Official Title: Esophageal Food Impaction (ONEFIT)

NCT#: NCT03305848

Study Protocol and Statistical Analysis Plan

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Participant Contact Project Narrative

1. *Summary*

   A piece of food stuck in the esophagus (the tube connecting the mouth to the stomach) is a relatively common occurrence, estimated at a rate of 13 episodes per 100,000 people per year, mostly men, and usually attributed to swallowed meat. The current standard of care for patients presenting to an Emergency Department with this problem includes a trial of medication, usually glucagon but sometimes a carbonated beverage, an injection of nitroglycerin, or benzodiazepines. The medical interventions mentioned above have not been shown to be significantly effective and have unwanted side effects; glucagon is known to cause nausea and vomiting and benzodiazepines can cause sedation and depressed breathing. If the medication fails to relieve the problem, the patient may require a procedure called endoscopy, where a video scope and retrieval tool are inserted into the esophagus to remove the piece of food. There is significant risk associated with endoscopy, including the risks of anesthesia as well as with the physical procedure itself. Endoscopy also results in a prolonged hospital stay due to the time required for the procedure, as well as from anesthesia recovery. The ideal treatment would be a safe, inexpensive, quickly effective medication without significant side effects that could be administered without sedation or extensive monitoring. Oral nitroglycerin solution might just be that intervention.

2. *Study aims*

   Obtain exploratory data on the safety and efficacy of oral nitroglycerin solution for the treatment of esophageal food impaction in a cohort of patients presenting to the ED with presumed esophageal food impaction.

   Aim 1: Efficacy. We will determine the success rate of oral nitroglycerin solution in relieving the food impaction by assessing the resolution of symptoms and the ability of the patient to swallow.

   Aim 2: Safety. We will calculate the frequency of adverse events from this medical intervention. We are mainly concerned with hypotension, lightheadedness, headache, allergic reaction, dyspnea, vomiting, and pain.

3. *Background, Rationale, Significance*

   Esophageal food impaction is a relatively common illness, estimated to occur at a rate of 13 episodes per 100,000 people per year, mostly men, and usually attributed to swallowed meat bolus. Current standard of care for patients presenting to an Emergency Department with presumed esophageal food impaction includes trial of medical therapy, usually glucagon but sometimes effervescent liquid, sublingual or intravenous nitroglycerin, or benzodiazepines, with a backup of endoscopy for definitive mechanical removal of the food bolus. Glucagon has significant uncomfortable side effects, chiefly nausea and vomiting. The medical interventions mentioned above have not been shown to have significant efficacy; endoscopy is frequently performed after failure of medical management. There is significant risk associated with endoscopy, including the risks of anesthesia as well as with the physical procedure itself. Endoscopy also results in a prolonged hospital stay due to the time required for the procedure, as well as from anesthesia recovery. The ideal treatment would be a safe, inexpensive, quickly effective medical intervention without significant side effects that could be administered without sedation or extensive monitoring. Oral nitroglycerin solution might just be that intervention.

   No published trials or case reports using oral nitroglycerin solution for esophageal food impaction were found. Two recent unpublished cases using oral nitroglycerin solution were remarkably and rapidly effective (within 2 minutes) in relieving esophageal food impaction symptoms. The currently proposed study would provide preliminary data which may motivate a larger controlled study.

4. *Approach*
   a. *Study design*

Prospective, unblinded, single-arm cohort of patients presenting to the Emergency Department with presentation consistent with esophageal food impaction.

b. Population

i. Inclusion/Exclusion Criteria [See Human Subjects items to be moved here]

1. Inclusion Criteria:
    a. Over the age of 18 years
    b. Presentation consistent with esophageal food impaction
    c. Ability to swallow a small volume of liquid.
2. Exclusion Criteria:
    a. Intractable vomiting
    b. Hemodynamic instability or SBP <100 mmHg
    c. Concern for or evidence of significant airway compromise
    d. Concern for or evidence of esophageal perforation,
    e. Concern for or evidence of coronary ischemia
    f. Presentation > 12 hours since onset.

ii. Sample size

1. Convenience sample of 20 patients.

c. Data collection process

i. Process steps for identification of patients or records

1. Study staff may access medical records of all potential subjects' identified (i.e., Workbench) to determine eligibility criteria using information that already exists in the medical record. During this process, no identifiable information may be recorded and any documentation made of a potential subject's information that would disqualify them will be destroyed. If an eligible patient is not being cared for by the PI, study staff must approach the patient's provider to determine if it is appropriate to proceed with the consent process.
2. If additional testing needs to be done to see whether a patient meets criteria for entry into the study, the PI or staff will need to consent the patient first.
3. If the preparation activity confirms a patient is a possible subject, PI/staff approaches the patient to begin the consent process.

ii. Recruitment

1. Study subjects will be recruited from the Emergency Department once their case has been identified as being preliminarily eligible by research assistants or medical providers. Once a potentially eligible patient is identified, the intern and/or CCRC research staff will screen the patient for eligibility based on the inclusion/exclusion criteria. If an eligible patient is identified, research staff will consult with the treating team to determine if the patient is a candidate for enrollment. The research team will use Epic to facilitate the screening process under the preparation for research guidelines. If the patient is eligible and a physician on the study team approves the patient's inclusion into the trial, a member of the research team will approach the patient/family, explain the study verbally, and review the informed consent document. The patient and, if present, legally representative family member, will be given sufficient time to privately review the consent form and discuss potential involvement in the trial. The research team member will again meet with the patient/family to address any questions and discuss enrollment. If appropriate, the research staff member will obtain consent from the patient or family member and begin the enrollment process. Critical Care Research staff is on site and has on-call staff 24/7/365.
2. No recruitment tools will be used in this study.

iii. Consent

1. Study subjects who meet all of the inclusion criteria and none of the exclusion criteria will be approached for consent by study staff prior to enrollment. If an eligible patient is not being cared for by the PI or a Co-I, study staff must approach the patient's provider to determine if it is appropriate to proceed with the consent process. If additional testing needs to be done to see whether a patient meets criteria for entry into the study, the PI, a Co-I, or staff will need to consent the patient first. If the preparation activity confirms a patient is a possible subject, PI/research staff approaches the patient to begin the consent process.

iv. Data sources
    1. 1. Study subjects will be interviewed prior to treatment and again after treatment. Medical records from the visit will be collected.
    2. Please see attached chart titled "Data Collection Form" describing the variable name, data source, purpose, and measurement scale in the initial application submission

v. Process steps for data acquisition
    1. The study subject's demographical, medical, and surgical history, and symptom data will be initially collected from medical record and interview by investigators and/or research assistants during the Emergency Department visit. First at enrollment, then after each administration of study medication. Data will be collected by study investigators and/or research assistants. Data collected includes:

        Medical record number (MRN), Age, Gender, Visit date, Allergies, Blood pressure, Presenting complaint / HPI, Symptoms throughout the ED visit, medical history, surgical history, time and dose of medications administered
    2. The patient's ED provider will be asked for appropriateness for inclusion in the study (yes to any answer will count as an exclusion). They will be asked:
        a. Is symptoms onset more than 12 hours ago?
        b. Is there concern for airway obstruction?
        c. Is there concern for esophageal perforation?
        d. Is there concern for coronary ischemia?
        e. Are there any other concerns about including this patient in the study?
    3. After discharge of the patient (either from the ED or after admission), their medical record will be accessed for data abstraction by investigators and/or research assistants. The following data will be collected:
        a. Disposition from the ED
        b. Length of stay
        c. Procedures performed during the visit
        d. Medications given during the visit
        e. Condition at discharge
    4. A single follow-up phone call will be made by investigators and/or research assistants between 4-7 days after discharge to obtain:
        a. Symptoms at discharge
        b. Symptoms currently
        c. Any other treatment required since hospital discharge
        d. Satisfaction survey

d. Intervention, treatments

i. Up to 3 administrations of 0.4mg sublingual nitroglycerin tablets, dissolved in 10mL tap water, given orally in a single swallow. Each administration is separated by at least 5 minutes, and only if systolic blood pressure > 100 mmHg. The patients then have to pass a swallow test before discharge. The passing of the swallow test will indicate a treatment success. Treatment failure is

defined as lack of symptom resolution 10 minutes after the last dose of nitroglycerin OR inability to tolerate administration OR intolerable side effects.

e. Outcomes/endpoint and other variable definitions, and instruments used

i. Primary Endpoint is the patient is able to swallow without difficulty within 10 minutes after nitroglycerin administration.

ii. Secondary endpoint is adverse events during the hospital stay.

f. Statistical analysis plan

i. Descriptive statistics will be used to summarize the study sample and to evaluate efficacy of the study intervention and frequency of side effects. Specifically, we will first calculate summary statistics (mean ± standard deviation, frequency counts and percentages) for relevant patient factors (demographics, etc.) at the time of presentation to the ED. We will then calculate the proportion of study patients who achieve resolution of food impaction, with a corresponding 95% confidence interval. Similarly, we will also report frequencies of adverse events, overall and by type of adverse event, along with appropriate measures of variance (including headache frequency and change in blood pressure). Finally we will report outcome statistics (frequency counts and percentages) for repeat symptoms subsequent to the hospital visit (from follow up phone call). Symptom data from follow-up phone call will be used, non-statistically, to identify possible delayed complications of oral nitroglycerin use.

g. Power analysis or statement of precision

i. No formal hypothesis testing will be pursued, thus we have not conducted a power analysis.. Given the proposed sample size (n=20), and projecting 90% success in resolving food impaction (18/20), we anticipate a 95% confidence interval of (68.3%, 98.8%).

h. Strengths and limitations

i. Strengths

1. New, promising medical intervention for esophageal food impaction with a strong theoretical likelihood of success.

ii. Weaknesses

1. Being a pilot study, further research will need to be undertaken to fully assess the safety and efficacy of the proposed intervention. We will not enroll a comparison group, statistical precision will be limited due to small sample size, and all results will be descriptive (no control for covariates).

5. Setting/Environment/Organizational feasibility
   a. This study is easily achievable, as the study cohort regularly presents to the Emergency Department, the study medication is inexpensive, universally available, and very easily administered.
   b. Research assistants are available 24/7/365 to help with enrollment and data collection.
6. Risks and Benefits
   a. The risks to study subjects are minimal. As with any medication, there is a risk of allergic reaction. Nitroglycerin causes vasodilation and has been associated with modest reduction in blood pressure, however this medication has been safely used for many years. The theoretical systemic absorption of oral nitroglycerin solution is slower than sublingual, and since its half-life is very short, systemic effects may very well be less prominent than with sublingual or intravenous administration.
   b. The benefits to study subjects include potentially rapid reversal of symptoms and food impaction with minimal delay or side effects, avoidance of admission and endoscopy, and avoidance of use of glucagon.
7. Data Confidentiality and Privacy
   a. This study is being conducted in accordance with the ethical principles that are consistent with the ICH and Good Clinical Practice. Once a patient is identified, they are assigned a unique identification number that is assigned to the patient for the duration of the study. The master database linking the patient MRN with the unique identification number is stored on a password-protected, secure share drive housed in the Critical Care Research Center. The CCRC is a locked office with limited accessibility. All

CCRC research staff have EPIC access via a unique user name and password that is monitored by IS&T Security. All research staff are fully trained on the elements of patient privacy, HIPAA and confidentiality.

b. Because of the protective safeguards in place to protect patient privacy, there is a very low risk to a patient's loss of privacy, risk to reputation or other social risks. The only data that will be accessed from the patient's medical record will be data that is related to the specific admission and meet the defined data abstraction elements.

c. All eligibility screening, enrollment, randomization, and data entry will take place in the CCRC. The CCRC is a secure, locked department with limited access for security purposes. All patient charts and paper case report forms, including signed consent forms, will be stored in locked file cabinets in the CCRC. A master database linking the subject number and patient name will be maintained on a password-protected server only available to research staff. This is a secure, electronic system that is currently used at Regions Hospital and is approved by IS&T Security. All study data will be coded and de-identified.

8. Timeline
    a. This study is proposed to be completed within 1 year.
        i. April 2017: IRB Submission
        ii. May 2017: IRB Approval
        iii. August 2017: Educate providers and CCRC research staff on enrollment criteria
        iv. August 2017- August 2018 Enroll patients and collect data
        v. July 2018 Analyze data and write abstract/manuscript for submission
9. Dissemination/Sharing Results/Integration and Impact
    a. We will prepare the results of the study for publication, with potentially significant impact on routine management of esophageal food impaction by Emergency medical providers.
10. References

    a. Robbins M, Shortsleeve M. Treatment of Acute Esophageal Food Impaction with Glucagon, an Effervescent Agen, and Water. *Am J Roentgenology*. 162:325-28. 1994.
    b. Management of Ingested Foreign Bodies and Food Impactions. *Gastrointestinal Endocscopy*. 73(6):1085-91. 2011.
    c. Ko HH, Enns R. Review of Food Bolus Management. *Can J Gastroenterol*. 22(10):805-8. 2008.
    d. Dellon ES, et al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). *Am J Gastroenterol*. 108:679-92. 2013.
    e. Weant KA, Weant MP. Safety and Efficacy of Glucagon for the Relief of Acute Esophageal Food Impaction. Am J Health-Sys Pharm. 69:573-77. 2012.