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SYSTEMATIC REVIEWS AND META-ANALYSES

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No Evidence for Efficacy of Radiofrequency Ablation for Treatment of Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis

Seth Lipka,[*] Ambuj Kumar,[‡] and Joel E. Richter[§]

*Division of Digestive Diseases and Nutrition, ‡Department of Medicine, Division of Evidence Based Medicine and Outcomes Research, §Department of Digestive Diseases and Nutrition, Joy McCann Culverhouse Center for Swallowing Disorders, University of South Florida Morsani College of Medicine, Tampa, Florida

BACKGROUND & AIMS: **A radiofrequency ablation technique known as Stretta was recommended by the Society of American Gastrointestinal and Endoscopic Surgeons as an alternative treatment for gastroesophageal reflux disease (GERD). However, randomized controlled trials of the efficacy of Stretta have produced conflicting findings, and those from previous systematic reviews were compromised as a result of deficiencies in study conduct and reporting of findings. We performed a systematic review to evaluate all evidence on the efficacy of Stretta for the management of GERD.**

METHODS: **We searched MEDLINE and the Cochrane Central Register of Controlled Trials (The Cochrane Library) from inception until February 28, 2014, along with other databases, for randomized controlled trials of Stretta in patients with GERD. Primary outcomes were physiologic parameters of GERD, including normalization of esophageal pH values and augmentation of lower esophageal sphincter pressure (LESP). Secondary outcomes were health-related quality of life (HRQOL) and ability to stop the use of proton pump inhibitors (PPIs). For quality assurance purposes, 2 investigators were involved throughout the study. Data were pooled under a random-effects model. The systematic review was performed as per the standards of the Cochrane collaboration.**

RESULTS: **We collected data from 4 trials and a total of 165 patients (153 patients were analyzed). Three trials compared Stretta vs sham, and 1 trial compared Stretta with PPI therapy. The overall quality of evidence was very low. The pooled results showed no difference between Stretta and sham or management with PPI in patients with GERD for the outcomes of mean (%) time the pH was less than 4 over a 24-hour time course, LESP, ability to stop PPIs, or HRQOL.**

CONCLUSIONS: **In a meta-analysis of trials, we found that Stretta for patients with GERD does not produce significant changes, compared with sham therapy, in physiologic parameters, including time spent at a pH less than 4, LESP, ability to stop PPIs, or HRQOL.**

Keywords: Comparison; Treatment; Gastric; Esophagus.

Gastroesophageal reflux disease (GERD) is defined as "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung."[1] It is one of the most common problems gastroenterologists face, with an estimated prevalence of 10% to 20% in the West.[2] GERD accounts for 8.9 million annual outpatient visits, with upper gastrointestinal endoscopy alone costing the health care system an estimated $12.3 billion annually.[3] First-line therapy for GERD includes a combination of lifestyle modifications and medical therapy, with antireflux medications accounting for approximately $7.7 billion in annual US health care costs.[4] Symptoms may be refractory to medical therapy requiring lifelong treatment and there are serious risks associated with GERD including esophagitis, esophageal stricture, Barrett's, and adenocarcinoma of the esophagus. Approximately 25% to 42% of patients with GERD do not

Abbreviations used in this paper: **CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GERD, gastroesophageal reflux disease; HRQOL, health-related quality of life; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; LNF, laparoscopic Nissen fundoplication; MD, mean difference; MESH, medical subject heading; PPI, proton pump inhibitor; SAGES, Society of American Gastrointestinal and Endoscopic Surgeons.**

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respond to an initial 4 to 8 weeks of proton pump inhibitor (PPI) therapy, and only about 25% respond to twice-daily dosing, presenting a major challenge to clinicians.[5]

Compared with medical treatment of GERD, surgery offers the advantage of eliminating reflux and the need for PPI therapy and lifestyle changes. Laparoscopic Nissen fundoplication (LNF) is the standard surgical intervention for GERD in adolescents and adults.[6,7] Despite the success of surgery, LNF is invasive, requiring hospitalization, and carries the risk of long-term complications including dysphagia, diarrhea, and gas bloat syndrome.[8,9] Endoscopic therapies can reduce the morbidity associated with LNF. These include radiofrequency augmentation to the lower esophageal sphincter (LES), endoscopic suturing of the LES, and silicone injection into the LES. Despite the less-invasive nature of these techniques, they have produced mixed results, and there is conflicting evidence for long-term efficacy. Most have been withdrawn from the market.

Stretta, a form of radiofrequency ablation to the LES and cardia, returned to the market in 2010 after Mederi Therapeutics, Inc (Greenwich, CT) purchased the assets from Curon Ltd (Bury St Edmunds, UK), which filed for bankruptcy in 2006 as a result of financial and reimbursement problems. The Stretta procedure is expensive, costing $2000 to $3500. However, reimbursement from insurance companies is a secondary issue, compared with the controversial clinical data on this procedure.[10] For these reasons, gastroenterology societies, including most recently the American College of Gastroenterology,[1] have not recommended Stretta for the treatment of patients with GERD.[11,12]

Recently, the Stretta procedure was recommended by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). This recommendation was graded as "strong" with a "high level of evidence" as a therapeutic modality in adult patients with GERD who have had symptoms of heartburn, regurgitation, or both for 6 months or more; who have been partially or completely responsive to antisecretory pharmacologic therapy; and who have declined laparoscopic fundoplication."[13] This was based primarily on a recent meta-analysis by Perry et al,[14] which pooled data from 20 studies (2 randomized controlled trials and 18 case series) and concluded that Stretta is an effective procedure for the management of GERD.

However, these positive results were not based on the findings of a systematic review and have serious methodology issues in study conduct and analysis. For example, the systematic review did not perform a meta-analysis despite the availability of data from 2 randomized controlled trials. In addition, most of the studies were single-arm case series and did not involve a control or comparator, making it impossible to deduce the effect of the Stretta procedure. A key purpose of the systematic review and meta-analysis is to determine whether results are observed because of the intervention or because of bias, owing to poor study design. Therefore, assessment of the methodologic quality of included studies is an important requirement for a systematic review and is recommended by the Cochrane Collaboration. The research synthesis by Perry et al[14] did not include a formal assessment of methodologic quality.

Since the publication of the systematic review by Perry et al,[14] 2 more randomized controlled trials have been published. A synthesis of all available evidence on the efficacy of Stretta for the treatment of GERD is essential for informed decision making.[15,16] Because of the cost, irreversibility, potential serious adverse events, and conflicting results from randomized controlled trials, we performed a systematic review of all evidence from these trials to assess the efficacy of Stretta for the management of GERD in light of SAGES' recommendations.

Methods

Selection Criteria

Any randomized controlled trial evaluating the efficacy of the Stretta procedure compared with sham or medical treatment for the management of GERD patients requiring PPIs regardless of publication status (eg, abstracts, unpublished studies, and so forth) was eligible for inclusion in the systematic review. Studies that were not a randomized controlled trial or did not have a control or included specialized treatment groups such as postreflux surgery or obese patients were excluded. There was no restriction on patient age, ethnic group, or sex.

Two authors (S.L., A.K.) independently extracted data on outcomes from all studies. Data were extracted using a standardized data abstraction form. Three authors (S.L., A.K., J.R.) independently reviewed all titles/abstracts and selected full-text articles for inclusion. We included all references that reported the results of randomized controlled trials of Stretta vs sham therapy or medical management in this review.

Types of Participants

We included studies that enrolled participants with GERD established by the presence of erosive esophagitis on endoscopy, or abnormal ambulatory esophageal pH monitoring (defined by DeMeester score > 14.7 or percentage total time pH < 4 of $\geq 4.0\%$). Participants also were defined as having GERD by scores on health-related quality of life (HRQOL) surveys or by symptom scores, who previously were on PPIs, and treated with Stretta vs either sham or PPI therapy (controls).

Outcomes

The primary outcomes were physiological parameters, including normalization of the percentage of a 24-hour time period spent at a pH less than 4 and augmentation of the lower esophageal sphincter pressure (LESP).