

Efficacy of endoscopic anterior fundoplication with a novel ultrasonic surgical endostapler for gastroesophageal reflux disease: Six-month results from a multicenter prospective trial

Lihua Peng¹, Rong Wan², Shengliang Chen³, Jimin Wu⁴, Jing Yang¹, Xiaoxiao Wang¹, Bin Yan¹, Huijun Zhao¹, Fei Pan¹, Yichao Shi¹, Weifeng Wang¹, Jie Ai¹, Yunsheng Yang¹

¹Department of Gastroenterology and Hepatology, The First Medical Center, Chinese PLA General Hospital, Beijing, China; ²Department of Gastroenterology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; ³Department of Gastroenterology, Renji Hospital of Shanghai Jiaotong University School of Medicine, Shanghai, China; ⁴Department of Gastroesophageal Reflux Disease, Chinese PLA Rocket Force Characteristic Medical Center, Beijing, China

ABSTRACT

Background and Objectives: Endoscopic therapy is an option for the treatment of refractory gastroesophageal reflux disease (GERD). We aimed to evaluate the efficacy and safety of transoral incisionless fundoplication with the Medigus ultrasonic surgical endostapler (MUSE™) for refractory GERD. **Materials and Methods:** Patients with 2 years of documented GERD symptoms and at least 6 months of proton-pump inhibitors (PPIs) therapy were enrolled in four medical centers from March 2017 to March 2019. The GERD health-related quality of life (HRQL) score, GERD questionnaire score, total acid exposure on esophageal pH probe monitoring, the gastroesophageal flap valve (GEFV), esophageal manometry, and PPIs dosage were compared between the pre- and post-MUSE procedure. All of the side effects were recorded. **Results:** A reduction of at least 50% in the GERD-HRQL score was observed in 77.8% (42/54) patients. Most patients 74.1% (40/54) discontinued PPIs and 11.1% (6/54) reported a ≥50% dose reduction. The percentage of patients who had normalized acid exposure time after the procedure was 46.9% (23/49). The existence of hiatal hernia at baseline was negatively correlated with the curative effect. Mild pain was common and resolved within 48 h postprocedure. Serious complications were pneumoperitoneum (one case), mediastinal emphysema combined with pleural effusion (two cases). **Conclusions:** Endoscopic anterior fundoplication with MUSE was an effective treatment for refractory GERD, but still needs refinement and improvement in safety aspect. Esophageal hiatal hernia may affect the efficacy of MUSE. (www.chictr.org.cn, ChiCTR2000034350)

Key words: fundoplication, gastroesophageal reflux disease, ultrasonic surgical endostapler

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Peng L, Wan R, Chen S, Wu J, Yang J, Wang X, *et al.* Efficacy of endoscopic anterior fundoplication with a novel ultrasonic surgical endostapler for gastroesophageal reflux disease: Six-month results from a multicenter prospective trial. *Endosc Ultrasound* 2023;12:128-34.

Access this article online

Quick Response Code:



Website:

www.eusjournal.com

DOI:

10.4103/EUS-D-21-00244

Address for correspondence:

Dr. Yunsheng Yang, Department of Gastroenterology and Hepatology, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China.

E-mail: sunnyddc@plagh.org

Received: 2021-11-24; **Accepted:** 2022-02-27; **Published online:** 2022-06-08

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic and recurrent disease defined as the injury or complications arising from the retrograde flow of gastric content into the esophagus, oropharynx, and/or respiratory tract. Among many proposed therapies, proton pump inhibitors (PPIs) remain the preferred option, however, 30% to 40% of patients have an incomplete or null response to pharmacologic therapy,^[1,2] and GERD symptoms recur in a large proportion of patients after PPI withdrawal. Moreover, prolonged PPI use has been related to increased risks of *Clostridium difficile* infection, community-acquired pneumonia, hip fracture, Vitamin B₁₂ deficiency, and hypomagnesemia.^[3,4]

When PPIs fail, endoscopic therapy is often considered. In recent years, minimally-invasive endoscopic therapies such as the Stretta (Mederi Therapeutics Inc., Greenwich, CT, USA) procedure have showed certain utility in GERD, but their efficacy is limited and relapses are common,^[5] especially in cases of hiatal hernia. Transoral incisionless fundoplication (TIF) current used in clinical application included EsophyX device (TIF2.0),^[6] GERD-X^[7] and the Medigus ultrasonic surgical endostapler (MUSETM, Medigus[®], Omer, Israel),^[8] provides an opportunity to create a partial fundoplication via an endoscopic approach. The difference between MUSE and other TIF devices is that MUSE has an ultrasound transducer to help doctors determine when a proper stapling gap is achieved. MUSE as one of the TIF, has shown benefits in the treatment of refractory GERD through a limited number of studies.^[8-10] Systematic review also showed TIF appeared to be a safe and effective endoscopic procedure for patients with refractory GERD;^[11] however, previous studies rarely analyzed the factors that affect the efficacy. We conducted a multicenter prospective study to evaluate the efficacy and safety of endoscopic anterior fundoplication with MUSE in patients with refractory GERD, and analyzed the factors that affect the efficacy.

MATERIALS AND METHODS

Participants

This prospective study was conducted between March 2017 and March 2019 in four medical centers in China (The First Medical Center, Chinese PLA General Hospital, Beijing, Shanghai First People's

Hospital of Shanghai Jiaotong University School of Medicine, Shanghai, Renji Hospital of Shanghai Jiaotong University School of Medicine, Shanghai, Chinese PLA Rocket Force Characteristic Medical Center, Beijing). Each site obtained the corresponding institutional review board approval. This trial was registered on www.chictr.org.cn (registration number ChiCTR2000034350). Written informed consent was obtained from all participants.

We enrolled the refractory GERD patients who were adults aged 18–65 years with 2 years of documented GERD symptoms who responded to continuous PPI therapy of at least 6 months duration but showed symptom recurrence after therapy withdrawal. Pathological reflux (off PPI therapy) was defined as the total time of pH < 4.0 more than 4.5% and Demeester score more than 14.7 according to our recruitment criteria, which was confirmed through ambulatory esophageal pH monitoring during baseline evaluation. The hypersensitive esophagus was excluded. Esophageal manometry within 30 days before the study showed that esophageal peristalsis was sufficient and there was no motor dysfunction.

Patients with a body mass index (BMI) >35 kg/m² or substantial comorbidities (*e.g.*, heart disease, diabetes, cancer, previous gastric surgery, esophageal and gastric varices, autoimmune or hematological disease, and any condition that would prevent study completion) were excluded from the study. Endoscopic exclusion criteria included a hiatal hernia (the distance between the squamocolumnar junction and the diaphragmatic impression) >3 cm, Barrett's esophagus, Los Angeles grade D esophagitis, or esophageal luminal narrowing due to strictures, rings, or webs.

Device and procedure

MUSE system consists of a light source, control unit, and flexible surgical endostapler which resembles an endoscope. The procedures were performed under general anesthesia with endotracheal intubation in an operating room or a therapeutic endoscopy suite. Endoscopic anterior fundoplication was performed according to the standard operation procedure,^[8] as Zacherl, *et al.* described in 2015. The optimal stapling sites proximal to the Z line were detected through ultrasound or video imaging; subsequently, a partial anterior fundoplication was performed and wrap the gastric fundus around the lower end of the esophagus. In the first two patients, we used a

transnasal gastroscopy to facilitate visualization of the stapling positions.

Assessment of efficacy and safety

Efficacy data were analyzed at baseline and 6 months postprocedure. The primary endpoint was a $\geq 50\%$ improvement in the GERD health-related quality of life (HRQL) score. This validated instrument includes six heartburn-related items and questions relating to other GERD symptoms, medication use, and satisfaction with the present condition. The total score ranges from 0 to 50, with a higher score indicating more severe symptoms. All scores were assessed while patients were off PPI therapy for a minimum of 7 days.

Improvements in the GERD questionnaire (GERD-Q), reduction of total acid exposure on esophageal pH probe monitoring, elimination or $\geq 50\%$ reduction in the PPI dose, and changes in the gastroesophageal flap valve (GEFV) grading system (Hill grade) were considered as secondary endpoints. Esophageal pH measurements included the percentage of the total time with a pH < 4 , percentage of the total time with pH < 4 in the supine position, number of episodes of pH < 4 longer than 5 min, and the longest episode. Esophageal pH was considered normalized if after the procedure the time with pH < 4 was $\leq 4.2\%$ of total time. Lower esophageal sphincter (LES) pressure and length were recorded, as was peristaltic amplitude and residual LES pressure during relaxation. An evaluation of the Hill grade as compared with baseline was performed. A satisfactory flap valve was defined as a grade I or II in the Hill classification.

A safety evaluation was performed at time 0, 1 month, and 6 months postprocedure. This included registering the occurrence and duration of symptoms such as epigastric pain, reflux, dysphagia, fullness or early satiety after meals, inability to burp, anorexia, nausea, vomiting, nocturnal cough or wheezing, fatigue, and diarrhea. Serious adverse event (SAE) refers to events such as prolonged hospital stay, disability, affecting work ability, life-threatening or death during clinical trials. The SAE of this study included esophageal and gastric perforation, pneumothorax, pneumoperitoneum, bacteremia, gastrointestinal bleeding requiring blood transfusion, mechanical failure requiring surgery, etc.

Statistical analysis

SPSS version 23.0 (IBM, SPSS Incorporation, Chicago, IL, USA) was used for statistical analysis. Data with

normal distribution were expressed as mean $\pm$ standard deviation, and comparisons were performed using the paired *t*-test. Due to the nonparametric distribution of most of the continuous data, the data were expressed as median (range), comparisons between baseline and postprocedure results were made using the Wilcoxon signed-rank test. Counting data were expressed as the number of cases and percentage, and the Fisher's exact probability method or Wilcoxon rank-sum test was used for comparison and analysis. Univariate analyses were used to assess factors influencing procedure outcomes. The primary endpoint was considered as the dependent variable, while the gender, center of origin, age, BMI, HRQL, GERD-Q (normal distribution, divided into two groups by mean), pH measurement at baseline (abnormal distribution, divided into two groups by median), hiatal hernia (yes/no), and preoperative Hill grading were considered as independent variables. The test level was set as $\alpha = 0.05$ (bilateral test). When $P < 0.05$, the difference was considered statistically significant.

RESULTS

Baseline and procedural results

Among 54 patients (mean age, 48.1 ± 10.6 years; 26% females; mean BMI, 24.6 ± 3.4 kg/m²) enrolled in the study. MUSE procedure was technically successful in all patients with a procedure duration of 86.9 ± 15.91 min, and anesthesia time of 112.8 ± 10.32 min. Forty-nine (90.7%) completed the follow-up. Four patients who refused "off PPI" testing at the 6-month follow-up visit agreed to report the dosage of PPI usage. One patient was unable to contact at the 6-month follow-up. An intention-to-treat (ITT) approach was adopted for the primary endpoint, PPI dosage, and safety analysis. The comparison of objective testing indexes before and after the operation was conducted in the Per-Protocol (PP) population.

Gastroesophageal reflux disease-health-related quality of life, gastroesophageal reflux disease-questionnaire score, and pH monitoring at baseline and 6 months postprocedure

In the ITT population, a reduction of at least 50% in the GERD-HRQL score was observed in 42/54 (77.8%) patients, with 11 patients achieving a 100% reduction at 6-month follow-up. There were no differences between centers in this regard ($P > 0.05$) [Table 1].

In PP population, the median HRQL score significantly decreased from 22.0 (range 14.0–36.0) at baseline off PPI to 4.0 (range 0.0–24.0) at 6 months postprocedure ($P < 0.001$) [Table 2]. Similarly, GERD-Q scores significantly decreased from 13 (range 5–18) to 7 (range 1–15) ($P < 0.001$), and ambulatory esophageal pH monitoring showed a statistically significant reduction in the percentage of mean total time with pH <4 ($P = 0.004$) [Table 3]. The percentage of patients who had normalized acid exposure time after MUSE was 46.9% (23/49).

Anatomical structure changes

Anatomical structure changes included the comparison of GEFV and hiatal hernia pre and postoperation. The number of patients with unacceptable Hill grades (>2) decreased from 31 at baseline to 3 at 6 months postprocedure [Table 4]. Hiatal hernia disappeared in 7 of 10 patients [Table 5]. Figure 1 shows the endoscopic findings before, during, and 6 months after the procedure.

Esophageal manometry

No significant changes were observed after the procedure in LES pressure, LES length, integrated

relaxation pressure, distal contractile integral, or contractile front velocity.

Proton-pump inhibitor dosage

At 6 months follow-up, 74.1% of patients (40/54) discontinued PPIs or other acid-reducing medications, and 11.1% (6/54) reported a dose reduction of at least 50%.

Factors affecting outcome

The results of univariate analyses showed that the presence of hiatal hernia at baseline was negatively associated with the occurrence of the primary endpoint (odds ratio [OR] 0.125 [0.02–0.70], $P = 0.018$), and other factors included gender, center of origin, age, BMI, HRQL, GERD-Q, pH measurement at baseline, and preoperative Hill grading were not related ($P > 0.05$) [Table 6].

Safety results and side effects

All 54 patients completed the procedure without any technical complications related to the MUSE™ equipment. All reported tolerable pharyngeal or chest/epigastric dull pain within 48 h after the procedure.

Table 1. Patients achieving a gastroesophageal reflux disease - health-related quality of life score reduction of at least 50% reduction (primary outcome) according to the different centers

Center	n (ITT)	n (PP)	Number with hernia	Number of achieving primary outcome (PP%, ITT%)
1	10	9	2	8 (88.9, 80.0)
2	16	13	1	11 (84.6, 68.8)
3	14	13	3	12 (92.3, 85.7)
4	14	14	4	11 (78.6, 78.6)
Total	54	49	10	42 (85.7, 77.8)

PP: Per-protocol; ITT: Intention-to-treat

Table 2. Gastroesophageal reflux disease - health-related quality of life score analyses at baseline and 6 months postprocedure

	Baseline, on PPI median (range)	Baseline, off PPI median (range)	6 months, off PPI median (range)	P^*	$P^{\#}$
N	49	49	49		
GERD-HRQL	6.0 (0.0-23.0)	22.0 (14.0-36.0)	4.0 (0.0-24.0)	0.412	0.000
Q1: How bad is your heartburn?	1.0 (0.0-4.0)	4.0 (2.0-5.0)	1.0 (0.0-4.0)	0.695	0.000
Q2: Do you have heartburn when lying down?	1.0 (0.0-4.0)	3.0 (0.0-5.0)	0.0 (0.0-4.0)	0.200	0.000
Q3: Do you have heartburn when standing up?	1.0 (0.0-3.0)	3.0 (0.0-5.0)	1.0 (0.0-4.0)	0.790	0.000
Q4: Do you have heartburn after meal?	1.0 (0.0-4.0)	3.0 (1.0-5.0)	0.5 (0.0-4.0)	0.926	0.000
Q5: Does heartburn change your diet?	0.0 (0.0-4.0)	3.0 (0.0-4.0)	0.0 (0.0-4.0)	0.907	0.000
Q6: Does heartburn wake you from sleep?	0.0 (0.0-4.0)	3.0 (0.0-5.0)	0.0 (0.0-3.0)	0.185	0.327
Q7: Do you have difficulty swallow?	0.0 (0.0-1.0)	0.0 (0.0-3.0)	0.0 (0.0-2.0)	0.739	0.084
Q8: Do you have pain with swallowing?	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (0.0-1.0)	1.000	0.000
Q9: Do you have gassy or bloating feeling?	1.0 (0.0-3.0)	2.0 (0.0-4.0)	0.0 (0.0-4.0)	0.868	0.000
Q10: If you take medications, does this affect your daily life?	1.0 (0.0-4.0)	2.0 (0.0-4.0)	0.0 (0.0-4.0)	0.001	0.000

*6-months, off PPI vs. baseline, on PPI; #6-months, off PPI vs. baseline, off PPI. GERD-HRQL: Gastroesophageal reflux disease - health-related quality of life; PPI: Proton pump inhibitors

Table 3. pH monitoring analyses at baseline and 6 months postprocedure

	Baseline, off PPI median (range)	6 months, off PPI median (range)	P
N	49	49	
pH<4 (%) total	10.2 (4.5-74.5)	5.0 (0.2-71.4)	0.004
pH<4 (%) upright	12.2 (2.3-84.4)	6.7 (0.3-59.7)	0.009
pH<4 (%) supine	5.5 (0.0-84.8)	1.1 (0.0-88.7)	0.127
Total episodes	118.0 (45.0-672.0)	68.0 (3.0-730.0)	<0.001
Long episodes	5.0 (0.0-28.0)	3.0 (0.0-49.0)	0.019
Longest episode (min)	21.0 (5.0-198.0)	8.7 (1.0-111.0)	0.020
DeMeester score	38.4 (15.7-255.3)	18.5 (1.1-252.7)	0.003

PPI: Proton-pump inhibitors

Table 4. Hill grades at baseline and 6 months postprocedure (n=49)

Baseline (preprocedure)	6 months postprocedure		
	Grades≤2	Grade>2	Total
Grades≤2	18	0	18
Grade>2	28	3	31
Total	46	3	49

Table 5. Hiatal hernia at baseline and 6 months postprocedure (n=49)

Baseline (preprocedure)	6 months postprocedure		
	Hiatal hernia	No hiatal hernia	Total
Hiatal hernia	3	7	10
No hiatal hernia	0	39	39
Total	3	46	49

SAE rate was 5.6% (3/54). One patient had a mild pneumoperitoneum that required no treatment, other two patients had serious complications. One of them presented mediastinal emphysema and small amount of pleural effusion; antibiotic therapy was initiated and the patient recovered completely after hospitalization for 10 days. The other had a mediastinal emphysema and moderate pleural effusion, chest pain, and fever, which raised the suspicion of an esophageal leak; chest tube placement and antibiotic therapy were effective and the patient was discharged 50 days after the procedure. There were no long-term sequelae in the follow-up. Both of them had abnormal structure of cardia (2 cm hiatal hernia, GEFV Hill III) at the baseline.

DISCUSSION

In this study, we found that fundoplication with the ultrasonic surgical endostapler had a significant effect in refractory GERD, and hiatal hernia at baseline was negatively correlated with the curative effect. The procedure was overall safe, with only three patients suffering from significant complications.

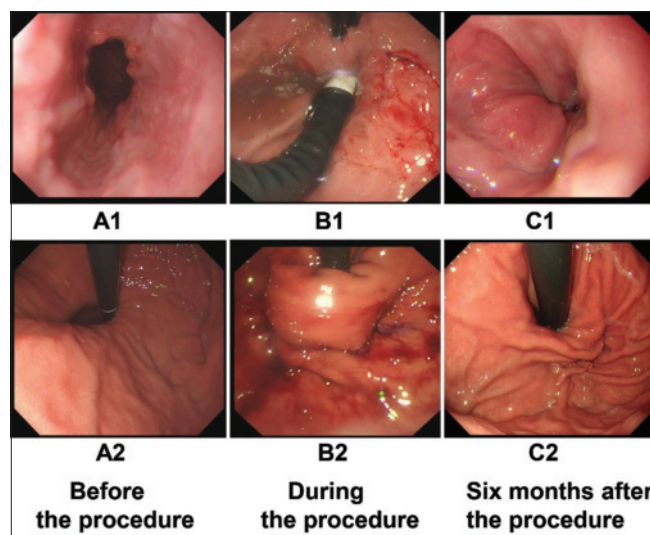


Figure 1. Endoscopic findings before, during, and 6 months after the procedure. B1 shows an endoscopic stapling with MUSE observed with transnasal gastroscopy

Endoscopic anterior fundoplication with this system is a type of local fundoplication in which the fundus of the stomach is wrapped around the lower portion of the esophagus, and at least two points are selected to sew the fundus of the stomach to the lower part of the esophagus. By binding the fundus of the stomach around the lower part of the esophagus, the pressure of the cardia is increased, and the His angle and the flap valve are restored to establish an effective barrier to prevent gastroesophageal reflux. Through the ultrasonic sensor, the device determines the distance between the nail box and the distal end of the endoscope (that is, the thickness of the nailed tissue), effectively avoiding the complications derived from nailing insufficient or excessive tissue.^[12] Despite these advantages, it is important to bear in mind that the limited space for stapling the gastric fundus restricts the maximum folding to 180°. For this reason, esophageal Hiatal hernias of more than 3 cm are difficult to reduce, and in these cases, laparoscopic Nissen or Toupet procedures are preferred.^[13]

Table 6. Univariate analyses of factors influencing the effect of endoscopic anterior fundoplication with medigus ultrasonic surgical endostapler (n=49)

Factors	HRQL score improvement<50%	HRQL score improvement≥50%	P	OR	95% CI
Gender (male/female)	5/2	31/11	0.895	1.13	0.19-6.67
Center distribution (1/2/3/4)	1/2/1/3	8/11/12/11	0.591	0.81	0.38-1.74
Age (≥48/<48 years)	2/5	25/17	0.145	3.68	0.64-21.19
BMI (≥24.9/<24.9 kg/m ²)	5/2	24/18	0.481	0.53	0.09-3.07
HRQL at baseline (≥23.53/<23.53)	3/4	19/23	0.907	1.10	0.22-5.54
GERD-Q at baseline (≥12.82/<12.82)	4/3	26/16	0.811	1.22	0.24-6.17
pH at baseline (≥10.4%/<10.4%)	4/3	21/21	0.727	0.75	0.15-3.77
Hernia at baseline (yes/no)	4/3	6/36	0.018*	0.125	0.02-0.70
Hill grade at baseline (Grade 4/3/1-2)	1/4/2	1/25/16	0.346	0.48	0.11-2.19

*Hernia at baseline was significantly associated with the effect of MUSE ($P<0.05$). HRQL: Health-related quality of life; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; GERD-Q: Gastroesophageal reflux disease-questionnaire

In recent years, there are only a few reports on the treatment of refractory GERD with MUSE. Zacherl *et al.*^[8] reported that its efficacy at 6 months is 72.7%. Another 5-year follow-up study found that 77% of patients stop using PPI or reach a dose reduction of more than 50% at 4–5 years after fundoplication with the ultrasonic surgical endostapler.^[9] Testoni *et al.*^[10] reported TIF with MUSE significantly improved symptoms at 1-year follow-up, allowing the consumption of PPIs to be stopped or halved in 78.3% of the ITT population. Although the follow-up time of these studies is different, the total effective rate is about 72%–78%. With a short-term (6 months) effective rate of 77.8%, our study is in accordance with these results.

Judging from the above results, endoscopic anterior fundoplication with the ultrasonic surgical endostapler, may be more effective than radiofrequency in increasing the pressure of the cardiac region and establishing an effective antireflux barrier. A randomized controlled study reported that 3 months after a radiofrequency procedure, 60% stopped PPI use.^[5] Similarly, a systematic review and meta-analysis of 28 studies including 2468 patients found that 51% of individuals can stop or reduce PPI use after radiofrequency treatment.^[14]

TIF using the EsophyX[®] device (EndoGastric Solutions, Redmond, WA, United States) is a similar method with MUSE. It reconfigures the tissue to obtain a full-thickness gastro-esophageal valve from inside the stomach, by serosa-to-serosa plications which include the muscle layers; the new valve boosts the barrier function of the LES with potentially fewer procedure-related side effects than surgery. Sixteen studies found TIF enabled patients to discontinue anti-reflux medications or markedly reduce their doses; 6-and 12-mo outcomes after TIF showed that 75%–

93% and 72%–85% of patients had either discontinued PPI or halved the dose. Normalization of esophageal acid exposure, in terms of total acidic refluxes, number of refluxates, and DeMeester score was reported in 37%–89% of patients.^[12] But there is a limitation compared with MUSE, which is the procedure requires two operators: One handles the device and the other the endoscope.

Differed from the indication of MUSE, Anti-reflux mucosectomy (ARMS) is another effective minimally invasive therapy for patients with poor therapeutic effect of PPIs and no sliding esophageal hiatal hernia, even for the patients who were complicated with Barrett's esophagus or high-grade epithelial neoplasia. It involves resection of the gastric cardiac mucosa, reduces the opening of the gastroesophageal junction through the healing process of the resulting scar. A retrospective analysis of 109 GERD patients treated with ARMS showed that more than 40% of patients could stop PPIs and the curative effect could be maintained until 3 years after the procedure.^[15]

In our MUSE study, outcomes were better in patients without hiatal hernia. Although there were no efficacy differences between centers, we noted that centers which included more patients with hiatal hernia showed a trend toward poorer results. Considering this finding and the fact that 3 of 10 patients still presented hiatal hernia postoperatively, we should carefully evaluate the presence of this condition when selecting the appropriate therapy for GERD. As we mentioned above, laparoscopic fundoplication may be a better choice in cases with large hernia diameters. Unfortunately, due to the small number of cases, we were unable to conduct a stratified analysis to determine the impact of different sizes of hiatal hernia on efficacy.

The incidence of complications is different among different endoscopic therapy for GERD. Stretta rarely reported SAE,^[5] usually AE, such as dysphagia, bloating, chronic stomach pain, etc.^[16] The incidence of SAE in MUSE and TIF2.0 was about 4.2%^[6] and 3.2%,^[7] respectively. Although all procedures were completed successfully with no mechanical failures related to the equipment, prolonged selection of the nailing site and repeated nailing may cause a small amount of gas to overflow into the peritoneal space, leading to pneumoperitoneum. It is worth noting that both cases of mediastinal emphysema and pleural effusion had esophageal hiatal hernia before the procedure. These complications may have been caused by the presence of a sliding hiatal hernia, change of mucous membrane position, poor location of stapling, or excessive stretching of the local mucous membrane in the process of pressing and stapling mucous membrane, resulting in small perforations or gas overflow.

There were some limitations in this study. As this procedure is still in a clinical research stage, strict inclusion and exclusion criteria were necessary, and patients were required to adhere to follow-up exactly as scheduled; this resulted in a slow selection process and small sample size. In addition, as we set a follow-up period of 6 months, long-term outcomes were not considered.

CONCLUSIONS

This study showed that fundoplication with the ultrasonic surgical endostapler is an effective procedure, especially for patients with refractory GERD who have been using PPI for more than 6 months. However, there are still some risks, and hiatal hernia at baseline may affect the curative effect, so we should exclude any patients with large hiatal hernia who reduce the efficacy and safety. This procedure still needs refinement and improvement in the safety aspect, so we must strictly grasp the indications of MUSE. Future studies with larger sample sizes and extended follow-up periods should be conducted to confirm our results and deepen the understanding of this new technology.

Financial support and sponsorship

The funding for this study was provided by the Key Project of PLA Healthcare Program China, No. 18BJZ33 and Science and Technology Innovation Nursery Fund of PLA General Hospital, No. 18KMM03.

Conflicts of interest

The devices of this study were provided by Medigus® Ltd., Omer, Israel, and Shanghai Golden-Grand Medical Instruments Co. Ltd., Shanghai, China.

The technological support was given by Amir Govrin, a senior engineer from Medigus®.

REFERENCES

- Hillman L, Yadlapati R, Whitsett M, *et al.* Review of antireflux procedures for proton pump inhibitor nonresponsive gastroesophageal reflux disease. *Dis Esophagus* 2017;30:1-14.
- Garros A, Mion F, Marjoux S, *et al.* Factors associated with nonresponse to proton pump inhibitors therapy in patients referred for esophageal pH-impedance monitoring. *Dis Esophagus* 2016;29:787-93.
- Hastrup PF, Thompson W, Søndergaard J, *et al.* Side effects of long-term proton pump inhibitor use: A review. *Basic Clin Pharmacol Toxicol* 2018;123:114-21.
- Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. *J Neurogastroenterol Motil* 2018;24:182-96.
- Kalapala R, Shah H, Nabi Z, *et al.* Treatment of gastroesophageal reflux disease using radiofrequency ablation (Stretta procedure): An interim analysis of a randomized trial. *Indian J Gastroenterol* 2017;36:337-42.
- Gerson L, Stouch B, Lobonțiu A. Transoral incisionless fundoplication (TIF 2.0): A meta-analysis of three randomized, controlled clinical trials. *Chirurgia (Bucur)* 2018;113:173-84.
- Nicolau AE, Lobonțiu A, Constantinoiu S. New minimally invasive endoscopic and surgical therapies for Gastroesophageal Reflux Disease (GERD). *Chirurgia (Bucur)* 2018;113:70-82.
- Zacherl J, Roy-Shapira A, Bonavina L, Bapaye A, Kiesslich R, Schoppmann SF, *et al.* Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. *Surg Endosc* 2015; 29:220-29.
- Roy-Shapira A, Bapaye A, Date S, *et al.* Trans-oral anterior fundoplication: 5-year follow-up of pilot study. *Surg Endosc* 2015;29:3717-21.
- Testoni PA, Testoni S, Mazzoleni G, *et al.* Transoral incisionless fundoplication with an ultrasonic surgical endostapler for the treatment of gastroesophageal reflux disease: 12-month outcomes. *Endoscopy* 2020;52:469-73.
- McCarty TR, Itidiare M, Njei B, *et al.* Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: A systematic review and meta-analysis. *Endoscopy* 2018;50:708-25.
- Testoni PA, Mazzoleni G, Testoni SG. Transoral incisionless fundoplication for gastro-esophageal reflux disease: Techniques and outcomes. *World J Gastrointest Pharmacol Ther* 2016;7:179-89.
- Siegal SR, Dolan JP, Hunter JG. Modern diagnosis and treatment of hiatal hernias. *Langenbecks Arch Surg* 2017;402:1145-51.
- Fass R, Cahn F, Scotti DJ, *et al.* Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. *Surg Endosc* 2017;31:4865-82.
- Sumi K, Inoue H, Kobayashi Y, *et al.* Endoscopic treatment of proton pump inhibitor-refractory gastroesophageal reflux disease with anti-reflux mucosectomy: Experience of 109 cases. *Dig Endosc* 2021;33:347-54.
- Ma L, Li T, Liu G, *et al.* Stretta radiofrequency treatment *vs.* Toupet fundoplication for gastroesophageal reflux disease: A comparative study. *BMC Gastroenterol* 2020;20:162.