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Original Article

Comparison of EsophyX2.0 and MUSE systems for transoral incisionless fundoplication: Technical aspects and outcomes up to 3 years

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Objectives: We compared the efficacy and safety of transoral incisionless fundoplication (TIF) with the EsophyX2.0 and MUSE systems for treatment of gastroesophageal reflux disease (GERD).

Methods: TIF outcomes from prospective protocols (Esophy2.0X: 2007–2012; MUSE: 2015–2019) were retrospectively compared regarding technical success, moderate/severe adverse events, morpho-functional findings up to 1 year, and clinical outcomes up to 3 years. Inclusion criteria were: (i) at least 6-month symptomatic GERD, full/partial response to proton pump inhibitors (PPI), esophagitis, and nonerosive reflux disease/hypersensitive esophagus (both protocols); (ii) hiatal hernia <3 cm (Esophy2.0X) and ≤2.5 cm (MUSE); and (iii) Barrett's esophagus <3 cm (MUSE).

Results: In the 50 EsophyX2.0 and 46 MUSE procedures, technical success and adverse event rates were similar, but MUSE-related adverse events (4.4%) were life-threatening. At 12 months, hiatal hernia recurred more frequently after EsophyX2.0 ($P = 0.008$). At 6 months, significantly fewer total and acid refluxes were reported after both TIF, but not more significantly at 1 year. Symptoms improved after both TIF up to 1 year ($P < 0.0001$), but to a greater extent in MUSE patients up to 3 years ($P < 0.0001$ vs. $P < 0.01$ for EsophyX2.0). The rates of 3-year off-PPI therapy patients were 73.5% in the MUSE and 53.3% in the EsophyX2.0 series ($P = 0.069$).

Conclusion: Although no conclusion could be drawn from this limited study, the MUSE technique seemed more effective in the long term in patients with hiatal hernia; however, there were more severe adverse events than with EsophyX2.0.

Key words: endoscopic gastrointestinal surgical procedure, fundoplication, gastroesophageal reflux disease

INTRODUCTION

TRANSORAL INCISIONLESS FUNDOPLICATION (TIF) is an effective alternative for the treatment of gastroesophageal reflux disease (GERD) in patients without hiatal hernia or hernia ≤2.5 cm, and with diaphragmatic hiatus <3 cm, fully/partially responsive to proton pump inhibitors (PPI). Current indications for TIF are erosive esophagitis, nonerosive reflux disease (NERD), and hypersensitive esophagus.[1,2] TIF has also been proposed in Barrett's esophagus <3 cm.[3]

TIF creates a full-thickness gastroesophageal (GE) valve, mimicking a 180° to 270° surgical fundoplication (depending on the technique adopted).[4] TIF can be done with the EsophyX (EndoGastric Solutions, Redmond, WA, USA) or Medigus Ultrasonic Surgical Endostapler (MUSE; Medigus, Omer, Israel) device.[5–10] We have used both techniques, with 10-year (EsophyX) and 3-year (MUSE) clinical follow-up.

There are as yet no studies comparing the two techniques, so it is still not clear whether one TIF technique is superior to the other. Therefore, we compared the two techniques looking at technical aspects and procedure-related adverse events, morpho-functional findings, and clinical outcomes.

METHODS

Study patients and design

CONSECUTIVE PATIENTS WHO had undergone TIF by EsophyX2.0 or MUSE, in two prospective protocols, followed up to 3 years,[3,11] were retrospectively reviewed.

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In both protocols, patients had had GERD-related symptoms for at least 6 months and were full/partial responders to PPI, with esophagitis, NERD, or hypersensitive esophagus at 24 h pH-metry and multichannel intraluminal impedance (24 h pH-MII) recordings. Barrett's esophagus <3 cm was considered an inclusion criterion only in the MUSE protocol. Hiatal hernia ≥3 cm, and >2.5 cm or nonreducible regardless of size, were considered ineligible, respectively, for TIF in EsophyX2.0 and MUSE protocols. Other exclusion criteria for TIF have been reported elsewhere.[3,11]

TIF patients were assessed regarding: (i) daily PPI consumption and symptoms, with the GERD-Health Related Quality of Life (GERD-HRQL) questionnaire,[12] 14 days after stopping PPI; (ii) functional parameters by esophageal stationary manometry (EsophyX2.0) or high-resolution manometry (HRM) and 24 h pH-MII (off-PPI)[13,14]; and (iii) the presence and severity of esophagitis (Los Angeles classification), hiatal hernia, and Hill's grade of the neovalve by endoscopy.

TIF techniques are described elsewhere.[3,11] All procedures were performed by one expert endoscopist, with in-vivo experience in animal models; reported cases included those done in the training period under the supervision of the company's specialists.

In both protocols GERD-HRQL and PPI consumption was scheduled to be recorded at 6 and 12 months, then yearly after TIF. Esophageal manometry was scheduled at 6 months, 24 h pH-MII and endoscopy at 6 and 12 months.

Physicians other than those who performed the TIF and unaware of postprocedure outcomes were involved in the follow-up.

All patients gave written informed consent for procedures and data management for scientific purposes. Both protocols were approved by the Medical Ethics Committee of the San Raffaele Scientific Institute (Milan). The MUSE protocol (started in 2015) was registered at ClinicalTrials.Gov (NCT03669874), while registration was not required for the EsophyX2.0 protocol (started in 2007).

Study end-points

The primary end-point was to compare the technical success and procedure-related moderate/severe adverse events with EsophyX2.0 and MUSE, defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (US Department of Health and Human Services, 2017).[15]

Other study end-points were to assess the morphological (hiatal hernia, Hill's grade of the neovalve, esophagitis) and functional (lower esophageal sphincter's [LES] basal pressure, distal esophageal amplitude [DEA] for EsophyX2.0, or distal contractile integral [DCI] for MUSE, number of total, acid, weakly acid, alkaline, and proximal refluxes, Johnson–DeMeester score) outcomes up to 1 year, and symptomatic (GERD-HRQL score and PPI use) outcomes up to 3 years.

Statistical analysis

Continuous variables are reported as means with standard deviation (SD) or as median values with 95% confidence intervals (CI) (Shapiro–Wilk test). Differences were analyzed using the unpaired Student's *t*-test or Mann–Whitney *U*-test (continuous variables), and Fisher's exact test with Freeman–Halton extension (categorical data). Before versus after treatment differences were computed using the paired Student's *t*-test or Wilcoxon signed-rank sum test. *P*-values <0.05 were considered statistically significant.

RESULTS

FIFTY PATIENTS WERE enrolled in the EsophyX2.0 (period 2007–2012) and 46 patients in the MUSE (period 2015–2019) protocols.

Patients' pre-TIF clinical-, morphological-, and symptom-related features did not significantly differ between the two series (Table 1), but mean body mass index and GERD-HRQL score off-PPI were respectively significantly higher and lower in patients treated with EsophyX2.0 and MUSE. The rate of full-responder patients to PPI was higher in the MUSE series ($P = 0.037$), as well as that of the Hill's grade II of the GE valve ($P = 0.028$).

Forty-nine/50 and 45/50 patients in the EsophyX2.0 series attended up to 1- and 3-year follow-up. In the MUSE series, the figures were 42/46 and 34/46 at 2- and 3-year follow-up.

Technical aspects and procedure-related adverse events

Figures 1–4 show details of the two devices and the creation of the neovalve with the two systems.

The procedural success rate was very high for both techniques and similar: 98% and 97.8% for EsophyX2.0 and MUSE (Table 2). Fifty-one procedures were done with EsophyX2.0. Two procedures were interrupted: one because of the device's malfunction (subsequently repeated with success), the other because of intraprocedural pneumothorax. In one case it was impossible to pass the MUSE device through the esophagus, because of a cervical vertebral protrusion.

Table 1 Demographic, anatomical, and clinical characteristics of patients enrolled in the EsophyX2.0 and MUSE protocols

	EsophyX2.0	MUSE	*P*-value
No. patients	50	46	–
Sex, *n* (%)			0.141
Male	35/50 (70)	25/46 (54.35)	
Female	15/50 (30)	21/46 (45.65)	
Age (years), mean ± SD	45 ± 16	50 ± 8	0.059
Body mass index (kg/m^2), mean ± SD	22 ± 3	24 ± 3.2	0.002
GERD-related symptoms duration (years), mean ± SD	8 ± 5	9 ± 6	0.376
NERD diagnosis, *n* (%)	37/50 (74)	30/46 (65.22)	0.352
Hypersensitive esophagus, *n* (%)	2/50 (4)	0/46 (0.00)	0.173
GERD-HRQL score off-PPI, mean ± SD	46 ± 19	23 ± 10	<0.0001
PPI response, *n* (%)			
Responders to a standard dose twice a day	36/50 (72)	22/46 (47.80)	0.016
Partial responders to a standard dose twice a day	14/50 (28)	0/46 (0.00)	0.0001
Responders to a standard dose once a day	0/50 (0)	19/46 (41.30)	<0.0001
Occasional use	0/50 (0)	5/46 (10.90)	0.017
Esophagitis (Los Angeles classification), *n* (%)	11/50 (22)	14/46 (30.43)	0.349
Grade A	10/50 (20)	14/46 (30.43)	0.241
Grade B	1/50 (2)	0/46 (0.00)	0.338
Barrett's esophagus (Prague classification), *n* (%)	0/50 (0)	2/46 (4.35)	0.138
C1M1	0/50 (0)	1/46 (2.20)	0.294
C1M2	0/50 (0)	1/46 (2.20)	0.294
Hiatal hernia, *n* (%)	28/50 (56)	18/46 (39.13)	0.100
≤2.5 cm	27/50 (54)	18/46 (39.13)	0.147
>2.5 cm	1/50 (2)	0/46 (0.00)	0.338
Hill's grade of gastroesophageal valve, *n* (%)			
Grade I	3/50 (6)	0/46 (0.00)	0.093
Grade II	34/50 (68)	40/46 (86.96)	0.028
Grade III	12/50 (24)	6/46 (13.04)	0.172
Grade IV	1/50 (2)	0/46 (0.00)	0.338

GERD, gastroesophageal reflux disease; HRQL, health related quality of life; NERD, nonerosive reflux disease; PPI, proton pump inhibitor.

The procedure's mean duration (minutes) was longer with MUSE, with a difference close to statistical significance. The neovalve obtained with EsophyX2.0 had a tighter circumferential closure than the one with MUSE (>240° vs. 180°), but its mean length was more variable and significantly shorter. With the MUSE device it is very likely the greater length of the neovalve than its pressure that acts as a barrier to reflux.

Hill's grade was reduced to grade I in all cases and hiatal hernias were all reduced too.

The rates of moderate/severe adverse events were comparable: 4.1% and 4.4% for EsophyX2.0 and MUSE, respectively. However, MUSE-related adverse events were life-threatening (CTCAE version 5.0 grade 4). One patient had intraprocedural perforation, 2 cm distally to the cardias, resulting from incorrect placement of the stapler due to difficult ultrasound-guided alignment; the other patient had postprocedural cough-induced esophageal perforation (>48 h), depending on fixation of the esophageal wall to a diaphragmatic pillar. Both patients required surgical repair, with prolonged hospitalization (>3 nights), and left the MUSE protocol. In the EsophyX2.0 series, two patients had CTCAE version 5.0 grade 2 adverse events: pneumothorax, rapidly resolved by immediate transthoracic drainage, with discharge from hospital within 3 days.

Morphological outcomes

Forty-nine EsophyX2.0 and 42 MUSE patients underwent endoscopy at both the 6- and 12-month follow-up.

Hiatal hernia recurred more frequently in the EsophyX2.0 series ($P = 0.04$ and $P = 0.008$ at 6 and 12 months, vs. MUSE); this included a pre-TIF 3 cm-long nonreducible hiatal hernia, confirming the lack of efficacy of TIF in patients with large hiatal hernia. Among patients with prior hiatal hernia ≤2.5 cm, 62.9% and 51.9% of EsophyX2.0 patients no longer had the hiatal hernia 6 and 12 months after TIF. This rate was higher in MUSE patients: 89.9% at 6 and 12 months ($P = 0.057$ and $P = 0.011$ vs. EsophyX2.0) (Fig. 5).

The Hill's grade and esophagitis rates were similar at 6 and 12 months. At 1 year, Hill's grade was still I in 65.3% and 59.5% and returned to grade II in 34.7% and 40.5% of EsophyX2.0 and MUSE patients, respectively (not significant) (Fig. 6A). EsophyX2.0 patients with pre-TIF Hill's grade IV returned to the preprocedure grade at 6 months (Fig. 6B).

At 6 months, grade A esophagitis was found in 12.2% and 16.7% of EsophyX2.0 and MUSE patients ($P = 0.543$), respectively. Prior esophagitis persisted or recurred in 27.3%

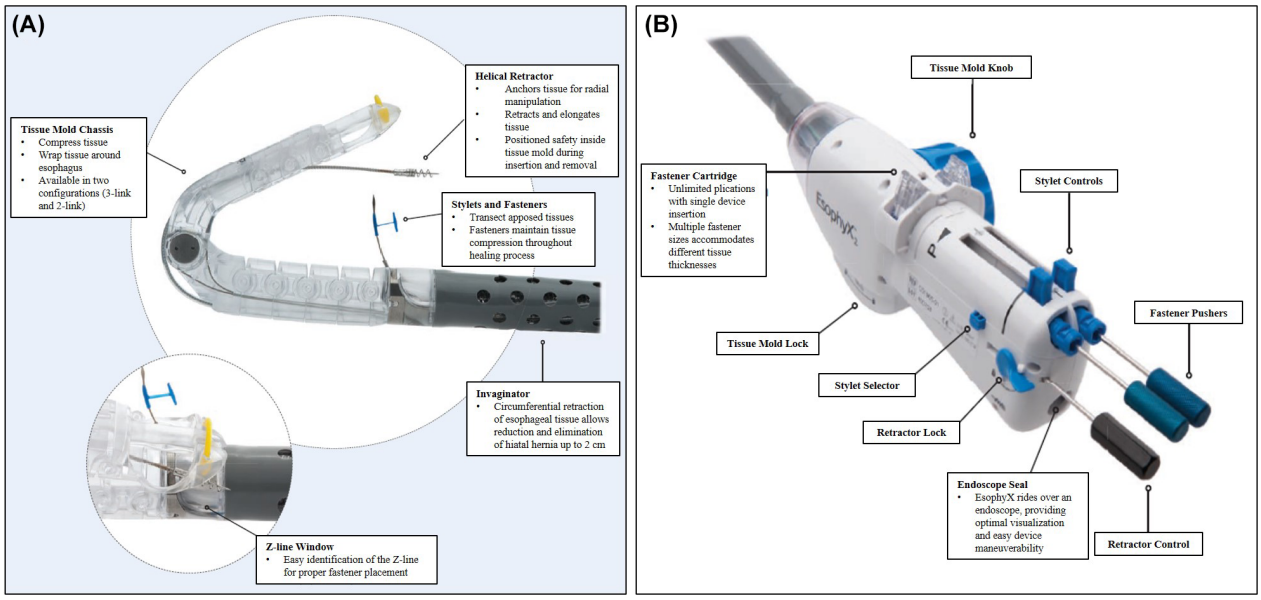

Figure 1 Details of the EsophyX2.0 device (courtesy of EndoGastric Solutions, Redmond, WA, USA). (A) A tissue invaginator; a tissue mold, that pushes the tissue against the shaft of the device; a helical screw, to retract the tissue between the tissue mold and the shaft; two stylets, that pass through the plicate tissue and the tissue mold, and H-shaped polypropylene fasteners can be deployed over them. (B) A handle that houses the controls; an 18 mm diameter chassis, including the operative channel through which a 9 mm diameter endoscope is inserted; a cartridge containing 20 fasteners.

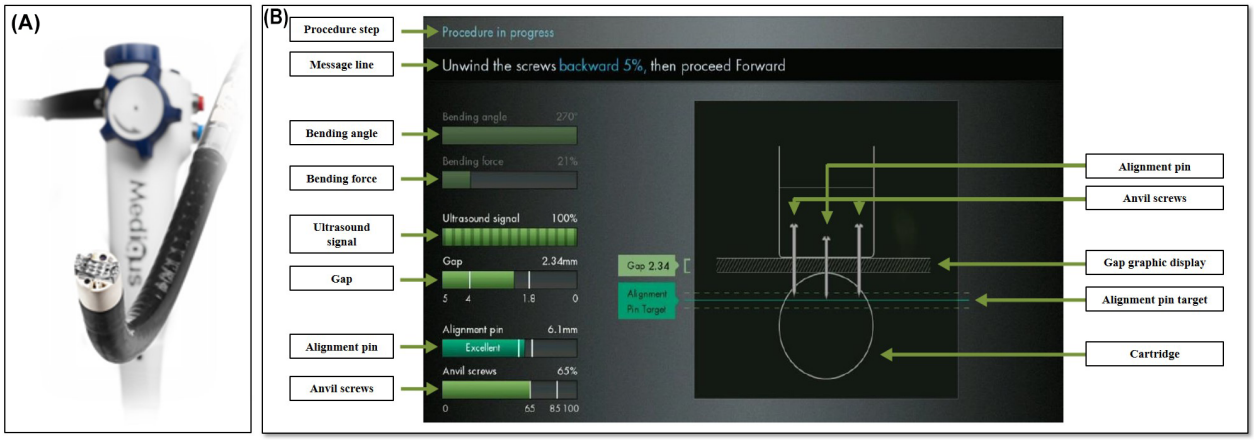

Figure 2 Details of the MUSE device (courtesy of Medigus, Omer, Israel). (A) A handle, housing the controls; a 15.5 mm diameter and 66 cm long insertion tube, containing suction and insufflation/irrigation channels, and electrical and mechanical cables; a 66 mm long rigid section containing the cartridge. (B) The endostapler contains a controller for the camera, ultrasonic range finder, and various sensors (bending angle, bending force, alignment pin, anvil screws, gap).

of EsophyX2.0 and 35.7% of MUSE patients up to 1 year ($P = 0.662$). At 1 year, esophagitis persisted in all EsophyX2.0 and 85.7% of MUSE patients ($P = 0.769$) (Fig. 7).

Functional outcomes

Functional findings were assessed at 6 and 12 months in 35/49 and 30/49 EsophyX2.0 and in 31/42 and 20/42 MUSE patients (Tables 3 and 4). Other patients, with symptomatic

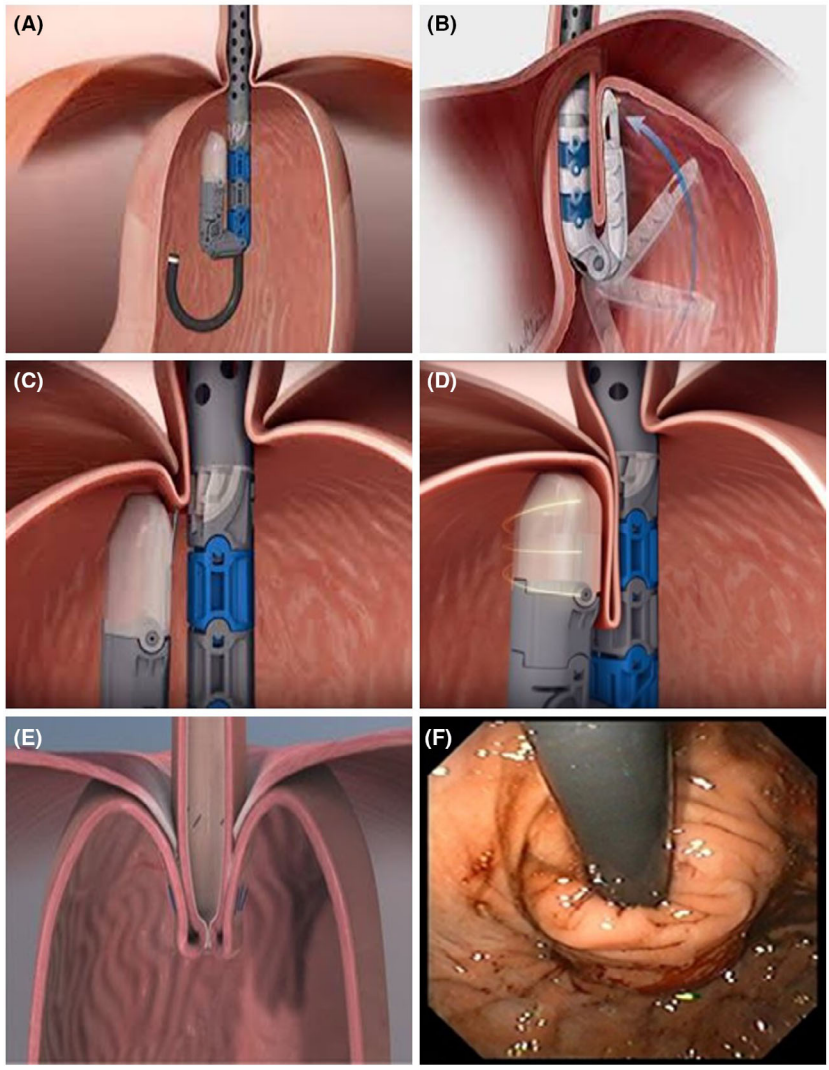

Figure 3 Schematic representation of the EsophyX2.0 procedure (courtesy of EndoGastric Solutions, Redmond, WA, USA). The procedure is done by two operators: one controls the device and the other operates the endoscope. With the endoscope placed in retroflex position (A), the device wraps the fundus around the distal esophagus (B) and fastens a tissue fold (C). This step is then repeated multiple times (D), placing at least 20 fasteners (E). The fastener deployment starts on the far posterior and anterior sides of the esophago-gastric valve, adjacent to the lesser curvature, and is then extended to the greater curvature. As a result, a robust tight >240° valve is reconstructed (F, an author's case).

improvement, refused functional investigation at the scheduled times.

LES basal pressure, DEA, DCI, and Johnson–DeMeester score did not change significantly. In the MUSE series the median LES length increased from 23.6 cm (95% CI 17.9–27.4) at baseline to 26.9 cm (95% CI 20–28.6) at 6 months (P = 0.03).

There were significantly fewer total and acid refluxes in both series at 6 months than at baseline. These differences were no longer significant at 1 year. There tended to be fewer proximal refluxes in both series at 6 and 12 months, but the difference was significant only in the MUSE series at 6 months.

Clinical outcomes

Symptomatic outcomes and PPI consumption were evaluated in 49 patients in the EsophyX2.0 series at 6 and

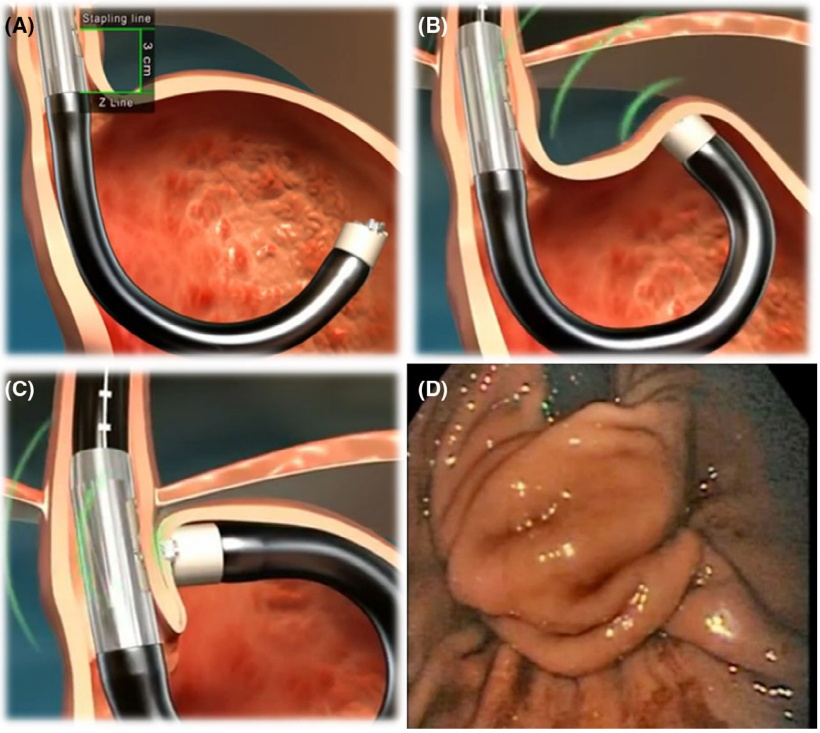

Figure 4 Schematic representation of the MUSE procedure (courtesy of Medigus, Omer, Israel). The procedure can be done by one operator. Steps of the procedure are all done under ultrasound guidance with the device in retroflex position (A, B) and include clamping tissue, deploying alignment pin, advancing anvil screw, stapling, and retrieving anvil screws (C). The most important stapling location is the leftmost location, which is typically done first. As a result, a tight 180° valve is reconstructed (D, an author's case).

12 months, and in 45 patients at 2 and 3 years. In the MUSE series, 42 patients were clinically examined at 6 months, 1 and 2 years, and 34 patients at 3 years (Table 5).

Both techniques achieved significant improvement of the GERD-HRQL score at 6 and 12 months ($P < 0.0001$ vs. baseline). Two and 3 years after TIF, the mean GERD-HRQL scores still showed significant improvement in both series, and more in the MUSE series (reducing it by 65.2% and 69.6% in the MUSE series, $P < 0.0001$ vs. baseline, and by 60.9% and 58.7% in the EsophyX2.0 series, $P < 0.01$ vs. baseline). At 6 months the improvement rate was 22.6% higher in the EsophyX2.0 series, and at 3 years it was 18.6% higher in the MUSE series. The mean GERD-HRQL score showed a 27.3% decrease—close to statistical significance—at 1 year compared to 6 months, maintained up to 3 years in the MUSE series. Conversely, in the EsophyX2.0 series the mean GERD-HRQL score rose slightly, although not significantly, up to 3 years.

At per-protocol analysis, PPI consumption did not significantly differ between the two techniques (Table 6). Three years after TIF, there was a trend in favor of MUSE in the rate of patients off-PPI, although not significant (37.9% over EsophyX2.0, $P = 0.069$) (Fig. 8).

Four of 49 patients in the EsophyX2.0 and 1/45 patients in the MUSE series were unresponsive to TIF and underwent Nissen fundoplication within 24 months.

DISCUSSION

TIF HAS BEEN seen to effectively treat GERD in selected cases,[16–19] with long-term outcomes comparable to surgical fundoplication, but without the risk of persistent side-effects.[20,21]

TIF by EsophyX2.0 has the widest worldwide experience so far (about 25,000 procedures, by market data). The learning curve is reportedly steep, with proficiency achieved after basic training and 18–20 independent procedures.[22] MUSE was introduced later in clinical practice, so experience with it is limited, as it has no longer been available since 2018 in the United States and Europe, but is currently used in China, Hong Kong, Taiwan, and Macao. Data about the learning curve are not available.

Table 2 Technical aspects and adverse events related to transoral incisionless fundoplication (TIF) with EsophyX2.0 and MUSE devices

	EsophyX2.0	MUSE	*P*-value
Technical success, *n* (%)	49/50 (98.00)	45/46 (97.80)	1.000
TIF procedure time (min), mean ± SD	69 ± 19	77 ± 22	0.059
New GE valve length (cm), mean ± SD	2.6 ± 0.8	3 ± 0	0.001
Reduction of GE valve's Hill's grade to grade I, *n* (%)	49/49 (100.00)	45/45 (100.00)	1.000
Reduction of hiatal hernia, *n* (%)	49/49 (100.00)	45/45 (100.00)	1.000
Post-TIF CTCAE version 5.0 grade ≥2 adverse events, *n* (% of TIF procedures)	2/49 (4.08)	2/45 (4.40)	1.000
Rate of CTCAE version 5.0 ≥3 adverse events requiring surgery	0/49 (0.00)	2/45 (4.40)	0.139

CTCAE, Common Terminology Criteria for Adverse Events; GE, gastroesophageal.

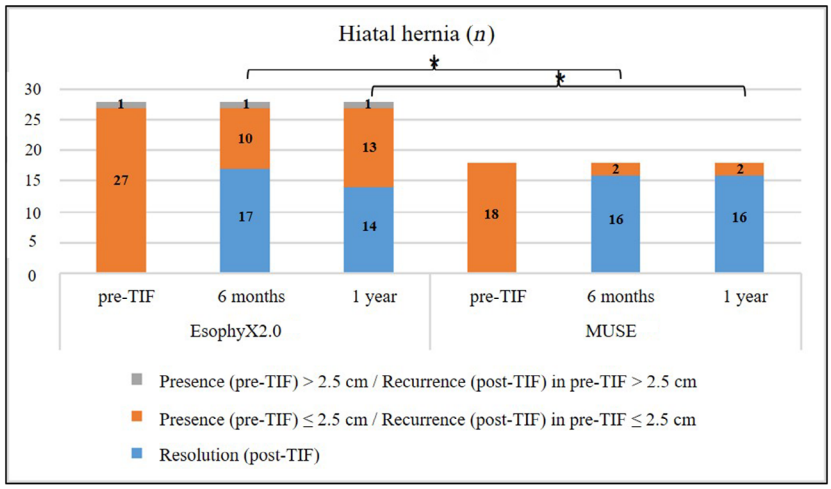

Figure 5 Hiatal hernia recurred more frequently in the EsophyX2.0 series at 6 and 12 months after transoral incisionless fundoplication (TIF) (P = 0.04 and P = 0.008 vs. MUSE). Among patients with hiatal hernia ≤2.5 cm before the intervention, MUSE was more effective at both 6 and 12 months (P = 0.057 and P = 0.011 vs. EsophyX2.0). In the EsophyX2.0 patient with hiatal hernia >2.5 cm, it recurred at 6 months. *Statistically significant.

To date, no studies have compared these TIF techniques. To our knowledge, ours is the only institution where TIF has been done by both EsophyX2.0 and MUSE techniques, with similar prospective protocols and 3-year follow-up at least.

The two techniques had comparable success rates (98% vs. 97.8%). Technical failure occurred in one patient in both series. MUSE seemed less maneuverable because it is stiffer, even though the diameter of the insertion tube is smaller (15.5 vs. 18.0 mm). The mean procedure time was 11.6% longer for MUSE than EsophyX2.0, and 10 min longer for both procedures than those reported in the literature (69 vs. 58 min for EsophyX2.0, 77 vs. 67 min for MUSE).[17,18,23,24] This was due to difficulty in identifying the correct position for the alignment and release of staples under ultrasound guidance, regardless of the operator's expertise. The neovalve's mean size varied more using EsophyX2.0 than MUSE (2.6 ± 0.8 vs. 3 cm), depending on the operator's subjective variability of the plication; this contrasts with the standardization achieved with ultrasound guidance and the software program with MUSE, regardless of the operator's skill.

The rates of adverse events with severity grade ≥2 according to CTCAE version 5.0 classification were similar (4.1% vs. 4.4%), but MUSE-related adverse events were life-threatening (grade 4), required surgery, and were not preventable by the operator, while the EsophyX2.0 adverse events were moderate (grade 2), healed spontaneously, and did not prolong the hospital stay. With EsophyX2.0, an expert operator can avoid adverse events because TIF is done under direct endoscopic vision and tailored based on the local anatomy. In our series, the mean rate of adverse events was double that reported so far in meta-analyses (2.4% and 2%),[16,17] but lower than in the postmarketing surveillance database from the FDA Manufacturer and User

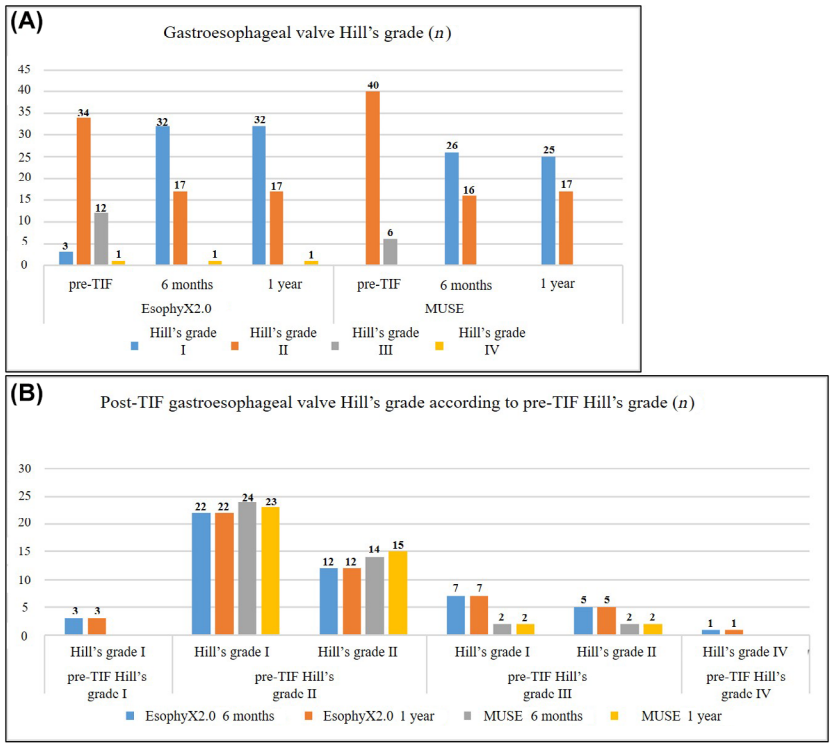

Figure 6 (A) Hill's grades of the gastroesophageal neovalve were similar in the EsophyX2.0 and MUSE series at 6 months ($P = 0.738$ for grades I and II, $P = 0.359$ for grade IV) and 12 months ($P = 0.571$ for grades I and II, $P = 0.359$ for grade IV) after transoral incisionless fundoplication (TIF). (B) The EsophyX2.0 patients with preprocedure Hill's grade I maintained grade I. Preprocedure Hill's grade II persisted at grade I in 66.7% of EsophyX2.0 cases up to 12 months, and in 63.2% and 60.5% of MUSE cases at 6 and 12 months ($P = 0.76$ and $P = 0.591$ at 6 and 12 months), but returned to grade II in 36.4% of EsophyX2.0 cases up to 12 months, and in 36.8% and 39.5% of MUSE cases ($P = 0.972$ and $P = 0.789$ at 6 and 12 months). Among patients with preprocedure Hill's grade III, grade I remained in 58.3% and 50%, and grade II in 41.7% and 50% of EsophyX2.0 and MUSE cases, respectively ($P = 0.779$), up to 12 months. The EsophyX2.0 patient with preprocedure Hill's grade IV relapsed to grade IV ($P = 0.359$).

Facility Device Experience (MAUDE) for 2011–2021.[25] No further adverse events were recorded during the 3-year follow-up, according to a recent report.[7]

Looking at the neovalve's competence, the Hill's grade was substantially similar for the two techniques at 6 and 12 months, even considering only Hill's grade II, the most common pre-TIF finding. The MUSE device was significantly more efficient in reducing hiatal hernia than EsophyX2.0 (88.9% vs. 51.9% at 1 year), even considering only hernias ≤2.5 cm long. Esophagitis rates (recurrent or persistent) were also similar at 6 and 12 months. Despite the greater efficacy of the MUSE system in reducing hiatal hernia, the rate of esophagitis was unexpectedly slightly higher in this series and unrelated to symptomatic improvement. This might possibly be due to impaired distal esophageal clearance, depending on the longer neovalve obtained with the MUSE system. However, discordance between relief of symptoms and morpho-functional findings was reported in most studies included in meta-analyses.[16–18]

Only about two-thirds and half of the patients returned for functional investigation after TIF in both series, and this could be a limitation. However, these low rates very likely reflect the symptomatic improvement with TIF, so patients prefer not to undergo a bothersome examination. Both techniques achieved significant reductions in the number of total and acid refluxes at 6 months, although the reduction of the total number of refluxes was similar with the two techniques (37.5% and 45.6% with EsophyX2.0 and MUSE, respectively), while the reduction of acid refluxes was 24.86% higher in the EsophyX2.0 series. The reduction of proximal refluxes was significant only with MUSE. Similar significant reductions of total refluxes are reported in the

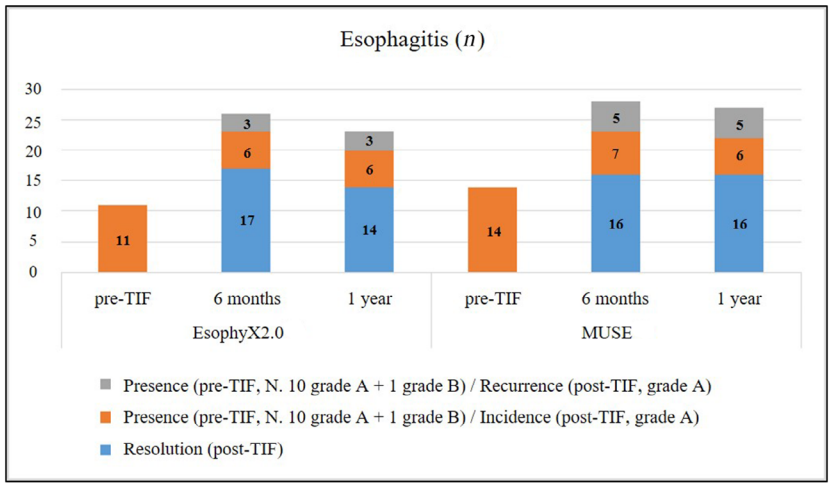

Figure 7 After transoral incisionless fundoplication (TIF), esophagitis (grade A) occurred in 12.2% of EsophyX2.0 cases up to 12 months, and in 16.7% and 14.3% of MUSE cases at 6 and 12 months (P = 0.543 and P = 0.769 at 6 and 12 months). Among patients with preprocedure esophagitis, it persisted or recurred in 27.3% and 35.7% of EsophyX2.0 and MUSE cases, up to 12 months (P = 0.662).

Table 3 Esophageal manometry and 24 h pH-metry and multichannel intraluminal impedance recordings at 6 months and 1 year after transoral incisionless fundoplication (TIF) with EsophyX2.0 device

	EsophyX2.0			*P*-value vs. pre-TIF		% Change vs. pre-TIF	
	Pre-TIF (49 pts)	6 months (35 pts)	1 year (30 pts)	6 months	1 year	6 months	1 year
LES pressure (mmHg)	9 ± 3	10 ± 3	NA	0.130	NA	11.11	NA
DEA (mmHg)	72 ± 30	73 ± 27	NA	0.740	NA	1.39	NA
Total refluxes, mean ± SD	64 ± 41	40 ± 41	44 ± 39	0.010	0.4	−37.50	−31.25
Acid refluxes,† mean ± SD	35 ± 22	14 ± 14	19 ± 17	0.001	0.5	−60.00	−45.71
Weakly acid refluxes,† mean ± SD	23 ± 20	13 ± 8	10 ± 10	0.250	0.7	−43.48	−56.52
Alkaline refluxes,† mean ± SD	4 ± 9	7 ± 20	12 ± 18	0.650	0.3	75.00	200.00
Proximal refluxes,† mean ± SD	25 ± 22	15 ± 11	15 ± 8	0.110	0.9	−40.00	−40.00
Johnson–DeMeester score,‡ mean ± SD	21 ± 13	18 ± 17	19 ± 19	0.570	0.6	−14.29	−9.52

†Definition of refluxes: "acid" if distal esophageal pH dropped to <4, "weakly acidic" if distal esophageal pH dropped to between 4 and 7, and "alkaline" if esophageal pH did not fall below 7, "proximal" if reached up to 15 cm from the gastroesophageal junction.
‡Parameters for DeMeester score: (1) total number of reflux episodes; (2) total number of reflux episodes ≥5 min; (3) longest reflux episode in minutes; (4) percentage of total time esophageal pH <4; (5) percentage of upright time esophageal pH <4; (6) percentage of supine time esophageal pH <4.
DEA, distal esophageal amplitude; LES, lower esophageal sphincter; NA, not applicable, because esophageal manometry was not done at 1 year; pts, patients.

literature.[17] However, in our series the differences were no longer significant at 1 year.

Clinically, no direct comparison could be made because of the significantly different symptom severity at baseline between the two series. Both techniques achieved significant symptom improvement at 6 months, 15.2% higher after TIF with EsophyX2.0. This improvement remained up to 3 years in both series. However, while the 1-year improvement rates were similar for the two techniques, there was a tendency toward slight worsening in the EsophyX2.0 series and improvement in the MUSE series at 3 years.

Daily PPI consumption is probably a more realistic indicator of the clinical impact of TIF than GERD-HRQL. Considering patients who stopped or reduced PPI

Table 4 Metrics at esophageal manometry and 24 h pH-metry and multichannel intraluminal impedance recordings at 6 months and 1 year after transoral incisionless fundoplication (TIF) with MUSE device

	MUSE			*P*-value vs. pre-TIF		% Change vs. pre-TIF	
	Pre-TIF (45 pts)	6 months (31 pts)	1 year (20 pts)	6 months	1 year	6 months	1 year
LES pressure (mmHg)	23.6 (17.9–27.4)	26.9 (20.0–28.6)	NA	0.8800	NA	13.98	NA
DCI (mmHg s cm)	530.4 (222.9–1288.4)	755.1 (133.6–1374.6)	NA	0.1400	NA	42.36	NA
Total refluxes, median (95% CI)	57 (38.3–79.4)	31 (24.5–54.1)	40.5 (24.7–69)	0.0002	0.37	−45.61	−28.95
Acid refluxes,[†] median (95% CI)	37 (24.5–54.2)	24 (12.3–41.2)	27.5 (13–46.6)	0.0020	0.15	−35.14	−25.68
Weakly acid refluxes,[†] median (95% CI)	11 (7–22.9)	8.5 (6–15.9)	10 (6–19.8)	0.2200	0.23	−22.73	−9.10
Alkaline refluxes,[†] median (95% CI)	2 (1–3.4)	1.5 (0–2.7)	1.5 (1–2.5)	0.8100	0.16	−25.00	−25.00
Proximal refluxes,[†] median (95% CI)	26 (12.8–37.8)	12 (5.8–20.3)	18 (7.2–30.5)	0.0020	0.31	−53.85	−30.77
Johnson–DeMeester score,[‡] median (95% CI)	21.1 (12–32.8)	20 (6–37.7)	16.4 (5.6–26.9)	0.5300	0.46	−5.21	−22.27

[†]Definition of refluxes: "acid" if distal esophageal pH dropped to <4, "weakly acidic" if distal esophageal pH dropped to between 4 and 7, and "alkaline" if esophageal pH did not fall below 7, "proximal" if reached up to 15 cm from the gastroesophageal junction.
[‡]Parameters for DeMeester score: (1) total number of reflux episodes; (2) total number of reflux episodes ≥5 min; (3) longest reflux episode in minutes; (4) percentage of total time esophageal pH < 4; (5) percentage of upright time esophageal pH < 4; (6) percentage of supine time esophageal pH <4.
CI, confidence interval; DCI, distal contractile integral; LES, lower esophageal sphincter; NA, not applicable, because esophageal manometry was not done at 1 year; pts, patients.

Table 5 Gastroesophageal reflux disease-health-related quality of life (GERD-HRQL) scores at 6 months and 1, 2, and 3 years after transoral incisionless fundoplication (TIF) with EsophyX2.0 and MUSE devices

	Pre-TIF	6 months	1 year	2 years	3 years
EsophyX2.0 series					
No. patients	50	49	49	45	45
GERD-HRQL score, mean ± SD	46 ± 19	15 ± 13	16 ± 13	18 ± 13	19 ± 14
P-value vs. pre-TIF		<0.0001	<0.0001	<0.0100	<0.0100
% Change vs. pre-TIF		−67.390	−65.220	−60.870	−58.695
P-value vs. previous follow-up	–	–	0.704	0.458	0.726
% Change vs. previous follow-up	–	–	6.670	12.500	5.560
MUSE series					
No. patients	46	42	42	42	34
GERD-HRQL score, mean ± SD	23 ± 10	11 ± 8	8 ± 7	8 ± 7	7 ± 7
P-value vs. pre-TIF		<0.0001	<0.0001	<0.0001	<0.0001
% change vs. pre-TIF		−52.170	−65.220	−65.220	−69.570
P-value vs. previous follow-up	–	–	0.071	1.000	0.538
% Change vs. previous follow-up	–	–	−27.270	0.000	−12.500

consumption, the outcomes were similar. The rates of PPI cessation at 6 months were similar too (61.2% vs. 64.3%), but MUSE achieved a 3-year 20.2% higher rate of patients off-PPI therapy, although not significant. The difference might be explained both by the pre-TIF lower severity of symptoms observed in the MUSE series, and by a possible longer duration of the neovalve created by MUSE with its suture system.

There were four times the number of patients who underwent surgical fundoplication in the 2 years after TIF with EsophyX2.0 than MUSE. Again, this can be justified by the greater symptom severity and the presence of patients

Table 6 Percentages of patients who had stopped, halved, or not changed the proton pump inhibitors (PPI) dose, at 6 months and 1, 2, and 3 years after transoral incisionless fundoplication (TIF) with EsophyX2.0 and MUSE devices

PPI consumption	TIF technique	6 months		1 year		2 years		3 years	
		PP	ITT	PP	ITT	PP	ITT	PP	ITT
Dose stopped + at least halved, *n* (%)	EsophyX2.0	41/49 (83.7)	41/50 (82.0)	39/49 (79.6)	39/50 (78.0)	39/45 (86.7)	39/50 (78.0)	38/45 (84.4)	38/50 (76.0)
	MUSE	37/42 (88.1)	37/46 (80.4)	38/42 (90.5)	38/46 (82.6)	37/42 (88.1)	37/46 (80.4)	29/34 (85.3)	29/38 (73.3)
P-value		0.552	0.842	0.153	0.574	0.845	0.774	0.913	0.774
Stopped, *n* (%)	EsophyX2.0	30/49 (61.2)	30/50 (60.0)	25/49 (51.0)	25/50 (50.0)	25/45 (55.6)	25/50 (50.0)	24/45 (53.3)	24/50 (48.0)
	MUSE	27/42 (64.3)	27/46 (58.7)	27/42 (64.3)	27/46 (58.7)	26/42 (61.9)	26/46 (56.5)	25/34 (73.5)	25/38 (65.7)
P-value		0.762	0.976	0.204	0.395	0.553	0.523	0.069	0.098
Dose at least halved, *n* (%)	EsophyX2.0	11/49 (22.5)	11/50 (22.0)	14/49 (28.6)	14/50 (28.0)	14/45 (31.1)	14/50 (28.0)	14/45 (31.1)	14/50 (28.0)
	MUSE	10/42 (23.8)	10/46 (21.7)	11/42 (26.2)	11/46 (23.9)	11/42 (26.2)	11/46 (23.9)	4/34 (11.8)	4/38 (10.5)
P-value		0.884	0.972	0.799	0.649	0.616	0.649	0.054	0.055
Dose unchanged, *n* (%)	EsophyX2.0	8/49 (16.3)	8/50 (16.0)	10/49 (20.4)	10/50 (20.0)	6/45 (13.3)	6/50 (12.0)	7/45 (15.6)	6/50 (12.0)
	MUSE	5/42 (11.9)	5/46 (10.9)	4/42 (9.5)	4/46 (8.7)	5/42 (11.9)	5/46 (10.9)	5/34 (14.7)	5/38 (13.2)
P-value		0.552	0.468	0.153	0.119	0.845	0.867	0.913	0.867

PPI consumption was considered "stopped," "halved," or "unchanged," when PPIs were no longer taken, taken at half the dose, or at the same dose as before TIF.
ITT, intention-to-treat; PP, per-protocol.

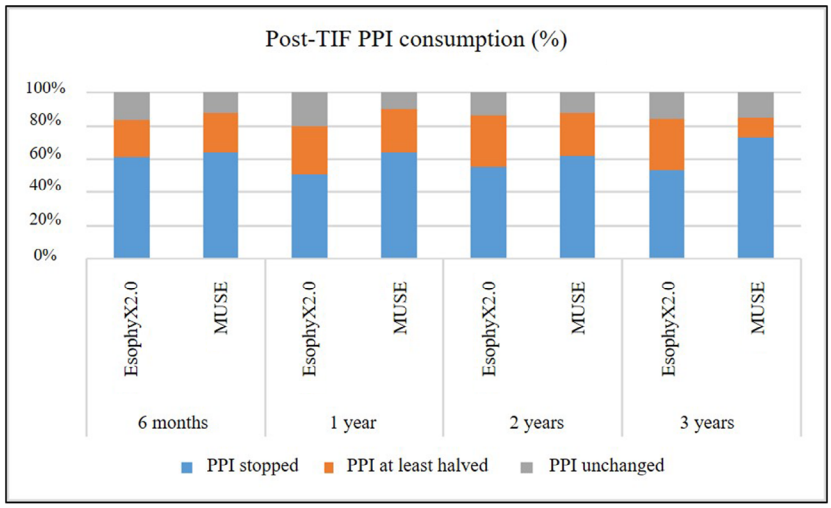

Figure 8 Proton pump inhibitor (PPI) consumption after transoral incisionless fundoplication (TIF), up to 3 years follow-up. Differences between EsophyX2.0 and MUSE techniques were not significant at any time.

with nonreducible or larger hiatal hernia in the EsophyX2.0 protocol.

In conclusion, despite the retrospective nature and small number of patients, this is the only study so far comparing the two TIF techniques, in patients enrolled in similar prospective protocols. TIF with EsophyX2.0 was easier to perform and took less time. The GE neovalve had a tighter circumferential closure after EsophyX2.0, but was longer after MUSE. The rates of complication were similar, but with EsophyX2.0 they were less severe and preventable by an expert operator, while MUSE-related ones were severe and not preventable by the operator.

Clinically, both techniques effectively controlled symptoms up to 3 years in selected patients, although the MUSE seemed more effective in the long term, especially in patients with hiatal hernia. However, we cannot draw any conclusion about the potential superiority of MUSE in the long term because baseline symptoms, rate of nonfully responders to PPI and hiatal hernias were more severe in the EsophyX2.0 series, potentially causing significant selection bias. Considering the severity of MUSE–related adverse events, the decision to use this device for TIF should be carefully evaluated, balancing benefits and risks, especially in subjects with mild GERD or at high surgical risk.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

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