Study Protocol and Statistical Analysis Plan

Official Title: Novel Management of Airway Protection in Parkinson's disease: A clinical trial

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Study Protocol

This prospective experimental study will include two participant groups; one group will receive EMST and the other smTAP. Briefly, once enrolled in the study, participants will undergo baseline testing consisting of airway protective measures, physiological measures of respiratory and laryngeal function, and patient-centered outcome measures. Participants will then be randomly assigned with allocation concealment to either the EMST or smTAP training groups. They will be further randomized to receive immediate training or delayed training where there is a 5-week wait to start with a second baseline performed at the end of the 5-week delay. Whether participants are in the immediate or delayed start groups, once treatment commences they will receive 5 weeks of intensive training including weekly meetings with a treating clinician in our clinical-research laboratory. Upon completion of the treatment arm, participants will return for a post-treatment assessment consisting of all tests and measures from the initial baseline assessment. All treatment and assessment visits will be completed 'on' optimal PD medication dosage which will be defined as one hour after medication administration. Participants may use diet and/or postural modifications as recommended by their treating Speech-Language Pathologist to maintain nutritional status and swallowing safety during enrollment in the study, but are not to participate in other dysphagia exercise-based rehabilitation including treatments such as the effortful swallow, mendelsohn maneuver, etc. that have been shown to have exercise training effects (e.g., [10]). Pre- and post-treatment procedures are described below. More specific information about the selected outcomes is included in the 'clinical protocol synopsis'.

Pre and Post Treatment Assessments

Swallowing Assessment Procedures. Three 10 cc thin liquid boluses by spoon and three 3-oz thin liquid sequential swallow challenges will be administered by cup. Our research team has extensive experience in the evaluation and measurement of swallowing dysfunction in PD (e.g., [20, 30, 31]). A recent retrospective analysis by our group of the swallowing performance of 50 participants with PD demonstrated that the 3-oz sequential swallow presentation was the best bolus presentation to detect change in swallowing performance. We will also include a smaller bolus (10 cc.) in the case that swallowing performance is so severe that it precludes the ethical presentation of the 3-oz liquid challenge.

Reflex Cough Assessment Procedures. Participants will be outfitted with a facemask covering the nose and mouth. The facemask will be coupled to a pneumotachograph, differential pressure transducer, and have a side port with a one-way inspiratory valve for nebulizer connection. The nebulizer will be a DeVilbuss T-piece connected to a dosimeter that delivers aerosolized solution during inspiration with a delivery duration of two seconds. The cough airflow signal will be digitized (Power Lab Data Acquisition System) and recorded (LabChart 7; ADInstruments, Inc) to a laptop computer.

Participants will be seated for an initial 30 seconds of quiet breathing in order to acclimate to the facemask. Participants will then complete a capsaicin challenge with three randomized blocks of 0, 50, 100, 200, and 500 μM capsaicin dissolved in a vehicle solution. Our preliminary data identified 500 μM as a supra-threshold concentration for eliciting the reflex cough in participants with PD. Participants will be given the instruction "cough if you need to" prior to capsaicin delivery. The solution will be administered automatically upon detection of an inspired breath and there will be a minimum of one minute between each trial. Participants will be provided water to drink between trials. Our research group has extensive experience utilizing this methodology to induce cough (e.g., [8, 22, 32, 33]). Our group holds an FDA IND # 76866 for the use of capsaicin in the study of cough reflex sensitivity and motor pattern.

Treatment protocols:

Every effort was made to match the two targeted treatments on amount of time with clinicians, home practice time, and number of repetitions.

Expiratory Muscle Strength Training (EMST)

EMST involves a calibrated device consisting of a mouthpiece with a one-way spring-loaded valve. The valve blocks airflow until a sufficient "threshold" pressure is produced to overcome the force. The pressure range is from 25 cm H_20 to 150 cm H_20. Participants will receive training at baseline, have the device set to 75% of his/her MEP, and then complete EMST five days per week for five weeks. During that time period they will be seen for weekly study-treatment visits in our clinical-research laboratory which will last approximately 45 minutes.

Weekly study-treatment visits:

During weekly visits, a study clinician will re-measure MEP, re-set the EMST device as appropriate (75% MEP), and observe the participant complete the targeted 25 repetitions. MEPs are completed by having the participants blow into a mouthpiece connected to a pressure manometer via tubing with a 14-guage needle air-leak. The participant blows into the manometer for two seconds.

Home practice:

The daily training sessions will be completed at home, with the assistance of the participant's primary caregiver if necessary. Each day approximately 20-30 minutes will be spent training. The daily training is identical to the protocol described above.

Sensorimotor Training for Airway Protection (smTAP)

Participants will complete 45 minutes of cough rehabilitation in the laboratory with a trained research clinician once a week for five weeks. During the weekly visits, participants will complete 25 'hard/long coughs' at sub-threshold levels of capsaicin. Level of capsaicin will be determined from baseline (pre-test) measures. Participants will train at the concentration just preceding their reflex cough threshold (C2). Attentional focus to the sub-threshold stimulus will be emphasized. Visual feedback will be provided in real time via LabChart 7 (ADInstruments, Inc) and will be displayed on a large 20 inch desktop computer monitor. A visual target line 25% above maximum PEFR (derived from baseline cough assessment; figure 5) will be provided during cough training in order to promote enhanced PEFR. PEFR was selected as a primary target given that it has been identified as a measure which can be modified through cueing of reflex cough [22], is related to swallowing outcomes [34, 35], can be visually targeted by participants, and is associated with increased cough effectiveness. The participants will only be provided with feedback regarding

their performance on the first five coughs trained within each session in order to reduce the influence of clinician bias on treatment outcomes.

Home practice: The daily training sessions will be completed at home, with the assistance of the participant's primary caregiver if necessary. Each day approximately 20-30 minutes will be spent training. Home practice will be completed 5 out of 7 days. Participants will complete 25 voluntary coughs (5 sets of 5 repetitions) using a peak flow meter [36]. Each week the target peak cough flow will be 25% above maximum PEFR as identified during the study treatment visits to the laboratory.

Statistical Analyses

Multilevel models with main effects of treatment, time, and their two-way interaction will be used. A randomeffect of participant will be used to include multiple trials (eg, three trials of MEP at each time point). In the presence of an interaction, differences in the magnitude of change between groups, as well as changes within each group, will be examined. For primary outcomes, separate models will be performed for delayed to pre-training and pre-training to post-training cohorts. More specifically, for participants randomized to the delayed treatment group, MEP and voluntary cough PEFR will be tested between delayed (first baseline) and pre-training (second baseline). For the active treatment phase, all outcomes will be tested between pre-training (which was the second baseline for those in the delayed treatment group) and post-training. α will be set at 0.05, and multiple pairwise comparisons were adjusted via Holm–Bonferroni corrections. Standardized effect sizes will be computed by dividing mean difference by the error and random effect variance. Single measure, absolute agreement intraclass correlation coefficients and weighted Cohen's kappa will be used for cough airflow and number of coughs, respectively, for reliability. Analyses will be performed in R.