

Therapeutic Effects of Laparoscopic Fundoplication for Nonerosive Gastroesophageal Reflux Disease

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Abstract

Purpose. Surgical treatments for nonerosive gastroesophageal reflux disease (NERD) have not been investigated sufficiently. We examined the results of laparoscopic fundoplication for patients with NERD.

Methods. We performed laparoscopic fundoplication for NERD in 22 patients. The severity of esophageal hiatal hernia, morphology of the cardiac orifice, and results of 24-hour continuous esophageal and gastric pH were evaluated. We used a four-point scale for the improvement rating of postoperative symptoms.

Results. There were 20 patients (91%) with a sliding hiatal hernia, and 21 patients (95%) with a loose cardiac orifice. Seven patients had acid reflux with 4.0% or higher esophageal fraction of time pH below 4. The surgical techniques used were Nissen fundoplication in 10 patients and Toupet fundoplication in 12 patients. Improvement of postoperative heartburn was rated as excellent in 16 patients, good in 5, and fair in 1. The overall efficacy rating was 95%, and discontinuation of proton pump inhibitor (PPI) was possible in 21 patients.

Conclusion. Our results of performing laparoscopic fundoplication in patients with NERD were excellent. Even if abnormal acid reflux cannot be confirmed preoperatively, sufficient therapeutic efficacy can be expected for patients with esophageal hiatal hernia or a loose cardiac orifice.

Key words Nonerosive gastroesophageal reflux disease · Endoscopy-negative gastroesophageal reflux disease · Hiatal hernia · Laparoscopic fundoplication

Introduction

Surgical treatment for reflux esophagitis began with Allison's anatomical repair¹: Nissen fundoplication,² Hill's posterior gastropexy,³ and the Belsey Mark IV technique⁴ were subsequently designed and improved,⁵ with excellent results.^{6–8} In 1991, Dallemagne et al.⁹ were the first to report laparoscopic Nissen fundoplication, which soon became adopted in Europe and the United States.^{10–12} Now, the standard surgical approach for treatment of reflux esophagitis is laparoscopic fundoplication; mainly with Nissen fundoplication or Toupet fundoplication.^{10–12} The long-term results (5 years or longer) have been reported as excellent.^{13,14}

Endoscopy-negative gastroesophageal reflux disease (endoscopy-negative GERD) is the generic name for a disease state in which GERD-specific symptoms such as heartburn are noted, but no esophagitis (mucosal break) is detected endoscopically. Recently, nonerosive GERD (NERD) and symptomatic GERD (sGERD) have come to be used as almost equivalent terms. The fact that NERD, which accounts for about 60%–70% of GERD,^{15,16} has a low rate of improvement of symptoms with proton pump inhibitors (PPIs)^{17,18} suggests that it differs slightly as a disease state from erosive GERD.¹⁹ It has been reported that since the proportion of patients with poor quality of life (QOL) and symptoms is equal to that for erosive GERD,^{20,21} the effective treatment of NERD is important. However, although there are the reports on the effects of PPIs or histamine H2 receptor antagonists,^{22–24} the results of surgical treatment for NERD remain largely unknown. Therefore, we evaluated the results of performing laparoscopic fundoplication for patients with NERD.

Patients and Methods

Patients

We performed 24-h pH monitoring and laparoscopic fundoplication in 22 patients with NERD, registered in the database of patients with GERD at our department up until October 2004. There were 10 men and 12 women with a mean age of 48.8 ± 17.3 years (range, 22–74 years), all of whom had received proton pump inhibitors (PPIs) preoperatively. We established the surgical indications for NERD as follows: positive acid reflux on pH monitoring (pH < 4 time fraction: 4% or more); positive bilirubin reflux detected by Bilitec2000 (abs > 0.14: 4% or more); improvement of symptoms by 50% or more with the administration of a PPI, but with a desire not to continue long-term administration; symptoms of esophageal hiatal hernia and reflux other than heartburn, including regurgitation, belching, and epigastric discomfort.

Surgery was performed for patients who met one or more of those criteria and who could provide sufficiently informed consent. The surgical indications for NERD in our department and the reasons for surgery in the 22 patients are shown in Table 1.

Table 1. Indications for surgical treatment in each patient

Patient no.	Surgical indications
1	4
2	1, 4
3	4
4	3
5	4
6	3
7	1, 3
8	1, 3
9	1, 3
10	3
11	1, 3
12	3
13	3, 4
14	3, 4
15	3, 4
16	4
17	1
18	3
19	2, 4
20	1
21	3
22	3

Criteria for surgical indications: 1, positive acid reflux detected by pH monitoring (fraction of time pH < 4: 4% or more); 2, positive bilirubin reflux detected by Bilitec2000 (abs > 0.14: 4% or more); 3, the patients did not wish to take long-term oral proton pump inhibitors even though they improved their symptoms by at least 50%; 4, esophageal hiatal hernia was observed, with reflux symptoms other than heartburn, such as regurgitation, belching, or epigastric discomfort

Selection of Surgical Procedure

We performed Toupet fundoplication in all patients aged 70 years or older, whereas the merits and demerits of Nissen fundoplication and Toupet fundoplication were explained to those younger than 70 years old and the appropriate procedure was chosen for each patient after individual consultation.

Endoscopic Evaluation for Hiatal Hernia and Valve Factor

The presence or absence, type, and severity of esophageal hiatal hernia were evaluated in each patient by upper gastrointestinal barium studies and upper gastrointestinal endoscopy using the A factor, according to the AFP classification by the International Society for Disease of the Esophagus;²⁵ namely, A0, no hiatal hernia identified; A1, small and/or intermittent sliding hiatal hernia; A2, constant sliding hiatal hernia, not reduced by barium studies or with the esophagogastric junction fixed more than 3 cm above the diaphragm on endoscopy; or A3, mixed or paraesophageal hiatal hernia. Morphology of the cardiac orifice was observed by gastric reverse imaging during upper gastrointestinal endoscopy to evaluate the “valve” factor;²⁶ namely, V0, no esophageal hiatal hernia detected, and the cardiac orifice not enlarged by supply with air; V1, esophageal hiatal hernia noted, and the cardiac orifice not enlarged by supply with air; V2, no esophageal hiatal hernia noted, and the cardiac orifice enlarged by supply with air; or V3, esophageal hiatal hernia noted, and the cardiac orifice enlarged.

24-h Continuous pH Monitoring

We performed 24-h pH monitoring after a 1-week wash-out period if patients had received acid antiseptory agents such as PPIs. The Diggitrapper Mk III (Medtronic Functional Diagnostic, Skovlunde, Denmark) was used as a pH meter, with a pH catheter equipped with a two-channel antimony electrode (15-cm interval of sensor). The pH catheter was inserted nasally under X-ray monitoring, with the catheter on the proximal side about 5 cm above the esophagogastric junction. The catheter on the distal side was introduced into the gastric body under X-ray monitoring, avoiding coil-up in the esophagus. As a rule, 24-h continuous monitoring was performed simultaneously for esophageal and gastric pH. Data were analyzed with Gastro software (Medtronic Functional Diagnostic). To monitor esophageal pH, we calculated mean pH, median pH, the number of episodes of acid reflux per day, the number of episodes of prolonged acid reflux for 5 min or longer per day, the longest acid reflux

time (min), and the fraction of time pH below 4.0. The standard value of esophageal pH monitoring was used according to the criteria of Johnson and DeMeester.²⁷ That is, when the esophageal fraction of time pH below 4 was 4.0% or more, patients were considered to have acid reflux. As gastric pH parameters, we calculated the mean pH, median pH, fraction of time pH below 3 (%), and fraction of time pH below 4.0 (%).

Evaluation of Surgical Outcome

Surgical technique, intraoperative complications, operative time, number of days of postoperative hospitalization, and postoperative complications were determined in the perioperative period. Improvement of postoperative symptoms was evaluated using a 4-point scale (excellent, symptoms completely disappeared; good, symptoms occur about once per month; fair, symptoms occur about once per week; poor, symptoms occur two or three times per week or more often than preoperatively). Patients who had acid reflux (with 4.0% or higher esophageal fraction of time pH below 4) and those who did not have acid reflux (with less than 4.0% esophageal fraction of time pH below 4) were classified into groups A and B, respectively, which were then compared.

Statistical Analysis

For statistical analysis, we used the unpaired *t*-test to compare each factor between groups A and B. The Spearman correlation analysis with determination of rank-sum correlation coefficient was used to examine the correlation of each gastric pH factor (mean pH, median pH, fraction of time pH below 3 and fraction of time pH below 4) with an esophageal fraction of time pH below 4. Differences were considered significant at $P < 0.05$.

Results

Patients' Characteristics

Twenty patients (91%) had a sliding hiatal hernia (A2: 5 patients; A1: 15 patients) and 21 (95%) patients had a loose cardiac orifice. Regarding the valve factor, V3 was noted in 19 patients and V2 in 2 patients. The results of esophageal and gastric pH monitoring are shown in Table 2. Nonstandard pH monitoring values, as categorized by Johnson and DeMeester,²⁷ were observed in 15 (68%) patients for 50 or more episodes of acid reflux per day, in 6 (27%) patients for three or more episodes of long acid reflux (5 min or longer), and in 5 (23%) patients for acid reflux times of 9 min or longer.

Table 2. Characteristics of the patients undergoing surgery for nonerosive gastroesophageal reflux disease

Male:Female	12:10
Age (years)	48.8 ± 17.3 (22–74)
Hiatal hernia	
A3	0
A2	5
A1	15
A0	2
Valve factor	
V3	19
V2	2
V1	1
V0	0
pH monitoring (esophagus, $n = 22$)	
Mean pH	6.0 ± 0.6 (5.0–7.0)
Median pH	6.1 ± 0.6 (4.9–7.2)
No. of episodes of acid refluxes (times/day)	101 ± 116 (2–463)
No. of episodes of long acid refluxes (times/day)	2.8 ± 4.7 (0–16)
Longest acid reflux (min)	11.8 ± 15.6 (0–63)
Fraction time pH below 4.0 (%)	5.7 ± 8.6 (0.1–31.1)
pH monitoring (stomach, $n = 18$)	
Mean pH	2.2 ± 1.0 (1.1–4.3)
Median pH	1.8 ± 1.0 (0.8–4.2)
Fraction time pH below 3.0 (%)	75.9 ± 19.1 (38.4–96.9)
Fraction time pH below 4.0 (%)	82.4 ± 17.4 (47.7–99.0)

A0–A3, anatomical factors in the AFP classification

We were able to analyze gastric pH in 18 of the 22 patients. Ten (56%) patients had a mean pH of less than 2.0, whereas 12 (67%) had a median pH value of less than 2.0. Ten (56%) patients had 80% or higher fraction of time pH below 3, whereas 13 (72%) had 80% or higher fraction of time pH below 4. For the gastric pH factors and esophageal fraction of time pH below 4, the correlation coefficients were as follows: $\rho = -0.123$ for the mean pH value; $\rho = -0.176$ for the median pH value; $\rho = -0.133$ for the gastric fraction of time pH below 3; and $\rho = -0.121$ for gastric fraction of time pH below 4, suggesting a lack of correlation between the gastric pH environment and the acid reflux time.

Comparison Between Groups A and B

A comparison between group A, with an esophageal fraction time of 4.0% or more ($n = 7$) and group B, with an esophageal fraction time of less than 4.0% ($n = 15$), is shown in Table 3. There were no significant differences in sex, age, hiatal hernia, valve factor, mean gastric pH value, median gastric pH value, gastric fraction of time pH below 3, or gastric fraction of time pH below 4 between the two groups. However, there were significant differences in the mean esophageal pH, number of episodes of acid reflux, number of long episodes of reflux, and longest acid reflux time between the two groups.

Surgical Technique, Time of Operation, Intraoperative Complications, Number of Days of Postoperative Hospitalization, and Postoperative Complications

We performed Nissen fundoplication in four patients from group A and six from group B, and Toupet fundoplication in three patients from group A and nine from group B. Overall, Nissen fundoplication and Toupet fundoplication were used in 10 and 12 patients, respectively. The mean postoperative follow-up period was 37 ± 24 (range 4–76) months. The mean operation times were 146 ± 48 (108–235) min in group A and 143 ± 46 (95–270) min in group B, with an overall mean time of 144 ± 46 (95–270) min. The intraoperative complications included pneumothorax and gastric perforation in one patient each in group B, but laparoscopic surgery was completed in each patient, with insertion of a thoracostomy tube or by suturing the gastric wall. The number of days of postoperative hospitalization was 7.6 ± 1.3 (7–10) days in group A and 7.6 ± 1.2 (7–11) days in group B; with a mean number of days of 7.6 ± 1.2 (7–11). The only postoperative complication was dysphagia, which lasted for 3 months or longer, in one patient each after Nissen fundoplication and Toupet fundoplication in group A. The dysphagia in the patient who underwent Nissen fundoplication was relieved by endoscopic dilatation, 6 months postoperatively. In the other patient with dysphagia after Toupet fundoplication, the

Table 3. Comparison of patients with nonerosive gastroesophageal reflux disease according to the presence or absence of acid reflux

	Group A (pH time fraction $\geq 4\%$)	Group B (pH time fraction $< 4\%$)	P value
Male:Female	4:3	6:9	0.4759
Age (years)	48.8 ± 20.2 (23–70)	50.1 ± 16.4 (22–74)	0.6025
Hiatal hernia			0.4489
A3	0	0	
A2	1	4	
A1	5	10	
A0	1	1	
Valve factor			0.3627
V3	6	13	
V2	1	1	
V1	0	1	
V0	0	0	
pH monitoring (esophagus)	($n = 7$)	($n = 15$)	
Mean pH	5.6 ± 0.3 (5.1–5.9)	6.2 ± 0.7 (5.0–7.0)	0.023
Median pH	5.9 ± 0.3 (5.5–6.5)	6.3 ± 0.7 (4.9–7.2)	0.1585
No. of episodes of acid refluxes (times/day)	207 ± 160 (71–463)	51 ± 31 (2–100)	0.0013
No. of episodes of long acid refluxes (times/day)	7.1 ± 6.4 (0–16)	0.7 ± 1.0 (0–3)	0.0009
Longest acid reflux (min)	23.9 ± 22.3 (2–63)	6.1 ± 6.8 (0–29)	0.0094
Fraction time pH below 4.0 (%)	14.4 ± 11.5 (4.3–31.1)	1.7 ± 1.2 (0.1–3.7)	—
pH monitoring (stomach)	($n = 5$)	($n = 13$)	
Mean pH	2.5 ± 0.8 (1.7–3.5)	2.1 ± 1.1 (1.1–4.3)	0.6084
Median pH	1.9 ± 0.8 (1.3–3.0)	1.7 ± 1.1 (0.8–4.2)	0.7838
Fraction time pH below 3.0 (%)	67.4 ± 14.6 (50.3–89.3)	79.1 ± 20.1 (38.4–96.9)	0.2558
Fraction time pH below 4.0 (%)	77.7 ± 16.4 (54.9–94.9)	84.2 ± 18.0 (47.7–99.0)	0.4901

passage of barium from the esophagus to the stomach was seen to be normal on upper gastrointestinal barium studies. This patient, who is taking antidepressant medication for diagnosed depression after a psychiatric consultation, is being followed up.

Symptoms

All the patients in this series suffered heartburn and were taking PPIs preoperatively. In group A, postoperative improvement was rated as excellent in 5 patients, good in 1, and fair in 1; as compared with excellent in 11 patients and good in 4 patients in group B. Overall, postoperative improvement of heartburn was rated excellent in 16 patients, good in 5, and fair in 1. The efficacy rating determined by the percentage of patients with improvement graded as excellent or good, was 95%, and discontinuation of PPIs was possible in 21 patients. In the patient with fair improvement who was diagnosed with depression postoperatively, the postoperative fraction of time pH below 4.0 improved to less than 4.0%, and a histamine H₂ receptor antagonist was still required.

Discussion

Excellent results of laparoscopic fundoplication in erosive GERD patients have been reported,^{13,14} with efficacy ratings of 90% or more. Since fundoplication is performed to reconstruct the mechanism preventing GER, it may be effective for the management of any kind of GER as well as for reflux esophagitis. Thus, it is important to determine if the symptoms of NERD are caused by GER. If the symptoms are caused only by GER, they can be resolved by fundoplication and excellent QOL can be expected. Fass²⁸ classified the characteristics of sGERD as follows: abnormal acid exposure; hypersensitivity to reflux events (pH < 4) within the normal range; hypersensitivity to minute pH changes (pH > 4); and non-acid-related intraesophageal stimuli. Improvement of symptoms can be expected after fundoplication in patients with abnormal acid exposure, in patients with hypersensitivity to reflux events (pH < 4) within the normal range, and in patients with hypersensitivity to minute pH changes (pH > 4), since this procedure improves the regulation of acid reflux. On the other hand, it can be predicted that PPIs will not be effective for patients with GERD caused by non-acid-related intraesophageal stimuli. When symptoms are caused by the reflux of duodenal juice, bile, or pancreatic juice, or reflux stimuli other than acid, the therapeutic effect of fundoplication should be sufficient. Therefore, it is important to understand the causal relationship between symptoms and reflux,

regardless of the composition of reflux acid or duodenal juice.

Generally, esophageal pH monitoring is a good standard testing method for assessing the disease state, but it does have some problems. We often encounter patients with no symptoms during 24-h esophageal pH monitoring. It is not necessarily easy to detect hypersensitivity to reflux events (pH < 4) within the normal range. Furthermore, there is no generally accepted criterion for the assessment of minute pH changes not reaching pH 4. Thus, hypersensitivity to minute pH changes (pH > 4) is not always easy to detect. In 30%–50% of patients with NERD, the results of pH monitoring have been reported to be within the normal range,^{21,29,30} but it is difficult to determine whether the symptoms are caused by GER alone using pH monitoring, for the above reasons. Hypersensitivity has therefore been examined by using the esophageal acid infusion test³¹ or the esophageal pressure sensitivity test.³² Hypersensitivity has in fact been reported in patients with NERD,³² but it is difficult to use these techniques for routine testing. We established the surgical indications for NERD based on the above-mentioned criteria. The overall efficacy rating was 95% for laparoscopic fundoplication, making discontinuation of anti-acid secretion drugs, including PPIs, possible.

There were no significant differences in findings other than those of esophageal pH monitoring between groups A and B. Sifrim et al.³³ reported that there was no difference in the incidence of reflux of gastric contents between patients with GERD and a healthy control group; however, the incidence of acid reflux was higher in the patients with GERD. They suggested that the symptoms might have been caused by the difference in gastric acid secretion and gastric acid distribution between the patients with GERD and the healthy control group. Although we studied the gastric pH environment in patients with NERD, we found no significant differences between groups A and B.

Regarding surgical results, Khajanchee et al.³⁴ compared the results of Nissen fundoplication in 15 subjects assessed by normal preoperative pH monitoring and 208 patients with acid reflux. They reported that the results of preoperative pH monitoring in the subjects with normal-range pH were inferior to those in the subjects with acid reflux, and emphasized the importance of preoperative routine pH monitoring. In their study, esophageal hiatal hernia was noted in 10 (67%) patients and 119 (57%) patients, respectively, in the two groups. On the other hand, Bell et al.³⁵ performed laparoscopic fundoplication with pH monitoring in 18 patients with an acid reflux time of less than 4%; as Nissen fundoplication and Toupet fundoplication in 9 patients each. They reported that 14 patients suffered remission of symptoms, which improved to some degree

in 3 patients, and concluded that fundoplication is effective for the symptoms of sGERD only if the indications for surgery are carefully determined. Bammer et al.³⁶ compared the results of laparoscopic antireflux surgery between patients with NERD and those with erosive GERD, and found no difference between the two groups. They also reported that laparoscopic antireflux surgery was effective for NERD. Our results for NERD were excellent, and supported the reports by Bell and Bammer et al.

The characteristics of patients undergoing surgery for NERD in our facility include a high incidence of esophageal hiatal hernia. Frazzoni et al.³⁷ reported that the rate of esophageal hiatal hernia as a complication was 25% in a control group, 31% in patients with functional heartburn, 49% in patients with NERD, and 68% in patients with erosive GERD. Cameron et al.³⁸ reported that the rate of esophageal hiatal hernia was 55% in patients with sGERD, 71% in patients with erosive GERD, 72% in patients with short segment Barrett's esophagus, and 96% in patients with long segment Barrett's esophagus. Compared with these percentages, our incidence was definitely high. Since the presence of esophageal hiatal hernia is an obvious risk factor for GER,³⁹ the inclusion of such a condition in the criteria for surgery at our department may be one of the factors predisposing to a high complication rate of hiatal hernia. However, the high incidence of esophageal hiatal hernia may be characteristic of Japanese patients with NERD. We noted esophageal hiatal hernia in 14 of our 15 group B patients, and the other patient had a valve factor of V2 and a loose cardiac orifice. Thirteen of 14 patients with esophageal hiatal hernia had a valve factor of V3 and a loose cardiac orifice. It is impossible to determine the percentage of group B patients with hypersensitivity to reflux events (pH < 4) within the normal range or patients with hypersensitivity to minute pH changes (pH > 4). However, judging from our results, esophageal hiatal hernia and loose cardiac orifice probably play roles in NERD.

In conclusion, our results of performing laparoscopic fundoplication for NERD were excellent. Even if abnormal acid reflux cannot be confirmed preoperatively, a good therapeutic effect can be expected if patients with esophageal hiatal hernia or a loose cardiac orifice are observed endoscopically.

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