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Original Article

Pilot study on anti-reflux mucoplasty: Advancing endoscopic anti-reflux therapy for gastroesophageal reflux disease

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Objectives: Anti-reflux mucosectomy (ARMS) and anti-reflux mucosal ablation (ARMA) were developed as interventions for proton pump inhibitor (PPI)-refractory/-dependent gastroesophageal reflux disease (GERD). Although ARMS and ARMA are established treatments for PPI-refractory GERD, reliance on natural healing for ulcer scar formation introduces uncertainty and bleeding risk. To address these issues, we introduced a novel approach called anti-reflux mucoplasty (ARM-P), which involves immediate closure of mucosal defects following mucosectomy. This pilot study aims to evaluate the safety, feasibility, and efficacy of ARM-P.

Methods: A retrospective single-center study was conducted using prospectively collected data from October 2022 to July 2023. Patients with PPI-refractory/-dependent GERD who underwent ARM-P were included. The study evaluated technical success of ARM-P, before and after ARM-P GERD-Health Related Quality of Life Questionnaire, GerdQ, and Frequency Scale for the Symptoms of GERD scores, along with PPI discontinuation and endoscopic esophagogastric junction morphology.

Results: A total of 20 patients with a median age of 61.5 years underwent the ARM-P procedure. The procedure achieved 100% technical success without adverse events. After ARM-P, 55.0% discontinued PPI usage and 15.0% reduced PPI dose by half. Median GERD-Health Related Quality of Life Questionnaire score improved from 21 to 6 ($P = 0.0026$), median GerdQ score improved from 9 to 7 ($P = 0.0022$), and median Frequency Scale for the Symptoms of GERD score decreased from 16 to 7 ($P = 0.0003$). Median Hill's Classification significantly improved from grade III to grade I ($P = 0.0001$).

Conclusions: This study presents the first pilot report of ARM-P, demonstrating its procedural safety, technical feasibility, and short-term efficacy.

Key words: anti-reflux mucoplasty, anti-reflux mucosal ablation, anti-reflux mucosectomy, endoscopic anti-reflux therapy, gastroesophageal reflux disease

INTRODUCTION

GASTROESOPHAGEAL REFLUX DISEASE (GERD) is a prevalent chronic pathological condition that persists in the upper digestive system.[1] Its occurrence is common, and it impacts up to 20% of the population in Western countries, with its prevalence steadily increasing globally.[2] Notably, approximately 15% of the Japanese population experiences weekly reflux symptoms, making GERD one of the most common upper gastrointestinal tract diseases in Japan's routine clinical practice.[3] Several minimally invasive endoscopic procedures have been developed[4–9] but there is currently no universally accepted standard treatment in development.

Although medical treatment with acid suppressive medications effectively addresses GERD symptoms, approximately 40% of patients still experience reflux symptoms even while on medication.[10] To overcome this challenge, we have developed two approaches of endoscopic anti-reflux therapy: anti-reflux mucosectomy (ARMS)[11,12] and anti-reflux mucosal ablation (ARMA).[13] In our 2004 study, we noted substantial scar retraction at the esophagogastric junction (EGJ) after gastric cardia mucosa resection, resulting in reduced EGJ diameter and an effective anti-reflux mechanism.[14] With this insight, we incorporated ARMS into endoscopic anti-reflux therapy,[6] which entails creating an

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intentional gastric cardia ulcer for mucosal regeneration through scar formation during the healing process.[11] Subsequently, it was found that artificial ulcers could be induced solely through mucosal cauterization, leading to the development of ARMA.[13] ARMA, chosen for its technical simplicity and similar effectiveness to ARMS, is now the primary choice for most patients over the complex ARMS mucosectomy. Long-term studies of ARMS have consistently shown efficacy up to 5 years. Both ARMS and ARMA have undergone thorough evaluation for efficacy and safety in three systematic reviews and meta-analyses,[15–17] confirming their safety and effectiveness. This has solidified their status as reliable therapeutic options for managing GERD.

However, ARMS/ARMA's mechanism for achieving cardioplasty relies on the natural healing process, making it challenging to predict ulcer shrinkage. Additionally, postprocedure, the induced ulceration persists for at least 3 weeks, potentially causing bleeding. To address these concerns, we introduced an innovative approach known as anti-reflux mucoplasty (ARM-P).[18] ARM-P involves directly closing the ulcer during initial mucosal resection. We hypothesize that ARM-P may promote the development of a more resilient mucosal flap valve compared with ARMS/ARMA. This pilot study aims to comprehensively assess the safety, feasibility, and efficacy of ARM-P.

METHODS

Study design

WE CONDUCTED A retrospective study using data from a prospectively collected database of patients who underwent ARM-P for proton pump inhibitor (PPI)-refractory/-dependent GERD at Showa University Koto Toyosu Hospital in Tokyo, Japan, spanning October 2022 to July 2023. Data were obtained from electronic medical records and participant questionnaires. The study was approved by the institutional review board of Showa University (approval number: 1205-6, 2023-089-B).

Patient selection

To fulfill the inclusion criteria, participants were required to have experienced at least one typical reflux symptom more than twice a week, regardless of receiving double-dose PPI treatment for a minimum of 6 months.

The inclusion criteria for this study were as follows. (i) Clinical: PPI/potassium-competitive acid blocker (P-CAB) refractory GERD, patients responding to PPI/P-CAB but unwilling to take them long term and refusing surgery. (ii) 24-h impedance-pH monitoring: positive symptom index (SI) or symptom association probability (SAP). Positive SI and SAP were defined as scores rated more than 50% and 95%, respectively. (iii) High-resolution manometry (HRM): no evident primary esophageal motility disorders. (iv) Even if the 24-h impedance-pH monitoring showed physiological acid reflux along with absent symptomatic correlation, symptomatic patients unwilling to take neuromodulators for the long term were included. In this study, there was no restriction on age. In case the applicant was younger than age 18 years, written consent was obtained from a surrogate.

High-resolution manometry (Star Medical Inc., Tokyo, Japan) was performed on all patients to verify the absence of esophageal motility disorders. The study excluded individuals with primary esophageal motility disorders but included those with ineffective esophageal motility diagnosed based on Chicago Classification version 3. Furthermore, all patients underwent various diagnostic procedures, including gastroscopy, barium esophagography, and 24-h impedance-pH monitoring while off PPIs (ZepHr; Sandhill Scientific Inc., Highlands Ranch, CO, USA). Our protocol for 24-h pH monitoring required patients to discontinue acid suppression drugs for a minimum of 7 days before the test. Esophageal biopsies were conducted to exclude the presence of eosinophilic esophagitis in cases in which typical endoscopic findings, such as edema, exudate, furrowing, concentric rings, or strictures, were observed.[19,20]

Primary and secondary outcomes

The primary end-points of our study are focused on the improvement in questionnaire scores (GERD-Health Related Quality of Life Questionnaire [GERD-HRQL],[21] GerdQ,[22] and Frequency Scale for the Symptoms of GERD [FSSG] score)[23] before and after ARM-P treatment, and the proportion of patients capable of discontinuing PPIs. Moreover, the secondary end-points of the study involved evaluating the improvement in EGJ morphology using Hill's Classification of gastroesophageal flap valve,[24] along with cardiac opening (CO) and sliding hernia (SH).[25] CO represents the diameter of the opening of the cardia, whereas SH represents the length from the diaphragmatic crus to the squamocolumnar junction. These measurements are assessed in the retroflex view, a method known to predict the presence of GERD. In addition to the changes in EGJ morphology, adverse events were also evaluated.

GERD definition

A conclusive GERD diagnosis was made when an abnormal acid exposure time (AET) value of >4.2%[26,27] or DeMeester scores >14.7 were calculated by 24-h impedance-pH

monitoring.[28] In cases where both AET value was <4.2% and DeMeester score was <14.7, positive SI or SAP were used. Those who had a positive symptom association were classified as having esophageal hypersensitivity,[29] whereas the remaining cases were considered as functional heartburn. Moreover, in Japan, the Los Angeles classification grade M (minimal change) has been incorporated,[30] and individuals classified as grade N and M are categorized as having nonerosive GERD. In this study, nonerosive GERD is exclusively determined by endoscopic findings.

Data collection

Patient data, including age, gender, duration of GERD symptoms, American Society of Anesthesiologists (ASA) physical status, use of antiplatelet or anticoagulant medications, Los Angeles classification for GERD, Hill's Classification, CO, SH, 24-h impedance-pH monitoring results for reflux parameters, EGJ morphology,[31] EGJ-contractile integral assessed through HRM, history of prior GERD interventions, perioperative details (total operation time, technical success, adverse events, hospital stay duration, perioperative pain), and PPI usage, were collected from electronic medical records. Additionally, questionnaire responses (GERD-HRQL, GerdQ, and FSSG) before and after the procedure were obtained. Endoscopic findings, including the Los Angeles classification system for GERD, Hill's Classification, CO, and SH, were verified by board-certified members of the Japanese Society of Gastrointestinal Endoscopy. Initial classification was conducted by K.Y. and I.T., with Y.S. intervening to resolve discrepancies when needed.

Statistical analysis

Continuous variables were presented as medians with ranges, whereas categorical data were reported as frequencies with corresponding percentages. Bivariate analyses were conducted using the Wilcoxon matched-pairs signed-rank test for comparisons before and after the ARM-P procedure. Statistical analysis was performed using Stata version 16.1 (StataCorp, College Station, TX, USA), with statistical significance determined at $P < 0.05$.

Anti-reflux mucoplasty

All patients received general anesthesia and endotracheal intubation, with prophylactic antibiotics and PPI administered 30 min before the procedure. A single operator (H.I.) performed all procedures using a therapeutic endoscope (H290T; Olympus, Tokyo, Japan) with an oblique distal attachment (MAJ-296) and a narrow crescent electrosurgical snare (SD-221L-25; Olympus) for endoscopic mucosal resection with cap (EMR-C).[32] The procedure involved injecting saline mixed with indigo carmine dye into the submucosa using a 4 mm tip, 25G needle (NeedleMaster; Olympus) before EMR-C. In conventional ARMS, approximately 3/4 to 4/5 of the mucosal circumference is removed.[11,12] In contrast, the ARM-P procedure entails removing approximately 1/3 of the mucosal circumference along the lesser curvature of the gastric cardia using the EMR-C technique, which is repeated three to four times.

Defect closure

Mucosal defect closure was achieved using the Loop-9,[33] Loop-10,[34] and Loop-11 closure technique.[18] The Loop-9 technique employs endoscopic purse-string suturing with a conventional surgical absorbable suture and a felt pledget to create a slip-knot loop for complete closure of large defects. Equipment and accessories included a 4-0 absorbable monofilament suture (PDS-II; Ethicon EndoSurgery, Cincinnati, OH, USA), the outer sheath of the QuickClip Pro Clip Fixing Device (HX-202LR; Olympus), and a disposable biopsy forceps (FB-231K; Olympus) designed to fit a 2.0 mm scope channel. The Loop-11 closure techniques are line-assisted methods using a support thread for traction during closure (Fig. 1),[18] involving a loop created with surgical suture (5-0 Nylon Suture, GA05NA; NescoSuture, Qingdao, China) around both arms of the repositionable endoscopic clip (QuickClip Pro, HX-202LR; Olympus), with a monofilament nylon line set within the loop. Loop-9 is an interrupted suture for mucosal defects in any direction, whereas Loop-11 is more continuous and suited for vertical suturing, chosen based on the mucosal defect's shape.

Postoperative management and follow-up

All patients underwent postoperative endoscopy (GIF-1200N; Olympus) on postoperative day (POD) 1 and 4 or 5 for complication monitoring. Clinical symptoms, including chest pain, dyspnea, hematemesis, melena, and abdominal pain, were closely monitored. Vital signs were checked every 6 h, and blood tests were conducted on POD 1. If no complications were found during the POD 1 endoscopy, patients were allowed to transition to a clear liquid diet. After achieving symptom-free oral intake and completing the second follow-up endoscopy, patients were discharged. The first follow-up endoscopy after discharge was scheduled 1–2 months postprocedure, with subsequent follow-ups planned at 3–4 months. Perioperative endoscopic images are shown in Figures 2–5, demonstrating mucosal remodeling

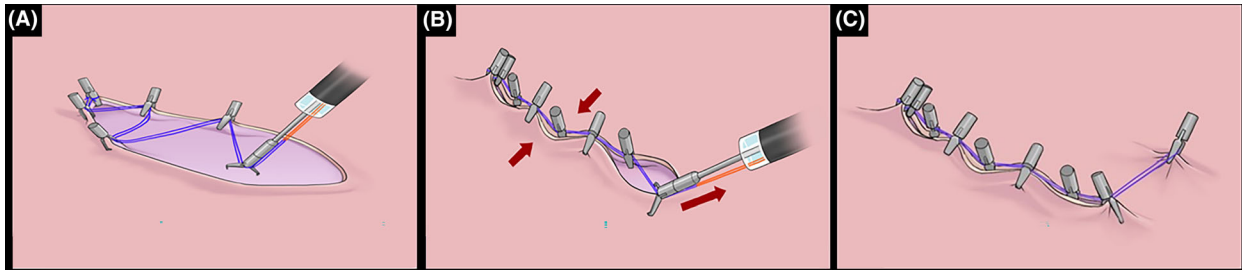

Figure 1 Loop-11 closure technique, which is a line-assisted closure method incorporating a support thread to ensure continuous traction throughout the closure. (A) Clipping is initiated at the most distal end, and the second clip is deployed adjacent to the first clip. Subsequent clips are then deployed in a zigzag fashion onto the contralateral side and continue in this manner until reaching the proximal end. (B) Continuous traction using a thread facilitates the mucosa and submucosa approximating together, allowing for complete closure, supplemented with the use of additional clips. (C) The last clip is applied to the mucosa to secure it firmly and prevent any potential loosening of the sutures.

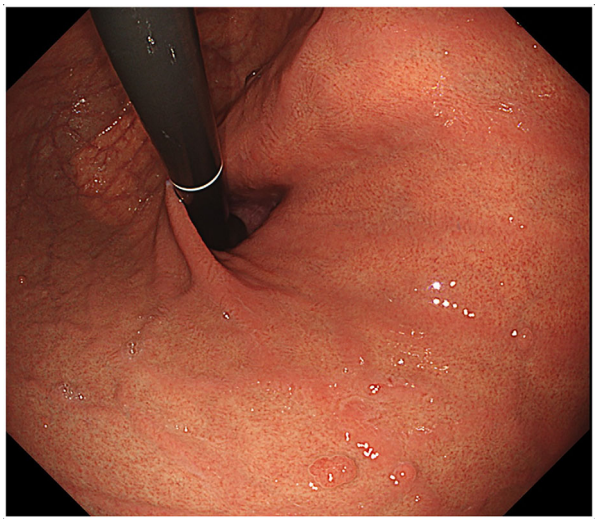

Figure 2 The upper endoscopy revealed a Hill's flap grade III hiatal hernia.

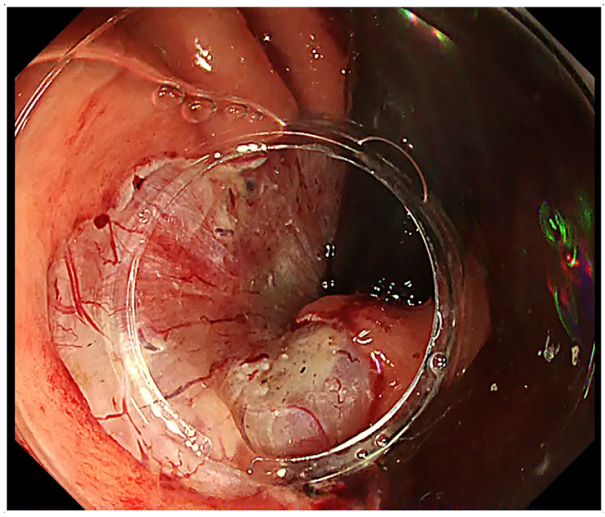

Figure 3 A partial mucosal resection (1/3 of circumference) with endoscopic mucosal resection with cap technique was performed along the lesser curvature of the cardia.

of the flap valve and a reduction in the prominence of the hernia.

RESULTS

A TOTAL OF 20 consecutive patients underwent the ARM-P procedure, with a median age of 61.5 years (range: 14–82). Before the ARM-P procedure, all participants were on a double-dose PPI or P-CAB treatment regimen. Two patients were on a double-dose PPI treatment, whereas the remaining participants were on P-CAB. The baseline characteristics of the patients are provided in Table 1. Of the total participants, 70.0% (14/20) were male and had a median duration of GERD symptoms of 4 years (range: 1–25). Among the patients, 50% were classified as ASA I, another 50% as ASA II, and only one patient was using regular anticoagulation medication. Furthermore, none of the patients in this study had underlying conditions such as scleroderma, other collagen diseases, or diabetes mellitus. Additionally, 80% (16/20) of the participants were classified as having nonerosive reflux disease endoscopically. The majority of Hill's Classification, CO, and SH were grade III (50%, 10/20), 2 cm (55%, 11/20), and 1 cm (40%, 4/20), respectively. According to the 24-h pH monitoring, 15% (3/20) were classified as having GERD, 45% (9/20) with esophageal hypersensitivity, and 40% (8/20) with functional heartburn (Fig. 6). Two individuals had undergone previous

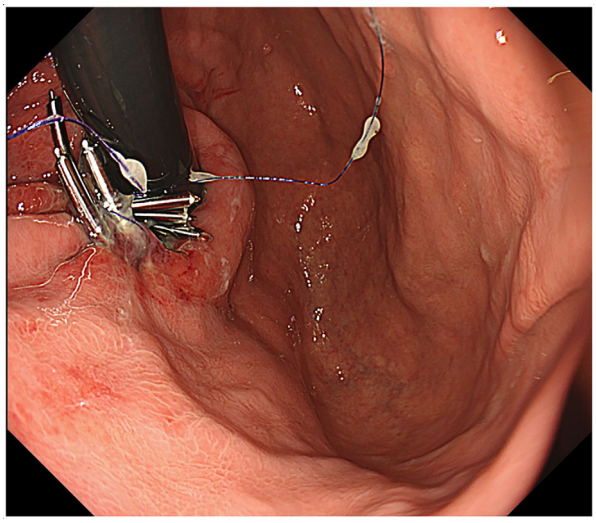

Figure 4 The closure of the defect was achieved by the Loop-9 closure technique, which involves an endoscopic purse-string suturing method.

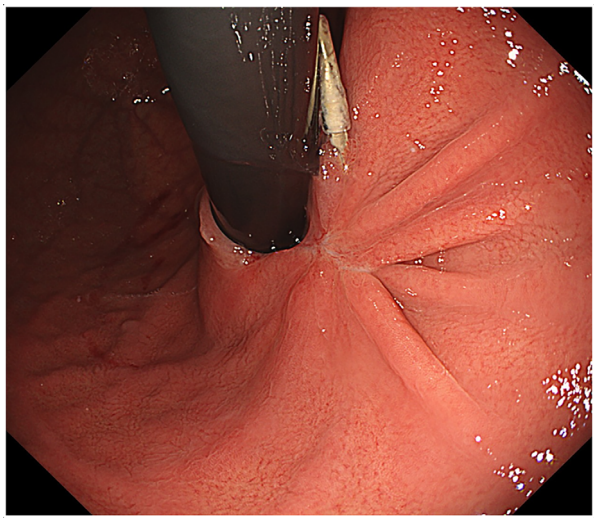

Figure 5 A subsequent endoscopy conducted 2 months after the procedure demonstrated an improved hernia tightening, along with a reshaped mucosal flap valve.

interventions for GERD treatment. One patient had a history of Toupet fundoplication, whereas the other had undergone ARMA procedure. The median total operation time was 75 min (range: 45–205), and we achieved 100% technical success (Table 2). The median hospitalization duration was 5 days (range: 5–9), and no adverse events, such as bleeding or perforation, were associated with delayed hospitalization or readmission following discharge. None of the patients

Table 1 Baseline patient characteristics in this study

Patients' demographics (*n* = 20)	
Age, median (range), years	61.5 (14–82)
Male, *n* (%)	14 (70.0)
Duration of GERD symptoms, median (range), years	4.0 (1–25)
ASA-PS score, *n* (%)	
Class I	10 (50.0)
Class II	10 (50.0)
Antiplatelet or anticoagulation use, *n* (%)	1 (5.0)
Endoscopic findings	
Esophagitis (LA classification), *n* (%)	
None or grade M	16 (80.0)
Grade A	3 (15.0)
Grade B	1 (5.0)
Hill's classification of gastroesophageal flap valve, *n* (%)	
Grade I	1 (5.0)
Grade II	5 (25.0)
Grade III	10 (50.0)
Grade IV	4 (20.0)
Cardiac opening, *n* (%)	
1 cm	3 (15.0)
2 cm	11 (55.0)
3 cm	6 (30.0)
Sliding hernia, *n* (%)	
0 cm	5 (25.0)
1 cm	8 (40.0)
2 cm	7 (35.0)
High-resolution manometry	
EGJ-contractile integral, median (range), mm Hg[†]	32.3 (9.2–65.4)
EGJ morphology, *n* (%)	
Type I	11 (55.0)
Type II	3 (15.0)
Type III	6 (30.0)
24-h impedance-pH monitoring	
Acid exposure time, median (range), min	27.5 (0–338.9)
Total number of reflux events, median (range)	53.5 (10–136)
Number of acid reflux events, median (range)	38.5 (0–88)
Number of non-acid reflux events, median (range)	16.0 (0–75)
GERD classification using 24-h impedance-pH monitoring, *n* (%)	
GERD	3 (15.0)
Reflux hypersensitivity	9 (45.0)
Functional heartburn	8 (40.0)
Previous intervention, *n* (%)	
None	18 (90.0)
Toupet fundoplication	1 (5.0)
ARMA	1 (5.0)

[†]Data for three patients are missing.
ARMA, anti-reflux mucosal ablation; ASA-PS, American Society of Anesthesiologists physical status; EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; LA, Los Angeles.

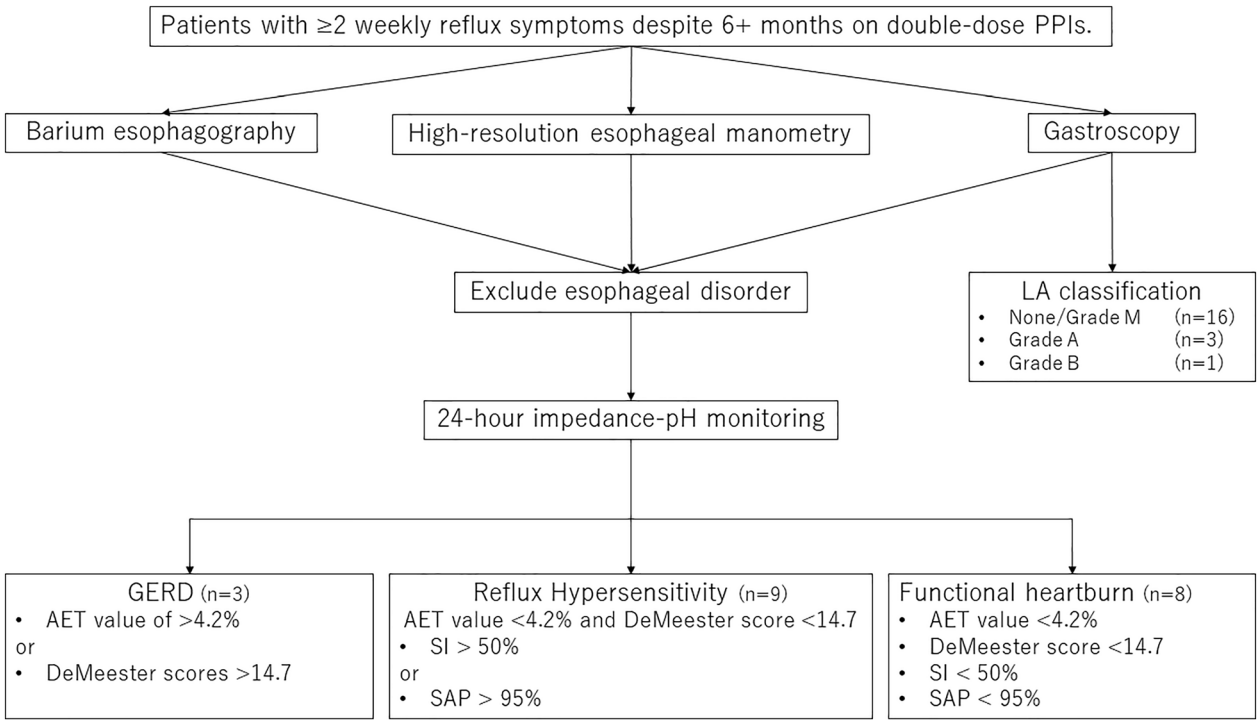

Figure 6 A study flowchart of patient population. AET, acid exposure time; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor; SAP, symptom association probability; SI, symptom index.

Table 2 Perioperative outcomes observed among patients in this study

Perioperative results (n = 20)	
General anesthesia, n (%)	20 (100.0)
Total operation time, median (range), min	75 (45–205)
Postoperative stay, median (range), days	5 (5–9)
Technical success, n (%)	20 (100.0)
Closure method, n (%)	
Loop-9 technique	3 (15.0)
Loop-11 technique	17 (85.0)
Mucosal resection, n (%)	
EMR-C	20 (100.0)
Adverse events, n (%)	
Perforation and bleeding	0 (0.0)
Pain requiring for opioids	0 (0.0)
Dysphasia requiring dilation	0 (0.0)

EMR-C, endoscopic mucosal resection with cap.

Table 3 Assessment of proton pump inhibitor discontinuation and endoscopic cardiac morphology following anti-reflux mucoplasty

Follow-up period	
Postprocedure to last endoscopy date, median (range), days	36 (19–211)
Postprocedure to date of last visit, median (range), days	56.5 (26–211)
Antireflux medications use, n (%)	
Discontinuation	11 (55.0)
50% dose reduction	3 (15.0)
Continuation	6 (30.0)
Hill's Classification of gastroesophageal flap valve (P = 0.0001), n (%)	
Grade I	13 (65.0)
Grade II	7 (35.0)
Cardiac opening (P = 0.0001), n (%)	
1 cm	16 (80.0)
2 cm	4 (20.0)
Sliding hernia (P = 0.0005), n (%)	
0 cm	15 (75.0)
1 cm	5 (25.0)

required opioids for postoperative pain management. Furthermore, none of the patients reported dysphagia requiring balloon dilation after the discharge from the hospital.

The median follow-up period from after the procedure to the last endoscopy was 36 days (range: 19–211), and to the last visit, 56.5 days (range: 26–211) (Table 3). After the procedure, 55.0% (11/20) of patients successfully discontinued PPI, whereas 15.0% (3/20) reduced their PPI dose by half. Significant improvements were observed in the

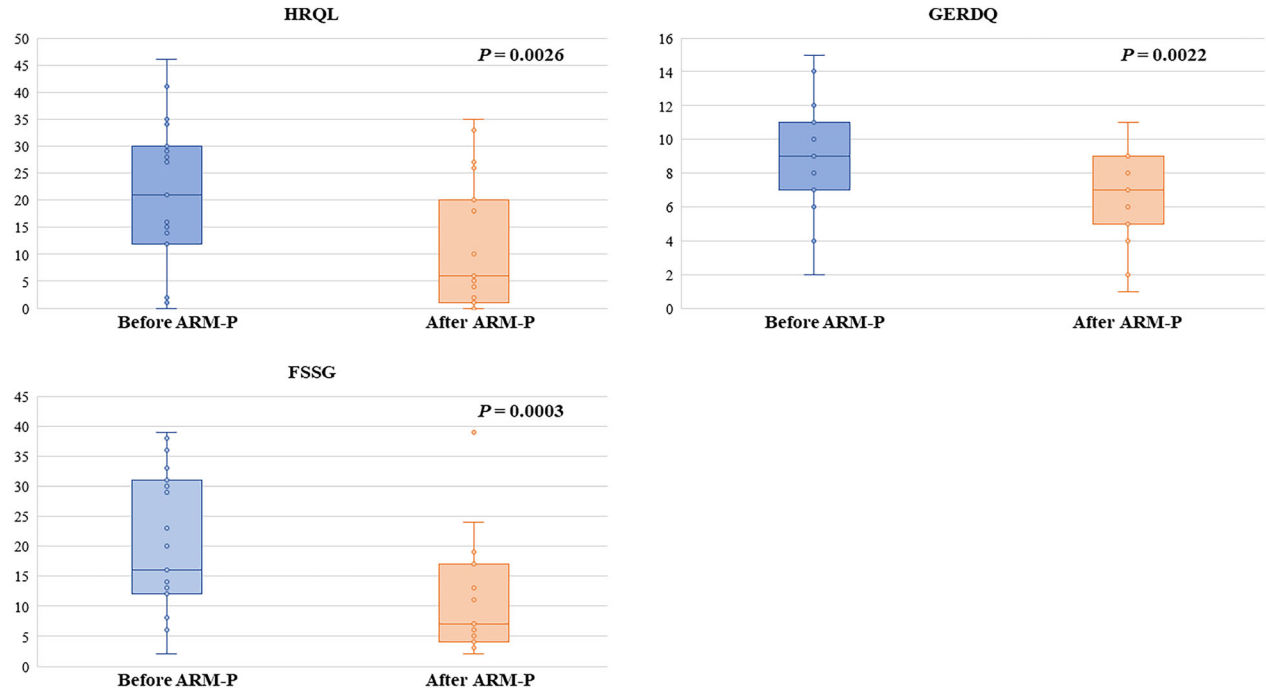

Figure 7 Median GERD-Health Related Quality of Life Questionnaire (GERD-HRQL) score improved from 21 to 6 (P = 0.0026), median GerdQ score improved from 9 to 7 (P = 0.0022), and median Frequency Scale for the Symptoms of GERD (FSSG) score decreased from 16 to 7 (P = 0.0003). ARM-P, anti-reflux mucoplasty.

median Hill's Classification, decreasing from grade III (range: I–IV) to grade I (range: I–II) (P = 0.0001). Median CO and SH[25] significantly decreased from 2 cm (range: 1–3) and 1 cm (range: 0–2) to 1 cm (range: 1–2) (P = 0.0001) and 0 cm (range: 0–1) (P = 0.0005), respectively.

A statistically significant improvement in the median GERD-HRQL score was noted, decreasing from 21 (range: 0–46) before ARM-P to 6 (range: 0–35) after the procedure (P = 0.0026) (Fig. 7). Additionally, the median GerdQ score significantly improved, shifting from 9 (range: 2–15) before ARM-P to 7 (range: 1–11) after ARM-P (P = 0.0022). The median FSSG score also showed a significant improvement, decreasing from 16 (range: 2–39) before ARM-P to 7 (range: 2–39) after ARM-P (P = 0.0003).

DISCUSSION

THE ONGOING PROSPECTIVE, interventional trial examining patients with PPI-refractory/-dependent GERD who underwent ARM-P has demonstrated encouraging results. ARM-P was well-tolerated and resulted in significant improvements in GERD-related symptoms and acid reflux.

The significant improvement in clinical outcomes can be attributed to the implementation of an additional closure technique following the mucosectomy. In ARM-P, the exposed submucosal layers are directly approximated using specific tissue apposition techniques. This approach may help build a more robust mucosal flap valve compared with ARMS. To achieve the closure, we used either Loop-9[33] or Loop-11[18] technique, which allowed us to capture the submucosal layer together. This approach prevents the occurrence of submucosal dead space underneath the approximated mucosa, which may otherwise result in mucosal dehiscence at a later stage if the mucosal defect is simply closed by pulling the bilateral mucosa with an endoscopic clip.

The progression of Hill's Classification of gastroesophageal flap valve has been identified as a known factor leading to refractory GERD.[20,24] Likewise, in our prior study, we established cut-off values for AET, with CO >3 cm and SH >2 cm.[25] Notably, a significant reduction in the grade of Hill's Classification, as well as in CO and SH measurements, could potentially play a role in improving the clinical outcome. We assumed that the likelihood of EGJ morphology narrowing is greater in ARM-P compared with ARMS/ARMA, as ARMS/ARMA achieves cardioplasty through natural ulcer scar formation. However, this potential difference has not been compared or evaluated yet, indicating the need for further research.

During the follow-up period, no adverse events (bleeding, perforation, or readmission) were observed, and no case of dysphagia requiring balloon dilation after hospital discharge. The risk of bleeding with ARMS or ARMA is known to be approximately 5%, and this risk is even higher for patients taking antiplatelet medications.[15–17] Open ulcers, persisting postprocedure for about 3 weeks,[11–13] elevate bleeding risk, possibly contributing to delayed bleeding. Unlike ARMS/ARMA procedures requiring 3/4 to 4/5 mucosal resection,[11–13] ARM-P involves resecting a smaller portion, approximately only 1/3. This reduced resection area in ARM-P, alongside mucosectomy closure, might lessen bleeding risk. Regarding dysphagia, none of the patients reported experiencing dysphagia or required balloon dilation after the procedure. The risk of dysphagia associated with ARMS or ARMA is approximately 7–11%.[16,17] This issue results from uncontrolled scar formation, varying by individual.

Currently, it is crucial to recognize study limitations: a pilot design with a single-arm approach, limited patients, and a short follow-up. For robust conclusions, larger randomized trials are needed. Another limitation is that the assessment was conducted by a single operator, which might limit the generalizability of the findings because of the potential impact of the operator's experience and learning curve. Involving multiple operators in future studies could address this concern. Technical difficulties in suturing an artificial ulcer may hinder its generalization. However, recent advances in closure technique allows for the possibility of mucosal closure with less difficulties. Although further refinements and clinical studies are needed with regard to the closure techniques, we believe that ARM-P has potential to be generalized among endoscopists with proficient skills.

Given our limited number of cases included in this study, deciding an optimal extent of mucosal resection is challenging. However, we believe that a 1/3 circumferential resection suffices for clinical improvement without postoperative dysphagia if the closure techniques are applied. Also, the absence of postprocedure 24-h impedance-pH monitoring data limits insights into treatment efficacy. Incorporating 24-h impedance-pH monitoring in future research could enhance outcome understanding. Nevertheless, we believe this technique can make a significant contribution, potentially improving GERD treatment by approximately 50–60%, building on the demonstrated efficacy of previous ARMS and ARMA procedures.[15–17] In the context of endoscopic anti-reflux therapy, ARMS will be transitioned to ARM-P. Nevertheless, considering its technical simplicity, ARMA will continue to be a robust contender for endoscopic anti-reflux treatments, alongside ARM-P.

CONCLUSION

THIS PILOT STUDY represents the initial clinical outcomes of ARM-P. The procedural safety, technical feasibility, and short-term efficacy of this approach has been confirmed with technical success in all cases with no adverse events encountered. With the ability to close mucosal defects, ARM-P will likely see its widespread use in the future.

CONFLICT OF INTEREST

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FUNDING INFORMATION

NONE.

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