Title: Cochlear Implantation During Vestibular Schwannoma Removal or During Labyrinthectomy Surgery for Treatment of Meniere's Disease

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Table of Contents

I. Objectives

The purpose of this study is to determine longitudinal benefits of listening with a cochlear implant placed during the time of tumor removal for patients with a vestibular schwannoma and/or with patients undergoing a labyrinthectomy for treatment of Meniere's disease

II. Background and Rationale

Cochlear implantation for patients with single-sided deafness is increasingly being performed. Combined electric stimulation in one ear with normal acoustic stimulation of the other ear has been shown to improve speech perception and sound localization abilities for patients with single-sided deafness, particularly in situations with background noise.

In patients with vestibular schwannomas, which grow on the balance nerves adjacent to the auditory nerve, hearing loss often occurs. Moreover, during surgical removal of the vestibular schwannoma through a translabyrinthine approach, the balance portion of the inner ear is destroyed (to access the tumor), which inevitably leads to profound hearing loss in that ear, a particular cause of single-sided deafness. However, after surgical removal, a viable cochlear portion of the inner ear remains, and often times the auditory nerve itself can be preserved anatomically, even if partially compromised by tumor compression or surgical manipulation. This leaves the potential to deliver signals through a cochlear implant electrode array placed into the cochlea at the time of tumor resection.

Meniere's disease is a disorder of the inner ear in which severe dizziness and hearing loss occur. One surgical treatment option for these patients is a labyrinthectomy. Labyrinthectomies, frequently performed for Meniere's disease, are very effective for treating the debilitating balance symptoms associated with this disease. However, as these surgeries involve opening of the inner ear by drilling of the labyrinth, they always result in single sided deafness. However, the cochlear portion of the inner ear and the auditory nerve is left intact. This leaves the potential to deliver signals through a cochlear implant electrode array placed into the cochlea at the time of the labyrinthectomy.

Evidence of the longitudinal effects of electric stimulation of a compromised inner ear and/or eighth nerve is limited. Tran Ba Huy et al. (2008) discussed the benefits of cochlear implantation in three neurofibromatosis type 2 (NF2) patients who underwent cochlear implantation after receiving treatment for their vestibular schwannomas. They reported each patient had improved postoperative speech perception with the cochlear implant, and that follow-up CT imaging studies did not show additional schwannoma growth. Zanetti et al. (2007) reported a single case study, where the patient underwent cochlear implantation at the same time as the vestibular schwannoma removal. They reported an improvement in nerve responses after extended listening experience with the cochlear implant. Hansen et al. (2013) reported 10 subjects who underwent cochlear implantation at the time of a

labyrinthectomy for Meniere's disease all had improved auditory function with the CI. Doobe et al. (2015) describe five patients who were simultaneously implanted with a cochlear implant during the same labyrinthectomy surgery for treatment of Meniere's disease and the patients were able to achieve up to 69% speech recognition in the implanted ear. The benefits of binaural hearing, including improved localization and speech understanding in noise, are well-known and documented in the literature. This study will more systematically assess whether this patient population will also receive these benefits.

Potential benefits to individual participants in this study include improvement in detection and speech perception of the surgical ear. Participants may also experience improved localization abilities and speech perception in noise as the result of having binaural hearing. Society may benefit from a better understanding of longitudinal outcomes of electric stimulation of a compromised inner ear and auditory nerve. This study will also help to determine if it is safe and effective to use cochlear implants in these patient populations.

III. Procedures

A. Research Design

This is a prospective, quantitative clinical study.

B. Sample

Fifteen adult participants, aged 18 – 70 years of age, with a diagnosed vestibular schwannoma or Meniere's disease will be recruited for this study. Eligible participants will meet the following criteria:

Inclusion Criteria:

- Have a diagnosis of a vestibular schwannoma confirmed by a physician with an MRI and/or CT scan; Or have a diagnosis of Meniere's disease by a physician
- be scheduled to undergo surgery to remove the vestibular schwannoma through translabyrinthine approach; Or be scheduled to undergo a labyrinthectomy
- Be English-speaking due to objective speech perception tasks. Non-English speakers may show a reduced speech perception score due to language differences
- For patients undergoing tumor removal, tumor removal must allow preservation of the auditory division of the VIIIth cranial nerve

Exclusion Criteria:

- Subjects with bilateral Meniere's disease or bilateral vestibular schwannomas
- Inability to preserve the auditory division of the VIIIth cranial nerve during removal of vestibular schwannoma
- Ossification or fibrosis of the cochlear found on preoperative imaging (CT or MRI) that precludes cochlear implantation
- Active middle ear disease
- Greater than 70 years of age
- Vestibular schwannoma greater than 2 cm
- Patient refusal of receiving pneumococcal vaccine
- Any contra-indication(s) for undergoing surgery.

There are no exclusion criteria related to race, gender or ethnicity, and recruitment will be directed to all participants that meet the criteria stated above.

C. Measurement/Instrumentation

In addition to the cochlear implant activation appointment, participants will have follow-up procedures/visits similar to the standard of care clinical procedures/visits of traditional cochlear implant recipients. Participants will return to the clinic for speech perception testing and programming at intervals of 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months post-implantation. Testing will include both detection and speech perception testing in quiet and in noise, along with assessment of sound localization. Following the first 12 months the subjects will then be routinely seen on an annual or as needed basis for routine follow-up care. No further testing as it pertains to this study will be performed at these intervals. However, clinical data obtained in typical routine cochlear implant visits will be collected by the investigators for four years from the time of subject enrollment.

D. Detailed Study Procedures

Potential participants will be identified by the study investigators, who are also the treating physicians, during a clinical visit for discussion of management of their vestibular schwannomas or Meniere's disease. The study will be described during the clinical visit only after the decision has been made by the treating physician and patient on the clinical management of the vestibular schwannoma or Meniere's disease. Potential participants will be provided the contact information of the study coordinator, who will review the consent form with the participant. Continued contact will be dictated by the patient, whether they prefer phone, mail, or email correspondence. All discussions regarding the study and possible participation will be conducted in a private, closed clinical exam room or office to protect the privacy of potential participants.

Informed consent will be obtained as part of a preoperative encounter. Interested participants will have the study, including all risks and benefits, described to them

by a research team member other than the patient's physician. The potential participant will be given a copy of the consent form and be given ample time to read it and ask questions that may arise. If the individual agrees to participate in the study, the consent form will be signed. The participant will be given a copy of the signed consent form. At this time, the participant will also be asked to complete the Tinnitus Handicap Inventory (THI) as a pre-operative measurement of his or her tinnitus perception.

The subjects will be patients who have been identified as having a vestibular schwannoma, diagnosed via a MRI or CT scan or diagnosed with Meniere's disease and is undergoing a labyrinthectomy surgery. They will receive extensive counseling regarding the goal of the surgery, and associated risks. It is recommended by the Centers for Disease Control (CDC) and is OSU's standard protocol that all patients' receiving a cochlear implant, due to the small risk of meningitis, be up-to-date on their pneuomococcal vaccinations. Meningitis is an infection in the fluid and tissue that surrounds the brain and spinal cord. If the patient is not up-to-date, then he/she will receive the pneumococcal vaccinations prior to undergoing surgery. All implantations will be performed under general anesthesia. The risks associated with this study are related to the surgery itself, which is already routinely performed by the treating physicians for patients with hearing loss. Implantation of these devices and subsequent management are not experimental.

Intraoperatively, following the procedure of translabyrinhthine approach and tumor removal, the surgeon will determine via visual microscopy whether there was preservation of the auditory division of the VIIIth cranial nerve. If determination is made that the auditory division is intact, then the surgeon will proceed with cochlear implantation only on the ipsilateral (operated) side. If the surgeon determines the auditory division is more likely than not to remain intact, then the subject with be discharged from the study and cochlear implantation will not be performed.

Intraoperatively, following the procedure of labyrinthectomy for treatment of Meniere's disease, the surgeon will proceed with cochlear implantation only on the ipsilateral (operative) side.

Approximately 4 weeks after surgery, subjects will be fit with an external speech processor to stimulate the cochlear implant. Prior to activating the cochlear implant, subjects will be asked to complete the THI as a post-operative measurement of his or her perception of tinnitus. Once activated, subjects will be encouraged to listen with the device to determine if electrical stimulation of a compromised auditory nerve offers improvements in detection and speech perception on the implanted side. Subjects will return to clinic for programming of the external speech processor and postoperative testing at the following intervals after the initial processor fitting: 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months post-implantation.

The following test batteries and questionnaires will be presented at each test interval:

- Detection Testing Determination of softest sound subjects can hear with the cochlear implant.
    - Sounds that vary in pitch (frequency) and loudness (intensity) will be presented in the sound field. The subject will then be asked to indicate when he/she detects/perceives a sound when listening with the cochlear implant.

- Speech Perception Testing - Subject listens and responds to recorded sentence and word lists in quiet and in noise.
    - AZ Bio sentences and CNC word lists will be presented through a sound field speaker and the subject will be asked to repeat back the sentences and/or word he or she heard. Background noise will be presented in conjunction with the sentences/words at various signals to noise levels.

- Sound Localization Testing - Subject listens to sounds presented from a number of speakers and identifies which speaker presented the sounds.
    - The subject will sit in the center of the sound testing booth. Speakers will be located at various degrees in the horizontal field varying from 0 to +/- 180 degrees. Sounds representing varying in acoustic properties will be presented at random through one speaker at a time. The subject is this asked to identify which speaker the sound came was generated from.

- The Speech, Spatial and Qualities of Hearing Scale (SSQ):
    - A subjective questionnaire which allows the user to report measures of a range of realistic hearing contexts, spatial hearing components (direction and distance judgements), and other listening qualities (listening effort, clarity/naturalness).

- Nijmegen Cochlear Implant Questionnaire (NCIQ)
    - The NCIQ encompasses hearing and speech, psychological, and social domains. Individual subdomain scores, as well as total scores across subdomains are used to evaluate the subject's quality of life.

- Tinnitus Handicap Inventory (THI)
    - A subjective questionnaire that identifies, qualifies, and evaluates the difficulties a subject may be experiencing due to tinnitus.

The data collected during the study will be kept in a filing cabinet in the locked office of the principal investigator, or on a password-protected medical center computer drive, and access to the data will be limited to authorized study

personnel. Data related to the research will be coded with a study number, and the code key will be stored separately from the research data. Only coded data will be transmitted between the research team. The data will be retained on file for at least seven years after the study is closed. The data will then be destroyed in accordance with the shredding/recycling procedures at The Ohio State Wexner Medical Center.

E. Internal Validity

All English speaking patients with a diagnosed vestibular schwannoma who have elected surgical resection by a translabyrinthine approach will be invited to participate in the study. Participants must be English speaking due to objective speech perception tasks. Non-English speakers may show a reduced speech perception score due to language differences. Eligible participants will not be selected based on gender, race, or ethnicity.

F. Risk Analysis

There is no significant added risk involved with performing a cochlear implant at that time of vestibular schwannoma resection or labyrinthectomy other than those risks associated with anesthesia due to the increased surgical time (maximum of 15-20 minutes additional). Given that hearing is believed to be sacrificed as part of translabyrinthine approach for tumor resection or treatment of Meniere's symptoms, the usual concerns of hearing loss, vertigo or dizziness or cerebrospinal fluid leak are already encompassed by vestibular schwannoma/labyrinthectomy surgery. Of the preliminary reports of simultaneous cochlear implantation, there have been no added or unforeseen complications. As such, the potential benefits of the knowledge that would be yielded from this proposal outweigh any added risks.

<u>Risks Associated with Surgery</u>
Risks associated with ALL operations include pain, scarring, bleeding, and infection. Anesthesia medication used during the operation also has risks for the heart, lungs, kidneys, liver, and brain and, in rare cases, can result in death.

<u>Possible risks associated with ALL ear operations including cochlear implantation:</u>
• damage to the facial nerve
• dizziness
• infection
• bleeding
• numbness or stiffness around the ear
• things may taste different
• increased ringing in the ear (tinnitus)
• neck pain
• skin reactions

• leakage of inner ear fluid, which may result in an infection called meningitis

Meningitis is a known risk of inner ear surgery. There are two main types of meningitis, viral and bacterial. Bacterial meningitis is the most serious type. It is the type that has been reported in some patients with cochlear implants.

Some conditions may increase the risk of meningitis. These conditions include:
• Mondini's malformation, an inner ear malformation
• cerebral spinal fluid (CSF) shunt or drain
• recurrent episodes of bacterial meningitis prior to cochlear implant surgery
• presence of a perilymph fistula
• some types of skull fracture and defects

The Centers for Disease Control (CDC) recommends that patients planning to receive a cochlear implant should be up-to-date on age-appropriate pneumococcal vaccinations 2 or more weeks before surgery (more information about the CDC's recommendations can be found by calling the CDC's National Immunization Information Hotline at 1-800-232-2522).

G. Data Analysis

Statistical analysis will be undertaken using standard repeated measures of analyses of variance. Fifteen participants will allow for the comparison of average speech perception performance with a cochlear implant over the course of 12 months. The fifteen patients will not have a "baseline" audiogram that is comparable pre- to post- surgery since the nature of the two surgeries result in profound hearing loss. However, the preoperative audiogram will be used during analysis since it will provide the investigators insight into the extent of neural compromise (as measured by word recognition scores) at the time of surgery.

Although the number of subjects is low we will employ descriptive statistics to measure variability and central tendency among the entire group as well as within the two groups when separated by etiology (Meniere's disease or vestibular schwannoma) at each interval on all performance measures including questionnaires. Other variables known to influence outcomes (age, duration of hearing loss, pre-operative audiogram) as well as new factors (size of tumor, duration of primary disease) will also be used in multiple analyses of the variance.

The primary effectiveness endpoint will include a statistically significant improvement in the AZ Bio sentences and CNC word recognition scores (in quiet) at the 12 month testing interval compared to the 6 month interval in the implanted ear. The secondary effectiveness endpoint will include significant device benefit for detection of sounds defined as a detection of sounds greater than 50% correct on correctly localizing location of the sound in space when listening through the implant at the 12 month testing interval.

The primary safety endpoint will be defined as the number and proportion of participants experiencing an adverse event, defined as any medical/surgical (i.e. explant due to infection, chronic dizziness) at the conclusion of the study. The secondary safety endpoint will be defined as the number and proportion of participants experiencing any adverse device events (i.e any open/short circuits, facial nerve tingling during stimulation) at the conclusion of the study.

H. Device Description

Cochlear implants (CIs) electronically process sound and transmit information to the auditory nerve, allowing dramatically improved perception of speech and environmental sounds for many individuals with severe to profound hearing loss. Approved by the United States Food and Drug Administration (FDA) in the 1980's, CIs have become widely used. For patients with sporadic vestibular schwannomas or neurofibromatosis Type 2 (NF2), an autosomal dominant condition prone to development of vestibular schwannomas, cochlear implantation is often performed as a separate surgery following tumor resection if there is preservation of the cochlear nerve (i.e., cranial nerve 8). Cochlear implants consist of an internal component, the receiver-stimulator, which receives a signal from the externally-worn, magnetically attracted head piece, and transduces this into an electrical signal delivered via an electrode inserted directly into the cochlea to interface with the cochlear hair cells and the spiral ganglion.

For this study all subjects will be implanted with an Advanced Bionics HiRes Ultra cochlear implant device for the internal portion. Subjects will also receive an Advanced Bionics Naida Kit which will include the Naida CIQ90 sound processor, 1 universal head piece (UHP), 1 UHP color cap, 1 T-mic, 1 charger, 1 power supply, 1 carrying case, 1 Dry 'n store, 1 brick, and 1 backpack.

I. Monitoring Procedures

The risks involved in cochlear implantation are not beyond the risks normally encountered in the intraoperative or postoperative course for vestibular schwannoma surgery or labryinthectomy for Meniere's disease, which all study participants will be undergoing. Standard intraoperative precautions and safety monitoring including, but not limited to nerve integrity monitoring and time outs, will be performed as per routine.

An Adverse Event will be considered any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with the use of the medicinal device, whether or not a causal relationship with the product has been established. Clinically significant laboratory abnormalities may be considered AEs if deemed appropriate by the Investigator. Worsening of a pre-existing

condition is also considered an AE as is the discovery of an abnormal finding during physical exam that was not included in the medical history.

Subjects will be encouraged to spontaneously report any AE. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented. All adverse events occurring after the initiation of the study treatment (treatment emergent adverse events) will be reported, including events present at baseline that worsened during the study.

Additionally, any serious adverse event considered by an investigator to be possibly, probably, or definitely related to the investigational device that is brought to the attention of the investigator at any time will be reported immediately to the IRB.

The Data and Safety Monitoring Board (DSMB) within the Clinical Trials Office at The Ohio State University Comprehensive Cancer Center (OSUCCC), will serve as the independent data and safety monitoring board for this study. The DSMB will meet quarterly to review progress of the study and will be available for emergent meetings if serious or unanticipated adverse events occur. The serious adverse events and responses will be reviewed by the DSMB.

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