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STUDY PROTOCOL

Exploring the Efficacy of the Effortful Swallow Maneuver for Improving Swallowing in People with Parkinson Disease

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LIST OF ABBREVIATIONS

ASPEKT	Analysis of Swallowing Physiology: Events, Kinematics and Timing
ES	Effortful swallow
H&Y	Hoehn & Yahr
IOPI	Iowa Oral Performance Instrument
LVC	Laryngeal Vestibule Closure
mSv	Millisieverts
NIH	National Institutes of Health
PD	Parkinson Disease
PhAMPC	Pharyngeal area at maximum constriction
RES	Regular effort swallow
SRRL	Swallowing Rehabilitation Research Laboratory
TWH	Toronto Western Hospital
UHN	University Health Network
VFSS	Videofluoroscopic Swallowing Study

Background Information

Parkinson Disease (PD) is a common neurological disorder that is expected to affect 9 million people by 2030. Dysphagia (swallowing impairment) is highly prevalent in PD and can result in aspiration pneumonia, malnutrition, and dehydration. The most common intervention for dysphagia is the use of thickened liquids and modified food textures.

However, due to dissatisfaction with their texture and taste, sensation of increased satiety and increased thirst with increasingly viscous fluids, this approach is reported by patients to negatively impact swallowing-related quality of life.

The purpose of this study is to determine if an exercise-based approach called the Effortful Swallow maneuver is an effective intervention for dysphagia in PD that will enable people with PD and dysphagia to continue to consume regular foods and liquids.

Research has found that while there are no optimal interventions, exercise-based interventions targeting improved swallowing efficiency and muscle strength hold promise (El Sharkawi et al., 2002; Miles et al., 2017; Pitts et al., 2009; Athukorala et al., 2014; Troche et al., 2008). To select targeted exercise goals for dysphagia therapy, it is important to identify the physiological mechanisms contributing to swallowing impairment in PD. Studies identify two key mechanisms of swallowing impairment in PD: 1) prolonged time-to-laryngeal-vestibule-closure (time-to-LVC)which is a risk for aspiration; and 2) reduced pharyngeal constriction, leading to pharyngeal residue after the swallow (Ellerston et al., 2016; Nascimento et al., 2020; Curtis et al., 2020; Gandhi et al., 2021). In other patients with dysphagia, the Effortful Swallow (ES) maneuver is commonly used to target faster airway protection and improved bolus clearance (Hind et al., 2001; Fukuoka et al., 2013).

Study Objectives and Hypotheses

The objective of this project is to determine the immediate (compensatory effect) and long term efficacy (rehabilitative effect) of a 4-week program of the effortful swallow maneuver intervention on physiological swallowing parameters in Parkinson Disease. The Videofluoroscopic Swallowing Study (VFSS) recordings will be analyzed in duplicate according to a rigorous standard procedure known as the ASPEKT Method (Analysis of Swallowing Physiology: Events, Kinematics and Timing), from which the following outcomes will be measured. .

Outcome measures:

Primary Outcomes:

- Time-to-laryngeal vestibule-closure (i.e., the time interval between onset of the hyoid burst movement at the beginning of a swallow and achieving airway protection via closure of the laryngeal vestibule
- Swallowing safety and airway protection status as measured by the Penetration-Aspiration Scale (Rosenbek et al., 1996)
- The degree of pharyngeal constriction during swallowing (“pharyngeal area at maximum constriction”)
- The amount of residue left behind in the pharynx after a swallow.

Secondary Outcomes:

- The number of swallows per bolus
- Maximum value across 3 repetitions of a maximum tongue-palate press using the Iowa Oral Performance Instrument in an anterior position.

Hypotheses

We expect that use and repeated practice of the ES will lead to show differences post-interventionin swallowing function and physiology compared to baseline, as listed in the following table:

Parameter	Prediction post-intervention of effortful swallow maneuver (**vs** baseline regular effort swallows)
Primary outcomes:	
Time-to-Laryngeal-Vestibule-Closure (time-to-LVC)	Earlier closure leading to shorter time to laryngeal vestibule closure
Penetration-Aspiration Score (PAS)	Lower frequency of airway invasion events due to earlier time-to-LVC
Pharyngeal Area at Maximum Constriction (PhAMPC)	Smaller pharyngeal area at maximum constriction (i.e. better constriction)
Residue	Reduced pharyngeal residue due to better constriction
Secondary outcomes:	
# of swallows per bolus	Lower number of swallows per bolus due to better bolus clearance
Maximum anterior isometric pressure	Increased tongue pressure

Study Design

Participants with Parkinson Disease will be recruited over 18-24 months to participate in a dysphagia intervention protocol. This protocol will be a single arm feasibility study to determine the impact of the ES maneuver intervention on swallowing physiology. Participants who display prolonged time-to-LVC, and/or poor pharyngeal constriction during their baseline videofluoroscopic x-ray of swallowing (VFSS) compared to healthy reference values will be enrolled in a 4-week intervention program, with two 30-minute sessions of ES practice daily, 5 days per week. See Figure 1 for a summary of participant recruitment and study procedures.

Selection of participants:

Potential participants will be identified by staff at the Toronto Western Hospital's Movement Disorders Clinic, who will make contact to introduce the research program and obtain verbal consent to provide the study team with the participant's contact information (phone number and/or email, as preferred by the participant). The Movement Disorders Clinic staff will select potential participants based on the following criteria:

Inclusion Criteria

- At least 18 years old
- English-speaking

- Able to follow study instructions
- Neurologist confirmed diagnosis of PD
- Hoehn and Yahr scale score of 2 or 3
- Self-report of one or more swallowing or related symptoms:
  - ➔ Difficulty with secretion management
  - ➔ Coughing at the meal time
  - ➔ Choking on food
  - ➔ Respiratory infection in the past 6 months (other than COVID)

Exclusion Criteria

- History of head and neck cancer
- Radical neck dissection (e.g. anterior cervical spine surgery) or neck/ oropharyngeal surgery (not excluded – tonsillectomy, adenoidectomy)
- Past medical history of any neurological disease other than PD (e.g. multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, stroke)
- Cognitive or receptive communication difficulties that preclude the participant's ability to follow study instructions provided in English. This will be determined by the participant's physician prior to referring them to the study.

The target sample size is 12 participants. We expect the ratio of males: females to be 1.5:1, reflecting the ratio of males to females in the PD population.

Review of consent form:

All participants that express interest in participating and have agreed to allow the Movement Disorders clinic to share their contact information with the study team will be contacted by study personnel of the Swallowing Rehabilitation Research Laboratory. Participants that show continued interest after a brief introduction will be provided with the study information and consent form ahead of a telephone or video-conference call (using MS Teams) to answer any questions. We will proceed to schedule a study appointment after the participant confirms they have understood all the information that is provided and after verifying they have no more questions and wish to proceed. The formal written consent will be obtained at the beginning of the baseline study appointment, and a copy of the consent form will be provided to the participant. If a participant does not wish to participate in the study, they will no longer be contacted by study personnel; a decision not to participate will have no impact on clinical services provided.

Baseline study appointment procedures:

1) *Demographic and medical history information*:
   Participants will be asked to complete a form capturing demographic, medical history and history of PD symptoms. The following data will be collected:
   i. Year of birth
   ii. Sex
   iii. Relevant medical history and ongoing treatments (e.g. presence/location of a deep brain stimulator).
   iv. Race/ethnicity
   v. Time post-onset of symptoms (initial and swallowing-specific);
   vi. Allergies to barium contrast, food thickeners or latex.

b. Participants will be requested to complete a 26 item validated questionnaire entitled the *Munich Dysphagia Test – Parkinson's Disease* to understand the nature of swallowing difficulties experienced and associated burden.

2) *Tongue strength:*
Bulbar muscle strength will be measured using 3 repetitions of a maximum effort isometric tongue-to-palate press task using the Iowa Oral Performance Instrument (IOPI). A clean, single-use disposable tongue bulb will be used for each participant.

3) *VFSS:*
Stimulus preparation: Bracco E-Z-Paque® powdered barium will be prepared in 20% w/v concentration with water, and thickened to target consistency using Resource Thicken-Up™ Clear (a xanthan gum thickener developed by Nestlé Health Science). Target consistency will be defined using the International Dysphagia Diet Standardisation Initiative definitions and Flow Test. All stimuli will be prepared no longer than 6 hours prior to scheduled use, according to a strict standard operating procedure.

Procedure: Three cups of each stimulus will be prepared for the experiment, each containing 40 ml and organized in a muffin tray placed in front of the participant (please see table below for the order of the exams). The participant will be asked to take a comfortable sip from each cup. The cups will be weighed on a digital balance at the conclusion of the session to derive estimates of sip volume.

Recording: The videofluoroscopic swallowing study will be captured in lateral projection using pulsed videofluoroscopy at a rate of 30 pulses per second, and recorded on a synchronized videocapture system at 30 frames per second.

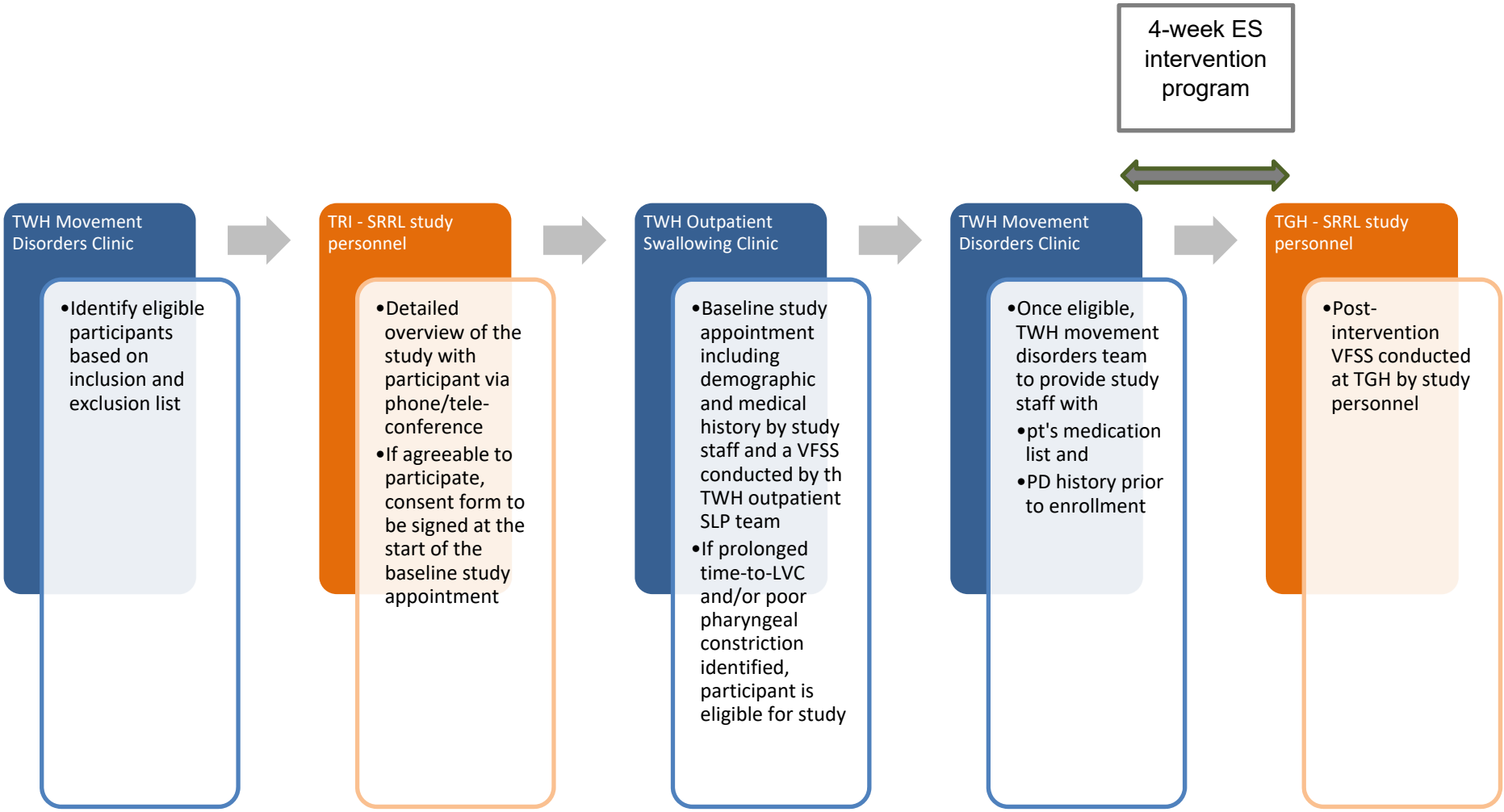
Timeline and location: A baseline VFSS will be conducted by speech-language pathologists at the Outpatient Swallowing Clinic at Toronto Western Hospital's Gastric Suite.

Order of stimuli:

i. Saliva swallow (with no external barium bolus) to be used for land-marking
ii. Up to 3 regular effort swallows of thin liquid
iii. Up to 3 effortful swallows of thin liquid
iv. Up to 3 regular effort swallows of mildly-thick liquid
v. Up to 3 effortful swallows of mildly-thick liquid

Intervention eligibility: Participants that display prolonged time-to-LVC measures and/or poor pharyngeal constriction measures compared to healthy reference values on the baseline VFSS with thin or mildly thick stimuli will be eligible for the intervention portion of this research study (described below). Once a participant has been deemed eligible, staff at the Toronto Western Hospital's Movement Disorders Clinic will then provide the study personnel with an updated Hoehn & Yahr scale score and medication list prior to proceeding with the intervention. Participants who do not display impaired time-to-LVC and/or PhAMPC on the baseline VFSS will be withdrawn and will not continue to the intervention portion of the study.

Figure 1. Summary of participant recruitment and study procedures



Study Intervention

A 4-week intervention program with two 30-minute sessions of ES practice daily, 5 days per week will be offered to eligible participants based on confirmation of intervention candidacy in the baseline VFSS.

Practice will be supervised on a reducing schedule (week 1: 5 sessions; week 2: 4 sessions, etc.), via a secure videoconference using Microsoft Teams. Which days the intervention will be performed and supervised will be dependent on the availability of the participant and the study team member. This will be determined at the start of the protocol with each participant. There is no requirement to practice at the same time each day or to practice on the same days of the week each consecutive week.

Intervention will involve biofeedback provided using the Iowa Oral Performance Instrument. An IOPI device will be loaned to each participant for home use at the end of baseline videofluoroscopy, and a set of disposable pressure bulbs will be provided to cover the course of intervention. Participants will not be held responsible for lost or broken devices. Additionally, a supply of thickener will be provided to each participant for use in home practice sessions. Instruction in use of all supplies will be provided.

Practice Sessions: Each session will include:

- 15 regular saliva swallows with the IOPI bulb in place. The mark on the connecting tube will be aligned with the upper incisors. A rest period of 20 seconds will be utilized between saliva swallow.
- 15 effortful saliva swallows with the IOPI bulb in place. The mark on the connecting tube will be aligned with the upper incisors. A rest period of 20 seconds will be utilized between saliva swallow.
- 15 effortful swallows of mildly thick liquid without the IOPI bulb in place, for generalization. A mandatory rest period of 20 seconds will be utilized between trials.

Participants will be encouraged to use a stopwatch/timer to ensure at least one swallow/30 seconds.

A homework log will be provided to each participant to document the number of tongue presses practiced in each session.

There will be two practice sessions per day. On days when direct supervision is provided, this will replace one of the home practice sessions.

Participants will be encouraged to contact the study team if they have any questions or need support.

Study intervention withdrawal rules:

Withdrawal rules for the intervention portion of the study are tied to participant absence from scheduled intervention sessions. A participant will be withdrawn from the study if they miss a total of 3 consecutive scheduled supervised intervention sessions, or develop a new health concern.

Post-intervention VFSS appointment:

Timeline and location: Participants that complete the intervention will be scheduled for a post-intervention VFSS at the end of the 4-week intervention protocol. The post-intervention VFSS will be performed at the Toronto General Hospital's Diagnostic Imaging Gastrics Suite by the SRRL study personnel.

Order of stimuli:

i. Saliva swallow (with no external barium bolus) to be used for land-marking
ii. Up to 3 regular effort swallows of thin liquid
iii. Up to 3 regular effort swallows of mildly-thick liquid

VFSS stimulus preparation, procedure, and recording details are as described for the baseline VFSS described above.

Risks

During the consent discussion, the following risks will be disclosed to all participants who are considering taking part in the study:

a) Participants may be experienced from continued practice of the Effortful Swallow maneuver, particularly during intervention sessions. Participants will be reminded at the beginning of each session to disclose any fatigue to the speech language pathologist (SLP) supervising the direct intervention session, and also that they are free to discontinue any session at any time or choose to leave the trial if they wish.
b) Participants may dislike the taste of the stimuli presented for swallowing during the data collection sessions; they will be reminded that they are free to discontinue participation at any time.
c) All x-rays, including the video x-ray in this study, involve low levels of radiation exposure. Radiation exposure always carries a risk of radiation effects (such as cancer). We manage these risks by following standard procedures and keeping radiation dose as low as possible. The following information should help to explain this risk:
    a. The risk of developing cancer changes based on sex and age. Lifetime cancer risks associated with a full clinical video swallowing x-ray are:
        i. for 60-year-old male: 4.9 per million
        ii. for a 60-year-old female: 7.2 per million
d) The x-ray is expected to show whether or not the participant has swallowing impairment. We are looking for two specific types of swallowing problem:
    a. Food or liquid going into their airway ("aspiration").
    b. Food or liquid getting stuck in their throat (which we call "residue").

    If either of these problems occur during the study, the SLP will follow standard procedures to encourage the participant to expel the material and decide when study VFSS trials and/or exams need to be terminated early.

Incidental Findings

A swallowing x-ray captures information regarding the structures of the neck and how they move during swallowing. It is possible that the VFSS may contain evidence of other, unexpected findings that are noticed by the study speech-language pathologist (such as a diverticulum or a mass). In such cases, the study licensed speech-language pathologist will follow routine clinical

procedures and ask the on-call radiologist to review the VFSS. If appropriate, the radiologist will generate a clinical report documenting the observation. The consent form includes a check box prior to the signature line, asking the participant to indicate whether or not they wish to be told about incidental findings

Benefits

There may or may not be benefits to taking part in the study. Benefits from participating in the study include potential amelioration of swallowing difficulties, and furthering knowledge regarding interventions for swallowing impairment in the Parkinson Disease population.

Honorarium

Once participants have completed all study steps, they will be given $100 in the form of an e-gift card for their time and effort. Participants that drop out early but have completed at least 2 weeks of the intervention protocol, will be given $50 in the form of an e-gift card. Compensation will be provided upon return of loaned study equipment.

Data processing and analysis

All data processing and analysis will take place at SRRL – TRI. Prior to data analysis, each VFSS will be de-identified by study staff at TRI and the audio signal will be removed to limit the communication of any information that might bias the raters. The de-identified recordings will then segmented into bolus clips which will be randomized for rating. Blinded rating will be completed by trained raters (minimum of 30% to be completed in duplicate to ensure reliability). Raters will additionally be blinded to VFSS time-point (pre vs post-intervention), time post Parkinson Disease diagnosis and bolus consistency. The bolus clips will be analyzed by the Swallowing Rehabilitation Research Lab using the ASPEKT method.

Statistics

We will use Wilcoxon signed rank tests to show differences between baseline regular effort swallow (RES), baseline ES and post-intervention RES in the frequency and severity of impairment in time-to-LVC, pharyngeal constriction, airway protection and bolus clearance.

Conflicts of interest

Professor Steele, the principal investigator, holds current and prior research contracts with Bracco Canada and Nestlé Health Science, who are manufacturers of the barium products and thickening agents that will be used in this study. She has also served in an advisory capacity on expert panels for Nestlé Health Science. All products for use in the study will be purchased. Neither Bracco Canada nor Nestlé Health Science will have any role as sponsors of this study. Professor Steele will not receive any financial payment, either personally or to the lab, related to the use of Nestlé or Bracco products in this study. Additionally, we will preparing liquids of different thicknesses (thin and mildly thick) in this study. The definitions of these thicknesses come from a recent framework developed by the International Dysphagia Diet Standardisation Initiative (www.iddsi.org). Professor Steele is a member of the board of directors for IDDSI.

Participants will be made aware of these relationships during the consent discussion.

Direct Access, Handling and Record Keeping of Source Data

All participant data will be coded using an alphanumeric study code. The master key linking the study code to participant identity will be maintained by Professor Steele for the Toronto site, and by the lead investigators at Toronto Western Hospital.

SRRL personnel involved in the study (recruitment, consent, and completing the intervention) will have direct access to the study related documents. VFSS studies will be de-identified and stored electronically on a secure, password-protected, encrypted research drive at Toronto Rehabilitation Institute. Any data collected on paper will be kept in a locked filing cabinet in addition to being entered into electronic documents and saved on the encrypted research drive. The research drive is backed up daily, which will protect against the loss of data.

VFSS data and scanned copies of paper study forms from Toronto Western Hospital site will be transferred to the SRRL using UHN's OneDrive and will then be stored in the same manner as the UHN records.

As participant VFSS studies are considered personal health information and are protected under the Personal Health Information Protection Act (PHIPA), they will be archived at the end of the study and stored at SRRL under the custody of Professor Catriona Steele for a period of 10 years after which they will be disposed of in a secure manner.

Quality Control and Quality Assurance Procedures

All VFSS ratings will be completed in accordance to Standard Operating Procedures (SOP) for parameters of swallowing physiology described. The individuals who will perform the ratings will all be SRRL trainees or employees. Duplication of ratings will be completed and interrater reliability will be calculated.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law

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