RANDOMIZED CONTROLLED TRIAL OF RADIOFREQUENCY ENERGY DELIVERY TO THE LOWER ESOPHAGEAL SPHINCTER FOR CHRONIC GASTROESOPHAGEAL REFLUX

Y. Alexis Choi

A. Introduction

a. Background

Gastroesophageal reflux disease (GERD) is the most common disorder of the esophagus (0. It affects as much as 40% of the American adult population and up to 50% of these patients are afflicted with a chronic, relapsing syndrome (1). The quality of life with GERD has been reported as being comparable to that with angina or heart failure (2). There are a number of factors that contribute to the pathophysiology of this disorder, including lower esophageal sphincter (LES) incompetence, esophageal body dysmotility, and dysfunctional gastric secretion and emptying (1).

Most medical therapies for GERD are directed at lowering the acidity of the refluxate. The most effective of these drug therapies is the proton pump inhibitor (PPI), which resolves symptoms in 80% of cases and heals esophagitis in 90 % (3-5). H2 blocker, which is much less efficacious, is sometimes helpful for nocturnal acid suppression (6). Unfortunately, with cessation of therapy, 80% of patients relapse and therefore many patients become committed to lifetime therapy (5). Therefore, many of the chronic patients face a dilemma of noncompliance with persistent symptoms or inconvenience and cost of indefinite medical therapy. Furthemore, although there is no suggestion epidemiologically of an association between long-term PPI therapy and gastric malignancies, there is also no definitive evidence that prolonged PPI treatment and its consequent elevated levels of gastrin are entirely benign (7) In fact in animal studies it has been shown to cause carcinoid tumors and enterochrornaffin cell hyperplasia (7). Also, omeprazole use has been associated with worsening of Helicobacter pylori-associated gastritis (8).

Anti-reflux surgeries, such as open and laparoscopic Nissen fundoplication, are available as alternative treatments for GERD. These procedures are directed at mechanically improving the competence of the LES by wrapping the fundal stomach circumferentially around the sphincter. Studies have demonstrated that laparoscopic fundoplication reduces symptoms in76-98% of patients and decreases esophageal acid exposure time on pH monitoring in 90 % (9). Also, this procedure has been shown to be efficacious in improving quality of life, and even to outdo some medical therapies in similar measures (10, 11). Unfortunately, these procedures are not without risk. Although the laparoscopic approach has significantly reduced mortality, these invasive procedures can cause esophageal or gastric perforation, pneurnothorax and other complications associated with surgery and general anesthesia (1). A number of investigations have focused on endoscopic interventions, which are less invasive and do not require general anesthesia, to achieve overall similar LES improvements. Some of these are suturing, injecting bulking agents or sclerosing agents, and radiofrequency energy (RFE)delivery (12-16).

Radiofrequency energy has been utilized for a number of clinical syndromes. Some of these applications include treatments for cardiac dysrhythmias and joint laxity (17, 18). These studies underscore the utility of RFE is in allowing targeted ablation of specific tissues and tissue tightening by thermally induced collagen contraction, collagen deposition, and wound healing (16). Recently, preliminary animal studies have suggested that RFE can be used as therapy for GERD (15, 16). In a canine model RFE reduced transient LES relaxation by 54% (15) and in a porcine model it increased the mean LES pressure and gastric yield pressure (gastric pressure required to induce reflux) (16). Similar effects were attained in a human study: RFE reduced transient relaxation of LES by 44% (14).

b. Rationale

As a less invasive alternative to anti-reflux surgeries, RFE may relieve symptoms, liberate patients from the inconvenience and possible risks of lifetime medication therapy and thereby improve their quality of life with chronic GERD. The primary endpoints of this study will be need for PPI medication pre- and post-RFE. The secondary endpoints will be quality of life, symptoms, mean acid exposure time on pl-I monitor, and resting LES pressures and frequency of transient relaxations on esophageal. manometry.

B. Methods

a. Recruitment of Subjects

Patients with chronic relapsing GERD requiring indefinite maintenance PPI therapy in the principle investigator's own clinical practice or referred to his office will be approached for enrollment.

b. Patient Selection/Screening

i. Inclusion criteria

- Age 18-80
- Previously diagnosed with GERD or who have chronic heartburn and/or regurgitation
- Currently on daily proton pump inhibitor therapy, with complete response to medication
- Failed taper or cessation of therapy with PPI in past
- On esophageal manometry, peristaltic amplitude >30 mmHg, LESP > 5 mmHg, complete relaxation in response to swallow
- On 24 hr ambulatory pH monitoring, > 4.0% acid time exposure
- Able to give informed consent

ii. Exclusion criteria:

- hihatal hernia > 2 cm on endoscopy
- Active peptic ulcer disease
- Previous esophageal/gastric surgery
- Active gastrointestinal hemorrhage
- Gastric/esophageal malignancy
- Mucosa suspicious for Barren's esophagus
- Moderate - severe (> Hetzel grade 2) esophagitis on pretreatment endoscopy
- Esophageal strictures
- History of caustic ingestion
- Achalasia
- Scleroderma, other collagen vascular disease
- Pregnancy
- Significant untreated comorbidity

C. Sample Size

The sample size of 100, 50 in each arm, was estimated based on detecting a reduction in medication use after procedure by 20% (with 80% power, p=0.5).

D. Study design

This study will be a prospective, randomized, controlled trial of radiofrequency energy to lower esophageal sphincter as therapy for chronic gastroesophageal reflux disease. All patients with chronic heartburn/regurgitation or diagnosed with chronic GERD dependent on PPI in the PI's practice or referred to his practice will be approached for enrollment. All patients enrolled in the study will undergo screening with baseline procedures of EGD/manometry and 24hr ambulatory pH monitoring off medications for 5-7 days. They will resume their medications immediately after the procedures. Those that meet criteria will then be randomized into either of two arms: the control group who will continue PPI use and the experimental group who will undergo RFE and discontinue PPI 2 weeks after RFE. Prior to RFE they will answer a questionnaire assessing for baseline symptoms, medication use, factors related to GERD (addressed in "Study Questionnaire") and quality of life on medication. Six months after the RFE (experimental group) or enrollment (control) both groups will be asked to return to the office for a repeat questionnaire session. Twelve months after RFE or enrollment both groups will be asked to return for another questionnaire, EGD/manometry and 24 hour pH monitoring, (again off medications). Patients in the experimental group will be taken off anti-acid therapy two weeks after RFE but will be allowed to resume it at starting doses (tapering up as necessary) if symptoms return. All procedures, screening and follow-up assessments will take place at the New York Presbyterian Hospital at Columbia Campus, specifically in the endoscopy suite and private clinical and research offices of the Pl. Finally, patients in the control group will be offered the investigational procedure after the trial once benefit of RFE has been established.

E. Statistical Analysis

For the discontinuous measures such as the primary endpoint of need for medication (i.e., the frequency of patients on acid suppressive medication) and the secondary endpoint of frequency of transient relaxations on manometry the chi square test will be used. For the continuous variables, the quality of life score and the mean esophageal acid exposure time, t-test analysis will be used.

The statistical analysis will include multiple logistic regression of the endpoints adjusting for the following variables: smoking, alcohol, diet compliance, HOB elevation, BMI, specific types of exercises, and use of medications affecting the LES or acidity of gastric content.

F. Study procedures

a. Investigational procedure

The procedure under investigation will be radiofrequency energy delivery to the lower esophageal sphincter by endoscopic means. It will be done on an outpatient basis in the endoscopy suite by the principle investigator. Agents for conscious sedation will be intravenous fentanyl or meperidine and midazolam. The RFE catheter consists of a bougie tip, a balloon-basket assembly, and 4 electrode delivery sheaths positioned radially around the balloon. The needle electrodes, 22 gauge and 5.5mm length, are made of nickel-titanium. The catheter will be passed to the level of 2 cm below the squamocolumnar junction (distance determined by passing the endoscope and measuring the length of scope from the incisors). The balloon will be inflated and the 4 needle electrodes will be deployed into the muscle of the GE junction. Proper deployment into muscle will be confirmed by measuring tissue impedance which should decrease from >500 Ohms to 100-300 Ohms once the electrodes move from simple mucosa to muscle. A 4 channel RF generator will deliver 465 kHz /2-5 Watts of radiofrequency energy to each needle electrode. Each needle tip is equipped to monitor the temperature for the purpose of modulating the power output to achieve a target tissue temperature of 85 degrees C for 2 minutes. The mucosal temperature will also be monitored and maintained below 30 degrees C with constant delivery and suctioning of chilled water through a separate channel. This process will be repeated multiple times to produce 12-15 lesion sets between 2 cm above and 2 cm below the squarnocolumnar line. After the delivery of RFE patients will undergo endoscopy for gross assessment of the mucosa. Preliminary data

from an as yet unpublished safety trial reports several complications observed at 6 month follow-up: fever, odynophagia, flatulence and bloating.

b. Other study procedures

After approximately a week of cessation of the medication(s) (5 days for H2 blockers, 7 days for PPI), patients will undergo esophagogastric-duodenoscopy (EGD) with manometry and 24 hour ambulatory pH monitor. These procedures will take place before RFE for the purposes of screening and attaining baseline information and repeated 12 months after treatment with RFE for follow-up information. EGD will assess grossly the presence and severity of GERD related esophageal disease and also screen for any lesions consistent with syndromes stated in the exclusion criteria. Esophageal manometry will be done during the same session as the EGD. It involves passing endoscopically a pressure sensitive probe to take the following measurements: LES pressure, length, relaxation and peristaltic amplitude will be measured. The 24 hour ambulatory pH monitor consists of transnasal passage of a pH sensor to the level of 5 cm above the manometrically established upper border of LES. The esophageal acid exposure time will be measured. The risks of these procedures include perforation, bleeding, and infection; the rates of these complications are less than 1% at this institution.

G. Study Drugs

The control group and failed experimental group will be treated with proton pump inhibitors (e.g., lansoprazole, omeprazole) with or without H2 blockers (e.g., famotidine, ranitidine). They are the most efficacious medical therapies for chronic, refractory GERD (described in "Background"). The proton pump inhibitors have a side effect profile including gastrointestinal symptoms, such as abdominal pain (2-5 %), nausea (2-7 %), diarrhea 3-8 %), flatulence (3 %), vomiting (1.5-3 %), acid regurgitation (1.9 %), and constipation (1-1.5%), headache (3-13%), dizziness (1.5 -3 %), and rash. Other less common side effects include decreased vitamin B 12 absorption in long-term users, Helicobacter pylori-associated gastritis, hypergastrinernia, parietal cell hyperplasia, minor increased risk of ocular toxicity, and ten-fold increase in risk of Campylobacter enteritis in >= 45 year olds. The H2 blockers can produce the following side effects: headache (1.3-2 %), constipation (1.4 %), diarrhea, dizziness, and fatigue. The dosage regimens used will be dependent on symptom control but will be within standard practice.

H. Study Questionnaires

The questionnaire will be comprised of five parts, as follows:

I. GERD Symptoms: **A questionnaire designed and validated for detecting changes in symptoms of upper gastrointestinal disorders will be used (19)**

II. **RFE related morbidity:** As a means of assessing for procedure related morbidity, part of the questionnaire will include evaluation of symptoms reported in studies of RFE and antireflux surgeries. The side effects of RFE (described in "Study Procedures") will be assessed along with other side effects reported in anti-reflux. surgery studies such as dysphagia, inability to belch, chest pain, nausea, diarrhea, signs of significant bleeding in stool (i.e., melena) (20, 21).

III. **Quality of Life (SF 12):** The validated questionnaire is scored to produce two summary measures: the physical component summary (PCS-12) and mental component summary (MCS-12). This generic measure is comparable in reliability and validity to SF-36 (22, 23).

IV. **Medication** Use: The frequency of patients who have continued/resumed acid suppression therapy with either PPI by 6 months and 1 year dose will be measured for both the control and

experimental arms. The frequency, start/dose change/stop dates will also be recorded at those time points.

V. **Factors related to GERD:** In order to adjust for possible dependent variables a simple questionnaire will be used to assess for smoking, alcohol, diet/meal schedule, HOB elevation, exercise, BMI, other medications - nitrates, calcium channel blockers, antihistamines, antiparkinsonian agents, tricylcic antidepressants, major tranquilizers, promotility agents, sucralfate, antacids, NSAID's, ASA.

I. Confidentiality

The results of the questionnaire will be kept strictly confidential, labeled by study subject number. The code will be kept separately, only accessible by PI and research assistant(s). The results of the study procedures will be accessible to health care professionals only.

J. Conflict of Interest

The only apparent source for conflict of interest is that with proven benefit of the investigational procedure, the principle investigator may experience an increase in the number of referrals to his practice.

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