Surgical outcome in gastro-esophageal reflux disease patients with inadequate response to proton pump inhibitors

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Abstract. Laparoscopic fundoplication (LF) has been shown to be effective in treatment of patients with gastro-esophageal reflux disease (GERD) requiring long-term medical therapy. Its effectiveness in patients with poor response to proton pump inhibitors (PPIs) has been questioned. We prospectively followed 445 patients with proven GERD inadequately controlled on PPI (up to 120 mg/day) and 274 GERD patients with good response to PPIs (20–120 mg/day) after LF. Patients in both groups underwent 24 h pH testing, esophageal manometry, symptom score evaluation, and quality-of-life (QOL) assessment (SF-36) before and at 6 months, 2 years, and 5 years after surgery. LF was associated with a marked improvement in percentage acid reflux, lower esophageal sphincter pressure, and symptom control in both groups of patients; however, the poor responders to PPIs also had a significant improvement in both physical and mental health component of the QOL assessment. Laparoscopic fundoplication provides an excellent symptom control for GERD patients, even those who have responded inadequately to large doses of PPIs. GERD patients who respond poorly to PPI therapy have significantly lowered physical and mental health QOL scores. Laparoscopic fundoplication in this group of patients leads to marked improvement of both components of QOL by 2 years after surgery.

Key words: Laparoscopic fundoplication — Proton pump inhibitor therapy — Outcome — Symptom response — Quality of life

Use of proton pump inhibitors (PPIs) for severe gastroesophageal reflux disease (GERD) has substantially reduced the number of medical nonresponders. PPIs have been shown to heal esophagitis in 90% of cases within 6 weeks in doses of 20–40 mg/day [4, 5, 8, 12], and it has been suggested that by increasing the daily dose to 60–80 mg the percentage of responders may reach close to 100% [10, 12]. However, in 80% of patients the symptoms recur once the medication is stopped [10], and although some may go on to be controlled on H2-blockers or prokinetic medication, a significant portion of patients do not achieve adequate symptom control on alternative therapies and require long-term maintenance therapy with omeprazole or other proton pump inhibitors [11]. This has led to a sharp increase in use of PPIs in most countries where the drugs are easily available and in which the cost of the drug does not act as a significant deterrent [14].

Surgery for GERD has been shown to be effective over long-term follow-up and was reserved for patients with complications of GERD or those who did not respond to maximum medical therapy [9]. In a prospective randomized controlled trial comparing surgical and medical therapy of GERD, Lundell et al. [13] found open fundoplication to be superior to maintenance omeprazole (AstraZeneca PLC, Sweden) therapy in GERD patients. However, with the high degree of acid suppression achieved on PPIs, some investigators have questioned whether patients with poor response to PPI (after adequate titration) have an acid-reflux problem and have suggested that these patients may not respond to acid-reflux surgery [5].

With recent introduction of laparoscopic techniques in performance of antireflux surgery, there has been a significant reduction in morbidity, postoperative pain, hospital stay, and recovery period. This has led to a resurgence in the use of antireflux surgery. Many centers that have offered this procedure over the past 10 years have reported an increase in referral of patients controlled on maintenance PPI therapy who choose to have the laparoscopic surgical option in preference to long-term medication. The result of surgery in this group of patients has been shown to be excellent [3, 5, 9].

The aim of this study was to evaluate the efficacy of laparoscopic fundoplication in patients with inadequate response to PPIs at doses of up to 120 mg/day in com-
parison to patients with good symptom response to maintenance PPI therapy who choose to have surgery.

Methods

Patients

Over an 8-year period from August 1992 to November 2000, 719 consecutive patients (444 female, 275 male) with mean age of 46.0 ± 13.6 have undergone laparoscopic fundoplication (LF) in our institution. All patients had proven gastroesophageal reflux disease and had been tried on proton pump inhibitor (PPI) therapy between doses of 20 and 120 mg/day. The primary indication for surgery was inadequate response (<70% relief on a visual analogue scale, defined by the patient's subjective impression) to PPIs titrated to a dose of 120 mg/day in 445 patients (308 female, 137 male) with mean age of 48.1 ± 13.8 (hereafter called the “poor responders”). This included 13 patients who were unable to tolerate PPIs due to side effects and who were on other antisecretory or prokinetic medications. As well, there were 35 poor responder patients who had stopped taking regular medications because of a lack of symptom control. These patients had all tried at least a 6-month course of PPIs at doses of up to 120 mg/day without adequate response.

The second indication for surgery was a need for long-term PPI therapy in 274 patients (136 female, 138 male) with mean age of 42.6 ± 12.5 years who despite a good (≥70% relief) symptom response chose to undergo LF for long-term control of symptoms (hereafter referred to as “good responders”). This group included 12 patients who were on H2-blockers and/or prokinetics because they could not tolerate PPIs due to side effects and who were on other antisecretory or prokinetic medications. As well, there were 67 poor responder patients who had stopped taking regular medications because of a lack of symptom control. These patients had all tried at least a 6-month course of PPIs at doses of up to 120 mg/day without adequate response.

The second indication for surgery was a need for long-term PPI therapy in 274 patients (136 female, 138 male) with mean age of 42.6 ± 12.5 years who despite a good (≥70% relief) symptom response chose to undergo LF for long-term control of symptoms (hereafter referred to as “good responders”). This group included 12 patients who were on H2-blockers and/or prokinetics because they could not tolerate PPIs (<70% relief) symptom response. In addition to the above tests, most patients underwent quality-of-life assessment (MCS). We used the published scoring algorithms and validated them with test data sets from the publishers of the questionnaire [17].

Proton pump inhibitor dose titration

Patients with proven GERD who had failed other antireflux medications were started on a daily PPI dose of 20–40 mg/day. They were asked to grade their symptom response after 6–8 weeks on a scale of 0 (none) to 100 (complete) on a visual analogue scale. Patients with ≥70% response to PPI drugs were considered as good responders, while <70% control of symptoms was considered as inadequate response and the dose was increased by steps of 20–30 mg/day up to a maximum dose of 120 mg/day. Patients who developed intolerable side effects were considered as failures and were put on alternative medication. Laparoscopic fundoplication was offered to all patients who had failed medical therapy, and as an alternative to PPI therapy to those requiring long-term (>2 year) maintenance therapy.

Operative technique and postoperative care

The procedure has previously been described. In short, a 2–3 cm 360° wrap is constructed, with the tightness of the wrap varied between 42 and 52 Fr depending on the status of esophageal motor function assessed by preoperative manometry [3].

Postoperatively, the patients did not receive a nasogastric tube and were started on a full fluid diet on the first postoperative day after a gastrografin (Bracco Diagnostics, Mississauga, ON) swallow. Patients were discharged from hospital when tolerating oral fluids and soft diet.

Follow-up investigations

Patients were invited to undergo follow-up investigations at 6 months and 2 years and 5 years following the surgery. The repeat studies included 24-h pH recording, esophageal manometry, GERD symptom assessment supervised by an independent observer using the scoring system described earlier [2, 3], and quality-of-life assessment using SF-36 questionnaire.

Esophageal manometry

Esophageal manometry was carried out with a seven-lumen sleeve-sidehole catheter. The basal pressure at the lower esophageal sphincter region was measured using the sleeve sensor (Dent Sleeve Pty Ltd, Adelaide, Australia) in relation to the gastric pressure.

24-h pH recording

All patients were asked to stop all antireflux medications for 5 days before 24-h pH testing using an ambulatory digitrapper (Synetics, Stockholm, Sweden). The pH probe was positioned 5 cm above the position of the lower esophageal sphincter, as determined earlier by manometry. Gastroesophageal reflux was considered as a drop in esophageal pH below 4, and the percentage reflux in 24 h below 4 was calculated for each patient.

Symptom score assessment

Patients were asked to score 5 specific GERD symptoms of heartburn, regurgitation, bloating, dysphagia, and epigastric/retrosternal pain. Each symptom was scored as a product of severity (0 = none, 3 = severe) and frequency (0 = none, 4 = daily). The preoperative scores were obtained on PPI (or other antireflux medication) and off PPI. All postoperative scores were obtained off all antireflux medication. This symptom score has been previously validated [2].

Quality-of-life questionnaire

We assessed quality of life using the SF-36 questionnaire. This is a general quality-of-life instrument with 4 domains of physical health and 4 of mental health. These 8 domains can be summarized into a Physical Health Component score (PCS) and Mental Health Component score (MCS). We used the published scoring algorithms and validated them with test data sets from the publishers of the questionnaire [17].

Statistical analysis

Data were analyzed using Statview 4.5 for the Macintosh. Data are expressed as mean (sd) in tables and text, and mean (95% confidence interval) on histograms. Comparisons of 2 variables were by unpaired t test. Follow-up data were analyzed by 2-way analysis of variance with post hoc comparisons by Fisher’s protected least significant difference.

Results

Success of follow-up

Although attempts were made to carry out follow-up evaluation on all patients, we could only achieve partial follow-up (Table 1), either because of patient refusal or inability to contact. There was, however, no difference in follow-up between the two groups.

Twenty-five patients (3%) have required redo fundoplication due to anatomic failure. The analysis of these patients was included in their original preoperative grouping.
Comparison between the two groups

Before surgery there were no differences in the symptom scores off medication between the “good responders” and the “poor responders” (Table 2). The 24-h pH study which was done off medication showed a slightly higher acid exposure in the good responders (Table 2). There was also no difference in the tone of the lower esophageal sphincter between the two groups (Table 2). When the symptom scores were assessed on medication, the responders showed much lower scores which were within the normal range for healthy subjects without reflux disease.

After surgery the responders showed excellent symptom control with reported reflux symptom scores off medication being similar to scores obtained on medication before surgery, and this improvement was maintained at 5-year follow-up (Fig. 1). The poor responders similarly showed excellent symptom control but consistently showed higher scores when compared to the good responders (Fig. 1).

GERD indices before and after surgery

Before surgery patients in both groups showed decreased lower esophageal sphincter tone (Fig. 2) and increased acid exposure (Fig. 3). As noted above, there was a slightly higher acid exposure in the good responders, but both groups responded equally well to surgery with sustained reduction in the lower esophageal pH scores to well within normal at 5 years after surgery. After surgery the poor responders had a small but significantly ($p = 0.0440$, 2-way ANOVA) higher LES pressures.

Table 1. Follow-up availability of patients

<table>
<thead>
<tr>
<th></th>
<th>Good responders ($n = 274$)</th>
<th>Poor responders ($n = 445$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>259</td>
<td>426</td>
</tr>
<tr>
<td>Followed up (%)</td>
<td>203 (78%)</td>
<td>342 (80%)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>0.80</td>
<td></td>
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<tr>
<td>5 years</td>
<td>0.0001</td>
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Table 2. Baseline data: Poor responders compared to good responders

<table>
<thead>
<tr>
<th></th>
<th>Poor responder ($n = 445$)</th>
<th>Good responder ($n = 274$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.1 (13.6)</td>
<td>42.6 (12.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>69%</td>
<td>50%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GERD symptom score off meds</td>
<td>34.3 (14.8)</td>
<td>33.7 (12.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>GERD symptom score on meds</td>
<td>22.6 (14.7)</td>
<td>13.2 (11.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h pH (% &lt;4)</td>
<td>8.5 (8.7)</td>
<td>10.2 (9.7)</td>
<td>0.0201</td>
</tr>
<tr>
<td>LES pressure (mmHg)</td>
<td>6.3 (5.5)</td>
<td>6.0 (5.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>QOL physical health</td>
<td>36.4 (10.8)</td>
<td>43.5 (10.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QOL mental health</td>
<td>43.5 (12.2)</td>
<td>47.2 (11.3)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Fig. 1. Improvement in reflux symptom score after surgery.
tone. Both groups showed a small downward trend in LES tone at 6, 24, and 60 months after surgery, but this was not associated with any loss of acid reflux control or symptom control.

**Quality-of-life score before and after surgery**

Before surgery the poor responders had a significantly lower physical health \((p < 0.0001)\) and mental health \((p = 0.0004)\) quality of life compared to good responders (Table 1, Table 3). Five years after surgery the good responders continued to enjoy, off medication, a quality of life that was unchanged when compared to baseline on medication for both physical health \((p = 0.1918)\) and mental health \((p = 0.8404)\) domains of the SF36 (Figs. 4 and 5).

Five years after surgery the poor responders had a significantly improved quality of life off medication for both the physical-health \((p = 0.0018)\) and mental-health \((p = 0.0039)\) domains as compared to preoperative values. By this time, the poor responders had

**Table 3. Quality of life before and after surgery**

<table>
<thead>
<tr>
<th></th>
<th>Pre-op mean (SD)</th>
<th>5 years post op mean (SD)</th>
<th>Mean change</th>
<th>(p)</th>
</tr>
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<tbody>
<tr>
<td>PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good responder</td>
<td>43.5 (10.6)</td>
<td>45.6 (11.3)</td>
<td>2.1</td>
<td>0.1918</td>
</tr>
<tr>
<td>Poor responder</td>
<td>36.4 (10.8)</td>
<td>40.3 (12.4)</td>
<td>3.9</td>
<td>0.0018</td>
</tr>
<tr>
<td>(p)</td>
<td>&lt;0.0001</td>
<td>0.0085</td>
<td></td>
<td></td>
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<tr>
<td>MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good responder</td>
<td>47.2 (11.3)</td>
<td>47.5 (9.9)</td>
<td>0.3</td>
<td>0.8404</td>
</tr>
<tr>
<td>Poor responder</td>
<td>43.5 (12.2)</td>
<td>47.3 (10.7)</td>
<td>3.7</td>
<td>0.0039</td>
</tr>
<tr>
<td>(p)</td>
<td>0.0004</td>
<td>0.8777</td>
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achieved such an improvement that their mental health scores were now similar to those of the responders ($p = 0.8777$).

**Antisecretory medication use after surgery**

It was noted that a number of patients continued to take PPIs or H2-blockers after surgery (Table 4). For the most part, this was initiated by the patients’ family doctors for a variety of dyspeptic symptoms without evidence of failed surgery. Although more poor responders than responders required antisecretory medication, the difference was not statistically significant. It should be noted that the objective tests and symptom score evaluations were performed after the patients had been off their medication for 5 days. Quality-of-life questionnaires were completed while the patients were on their medication.

**Discussion**

Laparoscopic fundoplication offers a suitable alternative to GERD patients who are unwilling to consider long-term medication but wish to enjoy symptom control comparable to that of proton pump inhibitors. Although studies have shown that surgery is effective in this group of patients, some investigators have suggested that surgery may not be effective in patients with poor response to medical therapy who often have multiple GI complaints [5]. This study demonstrates that laparoscopic fundoplication is effective in patients who had inadequate response to large doses of PPI therapy as

<table>
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<th>Good responder ($n = 274$)</th>
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<tbody>
<tr>
<td>6 months</td>
<td>12.5%</td>
<td>8.0%</td>
</tr>
<tr>
<td>2 years</td>
<td>13.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>5 years</td>
<td>16.0%</td>
<td>11.0%</td>
</tr>
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</table>

![Fig. 4. Change in quality of life — physical health component after surgery.](image)

![Fig. 5. Change in quality of life — mental health component after surgery.](image)
long as the diagnosis of GERD is objectively confirmed and correlation between symptoms and reflux events demonstrated.

Failure of response to proton pump inhibitor therapy may be due to inadequate acid suppression, or non-acid (including bile) reflux [6], or when regurgitation/aspiration is the primary symptom [5, 16]. In this study we titrated the dose of PPI therapy to a maximum of 120 mg/day, which should provide adequate acid suppression for most patients [5]. We also ensured not only that the patients had objective evidence of GERD (positive 24-h pH recording ± endoscopic evidence of esophagitis), but that there was a good correlation between patients’ primary symptoms and acid reflux events on 24-h pH recording or during a blinded randomized intrasophageal infusions of acid and saline (Bernstein test). Thus, the primary reason for failure in our patient cohort was either inadequate control of regurgitation/aspiration or the fact the symptoms were possibly due to non-acid reflux. Under these circumstances a fundoplication which augments the antireflux barrier at the lower esophageal sphincter is likely to produce significant symptom improvement, a fact confirmed by this study [7]. Our center has recently begun analysis of non-acid reflux using impedance technology, and further evaluation of poor responders is under way.

The symptoms of GERD can be chronic and incapacitating and significantly affect the quality of life [15]. In the North American population aged 45–54, the median score for the physical health component of the SF36 quality of life questionnaire is 52.6 (IQR 45.7–55.9) and the median score for the mental health component is 53.6 (IQR 46.3–57.2) [20]. Thus, both the good and poor responders had a significantly reduced physical health quality of life as has been described by Revicki et al. using the SF36 for patients with chronic GERD [15]. With regard to the mental health component, the poor responders were below the 25th percentile before surgery and both groups showed improvement over the 25th percentile after surgery [20].

The improvement seen in the poor responders in the mental health domain is similar to the change seen with the treatment of clinical depression (3.9) [19]. Not surprisingly, the change in the physical health domain in these poor responders is not as great as that seen after hip replacement or heart valve replacement but is similar to the changes seen with peptic ulcer treatment (3.2) [18]. These observations should lay to rest the concerns raised by some investigators that patients who respond poorly to large doses of omeprazole or other proton pump inhibitors and in whom acid suppression has not produced adequate symptom relief may also respond poorly to surgery.

While the poor responders did respond symptomatically to laparoscopic fundoplication, they had persistently higher symptom scores after surgery in comparison to good responders. This suggests that the poor responders are more complex patients and should be evaluated thoroughly before surgery is advised. Clear objective evidence of reflux and correlation between patients’ typical symptom and reflux events or acid infusion are essential to ensure a good outcome from surgery.

Although both groups received the same operation, the surgeon deliberately made a tighter (42 Fr) wrap in patients with primary respiratory symptoms (particularly cough) associated with GERD who were generally among the “poor responder” group. This was reflected in higher LES tone recorded in “poor responders” after fundoplication. Experience has shown that in patients with cough the percentage acid reflux in 24 h needs to be close to 0 to achieve excellent response [1].

Conclusion

Our data confirm earlier reports that laparoscopic fundoplication is an effective antireflux operation and that there is no significant deterioration in its function after 5 years. This study also confirms that patients with poor response to large doses of PPI should enjoy a good result from laparoscopic fundoplication when carried out in a specialized center and on appropriately selected patients.

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