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Endoscopic augmentation of the esophagogastric junction with polymethylmethacrylate: durability, safety, and efficacy after 6 months in mini-pigs

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Abstract
Background and aims Endoscopic augmentation of the esophagogastric junction (EGJ) with polymethylmethacrylate (PMMA) has been reported in an experimental short-term study. We assessed whether endoscopic augmentation of the EGJ with PMMA is durable, safe, and efficacious after 6 months in mini-pigs.
Methods Ten mini-pigs were studied under anesthesia. After a pilot study in two animals, eight mini-pigs underwent lower esophageal sphincter (LES) manometry and gastrostomy with measurement of gastric yield volume (GYV) and gastric yield pressure (GYP). Endoscopic implantation of PMMA was performed aiming for the submucosa of the EGJ. Six months later, LES manometry and GYV and GYP measurements were repeated and animals were sacrificed, followed by microscopic analyses of the EGJ.
Results Out of 32 implants (four per animal), 29 (91%) were identified as submucosal nodules postmortem. PMMA deposits were found at microscopic analysis in all animals and located as follows [mean (range)]: submucosa 61.5% (37.5–91%), muscularis propria 21.5% (0–58%), mucosa 11% (0–25%), and subserosa 6% (0–17%). Neither esophageal perforation nor death was observed. A

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significant increase in GYV (1,404 versus 905 ml; $p = 0.02$) and a borderline increase in GYP (8.1 versus 6.5 mmHg; $p = 0.057$) were detected 6 months later.

Conclusions Endoscopic augmentation of the esophagogastric junction with PMMA was durable and had no complications after 6 months. However, the occurrence of implants in the subserosa requires technical refinement before use in clinical trials.

Keywords Gastroesophageal reflux · Polymethylmethacrylate · Gastric yield volume · Gastric yield pressure · Esophagogastric junction · Endoscopic treatment

Abbreviations

PMMA	Polymethylmethacrylate
EGJ	Esophagogastric junction
GERD	Gastroesophageal reflux disease
LES	Lower esophageal sphincter
GYV	Gastric yield volume
GYP	Gastric yield pressure

Gastroesophageal reflux disease (GERD) has high prevalence in the Western world [1], impairs health-related quality of life [2, 3], and demands enormous costs for its management [4]. Current therapeutic modalities include medical and surgical treatments, but both are expensive and surgical therapy is associated with nonnegligible morbidity and mortality [5]. A number of endoscopic techniques have been developed, attempting to restore the competency of the antireflux barrier with acceptable costs [6, 7].

Implantation of biocompatible filler substances in the esophageal wall has been reported to decrease the use of proton pump inhibitors and ameliorates GERD symptoms [8, 9]. However, implant location has been a matter of major concern after reports of severe complications [10, 11]. These complications represented endoscopic misplacement of polymer into deeper layers of the esophageal wall or in the mediastinum, as described in case reports [12–14]. Furthermore, experimental studies with Enteryx® have failed to demonstrate polymer durability 6 months after its implantation [15]. Similar concerns were also described for Gatekeeper Reflux Repair System, based on procedure-related complications, such as pharyngeal perforation, as well as dislodgment of the hydrogel prosthesis over time, raising questions about its long-term safety and efficacy [9, 16].

PMMA is a nonresorbable biocompatible polymer largely used as intradermal implants by plastic surgeons [17]. Compared with other filler substances, PMMA microspheres seems to be the most stable and durable implant. Once injected, it cannot be broken down by enzymes, acting merely as a scaffold and a stimulus for constant production of connective tissue [18]. Because of its attractive characteristics, the use of PMMA has been expanded to other medical specialties, including ophthalmology, urology, and gastroenterology. As a consequence, endoscopic implantation of PMMA at the esophagogastric junction (EGJ) has been recently described to ameliorate symptoms and reduce esophageal acid exposure in GERD patients, without serious complications [19]. Additionally, a significant augmentation of the antireflux barrier after implantation of PMMA has been reported by us in an experimental short-term study. However, esophageal perforation followed by death raised concern about procedure safety [20].

The recent development of animal models for assessment of gastroesophageal reflux provided the opportunity to test new antireflux therapies, particularly those related with endoscopic interventions [15, 21, 22]. Most studies employed measurements of gastric yield volume (GYV) and gastric yield pressure (GYP) as markers of antireflux barrier competency. Reproducibility of GYV and GYP measurements were documented in our laboratory, providing a reliable experimental technique for assessment of antireflux efficacy after interventional studies [23].

In order to develop safer and efficacious endoscopic techniques for further application in clinical trials, studies in animal models are needed. Regarding implantation of filler substances in the EGJ, implant location must also be demonstrated. We hypothesized that endoscopic implantation of PMMA aiming for the submucosa of the EGJ may satisfy these requirements in an animal model. The aim of this study was to assess whether endoscopic augmentation of the EGJ with PMMA is durable, safe, and efficacious after 6 months in mini-pigs.

Materials and methods

A study with two phases was performed (Table 1) in ten mini-pigs after approval by the Animal Ethics Committee of the Post-Graduation and Research Group at the Hospital

Table 1 Study phases

	Pilot study		Survival study	
	Anatomical specimen ($n = 4$)	In vivo ($n = 2$)	Day 1 ($n = 8$)	6 months ($n = 8$)
LES manometry			X	X
Gastrostomy			X	X
GYV and GYP			X	X
PMMA implantation	X	X	X	
Necropsy/pathology		X		X

de Clínicas de Porto Alegre (number 04–077, GPPG-HCPA). The first phase served as a pilot study to acquire experience with the implantation technique. The second phase assessed the end points in a medium-term survival study, 6 months after the intervention.

Pilot study

The injection technique was developed by testing Teflon® catheters (1.8 mm diameter) with either 16- or 18-gauge needles in porcine anatomical specimens composed of the esophagus and stomach. In order to implant the high-viscosity PMMA solution, the catheters were tested either with 100-cm-long gastroscope (Endoview® EGV, Recife, Brazil) or 60-cm-long flexible fiber sigmoidoscope (Olympus® OSF, Tokyo, Japan). Feasibility and perforation rates were assessed during ex vivo implantation of PMMA in the wall of the distal esophagus. The sigmoidoscope combined with the 18-gauge needle catheter was chosen as the best system to implant PMMA. Subsequently, endoscopic implantation of PMMA at the submucosa of the EGJ was tested in two anesthetized mini-pigs and no signs of extramural or subserosal deposits were found at necropsy.

Survival study

Animal preparation and anesthesia

Eight Macau–Piau mini-pigs (female, 9 months old, 30–52 kg body weight) were studied after fasting for 24 h. All procedures were performed under anesthesia, induced with Zoletil® 50 (zolazepam + tiletamine) 4 mg/kg and Virbaxil® 2% (Xylazine) 0.5 mg/kg I.M. (Basso and Pancote, Co, Sao Paulo, Brazil). During the procedures, each animal was kept in supine position and anesthesia supplemented intravenously every 30 min allowing spontaneous breathing.

Manometry of the LES

LES pressure and location were measured using a perfusion multilumen catheter connected to external pressure transducers (Dynapack MPX 816, Dynamed, Sao Paulo, Brazil). Each lumen was perfused with distilled water (0.5 ml/min) using a pneumohydraulic pump. LES was studied by means of stationary pull-through technique, with its basal pressure measured at the respiratory inversion point. The distal border was determined at the station that demonstrated a consistent rise of pressure above the basal gastric pressure, and the proximal border identified at the station that showed a drop to basal esophageal pressure.

Gastrostomy

After laparotomy, the duodenum was tied up with wet gauze and a Foley catheter inserted into the stomach through a Stamm gastrostomy. The catheter balloon was filled with water and the abdominal wall closed with surgical clamps. After measurements of GYV and GYP, the Foley catheter was removed and both gastric and laparotomy incisions sutured.

Measurements of gastric yield volume (GYV) and gastric yield pressure (GYP)

GYV and GYP were measured immediately before and 6 months after PMMA implantation, using a technique whereby the duodenum was occluded and the stomach slowly filled with HCl solution (0.02 N with pH 1), dripped via Foley catheter. Both intragastric volume and pressure were followed by a real-time digital monitor (Bioengineering Service, HCPA, Porto Alegre, Brazil). Spilling of acid solution from the stomach into the esophagus was detected by a pH-metry recording system (Digitrapper MK III, Synetics Medical, Stockholm, Sweden) with a pH sensor located 5 cm above the proximal border of the LES. GYV and GYP were defined whenever intraesophageal pH dropped quickly from above 4.0 to below 3.0, corresponding to LES opening. This technique has been validated previously, showing reproducibility for both GYV and GYP measurements [23].

PMMA

A 30% solution consisting of PMMA microspheres (30% of total volume; mean sphere diameter 59.9 μm, range 34.2–103.3 μm) suspended in hydrogel of carboxy glyconate hydrolactic of magnesium (70% of total volume) was used as the implant material (donation of BioMedical Ltda, Porto Alegre, Brazil). The solution is characterized by a white color and high viscosity, determined by a resorbable hydrogel. PMMA was provided in 3-ml syringes, allowing easy adaptation to an "implant gun" as described elsewhere [20].

Endoscopic implantation of PMMA

Endoscopy was performed using a fiber sigmoidoscope with an instrumentation channel of 3.2 mm diameter (Olympus® OSF, Tokyo, Japan), connected to a micro-camera (Endoview®, Recife, Brazil). The injector system consisted of a 95-cm-long Teflon® catheter (1.8 mm external diameter) with a 5-mm-long needle (18-gauge), covered by an 82-cm-long polyvinylchloride (PVC) sheath (2.8 mm external diameter). The catheter was filled with

PMMA before insertion of the endoscope in the esophagus. After inspection of the esophageal mucosa, the catheter was inserted through the endoscopic biopsy channel and the needle exposed out of the sheath in the esophageal lumen. Each quadrant of the distal esophagus was punched at the level of the LES, with the needle angled approximately 30° to the mucosal surface. PMMA was slowly injected (0.7 ml per quadrant) with help of an implant gun, aiming for the submucosa of the EGJ. Implant was considered adequate when mucosal bulging was clearly observed after the first two shots. Otherwise, the injection was immediately stopped and the needle reinserted in an adjacent site.

Follow-up

Animals were kept in appropriate housing and were periodically monitored for eating pattern, body weight, and temperature. Six months later, LES manometry and gastric yield measurements were repeated and animals sacrificed as described elsewhere [20].

Necropsy and histological analysis

After sacrifice, dissection of the posterior mediastinum and diaphragmatic esophageal hiatus was carried out, searching for signs of PMMA extravasation in the external surface of the EGJ. The esophagus and stomach were removed en bloc and incised following the greater gastric curve. The inner surface of the EGJ was examined for ulcerations and nodules. Each specimen was fixed in 4% formalin for 2 weeks. Subsequently, a 30-mm-long segment containing the EGJ was cut longitudinally (Fig. 1), followed by staining of the microscopic slices with hematoxylin and eosin. Histological analysis was performed by two independent pathologists, describing for each slice: (i) presence of PMMA; (ii) location of PMMA considering mucosa, submucosa, muscularis propria or subserosa; and (iii) tissue reaction, including inflammatory cells infiltration, fibrous tissue deposit and presence of foreign-body granulomas. Discordant histological evaluation was solved by consensus.

Study end points

Implant of PMMA was considered "durable" when both of the following criteria were met: (1) at least three intramural nodules per animal identified by inspection of the EGJ at necropsy, and (2) PMMA microspheres identified at microscopic analysis in all animals. The procedure was considered "safe" when the following criteria were fulfilled: (1) no mortality, (2) uneventful clinical evolution, (3) absence of extra-esophageal deposits of PMMA at necropsy, (4) predominance of implantation in the submucosa layer, and (5) biocompatibility between PMMA and esophageal tissue. "Efficacy" was defined as a significant ($p < 0.05$) increase in GYV and/or GYP 6 months after implantation of PMMA.

Statistical analysis

Eight animals were considered an adequate sample size to detect an increase in GYV of 500 ± 274 ml and an increase in GYP of 2.5 ± 2.0 mmHg, with $\alpha = 0.05$ and power of 80%, according to data from our previous study [20]. Data are presented as mean ± standard error of the mean (SEM), unless otherwise stated. LES pressure, and GYV and GYP values were log-transformed due to asymmetry. GYV and GYP values were adjusted to LES pressure and body weight, whereas the LES pressure values were adjusted to body weight after each measurement. Pre- and post-implant adjusted log values were compared using Student's paired *t*-test, as no deviations from normality were detected in the differences. However, due to small sample size, results were confirmed by Wilcoxon non-parametric test for paired samples. PMMA location in the EGJ layers was performed as follows: for each animal, slices containing PMMA were first classified according to the EGJ layer in which PMMA was deposited, and then

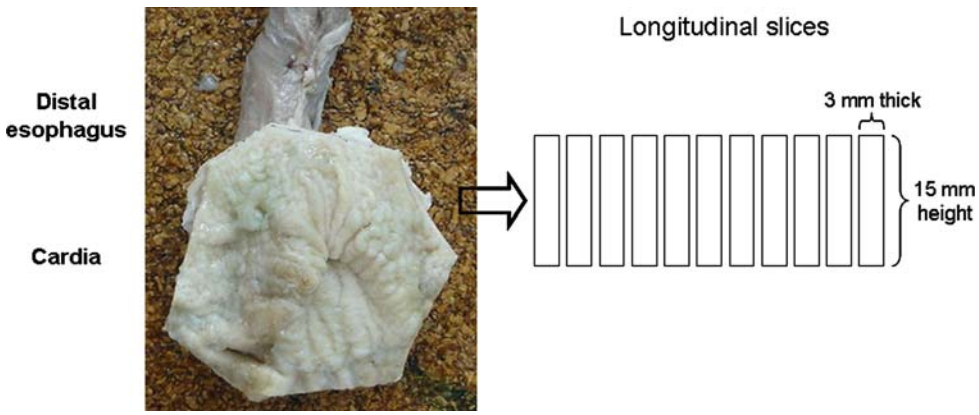

Fig. 1 Anatomical block containing the EGJ, which was sectioned in longitudinal slices

expressed as the percentage of slices containing PMMA in each layer. Comparisons between implantation in different layers of the EGJ were obtained by means of Friedman's test and subsequent Nemenyi's test, which accounts for multiple comparisons. Statistical significance was considered if $p < 0.05$.

Results

Endoscopic implantation of PMMA

Implantation of PMMA was performed in a single procedure lasting up to 20 min per animal. The 60-cm-long endoscope allowed easy visualization of the esophageal mucosa and frontal inspection of the proximal stomach. Out of 32 implants, 30 (94%) were successful at endoscopy, whereas two implants (6%) were considered to have reached deeper layers of the esophageal wall by the absence of mucosal bulging. The amount of PMMA implanted per animal was 2.73 ± 0.15 ml. An eventual extravasation of PMMA was precluded with slightly penetration of the needle into the wall. Neither bleeding nor cardiorespiratory instability were observed during the procedure.

Durability

Out of 32 implants, 29 (91%) were identified as submucosal nodules in the EGJ at necropsy. Four nodules were visualized in each of five mini-pigs and three in the remaining three animals (Fig. 2A). When the specimens were cut, a pale material compatible with PMMA deposit was identified at the center of the nodules (Fig. 2B). PMMA microspheres were easily identified in all animals at microscopic analysis.

Safety

There was no animal death. All mini-pigs showed uneventful clinical evolution, keeping habitual eating pattern with no signs of infection. A significant increase in body weight was observed, from an average of 37.6 ± 2.5 kg before implantation to 43.6 ± 1.4 kg 6 months later ($p = 0.012$).

Location of PMMA was described as mean percentage (range) of EGJ layers containing PMMA per animal (Fig. 3). PMMA microspheres were found mainly in the submucosa [61.5% (37.5–91%)], followed by muscularis propria [21.5% (0–58%)], mucosa [11% (0–25%)], and subserosa [6% (0–17%)]. In three animals implants of PMMA were found in the subserosa in a low percentage (12–17%) of slices. Among these animals, one had endoscopic implantation with no mucosal bulging, whereas two had implantations considered satisfactory. A significant difference was observed when comparing the layers with PMMA ($p = 0.003$). The percentage of submucosal deposits was higher when compared with either mucosal (61.5% versus 11%; $p < 0.05$) or subserosal implants (61.5% versus 6%; $p < 0.01$). The percentage of submucosal deposit was higher than that of muscularis propria (61.5% versus 21.5%), but failed to reach statistical significance ($p > 0.05$). At necropsy, no signs of PMMA extravasation were observed in the outer surface of the EGJ.

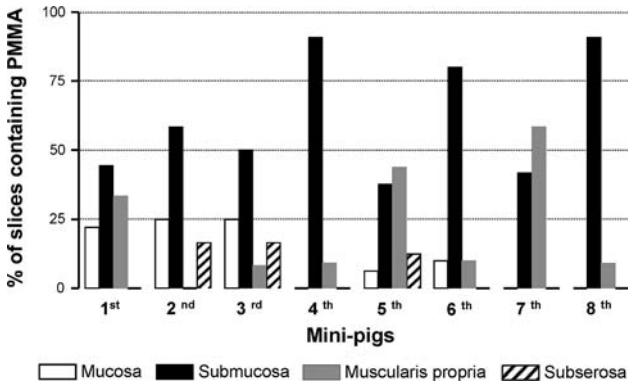

Fig. 3 Localization of PMMA in the layers of the EGJ. Each bar represents the percentage of slices containing PMMA in a singular layer ($n = 8$ animals)

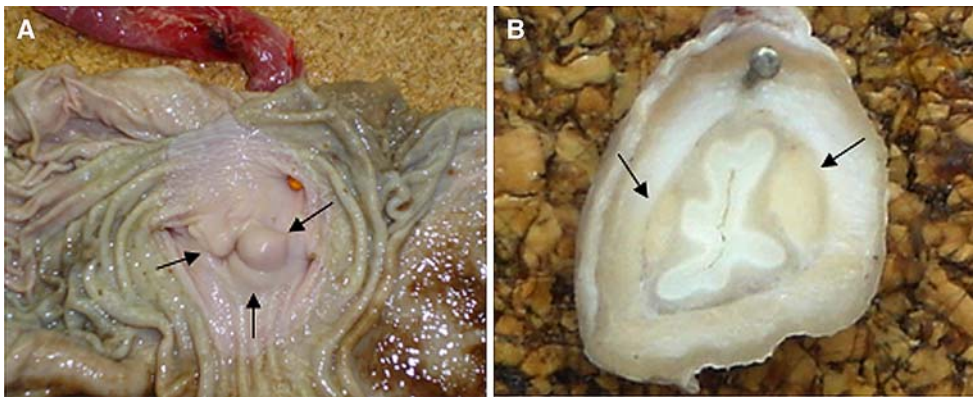

Fig. 2 Macroscopic analysis of EGJ after PMMA implantation. **A** Submucosal nodules of PMMA (*arrows*). **B** Intramural deposits of PMMA (*arrows*) in the submucosa

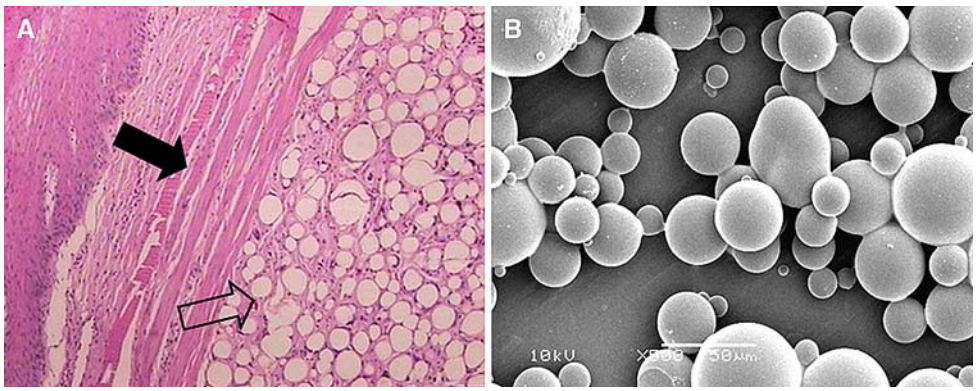

Fig. 4 Microscopic analysis of PMMA. **A** PMMA deposit in the submucosa (50×). The microspheres (*open arrow*) are limited superficially by the muscularis mucosa (*closed arrow*). **B** Electronic microscopy of PMMA. The microspheres are heterogeneous in size, including diameters <15 μm (500×)

Histological analysis of the EGJ revealed homogeneous innate chronic inflammatory infiltration involving PMMA microspheres (Fig. 4A), represented by macrophages and giant cells. Rare lymphocytes, plasmocytes, and eosinophils were identified. There were fibrous tissue deposits among the microspheres and around the implants, forming a capsule-like structure in all animals. Small amount of PMMA was found inside one periesophageal lymph node corresponding to animal number 1, in which the initial implantation was not followed by mucosal bulging.

The presence of PMMA microspheres in the lymphatic tissue prompted us to take a sample of nonimplanted polymer for morphometric analysis. A scanning electronic microscopy (JEOL-JSM 5800) showed microspheres smaller in size than expected (Fig. 4B). Subsequently, a granulometric analysis for particle size distribution (Cilas 1180 laser particle size analyzer) revealed microspheres with an average size of 39.68 μm, ranging from 1.87 μm (percentile 10) to 72.39 μm (percentile 90).

Efficacy

Unadjusted values for GYV, GYP, and LES measurements, obtained before PMMA implantation and 6 months later, are presented in Table 2. To account for possible effects of LES pressure and body weight on GYP and GYV, these variables were log-transformed for body weight and LES pressure at the time of measurements. A significant increase in GYV was observed 6 months after PMMA implantation compared with baseline measurements. An increase was also observed for GYP, but with a borderline *P* value. LES pressure and sphincter length were not significantly modified after PMMA implantation.

Table 2 Untransformed GYV, GYP, and LES data (mean ± SEM) before and after PMMA implantation ($n = 8$)

	Before	After	p*
GYV (ml)	905 ± 186	1404 ± 179	0.020
GYP (mmHg)	6.5 ± 1.2	8.1 ± 0.8	0.057
LES pressure (mmHg)	7.1 ± 1.3	7.7 ± 1.6	0.796
LES length (cm)	4.2 ± 0.4	4.9 ± 0.4	0.276

* Tests performed on log GYV and log GYP (adjusted for weight and log LES pressure), log LES pressure, and untransformed LES length

Discussion

We recently published an experimental study showing that endoscopic implantation of PMMA augments the gastroesophageal antireflux barrier 28 days after the procedure [20]. However, esophageal perforation and animal death pointed to the need for technical refinements. In the present study we assessed whether endoscopic augmentation of the esophagogastric junction (EGJ) with PMMA is durable, safe, and efficacious after 6 months in mini-pigs. For this purpose, we modified the implantation technique to improve procedure feasibility and safety. We then performed implantation of PMMA aiming for the submucosa of the EGJ and assessed study end points 6 months after the procedure.

Endoscopic implantation of PMMA as treatment for GERD was first published by Feretis et al. [19]. The authors implanted PMMA in the distal esophagus using a flexible sigmoidoscope in patients with refractory GERD and described a significant decrease in both symptom severity and esophageal acid exposure. Despite these promising results, further studies assessing PMMA implantation in humans have not been published. Furthermore, endotherapies for GERD were recently considered unsafe after reports of esophageal perforations and deaths, forcing a moratorium for these procedures [10, 12–14, 24, 25]. Therefore, animal studies focusing on safety and efficacy are needed before considering clinical trials.

The first end point of our study was durability of PMMA in the EGJ. After 6 months, submucosal nodules of PMMA were identified in all animals, confirmed microscopically with the finding of implant microspheres. This finding contrasts with an experimental study testing Enteryx®, in which the implanted polymer was not found in a subgroup

of animals [15]. Several factors may have contributed to PMMA durability in our study. First, its high viscosity may have diminished the occurrence of luminal dripping during and after implantation. Second, PMMA microspheres seem to be stable in soft tissues due to physical and chemical characteristics, precluding enzymatic degradation [18]. Third, it is known that PMMA activates collagen deposition in *anima nobile* after dermal implantation, favoring its stabilization in the tissue [18, 26].

The second end point was procedure safety, which was assessed by clinical evolution and mortality, as well as implant location in the layers of EGJ and PMMA-related tissue reaction. Neither death nor complications were observed after 6 months. There was no sign of extramural implantation at necropsy. Careful histological analysis showed that the submucosa was the main layer of implantation, followed by muscularis propria, mucosa, and subserosa. However, the finding of PMMA microspheres in the subserosa still points to a nonnegligible risk of esophageal perforation. Nevertheless, we believe that the current technique was improved in comparison with our previous experience, in which extramural implantation of PMMA was followed by animal death [20]. We attribute this improvement to the use of a thinner needle combined with a procedure learning curve. Experimental studies with Enteryx® have described implantation of polymer in the mediastinum, most likely due to esophageal transfixation [15, 27]. Early widespread use of Enteryx® in patients with GERD resulted in esophageal perforations and deaths [12, 14].

PMMA-related tissue reaction was described as innate chronic inflammation combined with fibrous deposits surrounding polymer microspheres in a capsule fashion presentation. Noteworthy, no foreign-body granuloma was seen 6 months after PMMA implantation. These findings are in agreement with studies that assessed biocompatibility of PMMA in dermal tissue [26, 28]. Intradermal injection of PMMA has been performed in more than 200,000 humans worldwide, with a low rate of local complications [17].

An unexpected finding was the presence of PMMA microspheres in periesophageal lymphatic tissue in one animal. Migration of PMMA to adjacent organs could be explained by accidental puncture of a lymph vessel during implantation. However, detailed microscopic analysis of PMMA deposits in the esophagus suggested the presence of microspheres with different diameters. It is known that PMMA microspheres smaller than 15 μm can suffer phagocytosis followed by transportation in macrophages [28, 29]. We performed electron microscopy and granulometric analysis of the employed PMMA material, which confirmed the presence of microspheres with heterogeneous dimensions, including microspheres below 15 μm in diameter. This finding supports the hypothesis that phagocytosis of smaller microspheres may have occurred, followed by transportation of PMMA to lymphatic tissue. The utilization of a PMMA solution containing microspheres with proper size might avoid polymer migration.

The third end point of our study was efficacy in augmenting the antireflux barrier. Study outcomes were GYV and GYP measurements, both considered physiological surrogates for LES competency. Using a validated animal model, we observed a significant increase in GYV and a borderline increase in GYP 6 months after PMMA implantation, indicating augmentation of the antireflux barrier. In agreement with other studies [15, 22, 30], both basal LES pressure and LES length were not modified following implantation of the polymer. These findings support the concept that antireflux barrier augmentation following implantation of filler substances is not mediated through modifications on LES pressure and/or sphincter length. A different mechanism must play a role and the most likely explanation for PMMA implants efficacy is a modification in the EGJ compliance or dimensions. Both fibrosis and inflammatory changes surrounding PMMA microspheres may have contributed to decrease the EGJ distensibility. Furthermore, the bulking effect of the submucosal nodules of PMMA in the EGJ lumen may have contributed to a mechanistic effect as proposed for the Gatekeeper® system [31, 32].

In conclusion, we assessed implant durability, safety, and efficacy following endoscopic augmentation of the esophagogastric junction with PMMA. We found that PMMA implantation was durable, located mainly at the submucosa, and augmented the antireflux barrier 6 months after the procedure. Neither death nor serious clinical complications including esophageal perforation were observed in this small study. However, the finding of PMMA in the subserosa points to the need for technical refinements before utilization in clinical trials.

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