USE OF AUTOMATIC PERIODIC STIMULATION AND CONTINUOUS EMG FOR FACIAL NERVE MONITORING DURING PAROTIDECTOMY

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Principal Investigators:

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STUDY SUMMARY

Title: Use of Automatic Periodic Stimulation and Continuous EMG for Facial Nerve Monitoring During Parotidectomy

IRB Protocol Number: 16-009380

Methodology: Prospective, investigational

Target subject accrual: 50

Expected duration of study: 6-9 months

Subject participation duration: 2 days (day of surgery and post operative day 1)

Primary Objective: Use of an automatic periodic stimulation electrode to correlate EMG changes during parotidectomy with post-operative facial nerve weakness.

Secondary Objective: Modification of intraoperative technique to decrease the incidence and/or severity of post-operative facial nerve weakness following parotidectomy.

Principal Investigator: Eric J. Moore

Head Study Coordinator: Daniel B. Noel

1 INTRODUCTION

This is a protocol to direct a prospective, investigational study which aims to evaluate the utility of a facial nerve monitor during parotidectomy in predicting intra-operative factors that portend post-operative facial nerve weakness. Intra-operative facial nerve monitoring has become the "standard of care" at most tertiary care centers but the current method of monitoring the facial nerve and predicting post-operative weakness has several limitations. In the trial, we aim to determine intra-operative factors that are associated with EMG changes on the facial nerve monitor in an effort to alter intra-operative techniques to decrease the incidence and severity of post-operative weakness.

2 BACKGROUND

Parotidectomy is a relatively common procedure for the practicing Otolaryngologist, especially at tertiary care facilities, where most of these procedures are performed. The most dreaded, yet relatively common, complication following parotidectomy is post-operative facial nerve weakness which results in functional, cosmetic, emotional, and financial burden on the patient as well as psychological burden on the surgeon. Transient post-operative facial nerve weakness, occurring in at least one major distribution of the facial nerve, occurs in approximately 20-40% of cases following parotidectomy. Permanent paralysis occurs in approximately 1-5% of cases.

The current method of facial nerve monitoring during parotidectomy was introduced during the late 1980's and its safety, application, effectiveness, and benefits have been described and documented (Metson et al, 1988, Terrell et al, 1997, Lopez et al, 2001). Current monitoring involves placing transcutaneous electrodes on the patient's face during general anesthesia in 2-4 muscles innervated by separate branches of the facial nerve. An electrophysiologic monitoring system, for example the NIM-Response 2.0 Nerve Integrity Monitor (NIM-2; Medtronic Xomed, Jacksonville, FL), then monitor facial muscle activity during parotidectomy and alert the surgeon to EMG changes using an integrated pulse generator for electrically- evoked EMG changes. This system has several benefits including identification of the nerve, differentiation between neural and non-neural tissue, alertness of potentially traumatic manipulation, and awareness of nerve proximity when it is not expected. A recent meta-analysis published in 2014 concluded that facial nerve monitoring is safe and effective, resulting in a statistically significant reduction in post-operative facial nerve weakness (Sood et al, 2014).

There are several limitations to the current method of facial nerve monitoring during parotidectomy. EMG changes using standard techniques of facial nerve monitoring are not reliably predictive of impending facial nerve damage and do not allow the surgeon to alter his or her technique to prevent adverse EMG events. Often times, the alert generated by the monitoring system is that of artifact, a change in the depth of the patient's anesthesia, or occurs after the damage is already done. In addition, the current technique does not allow for "real-time" identification of impending damage and requires the surgeon to use a handheld nerve

stimulator to active the nerve. This requires the surgeon to halt the operation and apply direct contact to the nerve with a handheld device. Changes in the nerve's neural integrity which may predict impending damage can not be detected until the surgeon stimulates the nerve either incidentally or with the handheld stimulator, after which permanent damage may have already occurred. Lastly, current techniques only reflect damage that occurs distal to the point of stimulation, and is not capable of monitoring the nerve's integrity along its entire course.

The use of an automatic-periodic-stimulating (APS) electrode has been proposed, designed, and implemented in thyroid surgery with success and safety. The use of an APS electrode allows for continuous monitoring of a motor nerve during surgery and provides the surgeon with real-time information regarding the integrity of the nerve and maneuvers which are associated with adverse EMG changes. The combination of changes in amplitude and latency (which is not provided by the current method) provide the surgeon with more accurate information regarding EMG changes that are associated with impending nerve damage. More importantly, this information allows the surgeon to alter techniques, in real-time, to avoid damage to the nerve being monitored. This method has been documented as safe and effective in thyroid surgery in monitoring the recurrent laryngeal nerve and preventing temporary vocal fold dysfunction following thyroidectomy (Dionigi et al 2013, Schneider et al 2013, Randolph et al 2014)

3 STUDY OBJECTIVES

Primary Objective: To determine if continuous intraoperative facial nerve monitoring during parotidectomy using an APS electrode is safe, feasible, and informative. We aim to determine if continuous facial nerve monitoring can identify intra-operative EMG changes that are associated with post-operative facial nerve weakness

Secondary Objective: To determine if the information garnered by intra-operative continuous facial nerve monitoring can arm the surgeon with information that may alter the surgical technique and prevent temporary post-operative facial nerve weakness.

4 STUDY DESIGN

4.1 General Design

This study will be conducted in three phases. The first will be that of a pilot study to document safety of this electrode during parotidectomy. This electrode has been used safely in other areas of head and neck surgery and has FDA approval for peripheral nerves throughout the human body. This phase will include 10-15 patients during which the electrode will be placed and either removed or inactivated to ensure that placement of the electrode itself is safe.

The second phase of the trial will aim to accrue approximately 25 patients who will undergo continuous intraoperative facial nerve monitoring with the Medtronic APS electrode. This is the same monitoring system, using the same receiving electrodes that is currently used during

parotidectomy and requires placement of the APS electrode as the only additional piece of equipment. During this phase, we will record intraoperative EMG data generated by the monitoring system as well as document intra-operative maneuvers that precede adverse EMG events. We hope to correlate both EMG changes as well as intra-operative techniques that predict facial nerve damage and post-operative paresis. During this phase, the surgeon will be blinded to the information provided by the APS electrode but will still have the monitoring system functioning in the current standard fashion, alerting the surgeon to stimulated EMG events.

The third phase of the trial will then aim to allow the surgeon to alter his or her techniques, with the information provided by the APS electrode, to reverse adverse EMG changes. The incidence of adverse EMG changes and their relationship to intra-operative maneuvers will be recorded in an effort to identify specific factors during surgery that cause post-operative facial nerve weakness. With this information, we aim to eliminate or minimize those factors so that the incidence of post-operative facial nerve weakness decreases.

4.2 Primary Study Endpoints

The primary study endpoints include adverse EMG changes, including amplitude and latency, and the degree of post-operative facial nerve weakness as recorded with the APS electrode and standard neural monitoring system.

4.3 Secondary Study Endpoints

The secondary study endpoints include adverse EMG changes as they relate to intra-operative techniques and maneuvers that their association with post-operative facial nerve weakness.

4.4 Early termination

If during the pilot study or during the main trial the placement or use of the APS electrode is documented or suspected by the surgeon to cause nerve damage or add unnecessary time or difficulty to the surgery, the study protocol will be revisited and re-written or the study will be terminated.

5 SUBJECT ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

- Age: 18 years of age or older
- Parotidectomy: Planned parotid gland surgery (superficial or total parotidectomy)
- Benign or malignant disease

5.2 Exclusion Criteria

- Age: less than 18 years of age
- Current pregnancy
- Preoperative facial nerve dysfunction
- Revision surgery
- History of preoperative radiation to the surgical field

- Retrograde or extracapsular dissection
- Intentional nerve sacrifice (ie. due to nerve involvement by tumor)
- Tumors with proximity to main trunk of facial nerve
- Inability to place electrode
- Presence of electrode alters surgical technique

5.3 Subject Recruitment

Patients being referred for parotid masses to the Department of Otorhinolaryngology will be identified at their initial pre-operative consultation by the consulting team, investigator, or study coordinator. All members of the clinic team, including consultants, residents, and nurses will be made aware of this study's inclusion and exclusion criteria and will identify appropriate patients. Consent to participate in the study will be obtained at the time of consultation or on the day of surgery, depending on availability of the investigator and/or research coordinator.

No specific recruitment material will be distributed for this study.

5.4 Withdrawal of Subjects

Patients who are not able to be evaluated on the day after surgery or those who should choose to withdraw for any reason will have the option to withdraw at any time.

6 STUDY PROCEDURES

6.1 Preoperative Visit

Eligible subjects will be identified for inclusion at their initial consultation. The study coordinator or departmental research staff will obtain informed consent to enroll in the study. The informed consent discussion will take place in a quiet and private room in the clinic environment, if possible. If no research personnel are available at this time, the patient may also be consented to participate the morning of surgery in the preoperative area by the research staff. If performed in the preoperative area, consent will be obtained at least 20 minutes prior to entering the operative suite and before any form of sedation is administered to the patient. If family or friends accompany the patient, the patient will have the opportunity to review the consent in or out of their presence. A copy of the consent form will be provided to the patient to keep, and a copy will be filed and stored. Once enrolled, the preoperative facial function of the subject will be recorded by the research staff.

6.2 Operative Visit

Patients enrolled in the study will proceed to the operating room according to the medical decision making between the patient and their surgeon. As a prerequisite for inclusion in the study, the planned operation will be a superficial or total parotidectomy with facial nerve preservation. The surgeon will complete whatever operation is needed for each specific patient, irrespective of their inclusion in the study. If the patient requires a less significant dissection for treatment (ie., partial parotidectomy without facial nerve dissection), or a more significant

dissection (ie., facial nerve sacrifice), then the surgeon will proceed accordingly. The facial nerve monitor will be used intraoperatively. The patient's operative experience will not deviate from standard operating room procedure in any way by their participation in this study, aside from the use of the APS electrode. If during the course of the patient's operation, any of the exclusion criteria are met, the patient will be withdrawn from the study, and will be notified of this on the first postoperative day visit.

6.2.1 Intraoperative Facial Nerve Monitoring

At the time of surgery, the facial nerve monitor (NIM-Response® 3.0; Medtronic, Jacksonville, FL) will be used, as is typical for parotid gland surgery. Four monitoring leads will be used, one in each of the following muscles: frontalis (frontal eminence), orbicularis oculi (lateral orbital rim), levator labii superioris (nasolabial fold), and depressor anguli oris (oral metnalis). Two grounding leads will be placed in the subcutaneous tissue of the patient's chest or shoulder per the standard fashion. The operative team will confirm accurate placement of leads and correct function of the system prior to making a surgical incision. When the main trunk of the facial nerve is identified, the APS electode will be placed by the primary surgeon (see Appendix A) when it is deemed safe.

The facial nerve monitoring system records the number of stimulations of the facial nerve during the operation and this data is stored on the device until it is shut down after the surgery is complete. With the APS electrode, the monitoring system will be able to record changes in amplitude in isolation or in combination with changes in latency. A 50% decrease in nerve amplitude combined with a 10% increase in nerve latency will be defined initially as an "adverse" EMG event as this combination has been identified in previous studies as predictive of post-operative nerve dysfunction. During the first phase of the trial, the surgeon will be blinded to these changes as the monitoring system will not be prompted to alarm. The surgeon, however, will still have the same feedback that is offered during the standard method of monitoring facial nerve function, which is an alarm generated by a stimulated amplitude generated, the threshold for which is selected by the surgeon.

During the last phase of the trial, the surgeon will be alerted to adverse EMG changes and will be allowed to alter the maneuver in an attempt to reverse or prevent further adverse EMG changes.

6.2.2 Facial Nerve Monitoring Malfunction

If the facial nerve monitor malfunctions during the operation, the circulator nurse will be asked to mark a timestamp on the nerve monitor indicating such. This occasionally occurs when the patient is not anesthetized deeply enough which can result in spontaneous activity on the nerve monitor without surgical manipulation. These events will not be scored as a stimulation of the nerve during data analysis.

6.3 Postoperative Visit #1

The primary investigator will visit with each patient on the morning after their operation in their hospital room. Almost all patients who undergo parotidectomy stay at least one night in the

hospital for surgical drain care.. At this visit, the study team member will grade the patient's facial function using the Facial Nerve Grading Scale 2.0 (Table 1). This grading scale is a validated adaptation of the most commonly used scale, the Facial Nerve Grading Scale, as described by House and Brackmann (Vrabec et al., 2009).

Table 1. Facial Nerve Grading Scale 2.0

	Region			
Score	Brow	Eye	NLF	Oral
1	Normal	Normal	Normal	Normal
2	Slight weakness >75% of normal	Slight weakness >75% of normal Complete closure with mild effort	Slight weakness >75% of normal	Slight weakness >75% of normal
3	Obvious weakness >50% of normal Resting symmetry	Obvious weakness >50% of normal Complete closure with maximal effort	Obvious weakness >50% of normal Resting symmetry	Obvious weakness >50% of normal Resting symmetry
4	Asymmetry at rest <50% of normal Cannot close completely	Asymmetry at rest <50% of normal	Asymmetry at rest <50% of normal	Asymmetry at rest <50% of normal
5	Trace movement	Trace movement	Trace movement	Trace movement
6	No movement	No movement	No movement	No movement

Secondary movement (global assessment)

Score	Degree of movement
0	None
1	Slight synkinesis; minimal contracture
2	Obvious synkinesis; mild to moderate contracture
3	Disfiguring synkinesis; severe contracture

Reporting: sum scores for each region and secondary movement

Grade	Total score
I	4
II	5-9
III	10-14
IV	15-19
V	20-23
VI	24

NLF, nasolabial fold.

7 DATA COLLECTION AND ANALYSIS

7.1 Data to Be Collected

Demographic data to be collected will include patient's age, sex, medical comorbidities (Charlson Comorbidity Index), and preoperative facial function.

Intraoperative data will include the type of surgery performed, length of anesthesia, tumor size, tumor histology, and the case log generated by the neural monitoring system, which will be recorded separately for each electrode (and therefore, muscle group).

Intraoperative maneuvers will be categorized to allow them to be recorded and compared statistically. For example, categories may include but are not limited to "thermal," "blunt dissection," "sharp dissection," "lavage," "pressure," "vessel ligation," and "traction."

8 DATA HANDLING

Data will be collected and handled in a manner to protect patient health information.

Intraoperative data extracted from the facial nerve monitoring system will be downloaded onto an encrypted flash drive and collected by the investigator. The data will then be extracted to a secure database on the Mayo Clinic server. Once the data has been transferred, the data will be deleted from the flash drive. Only the principal and co-investigators will have access to this data. Postoperative visit data will also be entered into this secure database. Access to the database will be restricted to research staff and will be unavailable to Medtronic or any other third party. Data will be deleted at the conclusion of the study.

The Head Study Coordinator will be responsible for handling of protected health information according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In accordance to this, a signed consent form by patient will be obtained that informs the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

9 STUDY FUNDING

Funding for this study will be obtained via internal research funds within the Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota in addition to funding provided by Medtronic for the payment of electrodes used in the study to avoid cost to the institution or patient. The study group has also requested funding from Medtronic either in part or in full for a research study coordinator. There will be no payments to patients for participation in this project.

There will not be any additional costs to the patient during their operation or postoperative care as part of participating in this research study.

10 REFERENCES

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parotidectomy. Head Neck. 2010;32(3):399-405.
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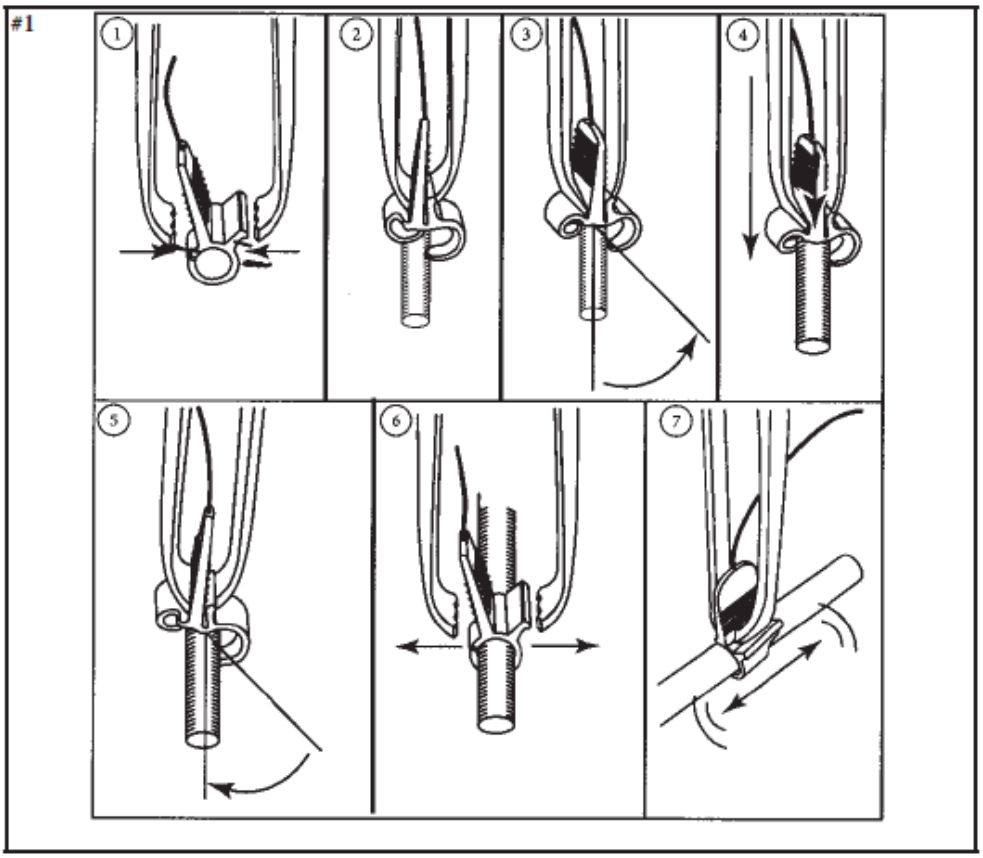
APPENDIX A. APS ELECTRODE PLACEMENT

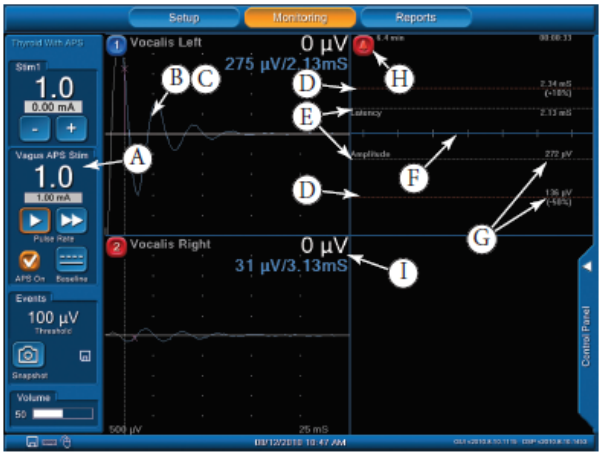
Illustrations

ILLUSTRATIONS / ILLUSTRAZIONI / ABBILDUNGEN / ILUSTRACIONES / AFBEELDINGEN / ILLUSTRATIONER / KUVAT / BILDER / ILUSTRAÇÕES / ΑΠΕΙΚΟΝΙΣΕΙΣ / ILUSTRACJE / OBRÁZKY / ILLUSZTRÁCIÓK / RESIMLER / ILLUSTRASJONER / РИСУНКИ



APPENDIX B. APS ELECTRODE PACAKGE INSERT, INDICATIONS FOR USE

#2



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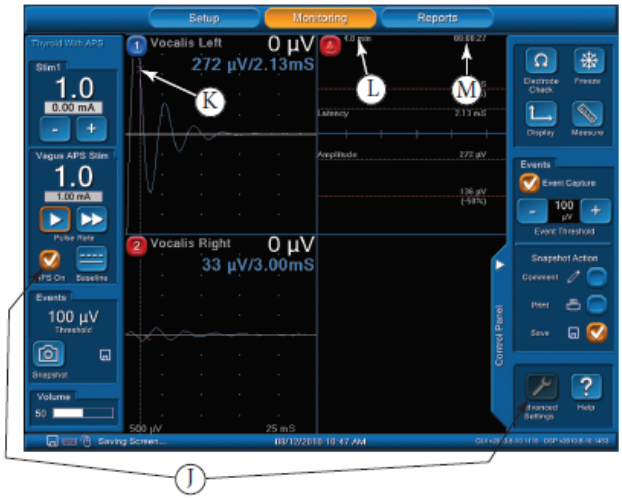

English

Indications for Use

The NIM 3.0 is intended for locating and identifying cranial and peripheral motor and mixed motor-sensory nerves during surgery, including spinal cord and spinal nerve roots. The APS™ electrode is an accessory intended for providing automatic periodic stimulation to nerves when used with the Medtronic Nerve Monitoring Systems.
Indications for NIM 3.0 EMG Monitoring Procedures include:
Intracranial, Extracranial, Intratemporal, Extratemporal, Neck Dissections, Thoracic Surgeries, and Upper and Lower Extremities
Indications for Spinal procedures which may use NIM 3.0 EMG monitoring include:
Degenerative Treatments, Pedicle Screw Procedures, Fusion Cages, Rhizotomy, Orthopedic Surgery, Open and Percutaneous Lumbar and Cervical Surgical Procedures, and Thoracic Surgical Procedures

Contraindications

The NIM 3.0 is contraindicated for use with paralyzing anesthetic agents that will significantly reduce, if not completely eliminate, EMG responses to direct or passive nerve stimulation.