The Effectiveness of Nissen Fundoplication in the Reduction of Asthma Symptoms and Need for Control Medication in Patients with Asthma Secondary to GERD.

Allyson Swann

Pacific University

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Abstract

Introduction: Asthma and gastroesophageal reflux disease (GERD) have been closely linked, but the association of one with the other is not completely understood. Though GERD contributes to and exacerbates asthma symptoms, best management has not been established. Many asthmatics have subjective and objective findings of GERD, but the use of antireflux medication may not reduce reflux-related asthma symptoms at all. Better management of GERD may lead to better management of GERD-induced asthma. Outcomes presented in the review will be evaluated using GRADE to assess the quality of evidence each study provides.

Methods: Articles for this review were chosen by relevance to the search terms “asthma” and “fundoplication”. Literature containing the relevant subject terms was evaluated, and articles were chosen for inclusion if they specifically addressed patients who underwent fundoplication for the primary indication of asthma and/or respiratory symptoms due to reflux disease.

Results: The studies all showed fundoplication to be superior over antacid medication of any kind. Patients undergoing fundoplicaton showed immediate improvement and continued improvement or cure through the course of follow-up periods. Postoperatively, most patients showed reduced asthma symptoms and required fewer asthma control medications.

Conclusion: Nissen fundoplication cures acid reflux in 90 percent of GERD patients, whereas medical management has only mediocre results and those results are not usually long-lived. Even though proton pump inhibitors (PPIs) and H2 receptor antagonists (H2 blockers) reduce acid production, reflux of acid and microaspiration of refluxate still occurs. This microaspiration continues to contribute to hypersensitivity of the airways. With fundoplication, the pressure of the lower esophageal sphincter is restored and further reflux is prevented, thus making fundoplication the most effective management of GERD, and of any asthma and respiratory symptoms associated with the reflux. While fundoplication does not cure or markedly improve every asthma symptom or pulmonary function test, these studies, assessed by GRADE criteria, provide good, though not excellent, evidence that fundoplication should be considered for patients with GERD-induced asthma, especially those whose symptoms interfere with daily living or those requiring use of oral corticosteroids.

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ALLYSON SWANN

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Faculty Advisor: Torry Cobb
Clinical Graduate Project Instructors: Torry Cobb, DHSc, MPH, PA-C & Annjanette Sommers MS, PAC
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Keywords: asthma, fundoplication
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INTRODUCTION

Background

Asthma and gastroesophageal reflux disease (GERD) are common conditions affecting millions of Americans. Asthma affects five percent of the population and its prevalence has increased over the past twenty years (Chesnutt, & Prendergast, 2010). Approximately twenty percent of the population experiences gastroesophageal reflux (GER) (McQuaid, 2010). A relationship between the two has been suggested and studied, however, their exact correlation to one another has remained controversial and unclear. It is estimated that 30 to 90 percent of those with asthma also have GER. It is becoming more clear that GER triggers asthma, possibly due to microaspiration of reflux or activation of vagal reflexes. The presence of acid reflux in asthmatics leads to poorer control of asthma and an overall reduced quality of life. A majority of asthmatics who experience GER, also have objective findings, in addition to the symptomatic manifestations. One particular systematic review of 28 patients with asthma found 59 percent had reflux symptoms, 51 percent had abnormal intraesophageal pH levels, 51 percent had hiatal hernias, and 37 percent had esophagitis (Havemann et al, 2007).

Medical management of acid suppression with proton pump inhibitors (PPIs) and H2 blockers, aimed at improving respiratory symptoms and reducing the need for asthma medication, has had varying degrees of success, ranging from no relief to complete suppression of reflux symptoms along with improvement of respiratory symptoms. Some asthma patients were able to reduce the need for control medications with successful acid suppression. Surgical management, specifically Nissen fundoplication, appears to be the most definitive intervention for treatment of GERD, as ninety percent
of patients reported resolution of reflux symptoms following the Nissen procedure. Nissen fundoplication, which has now become the surgical treatment of choice in controlling GERD symptoms, can essentially provide a cure for the majority of reflux patients. This procedure restores a physiologic equivalent of a lower esophageal sphincter, which becomes incompetent in patients with GERD. In contrast to GERD, asthma must be managed medically and there are no surgical interventions providing cure or relief. In patients with severe enough asthma, those medications include oral steroids, which have adverse systemic effects, especially with chronic use. Because there are better outcomes for reflux symptoms with surgical intervention, and given the established, albeit unclear, relationship between acid reflux and asthma symptoms, the use of fundoplication as an intervention for controlling respiratory symptoms and reducing the need for control medication should be analyzed and strongly considered. Determining the efficacy of surgical management with Nissen fundoplication to reduce or eliminate acid reflux, specifically for controlling asthma symptoms and reducing the need for control medication, is an important step for patients with asthma that is worsened by concomitant GERD.

Purpose of Study

The purpose of this paper is to conduct a systematic review of the literature to evaluate the effectiveness of Nissen fundoplication in reducing asthma symptoms and the need for control medication. These studies will also be analyzed with a GRADE assessment to evaluate the strength and/or weakness of the outcome.
METHOD

A literature search was performed using PubMed, Medline, and SpringerLink. These databases were accessed through the Uniformed Services University Learning Resources Center Electronic Resources System. The keywords search included “asthma” and “fundoplication” in combination. The search was limited to English language and full text journal articles. The initial results included 244 articles. Studies were sorted by relevance and reviewed for content that addressed the clinical question, including patients studied who had both gastroesophageal reflux and asthma and had undergone fundoplication to control reflux. Two articles that addressed patients with both gastroesophageal reflux and asthma who underwent fundoplication were selected. Another article that addressed gastroesophageal reflux and associated respiratory symptoms, including cough and wheezing, was also selected. Some studies looked at medication to control reflux in addition to fundoplication. Articles between 1999 and 2010 were selected. Case reviews were excluded. After exclusion criteria were applied, articles were reviewed for relevancy and three were chosen to review.

RESULTS

The first study reviewed was a retrospective study by Spivak et al. (1999). In this study, 39 patients met their inclusion criteria, which was asthma as their primary indication for undergoing fundoplication. The mean duration of asthma symptoms prior to surgery was fifteen years, and the mean duration of reflux symptoms was eight years. Sixty-four percent of these patients felt that there was a direct association between the two. Mean follow-up for this study was 2.7 years. All patients rated their asthma symptoms as severe and interfering with daily activities, and all patients used daily
control medication. Reflux symptoms of these patients were also rated as severe, and all patients were taking PPI or H2 blocker therapy prior to fundoplication. Outcomes measured were symptoms as measured by the National Asthma Education Program, medication use, and pulmonary function. Asthma symptoms, including asthma exacerbations, cough/wheeze, exercise tolerance, and nocturnal asthma all improved significantly (P<0.01). The only symptomatic outcome that was not significant was time missed from work or school. Frequency of medication use (inhaled bronchodilators, inhaled steroids, oral bronchodilators, and oral corticosteroids) decreased in all patients undergoing fundoplication, however, the only medication reduction to reach statistical significance was the use of oral corticosteroids (P<0.001). Of those taking daily oral corticosteroid therapy, 78% discontinued use of oral steroids completely. Pulmonary function tests did not see improvement postoperatively. Of note, although exact numbers and percentages were not discussed, all gastroesophageal reflux symptoms (heartburn, regurgitation, dysphagia) and use of reflux medication, either PPIs or H2 blockers, were reduced significantly postoperatively. The authors concluded that fundoplication effectively decreases asthma symptoms and allows for reduction in control medication, the most important of which being systemic oral steroids. In a patient with steroid-dependent asthma or one without GERD medication success, strong consideration for surgical referral for fundoplication should be given.

The next study reviewed, by Sontag et al. (2003), was a long-term follow-up on a randomized trial of 62 patients with gastroesophageal reflux and asthma to determine whether prolonged treatment of GER altered the long-term natural history of asthma in asthmatics with GER. Follow-up time was up to 19.1 years. The patients were
randomized to one of three antireflux groups; a control group to use antacids as needed, a medication group to use ranitidine 150 mg TID, and a surgical group who underwent Nissen fundoplication. Medication and control groups were treated for a duration of two years. In this trial, asthma was defined as prior diagnosis with discrete attacks of wheezing and 20% reversibility in airway disease, and GER was defined as an abnormal ambulatory 24-hour pH test and macroscopic or microscopic evidence of GERD. In terms of asthma symptom scores, improvement of at least 40% from baseline occurred in 75% of patients in the surgical group versus 20% in the control group and none in the medical group. Conversely, asthma symptoms worsened by at least 40% from baseline in 7% of the control group, 18% of the medical group, and none of the surgery group. The difference between improved asthma symptoms in the medical and control group versus in the surgical group was statistically significant (P<0.05). Only the surgical group reached statistically significant improvement in asthma symptom scores. Peak flow rates showed immediate improvement and long-term improvement in the surgical group, but not in either the medical or control groups. Although the difference between the surgical group versus the medical and control group appeared significant, the analyzable data was too small to demonstrate significance. Overall need for asthma control medication was reduced in the surgical group, slightly reduced in the medical group, but not reduced in the control group. Bronchodilator and inhaled corticosteroid therapy was not significantly reduced in the surgery group, however, 25% of patients requiring daily systemic corticosteroids and 50% of patients requiring intermittent systemic corticosteroids were able to discontinue corticosteroid use all together. While the reduction of oral steroid need is noteworthy, it
was not statistically significant. The authors of this study concluded that, while pulmonary function, control medication needs, and long-term survival did not overwhelmingly improve, overall clinical status in these patients was markedly improved in comparison to those patients in either the medication or control group.

The third study reviewed, a retrospective study by Patti et al. (2000), looked at the effect fundoplication had on GERD-induced respiratory symptoms. The study examined the correlation and predictive values of cough associated with reflux, pH, and respiratory symptoms. Thirty-nine of the 340 patients used in the study had coughing and wheezing associated with esophageal reflux within three minutes of reflux onset. Patients with cough associated with reflux (within three minutes of each other), as detected by pH monitoring, were most likely to benefit from antireflux surgery. Eighty-three percent of these patients had resolution of symptoms, compared to 57% when there was no correlation between cough and reflux. Overall, 74% of these patients had resolution of their cough and 64% had resolution of wheezing after undergoing fundoplication. This study suggested pH monitoring as the best way to predict postoperative resolution of respiratory symptoms. This is particularly useful when pH is measured at both the lower esophageal sphincter (LES) and upper esophageal sphincter. Outcomes were more dramatic when acidic pH was measured at the upper esophageal sphincter due to increased likelihood that respiratory symptoms were due to aspiration of refluxate. Seventy-seven percent of patients had resolution of respiratory symptoms when acidic pH was measured in the LES alone versus 90% of patients with respiratory symptoms resolution when acidic pH was measured in both the distal and proximal esophageal sphincters. The authors conclude that, while some patients may
or may not respond satisfactorily to medication therapy, more patients, including those who do not respond well to medication, will benefit from antireflux surgery. The challenge is deciphering who will benefit the most from surgery, and that surgery should be considered and completed before irreversible lung damage occurs.

DISCUSSION

While there is still an unclear connection between GERD and asthma, it appears an association exists, nonetheless. Because asthma seems to be exacerbated by gastroesophageal reflux, treating the reflux appears to be an effective means of improving or relieving asthma symptoms and reducing the need for control medication in those patients with both conditions. Each of the three studies reviewed, revealed improvement of asthma in some form or another. A significant portion of patients reported improvement of asthma symptoms following fundoplication. Not only did the patients who underwent antireflux surgery experience a higher rate of improvement over those taking antireflux medication, but they also experienced those improvements almost immediately and continued to maintain their improved or relieved state, rather than regressing at any period of time as did many in the medication groups. A great number of patients were also able to reduce or completely discontinue use of some or all of their asthma medications. The most impressive outcome from fundoplication in terms of medication reduction or elimination was that some patients no longer needed to take oral corticosteroids to manage their airways. Spivak et al. (1999) reported that, overall, 73 percent of the surgical patients were able to reduce their corticosteroid use. This is substantial for those who have been on or will need to be on systemic steroids long-term due to their long-term affects. Though these results seem very promising,
this study was limited by its sample size due to the nature of the Nissen procedure being primarily for GERD and generally not for the primary indication of asthma, which is the population this study was following. Only 39 of the 600 patients who had undergone fundoplication were doing so principally for asthma.

The theory that GERD-induced asthma is partially caused by microaspiration of reflux, whether symptomatic or not, has implications for long-term airway remodeling. The medication groups in all three studies did not show much improvement in asthma symptoms scores or medication use. Moreover, they did not show much improvement in GERD symptoms score, either. It is believed that, while acid-inhibiting medication may reduce or neutralize the acid, there is still refluxate migrating up the esophagus that is being aspirated due to an incompetent lower esophageal sphincter (LES), causing irritation to the airways. This, over time, can lead to airway remodeling, causing even further progression and exacerbation the patient’s asthma. The only way to prevent any microaspiration of reflux is to definitively eliminate the cause of refluxate. Fundoplication does this by increasing the LES pressure and restoring a reflux barrier.

When considering the GRADE criteria for evaluating outcomes, there were four outcomes that were similar among two or more studies. Frequency of exacerbations, including wheezing and coughing, were reduced in two studies, although the quality of evidence is low. Nocturnal asthma symptoms improved throughout two studies, and evidence of such proved to be of moderate quality. The need for control medication was reduced across two of the studies. These medications included inhaled bronchodilators, oral bronchodilators, and inhaled corticosteroids. One study yielded high quality evidence and the other yielded low quality evidence for a moderate overall
GRADE strength. Oral corticosteroids were given their own outcome category. This outcome is one of the most considerable of all outcomes due to its implications that one can reduce, or eliminate outright, the need for systemic steroids. Two studies that specifically addressed oral corticosteroid use showed a reduced need for such medication, with one study showing a statistically significant reduction in use. The outcome qualities for oral corticosteroid use were moderate and high, respectively, for an overall evidence strength of moderate. The evidence in support of fundoplication for improvement or relief of asthma symptoms or need for asthma medication, as determined by GRADE criteria, is of moderate quality based on the three studies in this review (Appendix A). By definition from the GRADE working group, evidence of moderate quality implies further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Generally speaking, studies looking at fundoplication success for the primary indication of asthma, will be limited in sample size because this is mainly a procedure indicated for GERD, and there are far fewer patients electing this procedure with asthma or respiratory symptoms as their foremost complaint, making it challenging to assess outcomes that are largely based on respiratory symptoms. What is known, is that fundoplication is the single most effective treatment for acid reflux, with 90 percent of patients reporting cure or significant improvement after the procedure (Patti, 2000). One should confidently be able to conclude that, if GERD exacerbates or potentially causes some asthma, the best treatment for GERD-induced asthma would be to cure the GERD and effectively eliminate the very cause of the hyper-reactive airway.
REFERENCES


### APPENDIX A

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quantitative &amp; type of evidence</th>
<th>Findings</th>
<th>Starting grade</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>GRADE for Evidence for Outcome</th>
<th>Overall GRADE of Evidence Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough/wheeze</td>
<td>1 ROS* Decreased incidence</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>+1 0 0</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>1 ROS^ Decreased incidence</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>0 0 0</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Nocturnal asthma exacerbations</td>
<td>1 ROS Decreased incidence</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>+1 0 0</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>1 RCT** Decreased incidence</td>
<td>High</td>
<td>0 0 0 0 0 0</td>
<td>0 0 0</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Control medications not including oral corticosteroids</td>
<td>1 ROS Somewhat reduced, but not significantly</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>0 0 0</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>1 RCT Somewhat reduced, but not significantly</td>
<td>High</td>
<td>0 0 0 0 0 0</td>
<td>0 0 0</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1 ROS Significantly decreased usage</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>+1 0 0</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>1 RCT Decreased usage</td>
<td>High</td>
<td>0 0 0 0 0 0</td>
<td>0 0 0</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*ROS- retrospective observational study
** RCT- Randomized control trial
^Cough and wheeze associated with reflux symptoms occurring within three minutes of onset of reflux