before the study starts, the involved personnel will be informed by e-mail and during a pre-study meeting about the study protocol, the research procedures, research member's duties, and functions.

26.0 Multi-Site Research*

Not applicable

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

- ☒ Name
- ☐ Complete Address
- ☐ Telephone or Fax Number
- ☐ Social Security Number (do not check if only used for ClinCard)
- ☒ Dates (treatment dates, birth date, date of death)
- ☐ Email address, IP address or url
- ☒ Medical Record Number or other account number
- ☐ Health Plan Beneficiary Identification Number

☐ Full face photographic images and/or any comparable images (x-rays)
☐ Account Numbers
☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☐ Device Identifiers and Serial Numbers
☐ Biometric identifiers, including finger and voice prints
☐ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?
Following publication of study results, research records will be stored for a period of 6 years and then will be destroyed by placing in a secure shredding bin.

4.0 Describe any plans to code identifiable information collected about each participant.
Not applicable.

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

☒ **Research records will be stored in a locked cabinet in a secure location**
☒ **Research records will be stored in a password-protected computer file**
☐ **The list linking the assigned code number to the individual subject will be maintained separately from the other research data**

☒ **Only certified research personnel will be given access to identifiable subject information**

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study. Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)
☒ Diagnosis
☐ Laboratory reports
☐ Radiology reports
☐ Discharge summaries
☒ Procedures/Treatments received
☒ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☐ Names of drugs and/or devices used as part of treatment
☐ Location of treatment
☒ Name of treatment provider
☐ Surgical reports
☒ Other information related to course of treatment
☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.

Demographics need to be recorded to describe the patient characteristics of the study cohort for publication of these data in scientific journals. Diagnosis and procedures need to be assessed for inclusion criteria.

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? ☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature? ☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? ☐ Yes ☒ No