Endoscopic implantation of Plexiglas (PMMA) microspheres for the treatment of GERD

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Background: A gelatinous implant containing polymethylmethacrylate (PMMA) beads is successfully used to augment the diminished thickness of the chorium in patients with skin defects and wrinkles. The aim of the present study was to determine whether submucosal injection of PMMA microspheres into the lower esophageal folds decreases the severity of symptoms and acid reflux in patients with GERD.

Methods: Endoscopic submucosal implantation of PMMA was carried out in 10 patients with GERD who were either refractory to or dependent on proton pump inhibitors. Symptom severity score, 24-hour pH monitoring, upper GI endoscopy, and EUS were performed to evaluate the efficacy of implantation.

Results: A significant decrease in the symptom severity score and mean total time with esophageal pH less than 4 was noted after the implantation of PMMA (p < 0.05). Seven of 10 patients were taking no medication after PMMA implantation. There were no serious procedure-related complications.

Conclusions: Endoscopic implantation of PMMA into the submucosa of the lower esophageal folds may be a new method for treating GERD. Further studies are required to determine the long-term efficacy of the procedure. (Gastrointest Endosc 2001;53:423-6.)
PATIENTS AND METHODS

The study was approved by the Scientific and Ethical Committee of our center, and all patients gave written informed consent. Ten patients (7 women, 3 men, mean age 52.6 years, range 23-73 years) who were proton pump inhibitor (PPI)-dependent or with refractory GERD were included in the study. All patients had been treated continuously with omeprazole for 6 months: 40 mg daily for the first 2 months and 20 mg daily for the following 4 months. Nine patients had symptomatic (heartburn, acid regurgitation) relapses 1 week after discontinuation of the treatment; 1 patient had symptom recurrence at least twice a month despite PPI treatment. All 10 patients had an abnormal 24-hour esophageal pH program with omeprazole. Exclusion criteria were pregnancy or lactation, a hiatal hernia of greater than 3 cm in length, known immune deficiency or current use of corticosteroids, known connective tissue disease, positive PMMA skin test, peptic stricture, and Barrett’s esophagus.

The primary outcome variable assessed was the severity of GERD symptoms before and after PMMA injection. The assessment method used was a GERD symptom core in which heartburn, regurgitation, pain, and dysphagia were scored from 1 to 5 (Likert scale) with 1 indicating absence of symptoms and 5 intolerable symptoms. The assessment was carried out 1 week before discontinuation of the treatment; 1 patient had symptom recurrence at least twice a month despite PPI treatment. All 10 patients had an abnormal 24-hour esophageal pH program with omeprazole. Exclusion criteria were pregnancy or lactation, a hiatal hernia of greater than 3 cm in length, known immune deficiency or current use of corticosteroids, known connective tissue disease, positive PMMA skin test, peptic stricture, and Barrett’s esophagus.

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1. 24-hour esophageal pH monitoring (Digitrapper MK III, Synectics-Medical, Stockholm, Sweden). The pH probe was positioned 5 cm proximal to the manometrically determined lower esophageal sphincter. A complete manometric study was not performed. The percentage of total time the pH was less than 4 and DeMeester score were used for evaluation. A pH of less than 4 for less than 4% of the total time and DeMeester score of less than 17.5 were considered normal.
2. Upper GI endoscopy.
3. EUS of the distal esophagus.

A test injection before implantation of PMMA is not required for plastic surgery. However, skin tests and antibody titers to gelatin (enzyme-linked immunosorbent assay) were performed in all patients because of the much larger volume of implanted PMMA. Antibiotics were not administered prophylactically.

With the patient under intravenous sedation and pulse oxymetry monitoring, endoscopy was performed with a flexible sigmoidoscope (CF-140, Olympus America Corp., Melville, N.Y.) to visualize the squamocolumnar junction (z-line). The sterilized PMMA implant material was prepared in 3-mL syringes and injected into the submucosa 1 to 2 cm proximal to the z-line through a shortened 90-cm catheter with a 4 mm long, 21 gauge retractable needle (GI Asp.N, Wilson-Cook, Winston-Salem, N.C.) (Fig. 1). Five to 6 injections in different sites were performed until the induced thickening of the esophageal folds resulted in their close approximation (Fig. 2). This was the end point of each implantation session. A second or even a third session, with the same treatment end point, was performed 2 weeks later if reflux symptoms (heartburn, regurgitation) were not controlled.

Statistical analysis included paired Wilcoxon’s signed ranks test analyzed on SPSS 0.8 statistical software (Microsoft, Inc., Chicago, Ill.). Statistical significance for p was fixed at equal to or less than 0.05 as standard.

RESULTS

Endoscopic injection of the PMMA implant was carried out successfully in all 10 patients. A mean volume of 31.77 mL (range 24-39 mL) was injected. Each ses-
A submucosal implantation of PMMA brought about a decrease in the GERD symptom score in 9 of 10 patients. The mean symptom severity score in the 10 patients declined significantly from 12.2 (range 9-16) before injection to 6.2 (range 5-8) after the implantation ($p=0.005$). There was also a fall in the mean total time with pH less than 4 as recorded by 24-hour pH monitoring. The mean preinjection value in the 10 patients was 24.51 (range 9.8-32) and the mean post-treatment value was 7.2 (range 5-10.4). This difference was significant ($p=0.007$). The mean DeMeester scores before and after the implantation were 74.6 (range 27-94.5) and 25.24 (range 16.5-32) (Table 1, Fig. 3). This difference was significant ($p=0.005$).

Complete discontinuation of medical treatment occurred in 7 of 10 patients. Three patients continued taking anti-reflux medication during the postimplantation period: 2 were using H2 receptor antagonists on demand and 1 continued regular use of a PPI.

By using the Los Angeles classification system, at initial endoscopy 5 patients had esophagitis (1 grade A, 3 grade B, 1 grade C). During follow-up (mean 7.2 months, range 5-11 months) healing of esophagitis was noted in 3 of 5 patients (2 grade B, 1 grade C). Improvement from grade B to A was noted in 1 patient, whereas the endoscopic findings (grade A) remained unchanged in 1 patient. Neither granulomas nor ulceration was detected in any patient. There were no serious complications.

EUS was performed immediately after injection to verify the submucosal position of the implant. At follow-up examinations, EUS demonstrated the continuing presence of PMMA particles at all sites in all 10 patients (Fig. 4).

After treatment, 9 of 10 patients were able to resume eating during the evening of the day on which the implantation was performed and to resume their normal activities on the next day. Chest pain requiring treatment for 2 days with an orally administered analgesic agent was experienced by 2 patients. Minor self-limited bleeding occurred in 1 patient. Minor transient dysphagia and gas-bloat syndrome of 3 weeks’ duration was recorded in 1 patient after treatment with a total volume of 39 mL of implant. Serum antibodies to bovine gelatin did not develop. Clinically recognizable early or late allergic reactions were not observed in any case.

**DISCUSSION**

Submucosal injections of the biologically and chemically inert, long-lasting PMMA implant in this small study proved to be a safe procedure. Implantation of PMMA was found to be moderately difficult because of the high viscosity of the compound. To overcome this, the shorter length flexible sigmoidoscope was chosen, which was capable of reaching the z-line while accommodating a large lumen needle-catheter. The procedure of submucosal injection with a 21-gauge needle and implantation of PMMA was well tolerated.
Over 4 to 6 months follow-up, implantation of PMMA resulted in significant improvement of GERD-related symptoms in 9 of 10 patients, as evidenced by a significant decrease in the mean symptom severity scale score. Although the percentage of total time of esophageal pH values less than 4 decreased significantly, this measurement did not normalize post-treatment in any patient. Similarly, DeMeester score values decreased significantly during the postimplantation period, but normalized in only 1 of 10 patients. Therefore, the discontinuation of PPI treatment in 7 of 10 patients cannot be easily explained. A possible explanation could be that reflux episodes, although not completely eliminated, were reduced significantly so that symptoms did not occur. Alternatively, there may be a placebo effect for the implantation procedure.

Only minor and self-limited complications occurred in 4 of 10 patients. Transient dysphagia and gas-bloat syndrome recorded in one case were thought to be due to excessive treatment with implantation of a total volume of 39 mL during a short period. This complication may have been prevented if incremental treatment with less than 20 mL of implant was used in each session. PMMA injection was not associated with local or systemic complications. There was absence of antibody response in the serum of all patients after treatment.

With regard to the long-term results of implantation, the nonabsorbable, nonmigrating particles of PMMA may decrease symptoms of GERD. Although the intermediate-term results of PMMA implantation look promising at 4 to 6 months follow-up, longer follow-up studies are needed before a sustained benefit can be established.

REFERENCES