Transmembrane Electromyography (TM-EMG) for the Assessment of Neuromuscular Function in the Oropharynx

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STUDY SUMMARY

Study Description: Transmembrane electromyography (TM-EMG) may be a feasible and valid non-invasive EMG technique for detecting neuromuscular (NM) impairment. This study will assess whether, in healthy volunteers and participants with known obstructive sleep apnea (OSA) and other NM diseases involving the oropharynx, the same characteristic motor unit potentials obtained on conventional needle EMG (NEMG) can be obtained using a TM-EMG sensor. The purpose of this study is to demonstrate whether the TM-EMG sensor can provide the same diagnostic accuracy as the concentric needle electrode for the diagnosis of NM diseases. Having demonstrated diagnostic similarity of TM-EMG to NEMG, the secondary aim of this study is to confirm that NM disturbance of oropharyngeal striated muscles in participants with OSA can be elicited with the TM-EMG sensor.

Objectives: **Primary Objective**: To validate the TM-EMG sensor as a non-invasive technique for the assessment of neuromuscular function in the oropharynx.

Secondary Objective: To elicit, using the TM-EMG sensor, neuromuscular findings that correlate to OSA in affected participants.

Endpoints: **Primary Endpoint**: Proof of diagnostic consistency using both the TM-EMG sensor and NEMG in neuromuscular disorders affecting oropharyngeal muscles.

Secondary Endpoint: Proof that participants with known OSA exhibit EMG findings different from healthy participants and that these findings can be detected using both the NEMG and the TM-EMG sensor.

Study Population:

- 15 total participants with disorders affecting the function of oropharyngeal muscles
    - 10 participants with one of the following neuromuscular disorders:

- ALS with the presence of bulbar symptoms
- muscular dystrophy with the presence of bulbar symptoms

- 5 participants with severe OSA

■ 8 healthy volunteer participants

Phase: Pilot

Description of Sites/Facilities Enrolling Participants: All study recruitment and screening will occur at the SENTA Clinic in San Diego, CA, USA; a tertiary referral center which focuses on diseases of the head, neck, brain and spine. All EMG testing procedures will be performed in this clinic under the supervision of an expert otolaryngologist who will obtain the EMG tracings. In-Laboratory polysomnogram (PSG) studies, if required, will be performed at AmeriSleep Diagnostics in San Diego, CA, USA; a comprehensive and ACHC accredited sleep diagnostic facility.

Description of Study Intervention: Medical device for use as novel diagnostic modality.

Examination of the electromyographic signal from oropharyngeal muscles obtained using an investigational TM-EMG sensor attached to a rigid probe and a very fine concentric needle electrode (Ambu Neuroline 25 mm x 30G).

Study Duration: Six months

Participant Duration:

- 60 minutes for in-office screening exam.
- 60 minutes for in-office EMG exam.
- Healthy participants: One overnight stay for In-Laboratory Polysomnogram (PSG).

STUDY BACKGROUND AND RATIONALE

Electromyography (EMG) is the electrophysiological examination of muscle used for the diagnosis of suspected neuromuscular (NM) disorders such as myopathies, neuropathies, neuronopathies and neuromuscular junction disorders. [1] Routine needle electromyography studies (NEMG) are mainly restricted to skeletal limb muscles, which are easily accessible, and are not performed routinely on less accessible muscles, such as striated muscles of the oropharynx. This limits the evaluation of neuromuscular involvement in disorders involving muscles of the oropharynx such as obstructive sleep apnea (OSA) and neurogenic oropharyngeal dysphagia. Surface EMG (SEMG) is a non-invasive EMG method that assesses muscle function by recording muscle activity from one or more electrodes placed on the surface of the skin above the muscle or muscles to be examined but lacks the signal quality to provide diagnostic information on individual motor unit morphology and recruitment. [2,3]

In-laboratory polysomnography (PSG) is considered the gold standard for diagnosis of OSA. [4] This study measures numerous sleep metrics including oxygen level, sleep stages, REM patterns, wakefulness, EKG, and leg movements. An apneic event is defined by a 4% drop in the level of oxygen associated with a pause in breathing of 10 seconds or longer. The diagnosis of OSA is determined by the apnea/hypopnea index (AHI) [normal ≤ 5, mild OSA 5-15, moderate 15-30 and severe OSA > 30]. [5]

A videofluoroscopic swallowing evaluation (VFSE) is currently considered the diagnostic gold standard for accurate assessment of oropharyngeal dysphagia arising from pharyngeal muscle dysfunction due to multiple etiologies including neurologic disorders such as stroke, Parkinson's disease (PD), multiple sclerosis (MS), multi-system atrophy (MSA), and amyotrophic lateral sclerosis (ALS); autoimmune disorders such as myasthenia gravis; and myopathies such as muscular dystrophy. Both PSG and VFSE are laborious, costly, and have limited accessibility for the diagnosis of muscular disorders of the oropharynx.

Our body contains more than 600 skeletal muscles as well as cardiac and smooth muscles with different properties and different selective vulnerability for certain disease processes, owing to structural or physiological differences. Disease processes that affect the limb muscles differ from those affecting cardiac, gastrointestinal, or urogenital muscles. From a practical and clinical point of view, it is essential in most clinical scenarios to be able to confirm and characterize the nature of muscle disease, to provide appropriate and effective treatment.

OSA is a collective term used for conditions that over time cause damage to the delicate soft tissues of the upper airway from turbulent air flow and can comprise anatomically obstructive processes that result in nocturnal narrowing of the upper airway leading to partial or complete obstruction of the airway. The upper airway encompasses the entire upper airway passages to include the nasal cavity, oropharynx and hypo-pharynx. Partial and total airway obstruction results in sleep arousals, sleep fragmentation and subsequent behavioral derangements such as excessive daytime sleepiness. Concurrently, pathophysiologic derangements usually

accompany the behavioral decrements with altered daytime performance and excessive daytime sleepiness. The cardiovascular derangements can cause in part high blood pressure, stroke, myocardial infarction and death. Decreased quality of life and a shortened life span are common in participants with untreated OSA.

Although the complications of OSA are well known, the physiological mechanism for upper airway collapse during inspiration and sleep is not clear. Nonetheless, there is substantial physiological, electrophysiological and histological evidence for neuromuscular impairment in the upper airway in participants with OSA, [2 6] and pharyngeal nerve injury has been proposed as a possible contributory factor in OSA development, [2] which might be related to vibratory trauma caused by sleep-disordered breathing. [7] Evidence for sensory involvement in participants with OSA includes the finding of abnormal two-point palatal sensory discrimination, [8] and disordered thresholds for warmth and cold detection in the oropharyngeal mucosa. [9] Although the activity of the genioglossus, an upper airway dilator muscle, was found to be significantly greater during wakefulness in OSA, possibly due to a reflex-driven neuromuscular compensation for an anatomically compromised airway, a greater decline was observed during the early and late sleep onset period, suggesting the loss of this reflex. [10] Evidence for motor nerve fiber loss was shown by needle electromyography (EMG), demonstrating longer duration motor unit potentials (MUP) with larger size index. [2] Histological evidence for neuromuscular impairment in the upper airways includes frequent focal degeneration of myelinated nerve fibers and axons,[9] increased number of sensory and motor nerve fibers, indicating peripheral sprouting secondary to neuropathy, [11] abnormal muscle fiber variability with increased amount of connective tissue, and alternation in myosin heavy chain compositions. [12,13]

Dysphagia is difficulty swallowing due to structural or functional impairment of the aerodigestive tract. Such impairment may arise from an underlying neurological disorder producing oropharyngeal dysphagia (OPD). Participants with OPD have difficulty initiating swallowing and present with choking, nasal regurgitation or coughing episodes while eating, and drooling due to difficulty managing saliva. In addition, neurogenic OPD may be complicated by aspiration pneumonia, dehydration and malnutrition, increasing the morbidity of the underlying neurological disorder. Participants with symptoms of oropharyngeal dysphagia undergo a VFSE, which in the case of neurogenic OPD, typically reveals impairment of oropharyngeal motor performance and/or laryngeal protection. [14]

Electrophysiologic examination of muscles can provide diagnostic information as to the underlying process: myopathy, neuropathy, neuronopathy or neuromuscular junction disorders. There are currently two primary types of EMG techniques or methods: intramuscular or needle EMG (NEMG) and surface EMG (SEMG). NEMG involves the insertion of a needle electrode directly into the muscle to be examined and is considered the gold standard for assessing the muscle attributes of neuromuscular diseases. NEMG allows the clinician the ability to provide a precise evaluation of key indicators of neuromuscular function such as

spontaneous activity and motor unit action potential (MUAP) recruitment and morphology. These indices are utilized to: 1) differentiate between primary muscle pathology and muscle dysfunction secondary to nerve injury 2) characterize the nature of the pathology by the assessment of denervation activity which is typically indicative of an active disease process 3) assess re-innervation changes indicating disease chronicity and 4) define the topographical distribution of the neuromuscular disorder. [1]

However, NEMG is invasive and painful. Insertion of the needle damages the pierced tissues causing swelling and bleeding and nociceptor activation causes pain. There is risk of infection, viscus perforation and disease transmission. [3] These drawbacks are especially evident in areas of the body that are sensitive or dangerous places to use a needle such as the mouth/pharynx, eyes, ears, GI tract, urinary system, and myocardium. Consequently, NEMG is not used in these areas routinely in EMG laboratories. In an awake participant, needle electrode placement into oral or pharyngeal muscles is constrained by the gag reflex, insertion pain, procedure fear, local trauma, and bleeding risk. Once inserted, the needle electrode must be optimally positioned to record muscle activity. This requires repositioning of the needle in the muscle which further challenges participant tolerance and compliance.

SEMG is a non-invasive EMG method that assesses muscle function by recording muscle activity from one or more electrodes placed on the surface of the skin above the muscle or muscles to be examined. The main advantages associated with SEMG are that it is a pain-free technique which is not associated with the bleeding and infection risks of NEMG. As a result, SEMG can be used to record signals from many sites and motor units at the same time, for prolonged periods of time, and during activity. An additional potential advantage, is a larger recording area, making possible the collection of data over a wider region of muscle.[5] Due to these attributes, SEMG is used routinely for obstetric monitoring, kinesiologic analysis of movement disorders and in rehabilitation.[3] However, the role of SEMG in the diagnosis of neuromuscular disorders is limited by lack of information on insertional activity, spontaneous activity, motor unit size and shape, and interference pattern. In fact, the American Academy of Neurology concluded that SEMG is substantially inferior to NEMG for the evaluation of participants with neuromuscular disorders. Furthermore, SEMG has limited spatial resolution, is more susceptible to mechanical and electrical artifact, and is more likely to show cross-talk between adjacent muscles than NEMG. [3] Finally, SEMG uses adhesive surface electrodes that are not appropriate for muscles located within internal body cavities and organ systems with moist mucous membranes. Development of surface sensors and probes for internal use has not been successful so far.

Electrophysiological examination of the muscles located in body cavities such as the oropharynx could provide physicians with valuable data to aid in diagnosis and treatment. For example, pharyngeal muscles located in the oropharynx that act to dilate the airway do not function properly in participants with OSA. These muscles can also be affected in gastrointestinal conditions such as dysphagia, which may involve dysfunction of pharyngeal muscles.

Due to the drawbacks and limitations of both NEMG and SEMG, routine clinical EMG examination of these types of muscles is not feasible or practical. Therefore, there is a need to provide an EMG sensor that can overcome the drawbacks of NEMG and the deficiencies of SEMG to provide accurate diagnostic data for the clinical evaluation of participants with neuromuscular disorders affecting muscles located in body cavities or associated with internal organ systems.

For that reason, we propose a pilot study to examine the diagnostic utility of a novel transmembrane surface sensor, and compare signals obtained with the TM-EMG sensor to conventional NEMG signals participants from healthy volunteers to those with documented neurologic pharyngeal muscle dysfunction (ALS and muscular dystrophy) and to those with severe OSA.

STUDY SETTING

Study recruitment will occur at the SENTA Clinic in San Diego, CA, USA; a tertiary referral center which focuses on diseases of the head, neck, brain and spine. All EMG testing procedures will be performed in this clinic under the supervision of an expert otolaryngologist who will obtain the EMG tracings. In-Laboratory polysomnogram (PSG) studies will be performed at AmeriSleep Diagnostics in San Diego, CA, USA; a comprehensive and ACHC accredited sleep diagnostic facility.

STUDY DESIGN

This is a prospective, cohort, pilot study of adults from healthy volunteers to those with documented neurologic pharyngeal muscle dysfunction (ALS and muscular dystrophy) and to those with severe OSA; assessing diagnostic properties of EMG studies using a conventional needle and TM-EMG sensor in pharyngeal muscles.

OBJECTIVES and HYPOTHESIS

Primary Objective

To validate the TM-EMG sensor as a non-invasive technique for the assessment of neuromuscular function in the upper airway.

Secondary Objective

To elicit, using the TM-EMG sensor, neuromuscular findings that correlate to OSA in affected participants.

Study Hypothesis

The primary hypothesis is that transmembrane EMG (TM-EMG) examination of muscles located within internal body cavities and organ systems such as the oropharynx using the TM-EMG sensor will have similar diagnostic findings to the conventional NEMG examinations and that neurogenic changes will be observed in OSA.

Eligibility Criteria

Inclusion Criteria

- Gender: Male and or female
- Age: 18-70 years
- Must be able pause use of anticoagulation, NSAID and multi-vitamins for appropriate period prior to study test. Timeline and safety to be determined by principal investigator.
- A cohort of participants with documented neurological disorders involving upper airway striated muscles including ALS and muscular dystrophy with the presence of bulbar symptoms.
- A cohort of participants diagnosed with moderate to severe OSA on in-lab PSG, including the following criteria:
    - AHI > 25 made up of primarily of obstructive apneas and hypopneas.
    - Nadir Sa02 < 85%
    - Untreated
- A cohort of healthy participants that meet the following criteria
    - Normal craniofacial anatomy
    - AHI ≤ 2
    - Epworth score ≤ 10
    - Stop-Bang score ≤ 2
    - BMI < 30

Exclusion Criteria

- Allergy to topical anesthetic agent.
- Heavy alcohol use – defined as 4 or more alcoholic drinks on the same occasion on 5 or more days in the past month.
- Any type of smoking with 10 days prior testing.
- The presence of any underlying medical, surgical or psychiatric disorder that would preclude participation in the study as determined study principle investigators.

- Prior radiation to the oral cavity.
- Craniofacial anatomical disorders.

Interventions (Diagnostic Procedure)

EMG Testing Procedure

Study participants will be seen by Dr. Mansfield in an outpatient otolaryngology clinic in San Diego, California (SENTA Clinic). Drs. O'Leary and Bril will serve as consulting physicians. All participants will be evaluated and selected as study candidates based on inclusion/exclusion criteria.

Baseline data obtained will include participant demographic information, a comprehensive history including HPI, medications, past medical history, allergies, family history, social history—including smoking and alcohol consumption, STOP-Bang, and Epworth sleepiness scale. A comprehensive physical examination will be performed. The data will be documented using Cerner Ambulatory Electronic Health Record. Once a candidate is selected for the trial, they will be presented with the risks and benefits of this study. This will be discussed with each participant prior to written consent being obtained. Risks include induction of a gag reflex and/or feeling of nausea, minor irritation or bleeding at the testing site, mild allergic reactions to the topical anesthetic or to the probe tip itself, infection at the needle insertion site. All reactions, if any, are expected to be minor.

Standard ENT examining room equipment and supplies will be available as part of the study.

The participant will be positioned in a powered reclining and elevating otolaryngology examination chair. The testing physician will stand to the left of the sitting participant, and the participant will be positioned at the appropriate height, head supported in a headrest, to allow the physician to adequately visualize the soft palate anatomy. The physician will use a headlight to illuminate the oral airway. Photographs of the participant and the participant's soft palate/tongue/dentition and oral airway will be taken, and anatomic findings documented. Participant's blood pressure, heart rate, and respiratory rate will be recorded prior to the start of testing.

The skin of the cheek on the zygomatic arch will be prepared and cleaned with an alcohol swab to optimize skin contact with the ground electrode. The investigational TM-EMG probe device is hooked up to the EMG system.

The participant will open his or her mouth adequately to allow for visualization of the soft palate musculature by the physician. For participants in which the palatopharyngeus/ palatoglossus or musculus uvulae are poorly seen, gentle tongue depression will be used to better visualize the anatomy.

Topical 20% Benzocaine will be applied to the mucosal surfaces overlying the muscles to be examined using the TM-EMG probe prior to the start of testing. With the participant's mouth open and in neutral position, the TM-EMG probe is positioned on the mucosal surface correlating to the expected midpoint of the palatoglossus by the co-investigator. Free run EMG recording of the palatoglossus will be obtained. Once an optimal EMG tracing is obtained the probe will be released off the mucosal surface. The same procedure is repeated on the contralateral palatoglossus.

The same protocol will be used to test the genioglossus. The TM-EMG probe is placed on the mucosa of the genioglossus until an optimal EMG tracing is obtained. The same procedure is repeated on the contralateral genioglossus.

The principal investigator will then take his turn at assessing the same muscles. The palatoglossus will be examined in the same location using the same TM-EMG probe. Once an optimal EMG recording is obtained, the TM-EMG probe will be released off the mucosal surface and a very fine concentric needle electrode (Ambu Neuroline 25 mm x 30G) will be placed into the palatoglossus using the procedure as described below. Needle insertion will be done in a straight line through the mucosal membrane into the midpoint of the muscle at the desired depth. 1-3 needle insertions will be used to obtain a diagnostic-quality EMG tracing from each muscle. The needle is placed in the same location tested by the TM-EMG probe. Once both tracings are recorded, the contralateral palatoglossus will be tested via both TM-EMG and NEMG. The principal investigator will then obtain bilateral genioglossus EMG using the same protocol that was used for the palatoglossus.

The principal investigator will also obtain EMG data from both left and right palatopharyngeus using the TM-EMG probe and associated protocol. However, due to anticipated difficulty with gag reflex associated with the palatopharyngeus, NEMG will not be used at this site, and testing of this muscle will only be performed by the principal investigator. In total, 6 muscles locations will be tested via TM-EMG, and 4 muscle locations by NEMG.

The free-run EMG tracing for both TM-EMG and NEMG will be displayed on an oscilloscope and heard through an audio-amplifier. All EMG recordings will be made using standard gain and sweep speed settings. Waveforms for both TM-EMG and NEMG tests will be recorded on a Cadwell Sierra Summit EMG system.

We anticipate the recording time per muscle will be approximately 10 seconds. If participant exhibits intolerance during an individual muscle test, that particular muscle test will be discontinued.

The participant will be examined at the conclusion of the EMG procedures for excessive bleeding or swelling. The participant will have blood pressure, heart rate, and respiratory rate checked for stability immediately upon completion of testing and prior to discharge. The participant will be given written instructions on how to contact the research staff should any adverse events arise, such as a sore throat, fever, testing site irritation or any other study

related concerns. The research staff will contact the participant 1 day and 7 days after completion of the EMG test to document any adverse events the participant may have had following the testing. Responses will be documented in the EMR and serious adverse events will be reported to the study sponsor and IRB within 24 hours. Adverse events which occur more than 5 days after the EMG test will not be considered related to the study intervention, unless the investigator suspects a potential link.

Sleep Study

All healthy study participants selected for the study will be required to complete an overnight stay for an in-laboratory Polysomnogram ("PSG").

Study Endpoints

Primary Endpoint

Proof of diagnostic consistency using both the TM-EMG sensor and NEMG in neuromuscular disorders of the oropharyngeal muscles.

TM-EMG and NEMG data will be analyzed offline upon completion of testing by Dr. Vera Bril. Analysis will include the presence of spontaneous activity (fibrillation potentials and positive sharp waves), MUP morphology (number phases, duration and amplitude) and recruitment pattern. MUP morphology will be analyzed manually. Each recording will be labeled as a normal or abnormal study. Abnormal studies will be classified into active or chronic neurogenic changes or myopathic changes.

Secondary Endpoint

Proof that participants with known OSA exhibit EMG findings different from healthy participants and that these findings can be detected using both the needle electrode and the transmembrane sensor.

Analysis results will be compared between the healthy cohort and the neurologic disorders cohort; and between the healthy cohort and the OSA cohort.

Sample Size Calculation

Given that this is a novel EMG testing technique, a formal sample size calculation was not performed. The sample size chosen for this study was based on what would be reasonably feasible given constraints in areas such as funding and recruiting. The results from this pilot study will enable design of a larger, multi-site study adequately powered to show the diagnostic usefulness of TM-EMG.

Statistical Methods

All data will be examined to determine if there are any missing or non-plausible values, and these will be removed. Summary statistics will be calculated, including means or medians, minimums and maximums, standard deviations, and interquartile ranges.

The distribution of EMG findings in OSA will be presented as descriptive statistics.

ADVERSE EVENT MONITORING

Documented above under Interventions.

STUDY DISCONTINUATION

Participants will be withdrawn from the study if they withdraw consent or if the study physician determines that there is a safety risk associated with their participation. If a participant exhibits intolerance during an individual muscle test, that particular muscle test will be discontinued.

ANCILLARY OR POST-TRIAL CARE

Following the trial, each participant will return to the clinical care of their original physician. We will also assume responsibility for any adverse effects or harms caused by the intervention.

ETHICS AND DISSEMINATION

Research Ethics Approval, Protocol Amendments, and Consent

Participants who are eligible for study participation will be approached by the research assistants, to avoid any coercion on the part of the investigators. Consent will be obtained in writing, with the risks and potential benefits of the study clearly explained in basic language in the consent form. The participant will be allowed ample time to review the consent form prior to signing; and if the participant wishes to discuss the study with family members prior to going forward, they may take the consent form home. The research assistants will be available to answer any questions about the study; and if the research assistants are unable to answer the question, this will be addressed by the study investigator. All participants will be re-assured that at any point during the study, they may withdraw consent and end their participation in the study. If consent is withdrawn, all data collected to that point remains as part of the study, however, will be de-identified.

The study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations

(CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality, Data Access, and Declaration of Interests

Participant confidentiality will be strictly maintained throughout the study. All study records will be de-identified to maximum capability, and all study charts will be kept under lock-and-key in a secure office. The study charts will not contain any protected health information (PHI), and each participant will be identified only according to initials and unique study identifier. Following completion of the trial, all data will be kept by SENTA Clinic for two (2) years, as mandated. Electronic data will be stored on password-protected computers using the SENTA Clinic's secure servers. Access to trial data will be available to study investigators, research assistants, and statisticians; however, this data will be de-identified to the maximum of the investigators' capabilities. Finally, each investigator will declare any financial or other conflicts of interests prior to study onset, and at completion.

Dissemination Policy

Any manuscripts derived from the study will be written by the investigators, without professional writers. The principal investigators (PI) will be the senior authors. Other investigators who have contributed to the planning and conception; manuscript writing or revision; participant recruitment; or data analysis may be named as co-authors on any publications. The results of the study may be presented at national or international scientific meetings. Participants will be informed about study results through local dissemination. In order to protect Sponsor's confidential information and intellectual property rights, any proposed publication, presentation or other public disclosure of study must be reviewed and approved in writing by Sponsor prior to submission or public disclosure, such approval not to be unreasonably withheld. Sponsor will respond to requests for publication or other public disclosure within sixty (60) days.

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