

# Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux

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**Background:** Both laparoscopic Nissen fundoplication (LNF) and proton-pump inhibitor (PPI) therapy are established in the treatment of gastro-oesophageal reflux disease (GORD). The aim of this study was to compare these two treatments in a randomized clinical trial.

**Methods:** Between July 1997 and August 2001, 340 patients with a history of GORD for at least 6 months were investigated by endoscopy, 24-h pH monitoring and manometry. Of these, 217 were randomized, 109 to LNF and 108 to PPI therapy. The two groups were well matched for age, sex, weight and severity of reflux. Twenty-four-hour pH monitoring and manometry were performed 3 months after treatment, and quality of life was assessed in both groups using the Psychological General Well-being Index and the Gastrointestinal Symptom Rating Scale at 3 and 12 months after treatment.

**Results:** At 3 months there was an improvement in lower oesophageal sphincter pressure from 6.3 to 17.2 mmHg in the LNF group but no change in the PPI group (8.1 and 7.9 mmHg before and after treatment respectively) ( $P < 0.001$ ). The mean DeMeester acid exposure score improved from 42.7 to 8.6 ( $P < 0.001$ ) in the LNF group and from 36.9 to 17.7 in the PPI group ( $P < 0.001$ ). The mean gastrointestinal symptom and general well-being scores improved from 31.7 and 95.4 respectively before treatment to 37.0 and 106.2 at 12 months after LNF, compared with changes from 34.3 and 98.5 to 35.0 and 100.4 respectively in the PPI group. The differences in both of these scores were significant between the two groups at 12 months ( $P = 0.003$ ).

**Conclusion:** LNF leads to significantly less acid exposure of the lower oesophagus at 3 months and significantly greater improvements in both gastrointestinal and general well-being after 12 months compared with PPI treatment.

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## Introduction

Gastro-oesophageal reflux disease (GORD) is most often treated medically. Many patients require long-term therapy with proton-pump inhibitors (PPIs) but in spite of this up to 30 per cent have a relapse of symptoms while on medication<sup>1</sup>. Antireflux surgery is an alternative to medical therapy, but has traditionally been reserved for

patients with persistent symptoms on medication, often due to volume reflux and regurgitation<sup>2</sup>. Laparoscopic Nissen fundoplication (LNF), which was first undertaken in 1990<sup>3</sup>, provides short- and medium-term control of reflux symptoms similar to that of open fundoplication<sup>4,5</sup>. Long-term results look likely to be similar to those reported for open surgery<sup>6-8</sup>.

Three randomized trials have compared open fundoplication with medical therapy<sup>8-11</sup>, but there has been no study comparing laparoscopic fundoplication with maximal medical therapy. The aim of this study was to determine

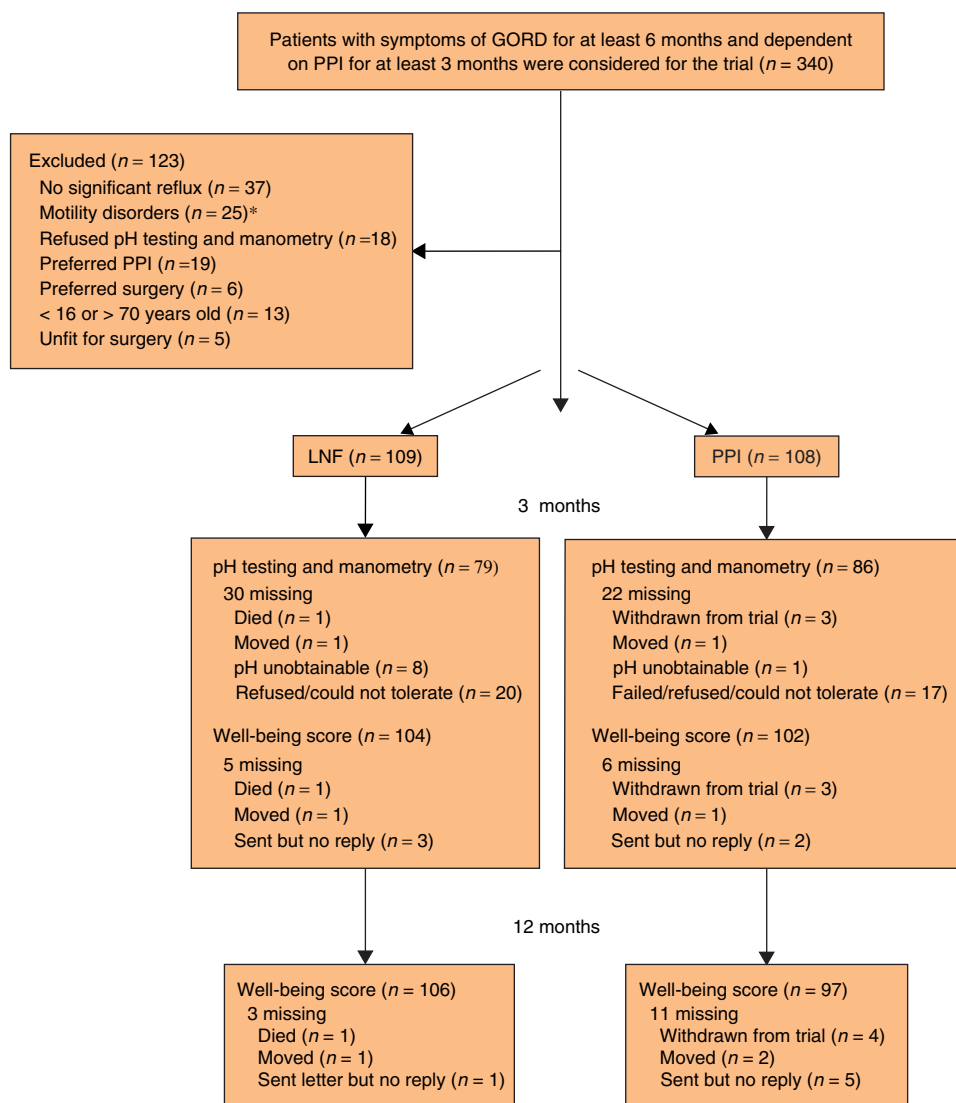
The Editors have satisfied themselves that all authors have contributed significantly to this publication

whether LNF or maintenance medication with a PPI provided better physiological and symptomatic control of GORD.

### Patients and methods

An outline of the study is shown in *Fig. 1*. Between July 1997 and August 2001, 340 patients with symptoms of GORD for at least 6 months and dependent on PPIs for at least 3 months were referred by primary care physicians to two university hospitals. To attract patients from primary care and to avoid patients referred specifically for surgery, letters, approved by the local medical gastroenterology

departments, that outlined the study invited referral of patients with reflux symptoms dependent on PPI treatment for investigation by endoscopy, 24-h pH monitoring and oesophageal manometry. All patients underwent these baseline investigations after stopping PPI therapy for a minimum of 5 days. Those with proven reflux disease who consented to randomization completed the general and gastrointestinal well-being questionnaires<sup>12</sup>. The study was approved by the Norfolk and Norwich University Hospital Ethics and Research and Development Committees as well as the University of Nottingham Ethics Committee. All patients gave informed consent before randomization.



**Fig. 1** Study design. \*Spasm, 12; non-specific motility disorder, nine; nutcracker, two; achalasia, one; scleroderma, one. GORD, gastro-oesophageal reflux disease; LNF, laparoscopic Nissen fundoplication; PPI, proton-pump inhibitor

After investigation, patients were eligible for the study if they were aged between 16 and 70 years, and had pathological reflux on the basis of endoscopic oesophagitis and/or 24-h pH studies with excess acid reflux and good symptom correlation (more than 50 per cent of episodes of heartburn associated with acid reflux). Patients with significant oesophageal dysmotility or morbid obesity (body mass index greater than 35) were excluded.

Patients were given written information about the study and computerized randomization followed consultation with one of five surgeons involved in the trial. Those randomized to medical treatment remained on the medication already prescribed by the primary care physician. Medical treatment involved any one of four different PPIs: rabeprazole 10 mg (Janssen Pharmaceuticals, Titusville, New Jersey, USA), pantoprazole 20 mg (Knoll Pharmaceuticals, Mount Olive, New Jersey, USA), lansoprazole 15 mg (Wyeth Pharmaceuticals, Madison, New Jersey, USA) and omeprazole or esomeprazole 20 mg (Astra Zeneca, Sodertalje, Sweden). The daily dose of the PPI was kept at or adjusted to a level that abolished all reflux symptoms and expressed as multiples of the above doses (omeprazole 10 mg daily = 0.5, lansoprazole 30 mg daily = 2).

Surgery was undertaken by two surgeons. LNF was performed using a five-port technique. Crural repair was performed in all patients and a short floppy wrap measuring 3 cm was created with division of the short gastric vessels as deemed necessary.

Patients on medical therapy completed well-being questionnaires at 3 and 12 months after entry into the study, and underwent repeat pH and manometry studies 3–4 months after entry. Repeat pH and manometry studies were carried out with the patients on their usual medication. Patients in the LNF group underwent all of these assessments using date of the first operation as the date of entry.

### Statistical analysis

Statistical power was calculated on the basis of a prospective randomized trial undertaken by Spechler in 1992<sup>9</sup> that compared open surgery with medical treatment. A sample size of 158 was calculated for a power of 90 per cent at a 5 per cent significance level. To allow for non-compliance in oesophageal physiology studies after treatment, 35 per cent more patients were randomized, giving a total of 215 patients.

Differences in outcome measures at 3 and 12 months in the LNF and PPI groups were assessed by analysis of covariance, using the corresponding pretreatment baseline

value as co-variate. Confirmatory non-parametric tests were also used where the distributional form for some of the outcome measures was not normal.

### Results

Of 340 patients who fulfilled the criteria for investigation, 217 were randomized. There were 123 exclusions (*Fig. 1*). Patients randomized to either LNF or PPI therapy were well matched for sex, age, weight, duration of symptoms and duration of PPI use. Their pretrial well-being scores were not significantly different. Pretrial investigations revealed similar endoscopic findings, pH profiles, lower oesophageal sphincter pressures and reflux scores between the two groups (*Tables 1 and 2*).

Surgery took a median of 79 (range 37–180) min and the median postoperative hospital stay was 2 (range 1–10) days. There were four major intraoperative complications (3.7 per cent; two splenic injuries, one oesophageal injury and one liver injury) resulting in one conversion to open surgery. There were six early postoperative complications (5.5 per cent; three wrap migrations related to forceful vomiting, two respiratory tract infections and one inadvertent inclusion of the nasogastric tube by a wrap suture) resulting in four reoperations. Two of these were open procedures, both for wrap migrations, and in one gastric resection was required owing to necrosis. Five patients (4.6 per cent) developed dysphagia that persisted for more than 3 months after surgery. There were no deaths in the surgical group.

The mean(s.d.) PPI dosage, calculated as a fraction of the recommended maintenance dose, was 1.47(0.80) at entry into the study and 1.57(0.88) at 3 months ( $P = 0.177$ ). Fifteen patients (13.9 per cent) required dose escalation to maintain symptom control,

**Table 1** Patient characteristics and preoperative investigations

	LNF	PPI
Sex ratio (F:M)	1:1.9	1:2.6
Age (years)	48 (39–56)	47 (35–57)
Weight (kg)	83 (74–83)	79.5 (71–88)
Duration of symptoms (months)	72 (36–126)	84 (36–183)
Duration of PPI use (months)	30 (12–56)	24 (12–16)
Hiatus hernia*	84 (94)	82 (93)
Hiatal hernia length (cm)	4 (2–5)	3 (2–5)
Oesophagitis		
Grade ≤ II	81	88
Grade III–IV	22	15

Values are median (interquartile range) unless indicated otherwise; \*values in parentheses are percentages. LNF, laparoscopic Nissen fundoplication; PPI, proton-pump inhibitor.

**Table 2** Summary statistics for efficacy variables measured

	LNF		PPI	
	n	Mean	n	Mean
Total well-being score				
Baseline	104	127.1(22.9)	108	132.8(21.2)
3 months	97	143.5(22.5)	101	136.3(20.8)
12 months	99	142.4(20.0)	96	136.8(22.4)
GI well-being score				
Baseline	104	31.7(6.7)	108	34.3(6.6)
3 months	92	37.3(5.9)	100	36.1(6.2)
12 months	80	37.0(5.4)	86	35.0(7.3)
General well-being score				
Baseline	104	95.4(19.0)	108	98.5(16.6)
3 months	92	106.0(18.2)	100	100.2(17.0)
12 months	79	106.2(16.3)	86	100.4(18.9)
LOSP (mmHg)				
Baseline	109	6.3(5.8)	107	8.1(7.6)
3 months	83	17.2(7.0)	87	7.9(7.7)
DeMeester score				
Baseline	102	42.7(33.1)	105	36.9(26.5)
3 months	77	8.6(16.3)	84	17.7(21.4)
% of time pH < 4				
Baseline	97	12.9(10.9)	98	9.5(7.3)
3 months	79	1.4(3.6)	85	3.8(7.8)

Values are mean(s.d.). LNF, laparoscopic Nissen fundoplication; PPI, proton-pump inhibitor; GI, gastrointestinal; LOSP, lower oesophageal sphincter pressure.

**Table 3** Comparison of changes in efficacy variables between surgical and medical therapy groups

	Analysis of co-variance		
	Adjusted difference	P	P*
Total well-being score			
3 months	+ 10.1 (+ 4.7, + 15.5)	< 0.001	< 0.001
12 months	+ 9.5 (+ 4.2, + 14.8)	< 0.001	< 0.001
GI well-being score			
3 months	+ 2.1 (+ 0.5, + 3.7)	0.010	< 0.001
12 months	+ 3.0 (+ 1.1, + 4.9)	0.003	< 0.001
General well-being score			
3 months	+ 8.2 (+ 3.8, + 12.5)	< 0.001	< 0.001
12 months	+ 7.1 (+ 2.5, + 11.7)	0.003	0.002
LOSP			
3 months	+ 10.2 (+ 8.4, + 12.0)	< 0.001	< 0.001
DeMeester score			
3 months	- 11.2 (- 16.9, - 5.5)	< 0.001	< 0.001
% of time pH < 4			
3 months	- 3.1 (- 5.0, - 1.1)	0.002	0.001

Values in parentheses are 95 per cent confidence intervals. GI, gastrointestinal; LOSP, lower oesophageal sphincter pressure. \*Mann-Whitney U test.

in 85 (78.7 per cent) the dose was unchanged and in eight patients (7.4 per cent) some dose reduction was achieved.

At 3 months mean gastrointestinal well-being scores improved from 31.7 to 37.3 in the surgical group ( $P < 0.001$ ) and from 34.3 to 36.1 in the medical group ( $P = 0.010$ ). General well-being improved from 95.4 to 106.0 in the LNF group ( $P < 0.001$ ) and from 98.5 to 100.2 in the PPI group ( $P < 0.001$ ). Mean DeMeester scores were lower in the surgical group than in the PPI group at 3 months (8.6 *versus* 17.7;  $P < 0.001$ ). The percentage of the total time at pH < 4 was 1.4 and 3.8 per cent respectively ( $P = 0.002$ ). At 12 months' follow-up mean gastrointestinal well-being scores were 37.0 in the LMF group and 35.0 in the PPI group ( $P = 0.003$ ), and mean general well-being scores were 106.2 and 100.4 respectively ( $P = 0.003$ ) (Tables 2 and 3).

## Discussion

Several studies have compared open antireflux surgery with maintenance medication for GORD<sup>13</sup>. This is the first randomized trial to compare laparoscopic surgery with 'optimal' medical therapy. There was significantly better physiological control of acid reflux at 3 months, and significantly better gastrointestinal and general well-being in the LNF group at both 3 and 12 months.

The study sought to recruit typical patients with chronic GORD from primary care with a minimum symptom duration of 6 months and a reliance on PPI medication for at least 3 months, although the median duration of treatment was 24 months in the PPI group and 30 months in the LNF group. Only 25 (7.4 per cent) of 340 patients refused to take part in the trial because of a preference for one type of treatment and only 18 (5.3 per cent) could not tolerate 24-h pH studies. The cohort of patients randomized seems representative of the typical chronic GORD population. Fundoplication in this trial was performed by two surgeons, both of whom had undergone formal laparoscopic training for 3 years and had performed over 50 LNFs independently before the trial was started. The results of surgery in this study compare favourably with large series of the procedure worldwide.

Laparoscopic fundoplication provides better physiological control of reflux than maintenance medical therapy. Although the differences are small, well-being scores measured 12 months into the trial also favoured surgery. Long-term follow-up of these patients is under way, as well as detailed economic evaluation of the relative costs of treatment.

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