1. General Information / Title Page

Title: Intratympanic Steroid Injection for Treatment of Idiopathic Facial Nerve Paralysis

Working Title: Facial Nerve Study

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Sponsor: *None*

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The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s). 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 IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to the IRB and the sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others. This trial will be performed in compliance with the protocol, GCP, and all regulatory requirements.

2. Schedule of Events

Recruitment of trial subjects will begin as soon as authorization is granted by the IRB. Clinic and emergency department patterns indicate that we can expect to identify and enroll 20- 25 participants per year. The goal of the study is to include 90 participants over the course of *four years* and follow until full facial nerve function is recovered or up to 12 months after the completion of treatment, whichever comes first. The expected length of the entire study will vary depending on when all subjects are identified and treatment is completed.
After obtaining consent, the study participant will undergo a complete history, head, neck, and cranial nerve exam. Facial function will be evaluated with House-Brackmann (H-B) scoring system. For participants with a high suspicion of Lyme disease based on history, Lyme disease serology will be drawn. Electroneurography (ENoG) and electromyography (EMG) testing will be performed on patients with complete facial nerve paralysis. Every participant will be treated with oral steroids (prednisone 60 mg for 5 days followed by a 5 day taper), unless they are unable to for medical reasons.
The study participants will then be randomized into the control group or the treatment group. If randomized to the treatment group, the patient will undergo one intratympanic steroid injection every 3-4 days over the course of 3 weeks for a total of 3 injections. A third group of patients will include those patients that are unable to take oral steroids for medical reasons (such as diabetes); these patients will only receive the intratympanic injection. An audiogram and tympanography testing will be performed on patients that are randomized to receive an intratympanic injection (Group 2) or are placed in Group 3 for medical reasons.

3. Abbreviations

All abbreviations will be defined in parenthesis following their first occurrence in the text.

4. Background Information

Facial nerve paralysis is due to inflammation surrounding the facial nerve. Current clinical practice guidelines for treatment of facial nerve paralysis recommend a 10 day course of oral steroids +/- oral acyclovir. Treatment should begin within 72 hours of symptom onset. In patients with complete facial paralysis, electrodiagnostic testing should be offered to the patient (1-2). In patients with 90% degeneration on electroneuronography (ENoG) testing, facial nerve decompression may be considered but is not a current recommendation.
In 1973, Bryant reported on ten cases where intratympanic steroid injection was used for the treatment of Bell's palsy (3). All but one of these patients had complete recovery of their facial nerve function. The remaining patient had 75% recovery. None of these patients suffered complications from the injections. The next study published on intratympanic steroid injection

for Bell's palsy was not published until 2014 (4). It was a randomized control trial that divided patients into standard treatment (oral steroids and acyclovir) versus standard treatment with intratympanic steroid injection. There was not a statistically significant difference between the complete recovery rate of the control group and of the intratympanic steroid group; however, the time to recovery was significantly shorter in the intratympanic steroid injection group as compared to the control group. Limitations of this study include small sample size and high attrition rate.
There have not been any other studies published in the literature looking at improving facial nerve recovery in idiopathic facial nerve paralysis with the use of intratympanic steroid injections.

5. Trial Objectives and Purpose

The question proposed by this study are:
Does intratympanic steroid injection improve the complete recovery rate of patients with idiopathic facial nerve paralysis?
Does intratympanic steroid injection hasten the time to recovery in patients with idiopathic facial nerve paralysis?
Are there significantly more adverse effects with the use of intratympanic steroid injection as compared to oral steroids in patients with idiopathic facial nerve paralysis?

The trial seeks to provide evidence that intratympanic steroid injection are acceptable and successful adjuncts to treatment of idiopathic facial nerve paralysis.

To answer this question, a prospective, single-blinded, randomized trial will be performed. The subjects will be randomized into the treatment group and the control group. The control group will receive oral steroids which is the current standard of care. Patients in the treatment group will receive oral steroids AND intratympanic steroid injections. The patient's will not be blinded because the patient will be undergoing an in-office procedure. It has been found to be unethical to perform sham procedures in patients. A third group of patients will consist of those patients that are unable to take oral steroids for medical reasons. These patients will only receive the intratympanic injection and they are placed in this group for medical reasons only (no randomization into this group). The patients will be examined and scored using House-Brackmann scoring system by a blinded investigator trained in otolaryngology.

6. Trial Design

Design:
Prospective, randomized, single-blinded clinical trial

End Points:
Complete recovery of facial nerve function
Time to complete recovery of facial nerve function
Improvement of facial nerve function within 3 weeks
Time to initial improvement of facial nerve function
Adverse effects related to the treatment

Methodology:
Screening
Patients age 18-99 will be identified in clinic as having an acute facial nerve paralysis of H-B IV or greater. Symptoms must have developed within a 72 hour period and be present for the last 21 days or less.

Baseline assessment
Patients who meet criteria will undergo a complete history, head, neck, and cranial nerve exam. Facial function will be evaluated with H-B scoring system. In patients where there is a suspicion of Lyme disease, Lyme disease serology will be performed. Electroneurography (ENoG) and electromyography (EMG) testing will be performed on patients with complete paralysis only.

Treatment Phase
Participants in groups 1 & 2 will be treated with steroids (prednisone 60 mg for 5 days followed by a 5 day taper). Patients will then be randomized into either control group (Group 1) or treatment group (Group 2). Patients in Group 2 will undergo intratympanic steroid injection. An audiogram and tympanography testing will be performed prior to injections.

Participants unable to take oral steroids for medical reasons (such as diabetes) will be placed in Group 3. These participants will receive intratympanic steroid injections only. An audiogram and tympanography testing will be performed prior to injections.

Injection will be up to 1cc of dexamethasone 24mg/mL. The procedure will be performed at supine position under a microscope. Local anesthesia will be achieved with topical phenol. A myringotomy will be made in the tympanic membrane. A 1 mL syringe connected to a needle will be used to slowly inject between 0.2 cc and 1.0 cc of solution through the myringotomy, with the subject's head turned 45 degrees to the opposite side. The subject will be asked to maintain positioning for at least 30 minutes and refrain from swallowing. The dose administered will vary due to subject-specific factors.

Follow-Up
Patients will be evaluated once a week for the first month after completion of treatment. From that point, patients will be evaluated monthly until complete recovery.

Procedures:
Participants are identified in clinic to have idiopathic facial nerve paralysis. If they meet inclusion criteria, they will then be asked to participate in the study and sign the consent form. Participants will undergo a complete medical history including facial nerve paralysis history, head, neck, and cranial nerve exam. Facial function will be evaluated with H-B scoring system. Lyme disease serology will be drawn on patients for which there is a suspicion of Lyme disease (SOC). Electroneurography (ENoG) and electromyography (EMG) testing will be performed only on patients with complete paralysis, as part of the standard of care (SOC) work-up. Next, patients in Groups 1 & 2 will be prescribed a course of oral prednisone. They will be randomized to Group 1 or Group 2. If randomized to Group 1, patient will come back weekly for a month for evaluation of facial nerve function. If randomized to Group 2 or placed into Group 3, patients will undergo an audiogram and tympanometry testing, which is SOC prior to any intratympanic injection. Patients will undergo intratympanic steroid injection to affected side after all details and risks of each procedure are discussed. There will be one injection every 3-7 days over the course of 3 weeks for a total of 3 injections. Follow-up will be once a week for the first month after the completion of treatment. From that point, patients will be evaluated monthly. All patients Group 2 & 3 will undergo a post-procedure audiogram and tympanogram approximately 1 month following the 3rd injection, which is SOC. Follow-up will be completed once full facial nerve recovery to H-B I or for up to one year, whichever comes first. At each clinic visit patients will undergo a complete head and neck exam, including H-B score. Extensive review of systems will be completed at every visit. Facial nerve exams will be video recorded pre-treatment and all post-treatment follow-up visits to allow for 2 independent blinded reviewers to determine facial nerve recovery and H-B score; a third unblinded review will be performed by the treating physician.

Adverse effects of the treatment will be assessed at each visit.

7. Selection and Withdrawal of Subjects

Inclusion Criteria:

1. 18 to 99 years
2. English as primary language
3. Acute unilateral facial palsy without skin lesions which developed within a 72-hour period and is present for 21 days or less.
4. Moderate to severe facial palsy [House-Brackmann grade IV or greater]

Exclusion Criteria:

1. Another cause of facial nerve paralysis that is not idiopathic
2. Otologic disease including otitis media, temporal bone fracture, a previous history of facial nerve palsy in either side, history of otologic surgery, and suspected Ramsay Hunt syndrome.
3. Systemic disease including history of tuberculosis, history of head and neck cancer, other neurological disorders, recent use of ototoxic medications, liver or renal dysfunction, and other illnesses that would contraindicate the use of high-dose steroid therapy.
4. Pregnancy

Withdrawal Criteria:
Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules or adverse events. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the case report form.

8. Treatment of Subjects

Participants in Groups 1 & 2 will be treated with steroids (prednisone 60 mg for 5 days followed by 5 day taper) as defined by the current standard of care. Patients in Group 1 will not have any further treatment. Patients in Group 2 & 3 will undergo intratympanic steroid injection. The patient will undergo one injection every 3-7 days over the course of 3 weeks for a total of 3 injections.

9. Costs

Participants will not be paid to be a part of the study. Subjects will be responsible for the normal cost of treatment associated with facial nerve paralysis, including any tests that the physician feels are necessary and all medications. Subjects who are randomized to one of the groups to receive the intratympanic injections will not be responsible for the added costs of the injection (which include the medication and phenol), the audiogram and tympanometry, and extra office visits to receive each injection.

10. Assessment of Efficacy

Efficacy of the treatment will be assessed by measuring facial nerve function using the H-B scale I-VI. Two blinded trained otolaryngologist or mid-level provider trained in otolaryngology will determine the efficacy by evaluating each individual study subject via video recording.

10. Assessment of Safety

Risks of intratympanic steroid injections include pain, bleeding, vertigo, otitis media, and tympanic membrane perforation.

The presence or absence of tympanic membrane perforation will be documented at 14 days and 1 month post-treatment. If a perforation is present, the extent of the perforation, type of treatment, and when resolved will be recorded.

All adverse events will be reported to the IRB and the Otolaryngology Department Quality Assurance. Admission of a trial participant to an emergency room or hospital will be recorded.

11. Statistics

A sample calculation was performed for the number of subjects to be enrolled in order to prove superiority of oral steroids + intratympanic steroids over oral steroids alone. The assumption was made that a 20% increase in primary outcome of complete recovery would be significant. A sample size of 25 subjects should detect a difference at a power greater than 80% and an alpha of 0.05. To account for potential testing or data collection errors, we will collect data on 30 subjects treated with oral steroids and intratympanic steroid injections, as well as 30 controls treated with oral steroids only, for a total of 60 subjects. Data will be collected on up to 30 additional subjects that are placed into Group 3 for medical reasons; therefore total number of subjects to be recruited is 90.

12. Direct Access to Source Data/Documents

The investigators will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

13. Quality Control and Quality Assurance

The integrity of the data collected will be maintained by the randomization of trial subjects to their groups (*control vs. treatment)*. All subjects are being treated using standard protocols. Even though participants will not be fully blinded, the data collected is reliable because it is randomized and objective measures will be obtained. Objective measures for this study include complete recovery of facial nerve function, time to complete recovery of facial nerve function, improvement of facial nerve function within 3 weeks, and time to initial improvement of facial nerve function. The University's biostatistics group can view any data collected prior to publication.

14. Ethics

A randomized study involving the adult population is subject to ethical as well as scientific considerations. The patients will not be blinded because it is unethical to perform a sham procedure. HIPAA guidelines will be followed in order to protect the privacy of study participants. The Otolaryngology community stands to benefit significantly from this study, as results will potentially yield information which will be used to improve outcomes of patients with facial nerve paralysis as this can be a debilitating disease process.

15. References

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