Improving Holding Function of the Hemiplegic Hand with Chemodenervation

NCT02459951

Date: 4-29-2016

Improving Holding Function of the Hemiplegic Hand with Chemodenervation

Specific Aims

Inserting and holding an object in the hand is what we mean by 'hand as a holder' function. After a stroke, the hand typically lacks voluntary finger extension that opens the hand. Simultaneously, the hand is also subjected to involuntary contraction of finger flexor muscles that close the hand, resulting in clenched fist and thumb-in-palm deformities. Despite these typical hemiplegic configurations, persons with stroke may be able to insert an object into the hand by wiggling and pushing it into the hemiplegic hand with their uninvolved hand, though struggle is often present and failure is frequent. A main goal of this project is to demonstrate that 'hand as a holder' function can be improved by blocking overactive muscles with medication. The main measure of hand function improvement will be 'transit time' i.e. the time it takes for the uninvolved hand to insert an object into the hemiplegic clenched fist and hold it independently.

This pilot study of 9 patients aims to demonstrate reliability and validity of a digital video method that will be used to measure 'transit time'. It also aims to establish initial statistical support for improved object transit time into the hemiplegic clenched fist after Botox A injections. [Botox A, injected directly into offending muscles, is a neuromuscular blocking agent that was approved by the FDA in 2010 to treat spasticity, a form of involuntary muscle contraction, in finger and wrist flexor muscles of persons sustaining a hemiplegic stroke.]

Experimental Design

Study hypothesis: Given hemiplegic patients, of stroke etiology, with a neurally driven clenched fist, who may also have a thumb-in-palm and/or a flexed wrist and who have severely impaired voluntary finger and thumb extension, we hypothesize that 'hand as a holder' function will improve after chemodenervation of relevant finger, thumb and wrist muscles selected by clinical examination.

The study objective is a pilot demonstration of the clinical hunch that objects will be inserted for holding by the hemiplegic hand more quickly and easily after chemodenervation, and, in some cases, insertion of larger diameter objects will be achieved as well.

Inclusion Criteria

1. Participant (or legal guardian) has been informed of the study procedures, participant is willing to comply with the study protocol and written informed consent has been given.
2. Age greater than 35 and less than 80 years.
3. Participant has experienced a documented, anemic or hemorrhagic, unilateral (right or left) hemiplegic stroke 1 year or more prior to enrollment.
4. While aphasia and hemianopsia are not absolute criteria for exclusion, a participant must be able to understand verbal and visual instructions and demonstration regarding task protocol.
5. A 'resting' wrist angle 0 is an inclusion criterion. It will be measured as follows: The forearm of a participant will be placed on a foam wedge, allowing the wrist and hand to hang down over the front wall of the wedge. Wrist angle will be measured with a clinical goniometer.
6. Spasticity is present in finger flexors and thumb coupled with marked voluntary paresis of finger extension (no finger has more than half range of active extension at any joint). By squeezing the examiner's finger, participants will have demonstrated, at least, some detectable voluntary contraction of finger flexors. Participants may have a flexed wrist (typical).
7. Impaired sensation is acceptable but participants must be aware that they are holding something, as tested clinically.
8. Participants present with at least two finger flexors with an Ashworth score ≥ 3
9. Participant will have moderate motor severity as defined by an upper limb Fugl-Meyer (14) motor scores between 21-50.
10. Participant does not have joint capsule_contractures as determined by clinical exam.

11. Participant may have tightness/shortening of extrinsic finger flexors but composite extension of wrist and fingers comes to at least neutral (i.e. fingers and wrist can be brought to neutral position simultaneously).

Exclusion Criteria

1. Profound sensory loss/absent touch sensation.
2. Known hypersensitivity/allergy to Botox A.
3. Acute illness or unresolved medical/psychiatric conditions at time of assessment.
4. Participant is pregnant or breast-feeding.
5. Participant had Botox injections 4 months previously.
6. Clenched fist associated with tenodesis of an extended wrist i.e. resting position of wrist is > 0

Project Design

9 participants with spastic hemiparesis greater than 12 month's duration will be studied using a repeated measures design. Two baseline sessions separated by at least 3 days will be conducted along with one post Botox treatment session, approximately 3 to 5 weeks later. [The peak response of Botox for spasticity has been reported as 4 weeks (1). Our clinical experience also confirms that four weeks is a reasonable time to expect a treatment effect. However, practical considerations such as participant schedules and transportation encourage us to target 4 weeks 7 days.] Each participant will use their uninvolved hand to insert cylinders with 5 graduated diameters into the receiving hemiplegic hand. The same scripted instructions will be used for all participants, including visual demonstration of cylinder insertion through the web space entrance of the hand. Cylinder diameters will range between 0.5 and 2.5 inches and will be approximately similar in weight and height. Each session will consist of 15 trials (5 cylinder diameter sizes times 3 insertions for each diameter → 15 trials, the order of diameter size being randomized). A 30 second trial duration will be allotted. Three synchronized Sony AS100VR recording cameras will provide side, front and top views, strategically placed to observe the "onset" time i.e. time of

initial object contact with the hemiplegic hand and the "offset" time i.e. the time the uninvolved hand lets go of the cylinder and the hemiplegic hand holds the cylinder independently. [The hemiplegic hand must visibly be holding the object independently for 5 seconds without being dropped or otherwise supported by contact with other parts of the body or the environment.] Using Final Cut Pro video software, playback of the synchronous views of the three cameras will be used by two independent coders to measure onset and offset times in order to calculate object transit time. Given that all insertions will be video recorded, it may be useful for coders to score qualitative aspects of performance when a participant doesn't meet the 5-sec criterion of unsupported grasp. In addition, we are unaware of another measure of holding function that could be administered to test convergent validity, emphasizing one aspect of the novelty of this project's work.

One reason why this pilot is exploratory and small in number is to learn more about variability in the primary measure. In addition, we will note stability of task performance as well the presence of short-term practice effects that may materialize across baseline sessions. In order to be informative, treatment effect would have to be greater than short-term practice effects. Since persons with hemiparesis would not have prior experience with insertion of the specific objects used in this project, we plan to give participants two practice trials prior to the experimental ones in each of the three sessions.

TREATMENT PLAN: Injection of Botox A will be done using customized dosing because participants typically present variable configurations reflecting the variability of underlying muscle involvement. Clinical assessment and judgment will be used to determine which muscles contribute to the hand deformities of a given participant. Therefore, we expect that any of the following muscles may be injected using the following typical ranges: 20-60 U into the flexor digitorum sublimis (up to 3 sites), 20-60 U into the flexor digitorum profundus (up to 3 sites), 10-40 U into the interossei (up to 4 sites), 20-40 U into flexor pollicis longus, 10-20 U into adductor pollicis, 10 U into flexor pollicis brevis, 40-70 U into flexor carpi radialis, 30-60 U into palmaris longus and 20-40 U into flexor carpi ulnaris. Maximum dose (if all

muscle were injected maximally) totals 400 U. Current clinical practice uses an upper limit of 600 U in adults.

Data Analysis Plan

Statistical Methods

Utilizing Final Cut Pro software, two coders independently used three synchronized camera views to identify onset and offset times of cylinder insertion in order to calculate cylinder Transit Time (Offset Time minus Onset Time). During a practice period, coding rules were established and coder training practice was done with hemiparetic volunteers. A concordance correlation coefficient (CCC) [Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989; 45:255-68] was computed as a measure of agreement between the two coders. Results indicated that the CCC for Onset Time was 0.961 (95% CI: 0.938, 0.996); the CCC for Offset Time was 0.998 (95% CI: 0.993, 0.999) and the CCC for Transit Times was 0.977 (95% CI: 0.945, 0.991).

Statistical Methods

Protocol 1: Analysis of Transit Time [time to insert a cylinder into the affected hand]

The log-transformed Transit Times were analyzed using a linear mixed effects (LME) model with the fixed effects of cylinder diameter (0.5, 1, 1.5, 2, 2.5 inches), evaluation session (Pre 1, Pre 2 and Post Treatment) and their interaction. The random effects of subject and evaluation session were included to allow for correlation among repeated measures for the same participant. Though two statistical models were considered, the model reported here included Pre2 and Post-treatment Transit Times as repeated measures of response variable, and Pre1 Transit Times as a covariate in the model, using the average of the three cylinder insertion trials for each cylinder diameter and evaluation session. The residuals of the LME model were evaluated for consistency with the assumption of the normal distribution.

The data included 69 (17%) of trials with missing transit times meaning that a subject was not able to do the insertion. A linear mixed effects methodology is appropriate for modeling data with missing observations if the 'misses' (i.e. participant was unable to insert a cylinder into the affected hand within 30 seconds) are ignorable or missing at random. For non-ignorable 'misses', it is required to specify the response mechanism (a probability model for missing indicator or non-response). A repeated measures logistic regression model was used to model the missing data indicator and investigate whether the 'misses' depended on cylinder diameter, evaluation session or Transit Times observed at the first baseline session (Pre1).

The data analysis was performed in SAS (SAS Institute Inc., Cary, NC, USA) and R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.)

Protocol 2: The counts of successful holds (i.e. participants had to hold a given cylinder independently with the affected hand for 5 seconds) in 3 trials for each cylinder diameter were modeled using a repeated measures negative binomial model with the 3 trials as an exposure.

The predictors of expected number of successful holds included the cylinder diameter and evaluation session (Pre-1 baseline session, Pre-2 baseline session, and Post-treatment). The interaction between cylinder diameter and evaluation session was also considered, but was not a significant predictor of mean successful holds. The model allowed for correlation among counts for multiple cylinder diameters and evaluation sessions for the same participant using an exchangeable correlation structure. Correlation among counts was estimated using the GEE approach (as implemented in SAS PROC GENMOD, SAS Institute Inc., Cary, NC, USA).

Primary Outcome Measure(s):

1. Geometric Ratios of Log-transformed Transit Time [Time Frame: transit times were measured at Pre-injection session 2 and Post-injection session]

Secondary Outcome Measure(s):

2. Incidence Rate of Successful Holds [Time Frame: evaluation sessions Pre1, Pre2, and Post]

3. Incidence Ratio of Successful Holds [Time Frame: evaluation sessions pre1, pre2, and post]

4. **Modified Ashworth Scores (MAS)** for injected muscles **[Time Frame: evaluation sessions Pre1, Pre2, and Post];** [MAS are obtained to verify that a biological effect of neurotoxin is, indeed, present] .

Subject Recruitment Plan: The MCAL treats over 400 patients a year and clenched fist problems occur in 20%. We anticipate no difficulty in obtaining 9 participants for this pilot study.