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In Adults with Gastroesophageal Reflux Disease, what is the efficacy of Surgical Versus Pharmacotherapy in reducing symptoms?

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by

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Table of Contents

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Abstract

The purpose of this systematic review is to explore the efficacy of pharmacotherapeutics and surgical interventions for the treatment of gastroesophageal reflux disease (GERD). In this systematic review, five electronic databases were used including AccessMedicine, PubMed, Cochrane library, Dynamed, and Clinical Key. Research criteria included work after 2010, peer reviewed, and only randomized control trials, systematic reviews, and meta-analyses were considered. Studies that were excluded included any that were before 2010, poor study design, and those that looked at other conditions or treatments outside of the research question in study. A total of 9 studies were selected for this systematic review. The research clearly shows benefits for both pharmacotherapy and surgical intervention for the treatment of GERD. The studies have shown a mixture of results when it comes to which treatment is more efficacious. Although both treatments have been shown to be effective, more research needs to be done to clearly identify risks and benefits of the different types of GERD treatments.

Keywords: GERD, gastroesophageal reflux disease. pharmacotherapeutics, surgery, heartburn, and PPI

Introduction

Gastroesophageal reflux disease is estimated to affect 20 percent of adults. In GERD, the lower esophageal sphincter is incompetent or relaxes and allows gastric acid to reflux up into the esophagus. Stomach acid on the cells of the esophagus can cause damage and lead to precancerous changes in the structure of those cells. When the cells become precancerous the diagnosis is termed Barrett's esophagus. The diagnosis of Barrett's esophagus has an 11-fold increase of developing adenocarcinoma of the esophagus. The purpose of this study is to reveal the most effective treatment for reducing symptoms and treating GERD.

Statement of Problem

There are many treatment options for gastroesophageal reflux disease. Pharmacotherapeutic drug classes approved by the United States Food and Drug Administration include proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA). Many surgical techniques are available including open fundoplication, transoral incisionless fundoplication, and magnetic sphincter augmentation. In recent years, many surgical techniques have shown promising results and are continually being researched for treatment in management of GERD. A question arises of is surgical or pharmacotherapeutic management more efficacious. Medical providers need to be up to date on the current research to provide the most efficacious treatment option for their patient.

Research Question

In Adults with Gastroesophageal Reflux Disease, what is the efficacy of Surgical Versus Pharmacotherapy in reducing symptoms?

Methods

A literature review was performed using electronic search databases: AccessMedicine, PubMed, Cochrane Library, Dynamed, and Clinical Key. Both keywords and mesh terms were used to define literature consisting of gastroesophageal reflux disease and the treatments including pharmacotherapy and surgical interventions. The search yielded 190 results and was narrowed to the last 10 years. Studies with age of population less than 18 were excluded. After selection criteria, a total of 9 studies were chosen. The keywords included GERD, gastroesophageal reflux disease. pharmacotherapeutics, surgery, heartburn, and PPI. These articles were reviewed and collected according to the pertinence to my research question, quality of research, and obvious bias.

Pathophysiology of Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is a condition in which contents from the stomach are refluxed into the esophagus. Common symptoms include regurgitation, heartburn, dysphagia, belching, dyspepsia, chest pain, cough, and hoarseness. Most patients have mild disease but there is potential for reflux esophagitis and precancerous changes within the esophagus. There are many potential mechanisms that that can cause GERD. The lower esophageal sphincter is a barrier between the esophagus and stomach. Some patients have inadequate lower esophageal sphincter pressure which fails to prevent stomach acid from refluxing into the esophagus. Another potential cause is an abnormality in the peristalsis of food. Peristalsis is the mechanisms in which food is carried from the esophagus to the stomach, if this mechanism is impaired there will be increased chances of reflux back into the esophagus.

Pharmacotherapeutics in the Treatment of Gastroesophageal Reflux Disease

Sigterman et al. (2013) published a systematic review consisting of randomized control trials with a single- or double-blind design, in which one of the intervention types was compared with a placebo or another type of intervention. This systematic review collected data from a total of 34 trials in North America, Europe, Australia, South Africa, and Japan. The participants were recruited from different sources: primary care physicians, secondary care centers, an ambulatory pH monitoring service, and potential anti-reflux surgery patients.

Two groups were used in these studies to compare treatment outcomes: empirically treated group and endoscopy negative group. The empirical treatment group included data from 6734 participants in nineteen trials. The mean age of these participants were 51 years of age (range 18-87) with 54% being male (Sigterman et al., 2013). Patients in the study were included with a mixture of GERD symptoms: heartburn, regurgitation, epigastric pain, acid eructation, pain on swallowing, and dysphagia. In other trials inclusion criteria included heartburn qualitative data such as severity, frequency, and duration. A mixture of testing methods were used to quantify GERD including Bernstein testing, x-ray, and oesophagoscopy. The endoscopy negative group included data extracted from 6406 participants in nineteen trials. The mean number of participants per trial was 337 (range from 19 to 947). The mean age was 48 years (range 18 to 80), with 41% being male (Sigterman et al., 2013). Like the previous group, many participants were selected with different GERD symptoms including heartburn, regurgitation, and dysphagia. Inclusion criteria were different depending on the study, some required one symptom while others required multiple of the above list. Additionally, one study required Bernstein testing, and another required 24-hour pH testing. Participants with any erosive oesophagitis were excluded from all studies in both groups. Other common exclusion criteria

were Barrett's oesophagus, oesophageal stricture, peptic ulcer disease and the recent use of antisecretory drugs (Sigterman et al., 2013).

The types of outcomes measured are PPI versus placebo, H2RA versus placebo, prokinetic vs placebo, PPI vs H2RA, PPI vs prokinetic, and H2RA vs prokinetic. In the empirical group, ten trials studied a proton pump inhibitor. Two studies compared PPIs to placebo, seven studies compared to H2RA, and one study versus prokinetics. Proton pump inhibitors tested were esomeprazole, omeprazole, and pantoprazole. These medications were tested at various dosages, treatment timeframes, and dosage intervals. Fourteen trials studied the H2RA: six studies versus placebo, seven studies versus PPI, and one study versus prokinetics. H2RAs included were cimetidine, famotidine, nizatidine, and ranitidine. These medications were tested at various dosages, treatment timeframes, and dosage intervals. Five trials studied the prokinetics. Four studies compared prokinetics to placebos, two studies versus PPI, and one study versus H2RA. Prokinetics studies included metoclopramide and cisapride. Like other trials, all prokinetics were tested at various dosages, treatment timeframes, and dosage intervals.

Outcomes of these interventions were primarily based on the relief of heartburn. Remission of heartburn was described as no more than one day of mild heartburn per week. Eleven trials use a quality-of-life instrument in assessing therapeutic response. The Gastro-intestinal Symptom Rating Scale (GSRS) was used in seven, the Psychological General Well-Being Index (PGWB) in two, the Short-Form Health Survey (SF-36) in four, and the heartburn specific questionnaire in one (Sigterman et al., 2013).

Results were compiled for all treatment options on heartburn remission, overall symptom improvement, daytime heartburn relief, nighttime heartburn relief, and quality of life within the empirically treated group. When comparing PPI to placebo, data suggested favor towards the PPI

with the risk ratio of 0.37. When comparing the H2RA to placebo, data suggested favor towards the H2RA with a risk ratio of 0.77. When comparing the prokinetics to placebo the relative risk ratio was 0.86. Seven trials compared a PPI with an H2RA. PPIs were significantly ($P<0.05$) more effective (RR 0.66) (Sigterman et al., 2013). Two trials compared PPI versus prokinetic, relative risk was 0.53. No trials measured heartburn relief when comparing H2RAs and prokinetics. Also, some studies reported data comparing overall symptom improvement. When compared against placebo, four trials with H2RA showed a relative risk of 0.72. Two trials studied prokinetics with a relative risk of 0.71. One study reported data comparing PPI and H2RA, relative risk reported was 0.29. Four trials compared treatments to daytime heartburn relief. The relative risk for H2RA versus placebo was 0.80 and prokinetics versus placebo was 0.63. When H2RA and prokinetic were directly compared, no significant difference in efficacy was demonstrated with a relative risk of 0.83 (Sigterman et al., 2013). No PPI was testing in this group. Three trials studied the treatment options for nighttime heartburn relief. Three trials compared H2RA to placebo with a relative risk of 0.77. One trial compared prokinetics to placebo with a relative risk of 0.51. PPI therapy was not tested in these trials. Quality of life was assessed by the PGWB, GSRS, and SF-36. No major difference was found between omeprazole 20mg daily, omeprazole 10mg daily, and cisapride 10 QID with respects to the PGWB and GSRS. However, improvement in the reflux dimension of the GSRS was significantly greater ($P<0.05$) with a PPI than with an H2RA (three trials) and greater with omeprazole 20mg once daily than with cisapride 10mg four times daily (Sigterman et al., 2013). One trial demonstrated significant GSRS four-week improvements ($P< 0.001$) with omeprazole 20 mg daily versus ranitidine 150 mg BID.

Results were compiled for heartburn remission, overall symptom improvement, daytime heartburn relief, nighttime heartburn relief, and quality of life in the endoscopy negative reflux disease group. The first data described was on heartburn remission. Ten trials looked a PPI versus placebo with a relative risk of 0.71. Two trials looked at H2RA versus placebo with a relative risk of 0.84. Four trials compared PPI to H2RA with a relative risk of 0.78. Only one trial was used to compare PPI to prokinetics with a relative risk of 0.72. Second data described was daytime relief of heartburn. Only one trial was reported comparing H2RA with placebo with a relative risk of 0.75. Thirdly, nighttime heartburn relief was studied. Only one trial studied H2RA versus placebo with a relative risk of 0.80. Regarding quality of life, PGWB, GSRS, and SF-36 were used to quantify results of treatments. Therapy with PPIs compared with placebo significantly improved the PGWB index and the GSRS reflux dimension ($P<0.05$), but not the global GSRS score and the SF-36 (Sigterman et al., 2013). PPI and H2RA therapy were compared by the GSRS and the SF-36 and no difference could be appreciated.

In summary, the study found that when patients are selected based on symptoms and diagnostic of GERD is high, that PPIs are superior to H2RAs and prokinetics. Also, the evidence shows that H2RAs are effective at promoting symptom relief. The authors included that the efficacy of prokinetics is unclear. Regarding endoscopy negative reflux disease, PPIs were superior to H2RAs at controlling symptoms.

This systematic review had a few weaknesses. There was limited data on prokinetics and its efficacy. Heterogenicity of statistics was tested and studied. When testing PPI versus H2RA, both the empirical treatment and endoscopy negative group, had only moderate heterogeneity because of a single study that no clear explanation was found. It is stated that one study tested a low dose omeprazole (10mg), which decreased the efficacy of the PPI trials. This study

concentrated on the short-term treatment outcomes of therapy and thus long-term therapy was not studied.

The variety of studies and population size this review provides is a strength. Numerous studies were created and compared against both placebo and competing therapies. Also, patient outcomes were quantified by numerous types of surveys. Two different subgroups were collected within the gastroesophageal reflux group and thus provided more research.

Surgical Interventions for the Treatment of Gastroesophageal Reflux Disease

Chen et al. (2017) published a meta-analysis consisting of four retrospective studies comparing the effects of Magnetic Sphincter Augmentation (MSA) and Nissen Fundoplication (NF) for gastroesophageal reflux disease (GERD). The selection criteria were based on direct comparison of the two surgical options between the years of 2005 to 2016. A total of four studies, 624 patients, in which 299 received MSA and 325 received NF were included in the meta-analysis. Inclusion criteria consisted of four standards: comparison of original outcomes of MSA and NF for GERD treatment, report on adverse events, complications, and proton pump inhibitor use, and only the most recent or highest quality of studies would be used for studies of the same institution or author.

The results of the study showed postoperative PPI usage between patients who underwent MSA or NF for GERD had no significant difference with a relative risk of 1.21. It is described that a fixed effect model was used because there was no heterogeneity between the four studies. Complications of the surgeries were measured by dysphagia because it is the most common complication with surgery. The meta-analysis also showed no significant difference of complications (RR=1.16) and severe dysphagia for dilation (RR=1.36) (Chen et al., 2017). No

statistical difference was found at the incidence of adverse effects with a risk ratio of 0.86. There was no significant difference in the ability to belch or vomit with a risk ratio of 1.33 and 1.66 respectively. The MSA study group had a lower trend towards gas and bloating with a risk ratio of 0.71 and $P<0.05$. Conclusion of this study showed no difference between MSA and NF except the MSA had decreased complications of gas and bloating.

Some weaknesses of this study are a limited amount of information regarding patient symptoms related to GERD after surgery. These studies looked mainly at complications and adverse events between surgery types but limited information on treatment of the condition of GERD. Also, there was no description on what symptoms and testing qualified someone to have the diagnosis of GERD. Strengths of the study included a good population size and homogeneity of outcomes.

Kaindlstorfer et al., (2013) published a randomized control trial comparing laparoscopic antireflux surgery with endoscopic full thickness gastroplication. Patients were selected based on long term GERD not responding to PPI therapy or unwilling to take long term medication. Questionaries were used to document quality of life, symptoms, and medication use. All patients were tested with gastroscopy, barium radiography, and esophageal manometry. Also, 24-hour pH impedance monitoring was considered the best way to quantify reflux types.

Seventy total patients were included in the study and were randomly assigned either the laparoscopic anti-reflux surgery group (LARS) or full thickness gastroplication. A total of 33 patients were selected in the LARS group, within the group patients were randomly chosen to receive either Nissen or Toupet fundoplication. A total of 37 patients underwent endoscopic antireflux gastroplication. Inclusion criteria of this study was documented via 24-hour ambulatory pH monitoring. This study required a total number of reflux events to be greater than

or equal to 73 per hour, a DeMeester score of greater than or equal to 14.7, a positive symptom index of greater than or equal to 50% with a frequency of at least 3 in 24 hours, and mucosal breaks seen on endoscopy.

Evaluation of patient severity was assessed by esophageal pH monitoring, symptoms and side effects monitoring, and quality of life evaluation. The esophageal pH monitoring measured GERD and was diagnosed if the total number of reflux events in 24 hours were at least 73. Fourteen different symptoms considered to be related to reflux, comorbidities, or postinterventional side effects, in particular heartburn, regurgitation, epigastric pain, cough, hoarseness, asthma, dysphagia, fullness, diarrhea, flatulence, constipation, bloatedness, and distortion of taste, were assessed using a standardized questionnaire (Kaindlstorfer et al., 2013). Quality of life was assessed by Gastrointestinal Quality-of-Life Index (GIQLI). A total of 34 of the 37 patients in the Plicator group reported for short term follow up on an average of 17 weeks. A total of 20 of 33 patients reported for short term follow up on an average of 14 weeks.

The results concluded little difference between the different surgery groups. At baseline there was no significant difference between reflux events at various positions before surgery. On follow up, the numbers were significantly lower ($P<0.05$) in both surgery groups. Reflux related acid scores were significantly lowered in the LARS group ($P<0.05$) while the Plicator group failed to reach a significant value with a $P=.078$. No significant difference was found with GIQLI scores when measuring quality of life between the two groups. There were no statistical differences in the surgery groups at baseline. Both surgical groups reported significant improvements in general, reflux specific, and gas related symptom scores.

Weaknesses of this study include a population size of seventy patients. No bias was studied or presented in this study. Strengths of this study include many objective measurements

of GERD as well as subjective measurements of patient outcomes. Selection was randomized appropriately and showed close equality to gender studies.

Skubleny et al., (2016) published a meta-analysis comparing LINX magnetic sphincter augmentation (MSA) to Nissen fundoplication (LNF). Articles were selected based on three criteria. The studies must directly compare MSA to LNF, one primary outcome of interest must be measured, and at least five patients must be enrolled. The primary outcomes of interest comprise GERD-Health-Related Quality of Life, DeMeester score, operative time, ability to belch, ability to emesis, discontinuation of proton pump inhibitors, need for endoscopic dilation, procedural satisfaction, presence of gas/bloating and dysphagia (Kaindlstorfer et al., 2013). After a thorough review process, three total studies were used with a total of 688 patients. Of those patients, 273 received LNF and 415 received MSA. Patients were encouraged to follow-up with a range of 7 to 16 months and 7 to 12 months for the LNF and MSA respectively.

Results showed main statistical differences in the ability to belch, emesis, and improvement in the GERD-Health-Related Quality of Life Index. MSA was statistically superior to LNF in preserving patient's ability to belch ($P<0.0001$) and ability to emesis ($P<0.0001$) (Kaindlstorfer et al., 2013). The Quality-of-Life Index showed symptom improvement in both surgical treatments. The MSA group showed a decrease in symptoms with preoperative score of 20.5 to a reduction to 3 postoperatively. The LNF group showed a decrease in symptoms with preoperative score of 19.7 to a reduction to 3.4 postoperatively. When testing gas/bloating, dysphagia, and PPI elimination, no statistical difference was found. One study looked at pH monitoring with the DeMeester score. The MSA group was found to be 49.5 preoperatively and 14.2 postoperatively. The LNF group was found to be 49 preoperatively and 5.1 postoperatively. Both treatment groups had postoperative morbidity. Major morbidity for LNF included a pleural

injury intraoperatively, two cases of retroesophageal abscesses and four cases of revision due to hiatal hernia recurrence (Kaindlstorfer et al., 2013). The MSA group morbidity included one pleural injury, two episodes of intraoperative bleeding, one pneumothorax and one gastroesophageal junction obstruction (Kaindlstorfer et al., 2013). Also, the MSA group had a total of two device removals, one due to treatment failure and one due to erosion 20 months later.

Weaknesses of this study include loss of patient follow-up of up to 10%. All the studies were case series without randomized control trial. Most of the data was reported subjectively through surveys thus creating variability. Also, no long-term data was reported. Strengths of this study include a methodological quality assessment. Gender distribution was well reported and appropriate.

Pharmacotherapeutics vs Surgical Interventions in GERD Treatment

Spechler et al., (2019) published a randomized control trial comparing efficacy of medical treatment versus surgical treatment of refractory heartburn. The population studied was patients who were referred to the Veteran Affairs (VA) office for refractory heartburn. Patients were treated with a 2 week, twice a day regimen of omeprazole 20 mg. If the patient continued to have heartburn after treatment regimen, further workup was provided. Patients recommended for the trials were those found to have reflux related heartburn investigated by endoscopy, esophageal biopsy, manometry, and impedance-pH monitoring. If patients were found to have reflux-related heartburn, we randomly assigned them to receive surgical treatment (laparoscopic Nissen fundoplication), active medical treatment (omeprazole plus baclofen, with desipramine added depending on symptoms), or control medical treatment (omeprazole plus placebo) (Spechler et al., 2019). Outcome was measured by the GERD-Health Related Quality of Life score improvement of greater than or equal to 50% at 1 year.

A total of 366 patients (mean age, 48.5 years; 280 men) were enrolled (Spechler et al., 2019). A total of 78 patients underwent randomization after a variety of exclusions. After randomization, the surgical group consisted of 27 patients at 85% male, active medical group consisted of 25 patients of which 72% were male, and the control medical group consisted of 26 patients of which 88% were male.

Results from GERD-HRQL score showed surgery to be superior to all other treatment groups. At least 50% GERD-HRQL score improvement occurred in 67% of the surgery group, 28% of the active medical group, and 12% in the control medical group. The incidence of treatment success with surgery was significantly superior to that with active medical treatment ($P=0.007$) or control group ($P<0.001$) (Spechler et al., 2019). The difference between the active medical group and control medical group showed no statistical significance. Five serious adverse events in four patients were described in the surgical group, four adverse events in four patients in the active medical group, and five adverse events in three patients in the control medical group.

Weaknesses in this study are a small sample size of 78 patients. Also, there was a limited number of female patients, predominantly white race of 63-80% of sample size, and all patients were part of Veteran Affairs. One of the treatment groups allowed the use of desipramine but all patients were not on the medication because of contraindications. Subjective survey was used to quantify success and can potentially create error. Strength of this study is methodological criteria for selection of patients. Selection of patients was determined by quantitative data from diagnostic evaluation.

Zhang et al., (2017) published a prospective, observational study comparing Nissen fundoplication to proton pump inhibitors for laryngopharyngeal reflux. This study population

included patients diagnosed with laryngopharyngeal reflux (LPR) with a hiatal hernia. This study was performed at the Second Artillery General Hospital of Chinese People's Liberation Army and Xuanwu Hospital.

A total of 70 patients with LPR and type I hiatal hernia were tested. Inclusion criteria includes all of the following: Patients complaint with laryngopharyngeal symptoms (hoarseness, globus, throat clearing/pain, mucus and chronic cough) suspected by the otolaryngologist, the LPR symptom occurred at least once a week, and lasted at least six months; Reflux Symptom Index (RSI) score at least 13, type I hiatal hernia; absence of significant esophagitis; abnormal Ryan score during 24 hour oropharyngeal pH monitoring; and an anormal esophageal sphincter pressure (LES) as detected by esophageal manometry (Zhang et al., 2017). Diagnosis of LPR using pH monitoring was assessed by using the Ryan score. The score consists of measurements of the number of reflux episodes, longest reflux episode, and percentage of time spent below a defined threshold. A score of greater than 9.41 in the upright position and/or 6.81 in the supine position was regarded as LPR (Zhang et al., 2017). Patients participating in the study were given a choice of PPI or LNF after description of such treatment. A total of 39 patients were treated with esomeprazole 40 mg daily for an average of 78 days. 31 patients elected to receive LNF. In the surgery group, a single dose of omeprazole 40 mg IV was given. For all patients, lifestyle modifications were suggested such as no nighttime eating, decrease consumption of fatty foods, smaller more frequent meals, and decreased cigarette, alcohol, and caffeine usage.

Results of symptom improvement were assessed by a pretreatment and posttreatment RSI and at a six month and two-year follow-up. All symptoms measured by the RSI were statistically insignificant between the treatment groups except globus, which was significantly more present in the LNF group compared to the PPI group (P=0.003). Diagnostic imaging including pH

monitoring, manometry, and endoscopy were performed pre and post treatment. No statistical difference was found in pH monitoring of the two treatment groups. The only difference found with manometry was the upper esophageal sphincter was lower in the LNF group compared to the PPI group (P=0.045). No differences were found when posttest endoscopy was performed when comparing groups. At 2-year follow-up, RSI score decreased significantly more in the LNF group compared to the PPI group (P=0.004). Also, there was a higher incidence of independence from PPIs at 2 years with the LNF group compared to the PPI group (P<0.001). When comparing baseline to 2 years follow up, Patients were more satisfied with their quality of life after undergoing LNF than with PPI therapy (P=0.004) (Zhang et al., 2017).

Weaknesses of this study include a lack of randomized control component to selection of treatment. The PPI used was designated to one type and treatment regimen. A small patient size of 70 patients was studied. There were multiple patients lost to follow-up. Strengths of the study include a 2 year follow up comparing a long-term treatment outcome.

Galmiche et al., (2011) published a randomized control trial comparing esomeprazole to Laparoscopic Antireflux Surgery (LARS). The studies conducted in academic hospitals in 11 European countries over eight years. Patients included were adults between 18 and 70 with chronic GERD. Diagnosis was classified based on mucosal breaks on endoscopy, pathological pH testing, and symptom grading.

A total of 554 patients were selected with a diagnosis of chronic GERD of which initially responded to acid suppression therapy. Patients were randomly assigned to a PPI group or the LARS group. A total of 372 patients (esomeprazole, n=192; LARS, n=180) completed 5 year follow up (Galmiche et al., 2011). The PPI group consisted of esomeprazole treatment 20-40mg. The PPI group consisted of 266 patients while the LARS group consisted of 248 patients.

Patients were expected to visit the clinic for 6 month follow up for a total time of 5 years. Endoscopy was performed at 1,3, and 5 years. Baseline, 6 months, and 5-year pH testing was done for both groups. Symptoms were assessed using the QOLRAD and GSRS at every follow up visit.

Results concluded that there was little difference in the treatment groups at 5 years. At 5 years, an estimated 85% in the LARS group and an estimated 92% in the esomeprazole group remained in remission (P=0.048) (Galmiche et al., 2011). At 5 years, acid regurgitation was significantly worse in the esomeprazole group than in the LARS group (P<.001) (Galmiche et al., 2011). Symptoms of heartburn, epigastric pain, and diarrhea seemed to show so statistical difference between the treatment groups. At 5 years, dysphagia remained significantly more common in the LARS group that in the esomeprazole group (P<.01) (Galmiche et al., 2011). Little statistical difference was found with endoscopy between the two treatment groups. No statistically relevant differences were found in safety of the two treatment groups.

Strengths of this study include randomized nature of treatments. A large population size of 552 patients were selected. The study tested long term outcomes over 5 years. Weaknesses of the study include loss of patients to follow-up. Also, a small portion of patients selected for surgery dropped out of the study.

Bell et al., (2019) published a randomized control trial comparing Laparoscopic magnetic sphincter augmentation to double dose proton pump inhibitors for the treatment of GERD related regurgitation. Patients were recruited from 21 different surgical clinics. Study inclusion criteria included patients aged at least 21 years, with moderate to severe regurgitation while taking once daily PPI therapy for at least 8 weeks and actively seeking alternative, surgical treatment for regurgitation symptoms (Bell et al., 2019). Other criteria included was a body mass index of less

than 35, abnormal pH testing, normal esophageal motility, a hiatal hernia less of at least 3 cm by endoscopy, no Barrett's esophagus, or late-stage esophagitis.

A total of 152 patients were selected for the study. Patients were randomly selected to either the PPI group or surgical group with a 2:1 ratio respectively. The PPI group consisted of 102 patient and the treatment regime is described as 20 mg of omeprazole twice daily. The surgical group consisted of 50 patients who underwent Laparoscopic magnetic sphincter augmentation. Both groups were tested at 6 months and 12 months for treatment outcomes. Study screenings included medical histories, physical examination s, GERD surveys, pH monitoring, Esophagogastroduodenoscopy (EGD), esophageal manometry or barium esophagram. Baseline quality-of-life surveys included the FSQ, Reflux Disease Questionnaire (RDQ), and GERD-Health-Related Quality of Life (GERD-HRQL) questionnaire (Bell et al., 2019).

Results showed increased improvements in the surgical group. Based on the 6-month endpoint and FSQ results, 89% of MSA patients achieved resolution of moderate-to-severe regurgitation compared with 10% of patients in the BID PPI arm (P<.001) (Bell et al., 2019). Eighty one percent of patients in the MSA arm achieved a reduction in a t least 50% from the baseline GERD-HRQL score compared with 8% of patients in the BID PPI arm (P<.001) (Bell et al., 2019). Impedance-pH testing was used to quantify the number of reflux events in a 24-hour period. The MSA group showed statistically superior to the PPI group with concerns to controlled reflux with a p value of less than .001. No statistical significance was found when comparing mean esophageal acid exposure or DeMeester scores between the two groups.

Weaknesses of this study included subjectivity of using questionnaires to assess symptom control. The study reported a level of potential referral bias as patients in this study were being

referred to a surgical clinic. A strength of this study is using pH impedance to quantify data associated with symptom control. The random control selection for treatments helped improve the efficacy of this study.

Garsk et al., (2015) published a meta-analysis of four randomized control trials comparing the treatment of Laparoscopic fundoplication to medical management. Four studies were selected from 2005 to 2011. Two surveys were used to assess treatment outcomes, the Health-related quality of life (HRQoL) and GORD-specific quality of life (QoL). Within these questionnaires both short (4 weeks to twelve months) and long term (one to five years) measurements were made. Specific symptoms studies were dysphagia, heartburn, and reflux. The same time frames were measured as short, medium, and the addition of a long term (five years or more) category.

Of the 4 trials, a total of 1160 participants reported outcomes. The mean age range was 43 to 48 years old. Three trials used laparoscopic Nissen fundoplication as the surgery intervention. One study gave physician preference to the laparoscopic fundoplication. All trials used proton pump inhibitors as the medical treatment. Three studies used PPI administration based in local protocol while one used esomeprazole in a choice 20-40mg administration. The HRQoL short- and medium-term testing showed no statistically significant evidence between the two treatment groups. When using the QoL, short term studies showed significant improvement in the laparoscopic fundoplication group compared to the medical treatment group (SMD 0.58). At medium-term, fundoplication group showed significantly better outcomes compared to medical treatment (SMD 0.28). When dysphagia was tested at short term and medium term, the proportion of people experiencing the symptom was significantly higher in the fundoplication group compared to the treatment groups with a relative risk of 3.58 and 5.36 respectively. No

statistical difference was found at long term follow-up. When comparing short-, medium-, and long-term reports of heartburn, the proportion of people was significantly less in the fundoplication group compared to the medical treatment group with a relative risk of 0.45, 0.19, and 0.56 respectively. When assessing reflux, both short- and medium-term data suggested that proportion of people experiencing reflux was significantly reduced with fundoplication compared to medical therapy with a relative risk of 0.10 and 0.15 respectively. Long term reporting showed no statistical difference between treatment groups.

Weaknesses of this study are two trials were funded by organizations with vested interests in the results and are subject to bias due to their source of funding (Garsk et al., 2015). Selective reporting was described to be appropriate in two studies and inappropriate in two suggesting the possibility of bias. A strength of this study is a large patient size of 1160 people. Gender reports in the study were near equal. Detailed systematic approach was used in this meta-analysis.

Discussion

Pharmacotherapeutic Efficacy

The systematic review by Sigterman et al. (2013) concluded that when patients present with symptoms consistent with GORD and diagnostic probability is high, PPI treatment is superior to both H2RA and prokinetics in achieving heartburn remission. Although less effective, H2RA treatment were also shown to promote symptom relief. Also, Sigterman et al. (2013) found that in the endoscopy negative reflux disease group, a short course of PPI or H2RA treatment is effective at achieving symptom relief. The PPI was again the most effective at achieving symptom relief.

Surgical Intervention Efficacy

The meta-analysis by Chen et al. (2017) concluded that when comparing MSA to NF, short term reflux symptom control was similar. This information helps the family medicine practitioner better educate patients with their treatment options. It was found that MSA can be recommended, short term studies have shown a shorter operative time and less complaints of gas and bloating compared to NF, (Chen et al. 2017).

The randomized control trial of Kaindlstorfer et al., (2013) found that general symptomatic improvements were similar when comparing laparoscopic antireflux surgery (LARS) and endoscopic full thickness gastroplication despite decreased acidic esophageal scores in the LARS group. Also, The LARS group experienced more reflux related relief while the endoscopic group had fewer side effect symptoms. (Kaindlstorfer et al., 2013)

The systematic review and meta-analysis by Skubleny et al., (2016) compared the effects of MSA and LNF and found that there was no statistical difference between gas/bloating, postoperative dysphagia, or PPI elimination between the two groups. The major difference in favor of MSA was increased preservation of the ability to belch and emesis. (Skubleny et al., 2016)

Pharmacotherapy versus Surgical Treatment

In the randomized control trial of Spechler et al., (2019), surgical (NF) and medical (omeprazole) treatment were compared for refractory heartburn and found that the surgical treatment was significantly superior to active medical treatment.

Zhang et al., (2017) compared LNF versus PPI therapy for patients with GERD and a hiatal hernia and found that significant improvements in the reflux symptom index (RSI)

occurred in both groups. The major difference was significant improvements in RSI and symptom scores of cough, mucus, and throat clearing with the LNF group compared to the PPI group. (Zhang et al., 2017) Also, the LNF group was found to have more satisfied quality of life compared to the PPI group but a significantly lower body mass index after treatment. (Zhang et al., 2017)

A randomized control trial by Galmiche et al., (2011) demonstrated that 5-year remission rates were similar between the LARS and esomeprazole group. The major differences were increased regurgitation with the esomeprazole group and increased dysphagia, bloating, and flatulence with the LARS group. (Galmiche et al., 2011)

A randomized control trial by Bell et al., (2019) showed significant regurgitation relief with MSA versus double dose PPI treatment at 6 months after treatment. Also, a significantly larger portion of patients in the MSA group had at least a 50 percent improvement in survey symptom scores as well as a decreased amount of reflux episodes. (Bell et al., 2019)

Garsk et al., (2015) found both positive and negative findings when comparing LNF versus PPI used for GORD. The LNF group reported significant improvement in short term quality of life, better short-, medium-, and long-term heartburn prevention, and decreased heartburn symptoms at short- and medium-term lengths. Also, the LNF group showed an increased proportion of people with serious adverse effects and short- and medium-term dysphagia compared to the PPI group. (Garsk et al., 2015)

Applicability to Clinical Practice

As discussed earlier, GERD is a common condition in the primary care setting that affects a large part of the population. First line treatments consist of short-term PPI use as well as weight loss and diet improvements. Long term PPI use may be necessary if no improvements after short term treatment. Surgical interventions are indicated only when a patient is intolerant to PPI with a strong recommendation.

Based on the research from this review, it can be suggested that surgical interventions may have a larger role in treating GERD. Also, new techniques are becoming less invasive with similar efficacy as previous techniques which may change future recommendations. Family practice practitioners are at an optimal position in healthcare to assess patient expectations, weigh risks and benefits, and encourage and educate patients to advocate for their health and quality of life.

Research on surgical outcomes continues to be released and the medical community learns more and more each day. There is still much that is unknown, it is important to investigate a clear reward over risk when considering a surgical procedure. More research needs to be done to assess long term effects and reliability of surgical techniques.

References

Bell, R., Lipham, J., Louie, B., Williams, V., Luketich, J., Hill, M., Richards, W., Dunst, C., Lister, D., McDowell-Jacobs, L., Reardon, P., Woods, K., Gould, J., Buckley, F. P., III, Kothari, S., Khaitan, L., Smith, C. D., Park, A., Smith, C., Jacobsen, G., & Katz, P. (2019). Laparoscopic magnetic sphincter augmentation versus double-dose proton pump inhibitors for management of moderate-to-severe regurgitation in GERD: a randomized controlled trial. *Gastrointestinal Endoscopy*, *89*(1), 14–22. https://doi-org.ezproxylr.med.und.edu/10.1016/j.gie.2018.07.007

Chen, M. Y., Huang, D. Y., Wu, A., Zhu, Y. B., Zhu, H. P., Lin, L. M., & Cai, X. J. (2017). Efficacy of magnetic sphincter augmentation versus nissen fundoplication for gastroesophageal reflux disease in short term: A meta-analysis. *Canadian Journal of Gastroenterology & Hepatology*, *2017*(9596342). https://doi.org/10.1155/2017/9596342

Galmiche, J. P., Hatlebakk, J., Attwood, S., Ell, C., Fiocca, R., Eklund, S., Långström, G., Lind, T., Lundell, L., & LOTUS Trial Collaborators (2011). Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA*, *305*(19), 1969–1977. https://doi-org.ezproxylr.med.und.edu/10.1001/jama.2011.626

Garg, S.K., & Gurusamy K.S. (2015). Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database of Systematic Reviews*. DOI: 10.1002/14651858.CD003243.pub3. Accessed 01 August 2021.

Kaindlstorfer, A., Koch, O. O., Antoniou, S. A., Asche, K. U., Granderath, F. A., & Pointner, R. (2013). A randomized trial on endoscopic full-thickness gastroplication versus laparoscopic antireflux surgery in GERD patients without hiatal hernias. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques*, *23*(2), 212–222. https://doi-org.ezproxylr.med.und.edu/10.1097/SLE.0b013e3182827f79

Papadakis, M., & McPhee, S. (2021). Current medical diagnosis & treatment (60th ed.). New York, NY: McGraw-Hill Education.

Sigterman, K. E., van Pinxteren, B., Bonis, P. A., Lau, J., & Numans, M. E. (2013). Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *The Cochrane Database of Systematic Reviews*, *2013*(5), CD002095. https://doi.org/10.1002/14651858.CD002095.pub5

Skubleny, D., Switzer, N. J., Dang, J., Gill, R. S., Shi, X., de Gara, C., Birch, D. W., Wong, C., Hutter, M. M., & Karmali, S. (2017). LINX® magnetic esophageal sphincter augmentation versus nissen fundoplication for gastroesophageal reflux disease: a systematic review and meta-analysis. *Surgical Endoscopy*, *31*(8), 3078–3084. https://doi-org.ezproxylr.med.und.edu/10.1007/s00464-016-5370-3

Spechler, S. J., Hunter, J. G., Jones, K. M., Lee, R., Smith, B. R., Mashimo, H., Sanchez, V. M., Dunbar, K. B., Pham, T. H., Murthy, U. K., Kim, T., Jackson, C. S., Wallen, J. M., von Rosenvinge, E. C., Pearl, J. P., Laine, L., Kim, A. W., Kaz, A. M., Tatum, R. P., Gellad, Z. F., … Huang, G. D. (2019). Randomized trial of medical versus surgical treatment for

refractory heartburn. *The New England Journal of Medicine*, *381*(16), 1513–1523. https://doi-org.ezproxylr.med.und.edu/10.1056/NEJMoa1811424

Zhang, C., Hu, Z. W., Yan, C., Wu, Q., Wu, J. M., Du, X., Liu, D. G., Luo, T., Li, F., & Wang, Z. G. (2017). Nissen fundoplication *vs* proton pump inhibitors for laryngopharyngeal reflux based on pH-monitoring and symptom-scale. *World Journal of Gastroenterology*, *23*(19), 3546–3555. https://doi-org.ezproxylr.med.und.edu/10.3748/wjg.v23.i19.3546