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Protocol for randomized controlled trial of electric stimulation with high-volt twin peak versus placebo for facial functional recovery from acute Bell's palsy in patients with poor prognostic factors

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Abstract

Background: Electric stimulation (ES) can prevent muscle atrophy and promote tissue healing and therefore may help prevent sequelae of Bell's palsy but due to lack of high-quality studies, the effectiveness of ES in Bell's palsy remains controversial. Here we describe a protocol to evaluate the effects of monophasic high volt ES in patients with Bell's palsy and poor prognosis for recovery.

Results: This is a protocol for a prospective, double-blinded, randomized, placebo-controlled study. Participants include adults with acute Bell's palsy with poor prognosis for full recovery due to complete paralysis or being over age 60. ES will be a monophasic, high-volt pulsed waveform, 100μsec pulse duration, 35 hertz, motor-level intensity. Follow up will be at months 1, 2, 3 and 6. The primary outcome will be the proportion of patients with complete recovery using the eFACES tool. Secondary outcomes include patient reported quality of life measured by FaCE and the synkinesis assessment questionnaires, objective photographs, time to complete recovery, adverse effects, and tolerability.

Conclusion: This protocol has the potential to provide high quality evidence regarding the effects, up to 6 months after onset, of pulsed monophasic high-volt ES for patients with acute Bell's palsy and poor prognosis for complete recovery.

Keywords

Electrical Stimulation, facial paralysis, Bell's palsy, synkinesis, clinical trial

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Background

Patients with Bell's palsy experience weakness of the muscles of facial expression with major functional and psychological consequences. Affected patients lose the ability to close their eyelids for eye protection and lose the ability to control their lips to articulate speech, smile, and retain food and saliva inside their mouth. One in 60 people experience Bell's palsy in their lifetime.[1,2] While most are expected to recover, up to 29% of patients with Bell's palsy experience life-long residual weakness, involuntary contractions, spasms, and unintentional movements that occur simultaneously with intentional movement known as synkinesis.[3] Electric stimulation (ES) could potentially reduce

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these sequelae by preventing muscle atrophy and improving the selectivity of motor nerve regeneration.

The benefits of ES for accelerating recovery after musculoskeletal injury or surgery have been studied extensively,[4,5] but the effectiveness of ES for Bell's palsy remains controversial. There are seven published human clinical trials evaluating ES in Bell's palsy.[6–12] Five of these found ES to be beneficial, although generally only weakly so[8–12] and two found ES to provide neither benefit nor harm.[6,7] However, these trials are limited by their quality. They are small, underpowered, and most are not controlled (only one is a randomized controlled trial[10]) Patient factors predicting recovery and outcomes, such as the initial severity of paralysis, age, and duration of paralysis are poorly reported. 94% of patients with initially incomplete paralysis recover fully while only 61% of those with complete paralysis,[3] and only one-third of those over age 60, recover fully.[3,13] The ES parameters used in prior clinical trials vary. Most used sufficient current intensity to produce muscle contractions but one used subsensory level stimulation.[9] The waveforms included biphasic[6,8,11,12] and monophasic pulses.[7–10] The outcome measures used also have substantial limitations. The most commonly used outcome measure, the House Brackmann (HB) scale, has low inter-rater reliability and does not adequately describe facial function.[14] Only one of the studies blinded the evaluators to group assignment[10] and only one blinded the participants.[12] Drop-out rates, tolerability, and adverse effects (AEs) were poorly reported or not reported at all. The follow up period was generally at most three months which likely underestimate late onset sequelae of Bell's palsy. The vast majority of patients with Bell's palsy (85%) recover facial movement within three weeks from the onset of paralysis[3] but, on average six months from onset, almost 40% of those who do not start to recover in the first 3 weeks after onset develop synkinesis.[15]

Clinicians are divided in their opinions regarding using ES for facial paralysis; some assert ES improves recovery while others are concerned by potential AEs and fear increasing the risk of synkinesis.[16–18] A recent Cochrane collaboration review of studies evaluating physical therapy interventions for Bell's palsy did not identify higher rates of synkinesis after ES but concluded that higher quality studies are needed to inform recommendations for ES for treatment of Bell's palsy and.[19] Such studies must include comparison with placebo and control for selection bias by intervening early, before participants have tried a wide and varying range of therapies.

ES generally uses transcutaneously delivered low amplitude, pulsed, electrical current to activate motor nerves innervating weak muscles, with the goal of producing contractions and thereby preventing or retarding the development of muscle atrophy[20–22] Monophasic electrical currents may also promote recovery from nerve injury by promoting tissue healing, including nerve healing.[23–25] Here we describe a protocol for a prospective, randomized, double-blinded study to evaluate the effects of monophasic pulsed current ES on patients with Bell's palsy and factors predicting poor recovery, with a 6 month follow up. Motor level stimulation with a pulse duration of 100 μsec and a frequency of 35 pulses per second were chosen as these parameters are similar to those used in most previous trials of electrical stimulation for Bell's palsy and other peripheral nerve injuries in humans.[6,12,26] Given that in Bell's palsy the damage to the peripheral neve is expected to recover, we chose a pulse duration that would be expected to activate the motor nerve when it recovered. We did not use a direct current to try to produce contraction by directly stimulating the dennervated muscle because this is uncomfortable in patients with Bell's palsy who have intact facial sensation where the trigeminal nerve is not affected.

Our hypothesis is that, in patients with poor prognostic factors for recovery, ES will be associated with improved recovery from Bell's palsy, compared to sham ES, as assessed by rigorous outcome measures.

Methods/design

Figure 1 shows a time-line of study related visits and activities including enrollment, allocation, intervention and outcome assessments.

Inclusion and exclusion criteria

Patients with acute Bell's palsy, within one month of onset, with poor prognostic factors of having complete paralysis or being over age 60, are eligible for this study (Table 1).[3,13] Patients under 18 years old, non-English speakers, and those with a pacemaker or deep brain stimulator will be excluded. Patients with adhesive allergy will be offered hypoallergenic electrodes. Since pregnancy, diabetes, and recurrent attacks of facial paralysis have been identified by some[3,27] but not all studies[28] as poor prognostic factors for recovery from Bell's palsy, these will be evaluated as potential confounders.

Recruitment

Automatic reporting from the EPIC electronic medical record (EMR) at a single medical center will be used to identify patients for screening based on newly entered International Classification of Disease (ICD) diagnostic codes for facial paralysis. This reporting will capture

	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
	Enrolment	Allocation					Close-out
Eligibility Consent	X						
Physical therapy appointments		X Intervention: ES vs placebo	X				
Photography	X			X	X	X	
Questionnaires	X			X	X	X	X

Notes: ES= electrical stimulation

Figure 1. Schedule of enrollment, intervention, and assessments.

Table 1. General inclusion and exclusion criteria.

Inclusion criteria
Paralysis < 30 days of duration
Any of the following:
Complete paralysis
OR
Age > 60 years of age
Exclusion criteria
Age < 18 years of age
Non-English speaker
Pacemaker
Deep brain stimulator

patients evaluated by providers in the emergency department, family medicine, internal medicine, gynecology and obstetrics, otolaryngology-head and neck surgery, neurology, and neurosurgery, all of whom are anticipated to treat patients with acute Bell's palsy.

The medical records of all patients identified by the EMR as candidates will initially be screened by the research assistant for meeting given diagnosis, communication, and age-based enrollment criteria. Study procedures and potential risks and benefits will be explained to these individuals and they will be invited to enroll. Those who consent and enroll will complete screening questionnaires to evaluate for contraindications and have standardized photographs with standardized facial expressions taken by the research assistant following eFACE scale guidelines.[29] The primary investigator will then review medical records and screening questionnaires to confirm the diagnosis of Bell's palsy and suitability for the study and review photographs to assess for complete paralysis. Subjects meeting all entry criteria will then proceed to treatment allocation.

Allocation and blinding

Enrolled subjects will be scheduled to meet with a physical therapist who will allocate them randomly, using a stratified, block design, with 2 subjects/block, with the following four strata 1) Over 60 years of age with incomplete paralysis, 2) Over 60 years of age with complete paralysis, 3) 60 years of age or younger and complete paralysis <14 days duration, and 4) ≤ 60 years and complete paralysis > 14 days duration., in a 1:1 ratio, to the active or sham ES group. The rates of synkinesis are higher in patients with longer duration of paralysis. Patients who begin recovery in the first weeks of paralysis rarely develop this problem; in contrast, patients who begin recovery on the third week developed synkinesis in nearly 40% of cases.[3] Outcome assessors and participants will be blinded to group allocation.

Active intervention

ES will be applied transcutaneously using a high-volt twin peak monophasic pulsed current with a 100 μsec pulse duration, 35 Hz pulse rate, 10 seconds on-time, 30 second off-time and 2 seconds ramp up and down. These parameters were derived from the previously described literature on ES for Bell's palsy and from focus groups with physical therapists who treat facial paralysis (MM, SS and MC). The device used will be the OrthoStim (VQ Ortho Care®, Vista, CA), a portable electrical stimulation device that outputs multiple waveforms and has highly adjustable treatment parameters. The high-volt waveform was delivered at constant voltage. Four facial muscles will be stimulated, one at a time: 1) Frontalis for brow elevation, 2) Orbicularis oculi for eyelid closure, 3) Zygomaticus major for oral commissure elevation superiorly and 4) Orbicularis oris for lip pursing. Figure 2 shows the electrode placement in the face. The negative polarity electrode will be placed on the target affected muscle belly and the positive polarity electrode will be placed just below the ipsilateral mastoid process. The current intensity will be increased until either maximum tolerated sensory stimulation or a visible contraction is produced. Ten contractions of each muscle group will be performed, or 7 minutes of sensory stimulation per muscle (the same amount of time as for 10 contractions) if no contraction is achieved. The devices will be programed so this protocol is the only one available.

After an initial treatment and instruction by a physical therapist, the subjects will perform ES for 20 minutes each day at home based on handout instructions

Table 2. Outcome parameters.

Variable	Scale	Timeline
Clinician graded facial function	eFACE[a] House-Brackman[a] Sunnybrook[a]	1, 2 and 3 months
Patient reported quality of life	FaCE and SAQ	1, 2, 3 and 6 months
Facial symmetry	FACE-gram measurements[a]	1, 2 and 3 months
Time to complete recovery	Proportion of patients	1, 2 and 3 months
Patient tolerability	VAS Likert scale	1, 2 and 3 months
Patient adherence	Based on the use diary[b]	1, 2 and 3 months
Adverse effects	Proportion	1, 2 and 3 months

[a]Based on standardized facial photography.
[b]If available, consider tracking use and intensity in the device to evaluate protocol adherence.

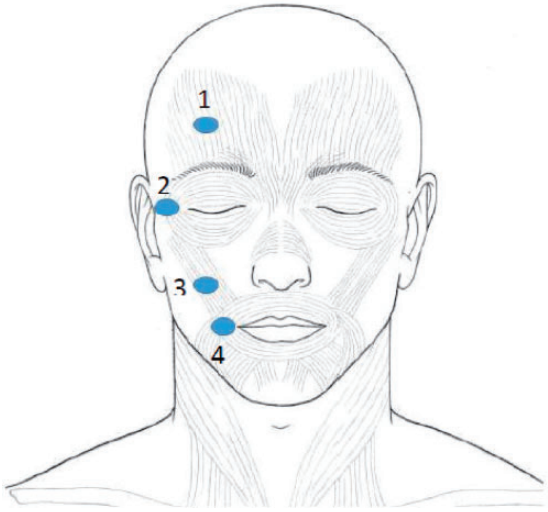

Figure 2. Electrode placement on the face for the both the ES and sham protocol. This diagram is included in the handout to be provided to patients.

(supplementary data 1). One week after the initial instruction session, participants will meet again with the physical therapist to review the treatment procedure, correct any errors, and have questions answered. ES will continue daily for three months or until complete recovery as judged by the primary investigator. Subjects will not have additional physical therapy during this study. Adherence (ES 5/7 days each week) will be tracked with a provided diary where participants will record stimulation use, muscles stimulated, current intensity, and ES duration (supplementary data 2).

Sham placebo intervention

The same device used for the active ES will be used to provide sham stimulation. The settings will be the same as for the active intervention except that the amplitude will be turned to sensation and then turned down by two clicks so the patient does not feels anything. To optimize subject blinding, subjects will be told that the study compares the impact of electrical stimulation settings that produces a sensation with those that do not. Although some evidence suggests that subsensory ES may enhance tissue healing, we know of no evidence supporting that subsensory pulsed high volt current enhances tissue healing.[30]

Standard of care

All subjects may receive standard of care of oral corticosteroids with or without oral antivirals.[31] We will record if subjects received and complete this therapy.

Assessments

1. Facial photograph evaluation: At baseline and monthly for the following three months, participants will have six digital frontal face photographs taken by the research assistant: 1) rest, 2) gentle eye closure, 3) strong eye closure, 4) strong smile, 5) brow elevation, and 6) lower lip depression. Three otolaryngologists blinded to group assignment will rate these photographs using the eFACE, HB and Sunnybrook Facial Grading System (SB) scales. eFACE rates facial function and symmetry on a 0–100 scale from 16 features of facial photographs.[29] HB rates facial nerve function from grade I to VI, from normal to total paralysis, based on symmetry at rest, eye closure, mouth symmetry and effort, and forehead function.[32] SB rates facial nerve function based on resting symmetry, voluntary movement and synkinesis.[33]
2. Patient reported, facial nerve specific, validated quality of life questionnaires including a) Facial Clinimetric Evaluation scale (FaCE)[34] and b)

Synkinesis Assessment Questionnaire (SAQ).[35] FaCE is a 15-item measures of facial palsy quality of life and the SAQ is a 9-item instruments specifically for self-assessment of synkinesis.
3. Facial symmetry measured in millimeters by the FACE-gram software program[36] including: a) resting palpebral fissure width and oral commissure symmetry b) brow elevation and c) smile oral commissure excursion.
4. Time to complete recovery as judged by the PI.
5. Subjective treatment tolerability rated 0 to 10 where 0 indicates completely comfortable and 10 indicates very uncomfortable/intolerable
6. Treatment adherence as measured by the use diary.

At 6-months, all participants will also have a standardized telephone interview where they will be asked about return of function and development or worsening of synkinesis and the FaCE and SAQ will be repeated.

Adverse effects (AEs)

AEs will be recorded on a standardized form. Contact information for the research assistant will be provided for participants to report AEs between visits.

Database management

Data will be safeguarded by using unique identificatiers and eliminating protected health information from all forms. Forms will be kept in locked cabinets in study personnel offices. Research Electronic Data Capture (RedCAP, Nashville, TN) web-based software will be used for digital data storage except for photographs which will be stored in a password protected file on a password protected institutional computer. The database and photographs will remain housed for the study duration and never be transferred. Published results will exclude identifying protected health information.

Statistical analysis

Descriptive statistics will be presented as means [±standard deviation] and prevalence (%) values. Within and between-subject bivariate comparisons will be performed using non-parametric tests due the small sample size. Average effect estimates and 95% confidence intervals (CI) will be reported. To compare treatment-related outcomes, between-subject differences across outcome responses will be evaluated using odds ratios (OR) and 95% CI. Dependent, repeated measures outcome data will be evaluated using simple linear, mixed-effects modeling after identification of appropriate random and/or fixed effects factors and maximum iterations. Discrete models will be completed for each separate, dependent variable to determine the predictive association of treatment assignment in the presence of other independent factors (e.g. pregnancy, diabetes, recurrent facial paralysis). Interaction terms will not be considered due to sample size. Mean estimates of fixed and/or random effects, standard errors, and 95% CI will be reported. Multicollinearity will be evaluated with correlation matrices. All comparisons will assume a 0.05 type-I error probability.

Power calculation: We propose recruiting 20 patients into each treatment arm for a total cohort of 40 patients. This will allow us to estimate the effect size for a future fully-powered multi-site trial. Complete recovery is expected in about 60% of patients with complete facial paralysis.[3] Assuming a similar recovery rate in our control cohort, a recovery rate above 48% (10/20 subjects) in the ES arm would assess the active treatment as no worse than standard-of-care at $\alpha = 0.05$ with 80% power. As this study lasts 6 months we anticipate some loss to follow-up and missing data. Missing data will be addressed statistically by imputation methods for small sample human trials including last observation carried forward or Bayesian least squares.[37]

Protocol feasibility evaluation

In preparation for this trial we collected preliminary data from four subjects with complete paralysis who underwent the active ES intervention. Two of these were over 60 years old and two were under 60 years old. One of the over 60 year olds had Ramsay Hunt syndrome (i.e. facial paralysis associated with varicella-zoster virus reactivation [shingles]), and, at enrollment, no longer had vesicles or skin irritation. Three subjects participated for three months; one of those under 60 years old exited the trial at one month because she attained complete recovery at this time. Troubleshooting during the trial included wetting the electrodes around facial hair to improve conduction and answering questions about the device. VAS scores for intervention tolerability were 6, 4, 1, and 0 at month 1 and lowered in subsequent months. All reported using the ES daily or almost daily. Treatment emergent AEs reported were severe pain (1), mild skin irritation (1), and mild headache (1) with only the skin irritation being judged as possibly treatment related. The reported severe pain was not treatment-related but was caused by post-herpetic neuralgia following Ramsay Hunt. The one subject who had developed Bell's palsy during pregnancy, developed synkinesis by the six-month follow-up that had not been present at the three-month follow-up. This synkinesis was reported by the patient on her questionnaires and was corroborated by the PI's evaluation of photographs.

Discussion

Currently, standard of care for patients with Bell's palsy is oral corticosteroids with or without antiviral medications, independent of prognostic factors.[31] This approach is associated with full recovery in almost all patients with good prognostic factors, including being younger and having incomplete paralysis. However, close to 40% of older patients and those with initially complete paralysis do not recover fully with standard of care. ES may further improve the potential for recovery in patients with these poor prognostic factors but the effectiveness of ES for Bell's palsy is still uncertain. This study protocol is designed to compare current standard of care to standard of care plus ES, using a high volt twin peak monophasic motor stimulation, in patients with acute Bell's palsy and poor prognostic factors. This trial will compare outcomes at 1, 2, 3 and 6 months, including recovery of motor function and synkinesis.

The trial has a number of strengths. It is a randomized, double blind, controlled trial with rigorous clinician and patient rated outcome measures and 6 months of follow up. Although most patients with Bell's palsy have an excellent prognosis for full recovery, this trial will select patients with factors associated with poor prognosis for full recovery. Enrolling patients shortly after diagnosis pragmatically allows one to reach out to potential participants when they are diagnosed, and is scientifically sound, minimizing confounding by other interventions between diagnosis and the study ES, and allowing ES to potentially retard disuse atrophy before substantial disuse occurs. Rigorous validated tools to evaluate facial function objectively through photographs as well as patient reported questionnaires are used. Additionally, the six-month follow up is likely to capture development of synkinesis.

This trial is only designed to evaluate the impact of a specific ES intervention, daily high volt twin peak monophasic motor level stimulation, and does not evaluate the impact of other ES parameters or protocols. The settings used were chosen based on review of the literature and a focus group with physical therapists with clinical expertise in the topic. Monitoring for adherence is limited to subject self-report because the stimulation device used cannot track use or provide sham intervention without allowing the participant to increase the stimulation intensity.

In conclusion, our randomized and placebo-controlled protocol evaluates the effects of high volt twin peak monophasic motor level ES for recovery for up to 6 months from Bell's palsy in people with poor prognostic factors for full recovery. The trial is novel in its selection of patients with factors that predict poor recovery and in its documentation of degrees of paralysis with methodical photography. Publishing the protocol, including precise description of the entry criteria, intervention and outcomes, should improve standards for researching interventions for facial paralysis that could be used in future multi-site collaborative studies.

Trial registration: Clinicaltrials.gov Identifier: NCT03836989 first posted 11 February 2019.

Declaration of conflicting interests

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ML.

Contributorship

ML and MC researched literature and conceived the study. MM was involved in protocol development and pilot data acquisition. JM calculated power and designed the statistical analysis. ML wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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