Ethics Protocol

Title: Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

NCT04112940

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1. Introduction

This protocol covers a subproject of a larger project entitled *Physiological Flow of Liquids Used in Dysphagia Management*. The larger project (henceforth referred to as the parent grant) has been reviewed and funded by the National Institutes of Health as a 5-year R01 grant awarded to the PI (Catriona Steele, Ph.D).

The overall goal of the parent grant is to collect measurements of liquid flow through the oropharynx (i.e., mouth and throat) during swallowing. The factors that are expected to influence liquid flow include the liquid consistency (i.e., thin, slightly-thick, mildly-thick, moderately-thick, extremely-thick) and the forces applied during swallowing (i.e., tongue pressures and swallowing muscle contraction). The overarching objective is to determine how these factors interact to influence the flow of a liquid through the oropharynx. The goal of this subproject is to explore this question in adults with head and neck cancer.

Work on the parent grant to date has included the development, characterization and testing of liquid stimuli to be used in the current project, in which measures of liquid flow and swallowing behaviour will be collected in patients with head and neck cancer. Data collection will take place at the Swallowing Rehabilitation Research Lab of the Toronto Rehabilitation Institute. Videofluoroscopy x-rays will be conducted on a purchased service basis in the diagnostic imaging department at the Toronto General Hospital. We will also use patient questionnaires to evaluate the acceptability of thickened liquids by people with head and neck cancer.

2. Purpose and Specific Aims

Dysphagia (swallowing impairment) involves two primary concerns: 1) the ability to swallow safely, without material entering the airway; 2) the ability to swallow efficiently, without leaving residue behind in the pockets of the pharynx. Impaired swallowing safety is linked to pneumonia while impaired efficiency contributes to risk of malnutrition. Dysphagia is common in patients with head and neck cancer prior to, and as a result of treatment. Radiation treatment for the cancer can cause and exacerbate symptoms of dysphagia. Due to an increase in the prevalence of oropharyngeal cancers secondary to the Human Papilloma Virus (HPV), a growing number of individuals are receiving radiation treatment for their disease. However, because of the typically young age at diagnosis, these individuals can expect longer post-treatment lifespans during which there is a significant chance for negative sequelae to develop, including dysphagia. When a person presents with dysphagia, a common intervention is to alter the consistency of the foods and fluids they consume. However, we lack evidence to guide the modification of food and liquid textures for clinical benefit. In particular, we lack studies demonstrating the effect of texture modification as an intervention in the head and neck cancer population. In this study, we propose to measure the flow of thin, slightly thick and mildly thick liquids in patients who have completed radiation treatment for base of tongue cancer, to understand whether or not thickened liquids provide benefit.

We have three specific aims:

Aim 1: To determine whether slightly-thick and mildly-thick liquids are palatable and acceptable to patients with base of tongue cancer. We will collect palatability measures for starch- and gum-thickened liquids with slightly-thick and mildly-thick consistencies, as defined by the International Dysphagia Diet Standardisation Initiative syringe flow test. We will also collect baseline quality of life measures to understand the impact of swallowing impairment on the participant's quality of life. Following a videofluoroscopy swallowing assessment (described under Aim 2), participants will be advised to use thickened liquids that are effective for improving their swallowing. A follow-up phone call will monitor compliance and acceptance of this recommendation. Significance: This will determine how likely participants are to adhere to a thickener recommended based on its efficacy to reduce aspiration.

Aim 2: To determine how slightly-thick and mildly-thick liquids flow and whether they reduce aspiration compared to thin liquids in patients with base of tongue cancer. We will collect concurrent videofluoroscopic x-rays of swallowing and physiological measures of tongue pressure in patients with head and neck cancer using thin, slightly- and mildly-thick liquid barium stimuli. This appointment will occur approximately 3-6 months after the completion of the participants' radiation schedule. Significance: This will demonstrate the impact of consistency on bolus flow through the mouth and pharynx, controlling for the forces used to initiate flow and propel the bolus. Additionally, the data collected will aid in characterizing swallow physiology after completion of radiation therapy.

Aim 3: To determine whether the use of starch vs. gum thickeners impact the results of aims 1 and 2 The thickened liquids used for aims 1 and 2 will be prepared using both starch- and gum-based thickeners. Additionally, we will collect measures of salivary flow to control for possible interactions between thickener type and oral dryness on the results. Significance: Individuals may find one thickener more palatable or comfortable to swallow. Understanding this may impact compliance, swallowing safety and quality of life.

3. Methods

Participants:

The protocol will involve a single sample of adults, aged 18 or older with an initial cancer diagnosis of base of tongue cancer (T1-T3, N0-N2c, HPV + or -). The eligibility criteria will include completion of bilateral radiation therapy to the neck 3 months prior to enrollment, and removal of enteral feeding tube.

Participants will be asked to attend appointments and complete all data collection sessions described in this protocol. Participation involves two appointments, and two follow-up phone calls.

Exclusion Criteria:

- Participants will be accepted into the study provided they have no previous health condition known to cause swallowing impairment (e.g., stroke; brain injury; neurodegenerative disease).
- Individuals with a previous history of radiation to the head and/or neck area (prior to the current radiation treatment) will be excluded from this study given the possibility of long-term radiation effects to the swallowing apparatus.
- Individuals with a previous cancer diagnosis will be excluded from the study.
- Participants who do not show impaired swallowing safety on thin liquids in the videofluoroscopy (Penetration Aspiration Scale scores of 1 and 2) will be withdrawn from the study.
- Participants who have had, or have a planned neck dissection will be excluded.
- Individuals with tracheostomy in situ will be excluded from the study.
- Individuals with cognitive communication difficulties that preclude the understanding of the protocol or following study instructions will be excluded from the study.
- Due to the requirement to swallow stimuli containing starch based thickeners, which carry a significant carbohydrate load, individuals with Type 1 Diabetes will be excluded.
- Individuals with known allergies to latex, dental glue or barium will be excluded, due to the probability that these items will come into contact with the oral mucosa during data collection.
- Children and pregnant women will be excluded from the study due to the use of radiation
- Occupational exposure to radiation exceeding half the limit specified for Ontario exposed workers within the past 12 months.

These exclusion criteria will be confirmed using a self-report questionnaire form at the time of intake into the study (see standard operating procedures [SOP], provided as an additional study document). Any questions will be clarified through discussion with the research assistant responsible for participant intake, and, where necessary with the principal investigator.

Recruitment:

This is a preliminary study that will demonstrate feasibility for a future planned extension. We propose to recruit 10-12 participants. Potential participants will be identified by study Co-PIs Dr. Andrew Hope and Dr. Douglas Chepeha through the current radiation therapy clinics and base of tongue cancer caseloads at Princess Margaret Cancer Centre.

Stimuli:

An array of barium and non-barium stimuli has been developed for this study. These stimuli include thin, slightly-thick and mildly-thick liquids, defined using the International Dysphagia Diet Standardisation Initiative (IDDSI) gravity flow measures. The barium stimuli used for videofluoroscopy will be prepared using E-Z-Paque® barium in 20% w/v barium concentration with starch and gum-based thickening agents (Nestlé Resource® ThickenUp® and ThickenUp Clear®). The non-barium stimuli will be prepared using Nestle's Lemon Spash® lemon-flavoured water and the same starch and gum-based thickening agents

(Nestlé Resource® ThickenUp® and ThickenUp Clear®). All stimuli will be prepared in the Swallowing Rehabilitation Research Laboratory not longer than 6 hours prior to scheduled use, according to a strict standard operating procedure (refer to additional reference documents). Following preparation, stimuli will be stored in the swallowing lab until needed. Barium stimuli will be transported to the radiology suite at Toronto General Hospital in a cooler, as per routine clinical procedures.

Data to be collected from each participant:

The following types of data will be collected from participants:

a) An intake questionnaire noting age, sex, ethnicity and race data and confirming eligibility based on the absence of reported exclusion criteria.
b) During the intake process, we will review a list of conditions that could alter the results of the research study and identify whether any of these conditions apply. This will include disclosing the use of any medications that the participant is are currently taking, in order to allow us to control for the possible influence of medication on oral sensory and motor function. Medications do not qualify as the basis for exclusion. However, it is important for us to collect information regarding the use of benzodiazepines and neuroleptic medications that are known to have possible effects on swallowing, particularly with respect to causing xerostomia (dry mouth).
c) Palatability ratings for thickened liquids (with barium and without barium).
d) The MD Anderson Dysphagia Inventory (a quality of life scale related to dysphagia)
e) The Performance Status Scale – Head and Neck (a scale capturing dysphagia and diet status)
f) The University of Washington Quality of Life Revised Version 4 (UW-WOL-R4).
g) Tongue-pressure waveform data, collected at the anterior, middle and posterior palate using the 3-bulb tongue-pressure bulb array of the KayPENTAX Swallowing Signals Lab.If the participant is unable to tolerate the attachment of the sensors, we will measure tongue strength using the Iowa Oral Performance Instrument (IOPI). This approach does not include adhered attachments to the oral mucosa.
h) A measure of stimulated saliva (the Saxon Test), using a 2x2 inch of folded gauze that is chewed for 2 minutes, expectorated and then weighed prior to being discarded.
i) A videofluoroscopy recording of swallowing collected at a pulse rate of 30 pulses per second and video capture at 30 frames per second.
j) Responses to follow-up phone calls exploring acceptance of thickened liquids.

Data Collection Procedures: Data Collection Session 1: The participant will arrive at the lab and will be asked to complete two questionnaires: the MD Anderson Dysphagia Inventory (MDADI), the Performance Status Scale for Head and Neck Cancer (PSS-HN) and the University of Washington Quality of Life Revised Version 4 (UW-WOL-R4).

Prior to data collection, saliva flow will be collected using the Saxon Test, for which the participant will chew on folded sterile gauze for 2 minutes. The gauze will be weighed before and after chewing to determine amount of saliva production. The participant will then be asked to swallow 6 non-barium

stimuli, and 2 barium stimuli thickened using starch and xanthan-gum based thickeners. After the participant has sampled each stimulus, they will be asked to rate palatability on a visual, hedonic scale (see study instruments provided).

Data Collection Session 2: Prior to data collection, saliva flow will be collected using the Saxon Test, for which the participant will chew on folded sterile gauze for 2 minutes. The gauze will be weighed before and after chewing to determine amount of saliva production. The participant will then be seated in the videofluoroscopy suite for tongue pressure sensor attachment. A silicon strip housing three 8 mm diameter pressure bulbs will be attached in midline to the roof of the participant's mouth, with the front sensor located immediately behind the participant's upper incisor teeth. The sensor strip will be attached using a medical adhesive (Stomahesive®, Convatec, St-Laurent, Quebec, Canada).

Following sensor attachment, the video output line from the fluoroscopy unit and the tongue pressure sensors will then be connected to the KayPENTAX Digital Swallowing Workstation Swallowing Signals Lab equipment, which is located on a properly insulated cart with an uninterrupted power supply and isolation transformer (see Image 1). If the participant is unable to tolerate the attachment of the sensors due to mucositis or general discomfort, we will measure tongue strength using the Iowa Oral Performance Instrument (IOPI) and collect the videofluoroscopy measures without the use of the adhered sensors.

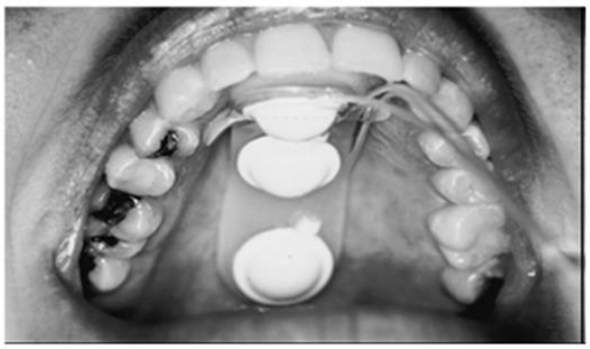


Image 1. Tongue pressure sensors.

Participants will be asked to swallow a series of thin, slightly-thick and mildly-thick barium stimuli 1 (3 boluses each of 5 stimuli, for a total of 15 boluses) in videofluoroscopy, with concurrent measurement of tongue-palate pressure. Videofluoroscopy will be performed at optimal temporal resolution (30 pulses/second) and captured at 30 frames/second. The stimuli will be presented in a randomized design, blocked by stimulus type. Participants will be allowed to take natural sized sips of each stimulus from cups containing 40 ml. Sip volume and mass will be calculated, by weighing the cups prior to and after the videofluoroscopic assessment.

Data Processing:

The tongue-pressure waveform will be segmented using an automatic segmentation algorithm developed previously in the PI's lab. Similarly, the videofluoroscopy recordings will be spliced into single bolus clips and the audio channel will be muted to remove cues that might bias rating. Blinded videofluoroscopy rating will then be performed in duplicate by trained raters in the Steele Lab following established procedures (see SOP provided as an additional study document). Discrepancies between raters will be flagged and resolved at consensus meetings, as required. These procedures will yield a

large number of parameters for each swallow. We will use established measures within our lab to collect and analyze measures related to kinematics and residue.

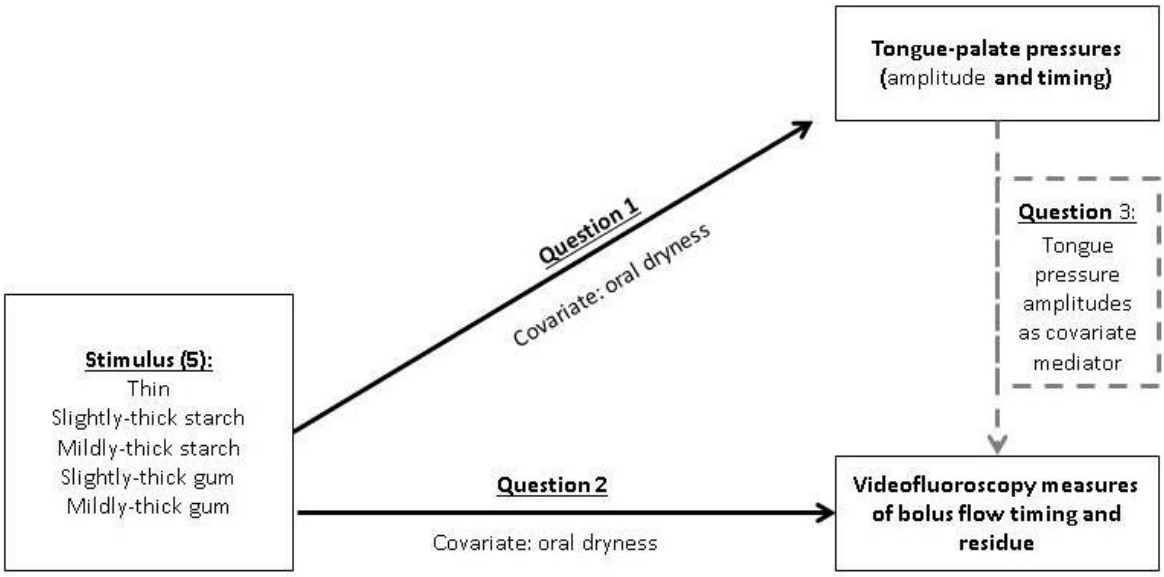
Follow-up phone calls: If deemed appropriate, the participant may be offered the opportunity to complete a follow-up component. For those willing to participate, this optional experiment will involve two follow-up telephone calls (at 2 weeks and 3 months following the videofluoroscopy) to determine compliance with use of thickened liquids recommended following the videofluoroscopy (see study instruments provided for questionnaires).

Data Analysis:

For Aim 1, we will compare hedonic ratings for the different stimuli using a univariate ANOVA. It is hypothesized that ratings will be significantly better for the thin and slightly thick stimuli compared to the mildly-thick stimuli, and that a preference will be seen for the gum compared to the starch thickened liquids.

For Aim 2, blinded videofluoroscopy rating will be performed in duplicate, and discrepancies between raters will be flagged and resolved at a consensus meeting. The frequency of aspiration will be explored with the thin stimuli and compared to the prevalence of aspiration when thickeners are introduced using chi-square statistics.

We will model the impact of stimulus on two timing measures of pharyngeal bolus flow from the videofluoroscopy (i.e., a) the interval from the bolus passing the mandibular ramus until laryngeal vestibular closure; b) the interval from the bolus passing the mandibular ramus until entering the upper esophageal sphincter) and on measures of post-swallow residue (Normalized Residue Ratio Scale). The Saxon test results regarding oral dryness will be used as a covariate for all analyses, as illustrated in the Figure below:



A path analysis approach will be used to first identify differences in tongue pressure across stimuli

(Question 1). If confirmed, this potential modulator will be added to the Question 2 model as a covariate (Question 3). The planned analyses will involve linear mixed model repeated measures ANOVAs with a factor of stimulus.

For Aim 3, we will use qualitative methods to describe participant reports of adherence to the prescribed thickener. Information from the quality of life and performance status scales collected in session 1 will be used to inform our understanding of variations on patterns of thickener acceptance.

4. Risks and Benefits

Risks

The following risks will be disclosed to all participants prior to obtaining their consent to participate:

a) Participants may experience local mucosal irritation from the glue on the adhesive strip used to attach the tongue-pressure bulbs for data collection. The glue usually wears off within 90 minutes following the conclusion of data collection. In the incidence that participants are unable to tolerate the attachment of the sensors, we will use the IOPI tongue bulbs to collect tongue measurements, and collect videofluoroscopic data using the same protocol.

b) Participants may dislike the taste or texture of some of the thickened liquid stimuli in the study. Participants will be reminded that they are free to discontinue participation at any time.

c) Participants may experience some fatigue during the videofluoroscopy data collection session. Participants will be reminded that they should disclose any fatigue or discomfort to the research team, and that they are free to discontinue any particular session or to withdraw from the study at any time.

d) Participants will receive additional exposure to radiation during the videofluoroscopy, in addition to their recent radiation treatment protocol. Based on a previous videofluoroscopic study that we have conducted in healthy adults, the study is expected to involve 118+/-18 seconds of radiation exposure (Molfenter & Steele, 2013), with an associated dose estimate of <0.35 milliSieverts. Moro and Cazzani showed that this dose (0.35mSv) corresponds to a risk of 1 in 39,000 of developing a radiation-induced stochastic effect from a videofluoroscopy. We will use a 2-minute warning bell to alert the data collection team to exposure time, and will terminate the protocol at the first opportunity following the bell.

e) Aspiration (entry of material into the airway) is a possible risk during the videofluoroscopic swallowing study that will be performed. This risk is always present for videofluorscopic swallowing studies, which are intended to document the presence and severity of swallowing abnormalities, including (but not limited to aspiration). When aspiration is observed, standard procedures will be followed to encourage coughing and throat clearing to expel the aspirated material. The protocol will be terminated immediately. Any participant who experiences aspiration will be counseled regarding aspiration prevention strategies and aspiration-risk following the videofluoroscopy.

f) Choking is an extremely unlikely event. However, in the event of choking, routine emergency procedures will be followed. All study personnel carry current CPR certification.

g) In the unlikely event that an incidental finding is noted on the videofluoroscopy (such as a diverticulum or a mass) the attending SRRL licensed speech-language pathologist will consult the on-call radiologist and generate a clinical report documenting the observation. These findings will be communicated with the participant as per usual clinical practice and follow up with their physician will be recommended.

Benefits

Participants who aspirate during the videofluoroscopy and demonstrate safer swallows using the thickened stimuli that are tested will be provided with 2 cans of the thickener-type from which they benefitted and instructions for use. Ongoing use of this thickener, as instructed, may reduce their risk for subsequent aspiration and related sequelae.

5. Privacy and Confidentiality

Routine practices for ensuring the confidentiality and privacy of all participants will be followed in this study. All research personnel at the Toronto Rehabilitation Institute are required to sign a confidentiality agreement at the time of hire.

Participants will be assigned a non-identifying alphanumeric study code, and the master key for this code will be retained separately by the PI in a password-protected file on a secure, password-protected, encrypted research server. Daily back-up of this research server is performed centrally at the Toronto Rehabilitation Institute to protect against data loss. Hard copies of the participant consent forms will be maintained in a folder, kept in a locked filing cabinet in the Swallowing Rehabilitation Research Lab.

All waveform and videofluoroscopic data will be stored electronically on the secure, password protected, encrypted research server. Any hard copy data will be transcribed into an electronic file (stored on the server), and the hard copy records will be stored in a locked filing cabinet in the Swallowing Rehabilitation Research Lab. Only the participant's alphanumeric study code number will appear on the data collection sheets and in the data collection files.

Access to participant information and experimental raw data will be restricted to the study personnel named in this application. All records will be destroyed after 10 years under the supervision of Dr. Steele.

In the event of inappropriate release of personal health information, further release of information will be stopped, any information that can be retrieved will be retrieved, the UHN Privacy Office and REB will be notified, and any recommended further actions will be taken.

6. Compensation

Data collection for each participant will involve 3 separate appointments and two post-study follow-up telephone call: a) intake; b) Session 1; c) Session 2 (videofluoroscopy); and d) follow-up phone calls at 2 weeks and 3 months following Session 2. Each face-to-face appointment is expected to last 1 hour. An honorarium of $50 will be provided per participant to cover expenses associated with participation in the study. This will be paid at the end of the videofluoroscopy session. Additionally, two cans of thickener will be provided to participants for whom thickening is shown to be effective for reducing aspiration.

7. Conflicts of Interest

Dr. 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. These relationships will be disclosed to participants in the study information sheet. 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. Dr. 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. Carly Barbon receives a stipend from the University of Toronto.

8. Informed Consent Process

All participants who show an interest in participating will be provided with detailed information about this study via the Participant Information Sheet and Consent Form two weeks prior to the scheduled intake appointment. Only after confirming they have understood all the information that is provided and after verifying they have no more questions, can they sign the consent form. A copy of the consent form will be provided to them. When the ability to comprehend the study is in question we will also request assent from the patient's substitute decision maker prior to enrolling a patient in the study.

The consent form includes a specific section requesting consent to use of study-related images for future educational and teaching purposes.

9. Scholarly Review

This parent grant of which this project is a subproject has undergone scientific review by the MFSR Study Section of the National Institutes of Health (USA).

10. Additional Ethics Reviews

There are no additional ethics reviews planned.

11. Contracts

There are no contracts required for this project, which will be conducted exclusively at the Toronto Rehabilitation Institute.

12. Budget

All costs for this study will be covered by the grant received from the National Institutes of Health.