OREGON HEALTH & SCIENCE UNIVERSITY

TITLE: Pilot clinical trial to study facial electrical stimulation to promote recovery in patients with Bell's palsy

DATE: 08/18/2017

NCT#:03836989

Protocol

1. Protocol Title

Pilot study of facial electrical stimulation to promote recovery in patients with facial paralysis from Bell's palsy

2. Objectives

PURPOSE: The primary goal of this pilot study is to collect preliminary data and optimize operations for a full-scale randomized controlled trial of electrical stimulation for the treatment of acute facial paralysis caused by Bells palsy at Oregon Health and Science University (OHSU).

In this study, patients with Bell's palsy and features suggesting they will have a poor recovery will receive either usual standard of care treatment, with medication and physical therapy and two different forms of electrical stimulation. Research subjects can receive either sensory stimulation (higher voltage that they can feel) or subsensory stimulation (minimal voltage that they cannot feel) after training by a physical therapist. We intend to recruit 40 patients for this study and to follow them for 3 months.

SPECIFIC AIMS:

AIM 1- To estimate the impact of 3 months of 15 minutes/day of home facial electrical stimulation on recovery of facial symmetry in patients with Bells palsy and poor prognostic factors for recovery as measured by objective photography.

We hypothesize that patients receiving sensory electrical stimulation will have better symmetry at rest and during facial expressions.

AIM 2- To estimate the impact of 3 months of 15 minutes/day of home facial electrical stimulation on recovery and quality of life in patients with Bells palsy and poor prognostic factors for recovery as measured by patient reported outcomes.

We hypothesize that patients receiving sensory electrical stimulation will have better self reported quality of life.

AIM 3-To estimate adherence and tolerability to a 3-month PT-instructed daily 15 minute home program of facial electrical stimulation in patients with Bells palsy and poor prognostic factors for recovery.

We hypothesize that there will be good adherence and tolerance of facial electrical stimulation when taught by an experienced physical therapist. Patients with facial paralysis are highly motivated to improve their probability of recovery.

PRIMARY ENDPOINTS

Primary outcome will be the proportion of patients with complete recovery at one, two, and three months post enrolment as judged by objective photography during facial expression by blinded evaluators.

SECONDARY ENDPOINTS

Secondary outcomes will be collected at one, two, and three months. There will be an additional 6 month post enrolment interview.

Secondary endpoints will include patient reported quality of life questionnaires, tolerability and adherence questionnaires, and time to complete recovery.

3. Background

Patients with facial paralysis experience weakness and drooping of the face. Bell's palsy is the most common form of facial paralysis with an incidence of 1 in 60 people in a lifetime (Holland NJ and Bersetin JM 2014). The drooping face has significant functional and physiological consequences to patients. Patients with eyebrow drooping have blockage of their vision, lose their ability to fully close and protect the affected eye, experience nasal obstruction, have difficulty with speech articulation, often drool, and have difficulty producing a smile that conveys their true emotions. Although most patients are expected to recover, up to 29% of patients with Bell's palsy experience life-long residual muscle weakness, involuntary contractions, spasms and unintentional movements that occur simultaneous with intentional movement (synkinesis) (Peitersen 2004). Facial paralysis affects young adults with a peak incidence in patients between the ages of 15 and 40 years resulting in many years lived with these sequelae. Social interactions and conveyance of emotions are extremely challenging for patients with facial paralysis who often experience isolation and depression (Nellis et al 2016).

The patient shown in Figure 1 has synkinesis and poor facial coordination after Bell's palsy. In the photo she is attempting to smile. She cannot symmetrically move her mouth, and her neck muscles show uncoordinated contractions on the affected side.

Figure 1- Patient with Bell's palsy attempting to smile. Her face is strained, and it is difficult for her to produce a meaningful smile. She is unable to symmetrically move her mouth, and her neck muscles show inappropriate and uncoordinated contractions on the affected side.

Electrical stimulation of the face could potentially reduce these sequelae. Electrical stimulation is thought to lead to selectivity in the regeneration of motor nerves and decreased muscle atrophy. Selectivity means the nerves regrow and innervate a specific muscle, as opposed to nerves that regrow aberrantly and innervate several muscles making fine control of movement difficult and spasms more likely to occur. By stimulating muscles deprived of electrical nerve input, atrophy is prevented and potentially muscles are more receptive to reinnervation. The theoretical benefits of electrical stimulation have been discussed extensively and replicated in laboratories, but the challenges have been in successfully incorporating electrical stimulation into the clinical setting. As our efforts in the clinic continue, our understanding of electrical stimulation has continued to improve. Successful examples of the use of electrical stimulation in other parts of the body are emerging. Gordon et al. used electrical stimulation acutely after injury to the median nerve for carpal tunnel syndrome patients with substantial axonal loss. Accelerated recovery was seen in this randomized controlled trial (Gordon et al. 2009). Electrical stimulation is also used to accelerate nerve re-growth after facial nerve reparative surgery in animal models when a nerve transection is being treated (Huang et al 2009, Hadlock et al 2010).

Five published clinical trials have examined electrical stimulation of the face during acute Bell's palsy (Tuncay et al. 2015, Alakram et al. 2010, Manikandan et al. 2006, Flores et al. 1998 and Mosforth and Taverner 1958). Two trials reported mild benefit from electrical therapy (Tuncay et al. 2015 and Manikandan et al. 2006), while the rest showed no difference in recovery. Worse recovery with electrical stimulation has not been reported. Given the design of the trials, the effect of electrical stimulation on the face could be underestimated. Patient selection in prior studies is a concern. Often patients with incomplete paralysis are the only patients included in the study, although 94% of patients with incomplete paralysis are expected to recover completely, in contrast to 61% of patients with complete paralysis (Peitersen 2004, Tuncay et al. 2015). Patients with complete paralysis who could

benefit the most are often not included in these studies. The number of patients in the prior trials ranges from 16 to 149, hence the some studies could be underpowered. The length of therapy in some of the studies could be insufficient to see an effect. For example, Alakram et al. only treated patients for 30 minutes weekly for 3 months and Manikandan et al. only treated patients for three times per week, for two total weeks. In severe cases of Bell's palsy, recovery may not begin for many months, making two weeks of electrical therapy potentially insufficient. Outcome assessment could be improved upon by using blinded objective measurements of standardized photographs at rest and with different facial expressions. Having two evaluators allows for better scrutiny of inter-rater reliability. Only one trial (Tuncay et al. 2015) reported treatment-blinded assessment of outcomes. Past trials have greatly relied on estimation of recovery by investigators using the House Brackmann scales. The House Brackmann scale is a well-established scale first described in 1958. It classified patients into 6 categories of global facial function from normal function to complete paralysis. Facial spasms and synkinesis are not considered in the scale. It is difficult to use this scale to describe intermediate levels of recovery, in which some degree of residual weakness exists. Finally, the time of follow up is an important consideration. Spasms and synkinesis tend to develop six months or longer after initial onset of paralysis in severe cases. Length of follow up in prior studies has averaged three months and often is not reported. We would like to perform a trial that addresses these limitations.

It is important to highlight that most current medical insurance covers electrical stimulation of the face. Electrical stimulation is delivered transcutaneously by placing self-adhesive electrodes on the face. Electrical current is used to produce a visible contraction. The device is easily portable and weighs less than 8 ounces. In general, patients pursue electrical stimulation to the face when recommended by their health care providers or find this resource themselves when frustrated by their poor recovery. The clinical community is divided, with some providers advocating the use of electrical stimulation of the face, while other strongly discourage. Clinicians discouraging electric stimulation site concern for worse outcomes based on their observational experience and one study of the facial nerve of mice (Skouras et al 2009). Evidence for the clinical recommendation of electrical face stimulation is much needed. However, this trial is a low burden intervention consistent with current practice.

4. Study Design

We propose conducting a pilot prospective randomized study for patients with Bell's palsy to receive either standard of care or standard of care plus electrical stimulation to include 30 patients. This would be a feasibility study for a larger study. The trial is described using the PICO Model.

Patients: Acute Bell's palsy with poor prognostic factors

We define acute Bell's and Ramsay Hunt syndrome (described two paragraphs below) as having patients present during their first week of paralysis.

Bell's palsy was defined as idiopathic lower motor neuron facial paralysis with absence of other central nervous system symptoms.

Poor prognostic factors for Bell's palsy defined by meeting **any** of the following factors:

- Complete paralysis
- Age > 60 years of age
- Ramsay Hunt

Patients with incomplete paralysis experience complete recovery 94% of time, while patients with complete paralysis only experience complete recovery 61% of time (OR 17.4 $P<0.05$). Complete paralysis affects 15% of patients with Bell's palsy. Patients over the age of 60 only experience complete recovery one-third of the time (Peitersen 2004 and Ikeda et al. 2004).

Exclusion criteria:

- Patients younger than 18 years of age
- Allergy to adhesive
- Non English speakers
- Patient with a deep brain stimulator or a pacemaker
- Patients who do not complete standard of care therapy with steroid therapy or patients who are determined to have a different etiology to explain their facial paralysis will not exit the intervention. We will continue to monitor and analyze separately in post hoc analysis.

Pregnancy, diabetes, and recurrent attacks of facial paralysis will not be considered exclusion criteria. These variables have been identified by some studies as negative prognostic factors (Peitersen 2004 and Navarrette et al. 2001) but not all studies confirm these factors as affecting prognosis (Fuijiwara et al. 2014). Pregnant women will be included in the analysis as the incidence of Bell's palsy is higher in pregnancy (Peitersen 2004). A separate post hoc analysis will be done analyzing these variables.

Patients will be identified for study eligibility through diagnosis billingcodes used at emergency room or urgent care and primary care doctor appointments at OHSU using EPIC reporting workbench (RWB). During a preliminary search of medical charts for cohort discovery, 350 patients were seen at OHSU for facial paralysis last year. 15% of these patients are expected to meet the criteria for complete facial paralysis (n=53 patients). Additional patients will be eligible based on the age risk factor (age greater than 60 years). We hypothesize we will be able to recruit 15 patients into each treatment arm in less than one year (total study members of 30). Emails and flyers will be used to raise awareness of the study at OHSU, community hospitals, and affiliated clinics. We will track how many patients were contacted for study participation, how many met inclusion criteria and how many chose not to participate and why.

A research assistant will contact the patients for recruitment. The PI will place a referral to physical therapy (under a telephone encounter).

Intervention: Electrical stimulation
Patients will be randomized to either electric stimulation or placebo.
Plan to use a monophasic waveform having 100microsec pulse rate, at a pulse rate of 35 Hz to voltage that generates twitch contraction or if the research subject can tolerate the voltage needed for a contraction then as high as tolerated. These parameters are taken from clinical trial showing improvement in patients with carpal tunnel (Gordon et al 2009). Electrical stimulation will be produced with the ortho 3 stim which has passes the inspection by the rehabilitation facility for use. The cathode will be placed over the ipsilateral facial muscle to stimulate and the anode behind the ipsilateral ear. All devices are noninvasive without any skin puncture.
Muscles stimulated were:

1) Frontalis (FM) to produce brow elevation
2) Orbicularis oculi (OOc) to produce eyelid closure
3) Zygomaticus major muscle (ZMM) to produce elevation of the oral commissure superiorly and posteriorly
4) Orbicularis oris (OOr) to produce lip pursing

Patients are asked to mimic the movements produced by electrical stimulation voluntarily on the non-paralyzed side of the face in front of a mirror during therapy. Electrical stimulation is performed concurrently with facial exercises and mirror therapy. Initially, electrical stimulation is performed with a therapist twice before transitioning to home patient-driven electrical stimulation (duration of first

appointment is 40 minutes). Ten contractions of each muscle group will be performed. A hand out will be provided for patients to take home and review the instructions on how to perform home electrical stimulation.
Home electrical stimulation is to be performed for 12 minutes daily (3 mins per muscle). Compliance is defined as performing the electrical stimulation 5 of 7 days of the week.

Duration of therapy: Therapy is to start during the first week of onset of facial paralysis and be used daily for three months or sooner until complete recovery is achieved, as judged by study personnel.
The design for electrical stimulation was derived from review of the literature and from focus groups with two physical therapists that treat facial paralysis. OHSU has a physical therapist, Margaret McReynolds, who is trained in electrical stimulation of the face and has been providing electrical stimulation for patients being treated at OHSU. Margaret McReynolds will be a collaborator in this trial.

The physical therapist will meet with patients twice. The first session will be 1 hr and will include evaluation and treatment showing patients how to use the electric stimulation machine. The second session will only be 30 min and will be 1 to 2 weeks after the first session. During the second session the participants will demonstrate how they perform electric stimulation.

Comparison: Subsensory electrical stimulation

The electric stimulation device has a placebo setting that delivers minimal electricity.
The settings will be the same as the intervention, the voltage will be below the earliest point at which patients feel the electricity.
The patient and physical therapist will not be blinded. The rest of the research team will be blinded.

All patients will receive steroids (prednisolone 25mg by mouth twice daily, or an equivalent regimen) and Ramsay Hunt syndrome patients should receive antivirals at standard doses (acyclovir 200mg five times a day) (Sullivan et al. 2007).

Outcome:
Primary outcome: Proportion of patients with complete recovery at one, two, and three months
Complete recovery is defined as symmetry at rest and symmetry during movement without evidence of synkinesis.
To evaluate for complete recovery, standardized photos of patients at rest, and during movement, will be evaluated by three treatment-blinded otolaryngologists. Recovery will be measured using the eFACES assessment with is a clinician-graded electronic assessment with high inter-rater reliability.
The photos will be standardized as follows:

1) Frontal face photo at rest
2) Frontal face photo with strong eyelid closure (which shows midface, chin and neck synkinesis)
3) Frontal face photo with strong smile (which shows periocular synkinesis and oral commissure movement)

Secondary outcomes:

1) House Brackmann scale scoring will be determined by the three otolaryngologists, reported as an average of their three scores after evaluating the three photos mentioned in the primary outcome.
2) Patient reported, facial nerve specific, validated quality of life questionnaires:
    a. FaCE scale (Khan et al. 2001) measured facial movement, facial comfort, oral function, eye comfort, lacrimal control, and social function.

b. Synkinesis Assessment Questionnaire (Mehta et al. 2007)

3) Objective measurements of facial symmetry at rest and with facial expression as measured by MEEI FACE-gram program.
    a. Reporting palpebral fissure width and corner of the mouth symmetry at rest
    b. Reporting brow elevation while raising the eyebrow
    c. Reporting commissure excursion during smile
4) Patient satisfaction and treatment tolerability will be reported at three-month intervals by patients using a Likert scale. Tolerability is rated as: very easily tolerated, easily tolerated, moderately tolerated, hardly tolerated, and not tolerated at all.
5) Patient reported treatment adherence through use of a diary and patient self-reporting at the three-month mark.
    a. Use tracking on the device to collect actual use time with date and time used
    b. Likert scale to report how frequently did the patient perform the electrical therapy: not at all, a little, rather regularly, very regularly, and as advised
6) Time to complete recovery
7) A standardized telephone interview will be conducted at six-month follow-up to evaluate any further progress and repeat patient reported questionnaires.

5. Study Population

a. Number of Subjects

Subjects planned to be included: 30 patients total with Bell's palsy (15 patients per treatment arm).

During a preliminary search of medical charts for cohort discovery, 350 patients were seen at OHSU for facial paralysis in 2016. We expect 15% of these patients are expected to meet the criteria for complete paralysis (n=53 patients) and additional patients will meet eligibility due to old age greater than 60 years. We believe we will be able to recruit the target number of 15 patients per group in less than a year.

b. Inclusion and Exclusion Criteria

Screening for eligibility

Patients will be identified for study eligibility through CPT billing diagnosis codes used at emergency room or urgent care and primary care doctor appointments at OHSU using EPIC reporting workbench (RWB). Patients with a diagnosis of Bell's will be reported to the researchers of the study, researchers will use EPIC to identify the contact information of the patient to conduct a telephone interview for screening and to check that patients are over 18 years of age.

A standardized screening telephone interview form is attached. During the interview patients are asked if they are over 60 or if they have complete paralysis. Either of these conditions makes the eligible to participate. If the patients do not have complete paralysis, the telephone interview will ask if they can contact them again in 3 to 5 days to see if the paralysis has worsened and they have developed complete paralysis and are now eligible to participate in the study (Both telephone interviews are included in the same file).

Emails and flyers will be used to raise awareness of the study at OHSU, community hospitals, and affiliated clinics.

We will track how many patients were contacted for study participation, how many met inclusion criteria, and how many chose not to participate and why. A screening database Excel file has been included with this application. The database will be kept under password protection at an OHSU computer and will only be accessed by researchers. The database will help prevent patients from being contacted multiple times to participate (EPIC reporting might not be able to differentiate old from new diagnosis). The data will also be evaluated to improve any future trials.

Inclusion and exclusion criteria

We define acute Bell's as having patients present during their first week of paralysis.
Bell's palsy was defined as idiopathic lower motor neuron facial paralysis with absence of other central nervous system symptoms.
Poor prognostic factors for Bell's palsy defined by meeting **any** of the following factors:

- Complete paralysis
- Age > 60 years of age
- Ramsey Hunt

Exclusion criteria:

- Patients younger than 18 years of age
- Allergy to adhesives
- Non English speakers
- Patients with a deep brain stimulator or a pacemaker
- Patients who do not complete standard of care therapy with steroid therapy or patients who are determined to have a different etiology to explain their facial paralysis will not exit the intervention. We will continue to monitor and analyze separately in post hoc analysis.

Pregnancy, diabetes, and recurrent attacks of facial paralysis will not be considered exclusion criteria. These variables have been identified by some studies as negative prognostic factors (Peitersen 2004 and Navarrette et al. 2001 and Philips et al. Onset of bell's palsy in late pregnancy and early puerperium is associated with worse long-term outcomes. Laryngoscope 2017) but not all studies confirm these factors as affecting prognosis (Fuijiwara et al. 2014). Pregnant women will be included in the analysis as the incidence of Bell's palsy is higher in pregnancy. Bell's palsy is three times more likely in pregnant patients than in the regular population (Peitersen 2004). A separate post hoc analysis will be done analyzing these variables.

c. Vulnerable Populations

- *Pregnant women will be included in the study*
- *No other vulnerable populations will be included in the study*

We consider including pregnant women important given that the incidence of Bell's palsy is higher in pregnancy. Bell's palsy is three times more likely in pregnant patients than in the regular population and in some studies pregnancy has been identified as a risk factor for worse outcomes (Peitersen 2004). A separate post hoc analysis will be done analyzing these variables.

d. Setting

Patient recruitment will take place at OHS. There will be an initial screening telephone interview.

All patients will receive two physical therapy appointments. Physical therapy (PT) will be at the rehabilitation center at in the CHH at OHSU with Margaret McReynold. The patients will be instructed in how to perform electric stimulation at home during these PT appointments.

Patient assessments will have an initial assessment prior to therapy initiation with follow up assessments at 1 month, 2 months and 3 months will take place at OHSU. The offices are also at CHH in the 5th floor where the division of facial plastic and reconstructive surgery is located.
A 6 month final assessment will be a telephone interview.

All data analysis will take place at OHSU.

e. Recruitment Methods

This study will use an Epic BestPractice Advisory (BPA) to recruit potential participants. Researchers will work with ITG to identify potential participants based upon the above eligibility criteria. Researchers will provide the list of inclusion and exclusion criteria and ITG will build the BPA in Epic based on these criteria.

During a clinical interaction in Epic, if a patient meets the criteria built into the BPA, an Epic In Basket message will be sent to the study contact containing a link to the patient's medical record. Study staff will contact identified patients to determine if they are interested in participating in the study. Once the BPA has identified a patient, it will not fire again for that same patient.

Epic records for patients identified through the Epic BPA will be queried for eligibility and will be contacted by study personnel about the study.

Emails and flyers will be used to raise awareness of the study at the OHSU main campus, and OHSU affiliated clinics. A research advertising flyer form and the blast email format is included in this application.

A telephone interview will be used to screen for eligibility. A recruitment telephone interview is included in this application. If the patient does not meet inclusion criteria during the phone call, there is still the possibility that their condition will worsen and they might develop complete paralysis and become eligible for the study. We will leave of contact information for the patients to reach out to use if complete paralysis does develop and ask if we can call at 1 week to follow up for eligibility. This is described in the recruitment telephone interview.

We will track how many patients were contacted for study participation, how many met inclusion criteria and how many did not including age and if they had complete paralysis or not and how many chose not to participate and why. A data collection form for the initial screening is attached.

Participants who are unable to comute to OHSU will be offerd the opportunity to use telemedicine with Cisco meeting.

Subjects will be paid during their outcome visits and during their physical appointment visits. There are a total of 4 outcome visit per patient: initial assessment and 3 follows ups (1,2 and 3 months). Each assessment patients will receive $50 dll. All patients will also complete 2 physical therapy appointments. All patients will be paid equality. Payment for physical therapy appointment will be $30 dll per session. Therapy sessions that are not placebo will be billed to medical insurance. Payment will be made via gift cards.

f. Consent Process

Consent will take place during the first appointment with the research team.

There will be two meetings with physical therapist to learn how to do therapy. Additional follow up happens once a month for 3 months.

The researcher will be conscientious to minimize undue influence.

To ensure understanding, the researcher will explain the project and a copy of the consent will be given to patients.

Non-English Speaking Subjects

- *Non- English speaking subjects will not be included in the study*

6. Procedures Involved

This is a randomized study for electric stimulation. Half of the patients will not receive electric stimulation. All patients will have a total of 6 visits that are detailed below (table). The first visit is a screening. The next two visits are with physical therapist to learn rehabilitation exercises and possibly electric stimulation. The next three visits are three follow up appointments to check on

If chosen to receive electric stimulation, subjects will use **electric stimulation at home for 15 min per day until you recover or for 3 months**. We will provide the equipment. The FDA approves the use of electric muscle stimulation.

	Visit 1 Day 1	Visit 2 Week 1	Visit 3 Week 2	Visit 4 Month 1	Visit 5 Month 2	Visit 6 Month 3	Phone call Month 6

Consent Discussion	X						
Physical therapy		X	X				
Photography	X			X	X	X	
Questionnaires	X			X	X	X	X
Total time	1 hour	1 hour	1 hour	30 minutes	30 minutes	30 minutes	20 minutes
Payment	$50	$30	$30	$50	$50	$50	$0

The quality of life questionnaires we will collect are called the SF-12, FaCE scale and Synkinesis Assessment Questionnaire. These questionnaires ask you about your own quality of life in relation to facial movement and facial spasms. It will take 20 minutes for you to fill both questionnaires. Additional questions about your general health will be asked at the consent and the follow up visits and if you are in the electric stimulation we will ask about tolerability and satisfaction. The FaCE scale, synkinesis assessment questionnaire, the initial screening questionnaire, the follow up questionnaires, and the electric stimulation satisfaction and tolerability forms are all uploaded with this application.

During this study we will obtain facial photographs at various facial expressions. A photo at rest, one with brow elevation, one with eye closure and another one with a smile will be takes. We expect it will take 10 minutes to take the photographs.

Total participation in the study is 3 months. We will also call you at 6 months for a telephone interview. The 6 month interview form is uploaded in this application as well.

To prevent loss of confidentiality, all of the information and photographs collected will be stored under password protected computer at OHSU and only study personnel will have access to these data. The data will be de-identify as early as possible.

If a subject withdraws from electric stimulation intervention, we will continue data collection.

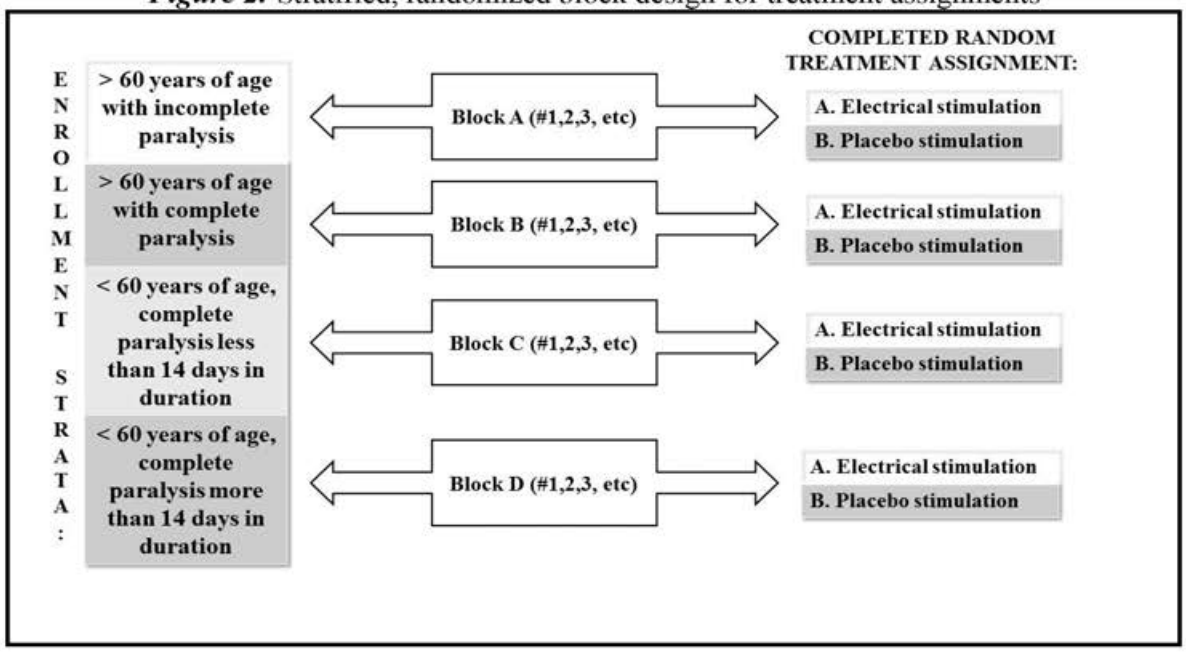
Physical therapy is part of routine Bell's palsy care. Physical therapy would be performed or used even if a subject was not in this study. The costs for these services or items will be billed to your insurance.

Block Randomization for Treatment Assignment

We will use stratified, randomized block design to randomly assign study participants into either treatment or control groups with a 1:1 ratio. Four strata will be utilized based on study participant disease status at enrollment: 1) > 60 years of age with incomplete paralysis, 2) > 60 of age with complete paralysis, 3) complete paralysis (≤ 60 years of age), less than 14 days in duration, and 4) complete paralysis (≤ 60 years of age),P greater than 14 days in duration (***Figure 2***). Study patients providing informed consent, meeting inclusion and exclusion criteria, will be assigned and evaluated in a single-blind fashion (i.e.research staff blinded but the patients and the physical therapist will be un-blinded). Due to the relatively small sample size (~20 patients for each treatment) and the number of

strata, we will utilize a minimum block size of 2 within each strata to minimize potential imbalances in treatment assignments. All block assignments will be completed to avoid treatment bias and provide even, but potentially unbalanced, numbers of enrollment subjects per strata.

Figure 2: Stratified, randomized block design for treatment assignments



7. Data and Specimens

a. Handling of Data and Specimens

All data and photos will be stored at OHSU computers under password protection.
Only research study members will collect and store information. Only study members will have access to the data for analysis.

b. Sharing of Results with Subjects

Results will not be shared with the subjects

c. Data and Specimen Banking

Data from surveys will be stored using a REDCap database.

8. Data Analysis

Please note Jess Mace, MPH, CCRP is a senior research analysis who is a collaborator in this study. We will provide guidance in statistical strategies and perform statistical testing. Results in the group that does receive electric stimulation will be compared to results in the group that did not receive electric stimulation.

Primary outcome: Proportion of patients with complete recovery at one, two, and three months

To evaluate for complete recovery, standardized photographs of patients at rest and during movement will be evaluated by three treatment-blinded otolaryngologists at the conclusion of the study. Recovery will be measured using the eFACES assessment with is a clinician-graded electronic assessment with high inter-rater reliability.
The photos will be standardized as follows: 1) Frontal face photo at rest, 2) frontal face photo with strong eyelid closure (which shows midface, chin and neck synkinesis), 3) frontal face photo with strong smile (which shows periocular synkinesis and oral commissure movement), and 4) brow elevation. The eFACES comes with a training video for the raters to use.

Secondary outcomes:

1. House Brackmann scale scoring will be determined by the three otolaryngologists, reported as an average of their three scores after evaluating the three photos mentioned in the primary outcome.
    a. Wilcox rank sum test will be used to compare House Brackmann results.

2. Patient reported, facial nerve specific, validated quality of life questionnaires:
    a. FaCE scale (Khan et al. 2001) measured facial movement, facial comfort, oral function, eye comfort, lacrimal control, and social function
    b. Synkinesis Assessment Questionnaire (Mehta et al. 2007)
    c. Medical Outcomes Study Short Form-12 (SF-12)
3. Objective measurements of facial symmetry at rest and with facial expression as measured by MEEI FACE-gram program.
    a. Reporting palpebral fissure width and corner of the mouth symmetry at rest
    b. Reporting brow elevation while raising the eyebrow
    c. Reporting commissure excursion during smile
4. Time to complete recovery as judged by researchers (which will be in 1 month intervals)_
5. Patient satisfaction and treatment tolerability will be reported at three-month intervals by patients using a Likert scale. Tolerability is rated as: very easily tolerated, easily tolerated, moderately tolerated, hardly tolerated, and not tolerated at all.
6. Patient reported treatment adherence through use of a diary and patient self-reporting at the three-month mark.
    a. Diary of use which will be handed in monthly
    b. Patient self-reported adherence using a Likert scale. The scale will have the following options for the patient to rate use: not at all, a little (1-2 week), rather regularly (3-5 week), very regularly (5 week on average), and as advised (daily).

Power calculations

When calculating the number of patients to be included in the pilot study, we wanted to have a realistic sample goal. This study is aimed at evaluating feasibility of recruitment and trial implementation. As mentioned earlier, our preliminary chart reviews show 350 patients were seen at OHSU for facial paralysis during 2014. We expect 15% of these patients are expected to meet the criteria for complete paralysis (n=53 patients) and additional patients will meet eligibility due to old age greater than 60 years. We believe we will be able to recruit the target number of 15 patients per group.

From this pilot trial we hope to gain more information on the effect size. Although adverse effects have not been documented in the prior clinical trials, clinicians in the community are still concerned about negative consequences of electrical stimulation that could have been missed by prior trials. In this trial we are aiming at including 15 patients per group for this pilot study, which would detect an adverse effect in 23% of the population with α for Type I error as 0.05 and power at 0.8.

9. Privacy, Confidentiality, and Data Security

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network. Electronic data will be stored on encrypted computers. Access to data/specimens is restricted to study personnel. Access to data requires OHSU ID/password authentication. Data from paper forms will be migrated to REDCap Database.

Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN) The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

Cisco meeting which has been approved for use with PHI will be offered to participants who cannot make the visit. Best practices will be used with the cisco meeting telemedicine.

Three years after the study all data will be destroyed.

Data will not be shared with researchers outside of this study.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

We believe electric stimulation of the face for Bell's palsy offers a minimal risk. It is currently a therapy covered by many insurances for this indications. Five different clinical trials have not reported a negative impact of therapy (the references from these studies are in the risk and benefits section).

Confidentiality breech is a risk and the measures taken to prevent a problem are described above.

11. Risks and Benefits

a. Risks to Subjects

Our hope is to study if electric stimulation decreases these risks, but there is a potential that electric stimulation might worsen these complications.

This study also has the risk of being futile. Electric stimulation may not be effective in helping to treat your disease. This means subjects might spend time in the study and experience side effects that may not provide you with any health-related benefits.

Five published clinical trials have examined electrical stimulation of the face during acute Bell's palsy (Tuncay et al. 2015, Alakram et al. 2010, Manikandan et al. 2006, Flores et al. 1998 and Mosforth and Taverner 1958). Two trials reported mild benefit from electrical therapy (Tuncay et al. 2015 and Manikandan et al. 2006), while the rest showed no difference in recovery. Worse recovery with electrical stimulation has NOT been reported. However, some clinicians discourage electric stimulation because they are concern for worse outcomes based on patients they have treated and animal studied (mice studies) (Skouras et al 2009).

Patients with Bell's palsy can experience residual weakness, facial spasms, inability to coordinate facial movements and unintentional facial movements (for example the eye can close when attempting to smile or the lip can twitch when closing the eye). Patients with Bell's palsy can experience pain and soreness on the side of the face that is paralyzed even if no electric stimulation is used. The complications from Bell's palsy happen even in patients who never receive electric stimulation.

Common side effects of electric stimulation are:

-Mild to moderate discomfort during the 15 min of stimulation.
-Skin redness from the stickers for the electrodes (NO needles are used)
-You might experience skin irritation for the adhesive
-You might experience worse soreness in the face

Investigational protocol for the device: There might be some side effects we do not expect because we are still learning about electric stimulation of the face. Effects of electric stimulation can take weeks to months to be noticeable. The FDA has approved the use of electric muscle stimulation.

Although it is highly unlikely the study will have an adverse effect on pregnancy given that it only affects the muscles being stimulated in the face. However, the following language was added to the consent to emphasize potential unknown risks. *For pregnancy/risk to fetus (For Women):* If you are nursing an infant or you are pregnant now, you can still participate in the study. Pregnant women have a higher risk of Bell's palsy than non-pregnant women and are suspected to have worse recovery than non pregnant women. (Reference: Petersen 2004 Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl.) This study may involve risks not yet known to an embryo, fetus, or nursing infant that are currently unknown. If you are sexually active and could become pregnant, you and your partner(s) can consider using birth control. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

Interviews/questionnaires/QOL assessments that discuss sensitive issues that may cause emotional upset: The questionnaires only revolve around facial paralysis and its consequences.

Loss of confidentiality. Although we are making efforts to protect subject identity, there is a small risk of loss of confidentiality. Photos will never be published with any associated patient identifier. There is a specific optional part of the consent to allow for photo to be used for educational material, publication or marketing. Even though there are confidentiality protections in both Oregon law and federal law, there is still a small chance that you could be harmed if a release occurred.

b. Potential Benefits to Subjects

In this study, patients with poor prognostic factor are being selected for intervention. By selected patients with the worst prognosis we are hoping to see a more dramatic effect. The size of the effect is currently not known. Five published clinical trials have examined electrical stimulation of the face during acute Bell's palsy (Tuncay et al. 2015, Alakram et al. 2010, Manikandan et al. 2006, Flores et al. 1998 and Mosforth and Taverner 1958). Two trials reported mild benefit from electrical therapy (Tuncay et al. 2015 and Manikandan et al. 2006), while the rest showed no difference in recovery. Better symmetry at rest and with movement (from House Brackmann 3 to 2 to a scale 3 to 1) and better social interaction (using facial disability index the scale went from 68 (20-96) to 88 (28-100) p0.001) have been reported. In all trials, only patients with good prognostic factors were included.

The length of therapy in some of the studies could be insufficient to see an effect. For example, Alakram et al. only treated patients for 30 minutes weekly for 3 months and Manikandan et al. only treated patients for three times per week, for two total weeks. In severe cases of Bell's palsy, recovery may not begin for many months, making two weeks of electrical therapy potentially insufficient.

Outcome assessment could be improved upon by using blinded objective measurements of standardized photographs at rest and with different facial expressions. Having two evaluators allows for better scrutiny of inter-rater reliability. Only one trial (Tuncay et al. 2015) reported treatment-blinded assessment of outcomes. Past trials have greatly relied on estimation of recovery by investigators using the House Brackmann scales. The House Brackmann scale is a well-established scale first described in 1958. It classified patients into 6 categories of global facial function from normal function to complete paralysis. Facial spasms and synkinesis are not considered in the scale. It is difficult to use this scale to describe intermediate levels of recovery, in which some degree of residual weakness exists.

Finally, the time of follow up is an important consideration. Spasms and synkinesis tend to develop six months or longer after initial onset of paralysis in severe cases. Length of follow up in prior studies has averaged three months and often is not reported. We would like to perform a trial that addresses these limitations.

It is important to highlight electric stimulation is currently an approved therapy for facial paralysis and worse recovery with electrical stimulation has NOT been reported in any clinical trials. However, some clinicians discourage electric stimulation because they are concern for worse outcomes based on patients they have treated and animal studied (mice studies) (Skouras et al 2009).

For the consent, the following language was used: You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

12. Resources Available

A physical therapist with experience and training is necessary. Margaret McReynold is a collaborator in the study and has been using these techniques for the last 10 years with patient. She is listed as part of the study personnel.

We will need to provide patient with the electric stimulation device and will need to have 15 machines available as well as electrodes.

Photographic camera and clinical space to conduct consent and follow up interviews is necessary. We have such resources available.

We are applying for funding for a research assistant and the personnel will be updated if we are able to secure a research assistant for the study.

Statistical support is also available as described in the statistics section. Jess Mace is part of the study personnel.