Original article

Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180° anterior partial fundoplication in a randomized clinical trial

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Background: **Laparoscopic 180° anterior fundoplication has been shown to achieve similar reflux control to Nissen fundoplication, with fewer side-effects, up to 5 years. However, there is a paucity of long-term follow-up data on this technique and antireflux surgery in general. This study reports 12-year outcomes of a double-blind RCT comparing laparoscopic Nissen *versus* 180° laparoscopic anterior fundoplication for gastro-oesophageal reflux disease (GORD).**

Methods: **Patients with proven GORD were randomized to laparoscopic Nissen or 180° anterior fundoplication. The 12-year outcome measures included reflux control, dysphagia, gas-related symptoms and patient satisfaction. Measures included scores on a visual analogue scale, a validated Dakkak score for dysphagia and Visick scores.**

Results: **Of the initial 163 patients randomized (Nissen 84, anterior 79), 90 (55·2 per cent) completed 12-year follow-up (Nissen 52, anterior 38). There were no differences in heartburn, dysphagia, gas-related symptoms, patient satisfaction or surgical reintervention rate. Use of acid-suppressing drugs was less common after Nissen than after 180° anterior fundoplication: four of 52 (8 per cent) and 11 of 38 (29 per cent) respectively ($P = 0·008$). The proportion of patients with absent or only mild symptoms was slightly higher after Nissen fundoplication: 45 of 50 (90 per cent) *versus* 28 of 38 (74 per cent) ($P = 0·044$).**

Conclusion: **The two surgical procedures provided similar control of heartburn and post-fundoplication symptoms, with similar patient satisfaction and reoperation rates on long-term follow-up.**

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Introduction

Laparoscopic fundoplication is the surgical approach of choice for gastro-oesophageal reflux disease (GORD)[1]. Total fundoplication according to Nissen provides excellent reflux control and is the most frequently performed operation for GORD[2–4]. However, laparoscopic Nissen fundoplication causes troublesome dysphagia and gas-related symptoms in a significant number of patients[5–9]. Partial fundoplications have been developed as alternatives to total fundoplication and aim to reduce the incidence of adverse post-fundoplication symptoms[5,7–9]. The 180° laparoscopic anterior fundoplication is the most commonly used anterior wrap[5,7–9].

Several trials[10–12] have been performed to determine whether anterior fundoplication is able to reduce post-fundoplication symptoms, without compromising reflux control. Short-term (2 years) and mid-term (5 years) analyses of current trials have been published[6,12]. A meta-analysis[7] of trials comparing laparoscopic Nissen with 180° anterior fundoplication concluded that the latter achieves similar reflux control to Nissen, with fewer side-effects up to 5 years. However, recent guidelines[13] for antireflux surgery concluded that there is a paucity of long-term follow-up data on this topic.

This study reports the 12-year results of a randomized double-blind trial comparing laparoscopic Nissen with 180° anterior fundoplication to evaluate whether differences in efficacy, side-effects, patient satisfaction and re-operation rate develop with extension of follow-up beyond 5 years.

Methods

The short-term[12] and mid-term[6] results of this double-blind RCT have been described previously. Patients with

proven GORD undergoing primary laparoscopic antireflux surgery were enrolled between June 1999 and August 2001. GORD was defined as unequivocal reflux disease during endoscopy associated with retrosternal burning discomfort and/or acid regurgitation. All patients underwent preoperative endoscopy. In patients who did not satisfy the endoscopic criteria, 24-h pH monitoring and manometry were performed to diagnose GORD objectively. In addition, all patients had an unequivocal response to proton pump inhibitor therapy. Patients who had undergone antireflux surgery previously or were younger than 18 years of age were excluded. All procedures were performed in a single centre by a single surgeon with extensive experience (more than 120 laparoscopic fundoplications before commencement of the study).

The trial was conducted in a double-blinded fashion. The type of fundoplication was concealed from all patients unless revisional surgery was required. Although patients underwent routine postoperative review by the surgeon, these data were not included in the trial database. Patients were interviewed in the years following surgery using a structured postal questionnaire administered by an independent investigator, who remained unaware of the operation each patient had undergone. The final analysis of these double-blinded data was performed jointly by the surgeon and the investigator. After informed consent had been obtained, randomization took place using sealed envelopes.

Operative technique and postoperative care

Procedures in both groups commenced with blunt dissection of the oesophageal hiatus with minimal use of diathermy and preservation of the hepatic branch of the vagus nerve, if possible. The short gastric vessels were left intact. Laparoscopic Nissen fundoplication was followed by routine posterior hiatal repair and the creation of a short loose 360° wrap over a 56-Fr bougie using 2/0 polypropylene sutures[12,14]. A 180° anterior fundoplication was created by suturing the anterior wall of the fundus to the right hiatal pillar and the posterior hiatal repair[15]. The angle of His was accentuated by a suture to the apex of the left hiatal pillar. Four to six 2/0 polypropylene sutures were used to create the wrap[12].

Follow-up

Outcome was assessed using a standardized set of questions, administered at 3 months and after each year, by either postal questionnaire or telephone interview. The questionnaires were analysed by an independent investigator, who was unaware of treatment allocation. Other events during follow-up were identified and recorded. Thorough efforts were made to track missing patients by reference to general practitioner records, next of kin, previous employers and the internet. Follow-up was abandoned at 12 years as these efforts became less successful and the number of patients lost to follow-up rose.

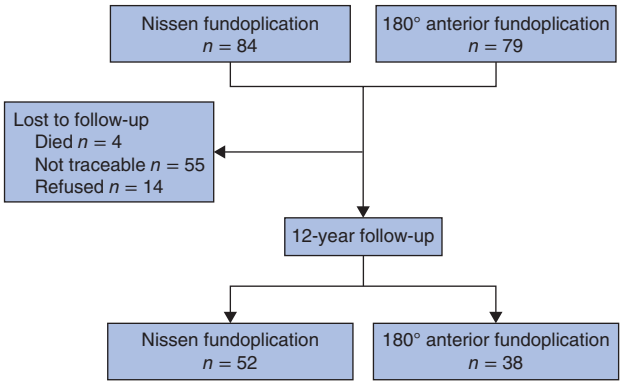

Fig. 1 Flow diagram for the long-term follow-up study

Heartburn was scored using a visual analogue scale (VAS; 0, no heartburn; 10, severe heartburn) and by determining the use of antisecretory drugs.

Dysphagia was scored in two ways: using VAS scores for solids and liquids (0, no dysphagia; 10, total dysphagia) and a validated Dakkak dysphagia score (0, no dysphagia; 45, severe dysphagia)[16].

Patients were asked whether they were able to eat a normal diet. Gas-related symptoms were assessed by the presence or absence of gas bloating, flatulence, and ability to relieve bloating and belch.

Patient satisfaction was scored using a VAS and a Visick score (1, no symptoms; 2, mild symptoms; 3, moderate symptoms; 4, moderate symptoms interfering with life; 5, symptoms as bad or worse after surgery)[17]. In addition, patients were asked whether they would choose to undergo the same procedure again under similar circumstances.

Statistical analysis

Data were analysed according to the intention-to-treat principle and non-normal distribution was assumed. Ordinal variables were expressed as percentages, and differences between groups were analysed using the χ^2 test. For continuous variables, data were expressed as median (range) and groups were compared using the Mann–Whitney *U* test. All tests were two-tailed and $P < 0{\cdot}050$ was considered statistically significant. Statistical analyses were performed using SPSS® version 22.0 (IBM, Armonk, New York, USA).

Table 1 Baseline characteristics of patients according to treatment group

	With long-term follow-up		
	Nissen fundoplication ($n = 52$)	180° anterior fundoplication ($n = 38$)	Lost to follow-up ($n = 73$)
Age (years)*	43 (16–69)	46 (27–66)	39 (22–70)
Sex ratio (M : F)	29 : 23	19 : 19	46 : 27
Follow-up interval (months)*	143·5 (130–158)	145·5 (132–183)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). Thirty-two patients (38 per cent) in the initial Nissen fundoplication group and 41 (52 per cent) in the original 180° anterior fundoplication group were lost to follow-up.

Table 2 Symptomatic outcome at long-term follow-up

	Nissen fundoplication ($n = 52$)	180° anterior fundoplication ($n = 38$)	P†
Reflux symptoms			
Heartburn (VAS)*	0·00 (0–4)	1·00 (0–9)	0·107‡
Acid-suppressing drugs	4 (8)	11 (29)	0·008
Dysphagia			
Dysphagia for liquids (VAS)*	0·00 (0–10)	0·00 (0–9)	0·428‡
Dysphagia for solids (VAS)*	1·50 (0–10)	0·00 (0–9)	0·128‡
Dakkak dysphagia score*	4·00 (0–40·0) ($n = 50$)	2·50 (0–37·5) ($n = 35$)	0·762‡
Normal diet	45 (87)	32 (84)	0·756
Gas-related symptoms			
Ability to belch	41 (79)	30 (79)	0·991
Gas bloating	21 (40)	20 (53)	0·249
Ability to relieve bloating	35 (67)	25 (66)	0·880
Flatulence	30 (58)	18 (47)	0·332

Values in parentheses are percentages unless indicated otherwise; *values are median (range). VAS, visual analogue scale. †χ^2 test, except ‡Mann–Whitney U test.

Table 3 Patient satisfaction at long-term-follow-up

	Nissen fundoplication ($n = 52$)	180° anterior fundoplication ($n = 38$)	P†
Satisfaction (VAS)*	10·0 (2–10)	10·0 (0–10)	0·852‡
Patient would opt for surgery again	47 (90)	31 (82)	0·225
Visick score			0·039
1 (no symptoms)	16 (32)	15 (39)	
2 (mild symptoms)	29 (58)	13 (34)	
3 (moderate symptoms)	1 (2)	7 (18)	
4 (symptoms interfering with life)	3 (6)	3 (8)	
5 (symptoms not improved)	1 (2)	0 (0)	
Visick 1 and 2 (symptoms absent or mild)	45 of 50 (90)	28 (74)	0·044

Values in parentheses are percentages unless indicated otherwise; *values are median (range). VAS, visual analogue scale. †χ^2 test, except ‡Mann–Whitney U test.

Results

A total of 163 patients were enrolled in the randomized trial, and underwent laparoscopic Nissen fundoplication (84) or 180° anterior fundoplication (79). The initial trial results and study design were published in 2005[12] and the 5-year results in 2012[6]. Fifty-five patients were untraceable, 14 declined to participate and four died during follow-up from causes unrelated to antireflux surgery. Ninety patients completed long-term follow-up (*Fig. 1*).

Baseline patient characteristics after 12 years of follow-up were similar in the two groups (*Table 1*). Characteristics of patients lost to follow-up were similar to those of patients who completed follow-up. Median age at time of surgery was 43 years in the Nissen group and 46 years in the 180° anterior fundoplication group. Median duration of follow-up was 144·5 months (Nissen 143·5 months, anterior 145·5 months).

Clinical outcomes are summarized in *Table 2*. Heartburn scores were similar for both procedures. The use of antisecretory drugs was significantly more common after anterior fundoplication: 11 of 38 (29 per cent) *versus* four of 52 (8 per cent) after Nissen fundoplication ($P = 0·008$). There were no clinical or statistical differences in dysphagia, with similar VAS and Dakkak scores in both groups and a similar proportion of patients on a normal diet. Gas-related symptoms, including ability to belch, gas bloating, ability to relieve bloating, and flatulence, were comparable in the two groups (*Table 2*).

The median score for overall satisfaction was similar and the vast majority of patients would undergo surgery again in the Nissen and 180° anterior fundoplication groups: 47 of 52 (90 per cent) *versus* 31 of 38 (82 per cent) respectively ($P = 0·225$) (*Table 3*). Overall, Visick scores were lower after Nissen procedures ($P = 0·039$), with more patients with absent or mild symptoms after Nissen compared with 180° anterior fundoplication: 45 of 50 (90 per cent) *versus* 28 of 38 (74 per cent) ($P = 0·044$) (*Table 3*).

There was a higher surgical reintervention rate after 180° anterior fundoplication but this did not reach statistical significance: four of 52 (8 per cent) after Nissen and six

Table 4 Surgical reintervention

	Nissen fundoplication ($n = 52$)	180° anterior fundoplication ($n = 38$)	P*
Surgical reintervention	4 (8)	6 (16)	0·227
Recurrent reflux	2 of 4	4 of 6	
Dysphagia	2 of 4	2 of 6	

Values in parentheses are percentages. *χ^2 test.

of 38 (16 per cent) after partial fundoplication ($P = 0·227$). In the Nissen group two of four reoperations were for dysphagia, whereas in the 180° anterior group four of six reoperations were for recurrent reflux (*Table 4*).

Discussion

In patients available for long-term follow-up in an RCT comparing two techniques of fundoplication for GORD, the effect on symptom control after 12 years was similar in both groups. Patients undergoing Nissen fundoplication had slightly better rates of absent or only mild symptoms than those having partial fundoplication.

The main goal of antireflux surgery is to establish durable reflux control with minimal side-effects. Several trials and a meta-analysis[6,7,10,18,19] have compared laparoscopic Nissen and 180° anterior fundoplication, demonstrating that the latter provides similar reflux control with fewer side-effects up to 5 years. There is, however, a paucity of long-term results[13], so it is not clear whether Nissen and 180° anterior fundoplication provide similar reflux control with minimal side-effects in the long run[20,21]. The 10-year results of one trial[21] did not demonstrate differences in efficacy between the two procedures. The present study was designed to compare the long-term differences between Nissen and 180° anterior fundoplication in a head-to-head comparison in an attempt to strengthen the evidence base. The results demonstrate similar heartburn scores for both groups, consistent with the comparable reflux control demonstrated at short- and mid-term follow-up of this trial[6,12]. These findings are in line with the 10-year results reported by Cai and colleagues[21]. With extension of follow-up, a higher rate of acid-suppressing drug use developed in the 180° anterior compared with the Nissen group. The percentage of patients using acid-suppressing drugs after 180° anterior fundoplication was high at 29 per cent in the present study, but similar to the rate in another trial (27 per cent)[20]. However, it has been demonstrated previously that only a small proportion of patients who have restarted acid-suppressing therapy suffer from objective recurrent reflux disease[4,22,23].

The reduced rate of dysphagia and gas-related symptoms after 180° anterior compared with Nissen fundoplication that was present at 2 years[12] and 5 years[6] disappeared with extension of follow-up to 12 years. This trend is consistent with the findings of other long-term studies[20,21]. The two procedures had similar patient satisfaction rates, with the majority in both groups willing to undergo surgery again in a similar situation. In general, patient satisfaction scores were similar at 5 years (mean 8·2 *versus* 8·5 for Nissen *versus* anterior fundoplication[6]) and after 12 years (mean 8·6 *versus* 8·1). Satisfaction rates were in line with the 10-year results of Cai *et al.*[21], who reported that 90 per cent of the patients who had a Nissen procedure and 98 per cent of those who underwent 180° anterior fundoplication would be willing to undergo surgery again. Patients in the Nissen group had lower Visick scores and a higher percentage had no or only mild symptoms. Reoperation rates were not significantly different between the interventions. The total reoperation rate of 11 per cent was slightly higher than that in another long-term study[21], which reported surgical reintervention in up to 9·3 per cent of patients.

Strengths of the present study are the double-blind randomized design and the duration of follow-up beyond 12 years (median 145 months). The present methodology has been consistently described and accepted as a valid form of double-blinding in all previous publications from the authors' group and the Adelaide group that first described this method of blinding[2,6,10,12].

One of the limitations of this trial is that it relied on clinical follow-up using validated questionnaires and did not use objective data to support the subjective findings. It would, for example, have been useful to perform 24-h pH monitoring in all patients who recommenced acid-suppressing drugs. However, these investigations are invasive and it has been well documented that a significant percentage of patients refuse invasive follow-up[21,24]. In addition, the present study had substantial loss to follow-up owing to a failure to return the questionnaires or an inability to contact patients by post or telephone despite multiple attempts. This loss to follow-up limits the validity of the study and might have increased the potential bias associated with incomplete follow-up[25]. South Africa's geography, high migration rates and infrastructure might have contributed to the loss to follow-up. However, the follow-up rate here is in line with that in comparable trials[25], considering the duration of follow-up of 12 years. A study by the authors' group[20] that also compared the long-term results of laparoscopic Nissen and 180° anterior fundoplication demonstrated no differences in outcome between patients who refused part of the study protocol and those who completed the entire long-term outcome assessment. The authors, therefore, feel that the results for the participants in the present study are representative of those who originally enrolled in the trial.

Disclosure

The authors declare no conflict of interest.

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