Progress in Gastroenterology

Endoscopic treatment of Gastroesophageal Reflux disease (GERD)

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INTRODUCTION

The lower esophageal sphincter (LES) and its surrounding structures normaly act as a reflux barrier between the esophagus and the stomach preventing the abnormal exposure of the gullet to the gastric contents. Gastroesophageal reflux disease (GERD) is common and is apparently being detected at an ever-increasing rate in the western world. Symptoms of GERD affect 19% of adults in the US on a weekly basis[1] and have a significant negative impact on patient's QoL.[2] To date, transient lower esophageal sphincter relaxations (TLESRs) triggered by gastric distension and mediated by a vagovagal reflex are considered the most important mechanism for reflux in up to 80% of the cases of normal and GERD patients.[3] In the most severe cases (<20%) the LES pressure is low or absent[4] and demonstrates little resistance to reflux. Reflux and its concequences may be further aggravated in the presence of a large hiatal hernia[5] that is associated with increased frequency of TLESRs and impaired esophageal clearance.

Current medical therapy of GERD, except for the requirement for often inconvenient life-style modifications, begins with proton pump inhibitors (PPIs). The inhibition of gastric acid secretion with PPIs, relieve heartburn in 80% of patients and heal esophagitis in 90%.[6] Reflux symptoms and/or esophagitis recur in 75-90% of patients six months of discontinuing PPIs therapy. A subgroup of GERD patients require life-long medical treatment with consequential difficulties in treatment compliance, particularly regarding, younger sufferers. Surgical management is an option for refractory or chronic GERD and for those unwilling to continue a life-long PPI therapy. Laparoscopic Nissen fundoplication with wrapping of the gastric fundus behind and around the LES, is the most commonly employed anti-reflux procedure. Fundoplication entails general anesthesia, a 2-5 hour operation time, 2-3 days of hospitalization and 3 weeks to return to normal activities. The laparoscopic operation effectively reduces esophageal acid exposure and obviates the need for anti-secretary drugs in 90% of patients.[7] Even if low morbidity and no mortality has been reported[8] the bulk of the evidence[9-11,13] suggests a perioperative complication rate of 20%.

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ENDOSCOPIC TREATMENT OF GERD

The appeal for an effective endoscopic modality that could decrease the esophageal acid exposure, relieve GERD symptoms and improve the QoL obviating the dependency on long time maintenance PPI treatment is obvious. The predominant presence of GERD in clinical practice, the need for prolonged acid suppressive therapy together with the possible risks of surgery, can easily explain the continuing pursuit of endoscopic treatment of GERD.

In ths connection a variety of endoscopic techniques attempting to prevent gastric reflux have been reported in the past. Collagen[14] and sodium morrhuate[15] have been injected in the lower esophagus or gastric cardia of animals and humans in order to create an anti-reflux valve and sutures have been placed to create a gastric fold plication barrier to reflux. Bulking of the lower esophageal rosette by submucosal injection of collagen in humans[16] has been associated with short-term relief of GERD

symptoms, but a sustained benefit was not achieved due to absorption of collagen. Polytetrafluoroethylene particles[17] have also been injected in the submucosa of the lower esophagus to increase the LES pressure in patients with GERD. The promising early results failed in the long-term, possibly due to phagocytosis and migration of the injected particles.

Recently three different means of endoscopy have been claimed to be effective in the treatment of GERD.

Endoscopic Gastroplasty

The development and application of an endoscopic sewing machine[18] and knot tying methods made it feasible to perform a variety of antireflux operations on animals. Among them, the less technically demanding, has been choosen to be performed on humans with GERD. Gastroplasty is accomplished by suturing together the anterior and posterior wall of the stomach below the Squamo-Columnar Junction (SCJ) to create an internal plication along the lesser curve. It is postulated that plication alone, through buffering the muscularis of LES could be as effective in preventing reflux, as is its counterpart in laparotomy. The procedure is performed by using a system including a sewing machine, a knot pusher and a suture cutter. The machine, 9mm in diam and 32mm in length, is mounted on any flexible endoscope with a biopsy channel of 2.8mm or greater diameter. The essential components of the machine include a suction capsule and a hollow needle. A first gastric fold is entrapped into the vacuum champer of the capsule. The hollow needle is pushed through the fold and a tilt stich comprising a metal tag with a long attached length of nylon thread is pushed through the hollow needle to be caught in the reception champer of the sewing machine. The suction is released allowing the first fold of tissue through which the stich has been placed, to fall out of the machine. The sewing machine is withdrawn retaining the thread and thus pulling the thread through the tissue. The thread and tilt stich are released from the sewing machine outside the mouth so that the thread passes from the mouth, through the gastric tissue and back up to the mouth again. The nylon thread and metal tag are reloaded onto the machine, and the suturing system is reinserted to stich a second gastric fold adjacent to the first one. The suturing system is withdrawn so that both suture ends are out of the mouth. A knot pusher mounted on the scope serves to tie the stich and secure the plication. The suture strands are divided with a cutter introduced through the working channel of the endoscope. In this way the fist plication is created 2-3 cm below the SCJ. Two to 3 plications are placed on the lesser curve approximately 1cm apart, and 1cm distal to the SCJ.

In a recent multicenter trial of Endoscopic Gastroplasty[19] in 64 patients with early-stage uncomplicated GERD and no hiatal hernia, the procedure was accoplished with safety in a mean time of 68 minutes. At a mean follow-up of 6 months after the procedure a statistically significant improvement in the mean heartburn severity score and in regurgitation was observed in 62% of the cases. A significant decrease in the percentage of total time with PH<4 was recorded post treatment but statistically significant differences in the pre and post therapy esophageal manometry, and grade of esophagitis reported in a previous study were not confirmed. The quality of life questionaire results showed significant improvement and furthermore the requirements for symptom control medication were decreased post-treatment in 62% of patients.

Adverse effects such as mucosal tears, gastric bleeding from stitch placement, suture perforation and hypoxia during the procedure requiring general anesthesia were noted in 13% of patient. In this study the mortality was zero.

Radiofrequency Energy (Rfe - Stretta procedure)

Thermocouple controlled Rfe causes well-circumscribed thermal lesions which alter the anatomy and function of the targeted tissue.[20,21] In the case of GERD the therapeutic effect of heating of OGJunction is thought to result from A) contraction of collagen fibers that are found in abundance within the submucosa and between the smooth muscle sublayers of OGJ. A 30% volume contraction occurs during RFe delivery when the lesion temperature reaches 65° C. This is followed by tightening of OGJ and reduction in its compliance. B) heat related disruption of vagal nerve afferent pathways within the myenteric plexus of cardia which are considered responsible for TLESRs. In this connection a 50% reduction in the frequency of TLESRs has been reported in dogs. The destroyed areas of smooths muscle tissue are thought to be regenerated by viable mononucleated smooth muscle cells that undergo mitoses and provide for the replacement of damaged cells. A four channel generator is used to deliver thermocouple-controlled RFe (465 KHZ, 2-5 Watts) to the OGJ via 4 independently controlled channels of a 30 Fr special flexible catheter. The RFe catheter is comprised of a bougie tip, a ballon four-basket arm assembly and 4 electrode delivery sheaths. After identifying the SQJ endoscopically the RFe catheter is passed transorally and positioned con-

sequtively in six levels from 1cm above to 2cm below the SCJ. When the balloon is inflated in each level, 4 nickel-titanium stilleto-like needle electrodes (22 gauge, 5.5cm) are deployed into the muscle of OGJ. Proper deployment is followed by immediate· decrease in tissue impedance to <500 Ohms. Thermocouples incorporated within each needle tip and base, allow automatic modulation of power output to maintain the desired target tissue temperatures in the muscle (85°C) and mucosa (<40°C) during RFe delivery that lasts 1:30 min in each level. The mucosal temperature is kept low by delivering chilled plain water through an irrigation pump integrated into the catheter while suctioning, via a separate channel, helps to avoid fluid accumulation. The built-in safety features automatically discontinue RFe delivery in the event that target temperature exceeds 100°C, impedance exceeds 1000 Ω or mucosal temperature exceeds 50°C. Taking into account the number of electrodes and the rotation of the catheter in each level of treatment, a total number of 56 well-circumscribed thermal lesions are created. Successful delivery of RFe under consious sedation has been recently reported[22] as a well tolerated, <86 min, out-patient procedure in 47 patients with GERD and absent or less than 2cm hiatal hernia. Manometry and 24h pH studies, demonstrating adequate esophageal peristalsis, LESP of >4% were 5mmHg, and 24h pHmetry showing total acid exposure time >4% were performed before the procedure in all patients. There was clinically and statistically significant improvement in heartburn scores, GERD scores and patient satisfaction at 6 month follow-up. 87% of patients were able to discontinue PPI therapy by 6 months after treatment and 70% no longer required any anti-secretory medications by this time. GERD symptom scores decreased steadily during the six month post-treatment from 26 to 7. The general quality-of-life scores, as measured by the Medical Outcomes Short form-36 were improved significantly, from 46 to 52 and from 41 to 52 for mental and physical SF-36 conditions respectively. Acid exposure time was significantly decreased (11.7% to 4.8%) and esophagitis was improved in 74% of cases. There was no effect in peristaltic amplitude or LES pressure. There were 3 self-limited complications: fever, odynophagia and mucosal laceration.

ENDOSCOPIC INJECTION OF IMPLANTS

Biocompatible materials acting as tissue bulking factors are injected into the lower esophagus to reinforce the defective Lower Esophageal sphincter (LES) and prevent GERD. Recently Polymethylmethacrylate (PMMA) microspheres of 100μ suspended (1:3) in a 3.5% bovine spongious encephalitis-free gelatin solution were injected into ten GERD patients with absent or <2cm hiatal hernial.[24] The choice of PMMA was based on its well-documented biocomplatibility, proven after its use in plastic surgery. Due to the size of michrospheres that hinders phagocytosis and migration aay from the implantation site and the almost completely smooth surface of the particles that evokes negligible foreign body reaction, PMMA incorporates two important properties of an ideal implant, durability and inertness. When PMMA is injected within the susmucosa of the lower esophageal folds, the microspheres are encapsulated in connective tissue wich replaces 50% of the volume of gelatin solution during a 4 month period. It is estimated that two thirds of the total injection volume remain at the implantation site, inducing bulking of the folds and coaptation of esophageal lumen. The sterilized solution of PMMA, prepared in 3mL syringes, is injected into the submucosa 1cm proximal to the SCJunction A short, wide-channel flexible sigmoidoscope (C-F-140 Olympus America Corp. Melville, N.Y.) and a shortened 90cm long needle catheter (GI Asp. N, Wilson Cook, Winston Salem, NC) were used to inject this viscous preparation. A mean volume of 31.7mL (range 24-39) was injected into each patient once or twice weekly. The implantation of PMMA was carried out under IV sedation as an out patient procedure and was accomplished in less than 30min in all patients. With a mean follow-up period of 7.2 months, implantation of PMMA resulted in significant improvement of GERD-related symptoms in 9 of 10 patients.

The mean symptom severity score declined significantly from 12.2 before to 6.2 post treatment. A significant decrease in both the mean total time with pH<4, from 24.5 to 7.2 and the mean De Meester score from 74.6 to 25.2 post-therapy was recorded. Complete discontinuation of PPI treatment was achieved in 7 out of 10 patients post-treatment. Except for minor self-limited complications such as chest pain, minor bleeding and transient dysphagia, serious adverse-effects were not observed. Endoscopic ultrasound performed immediately after the injection and repeated at the follow-up examination, demonstrated the continuing presence of PMMA at the implantation site. In this connection, it has been claimed that a sustained benefit of PMMA implantation is possible in the long-term due to the non-absorbable non-migrating nature of the particles.

Another implant, a formulation of Ethylene Vinyl Alcohol Co-polymer based in the solvent dimethyl sulfoxide (Enteryx) has also recently been used to augment

the Lower Esophageal Sphincter in GERD patients.[25] The biocompatibility of Enteryx has been tested in the past since the implant has already been used for the embolization treatment of Brain Arteriovenous Malformations. It is a non-biodegradable non-antigenic subsance that is mixed with radiopaque Tantalum powder to make it visible on plane x-ray. In its liquid form Enteryx, a low viscosity solution, is injected through a needle-catheter within the muscle layer of the lower esophagus under endoscopic and x-ray control. Upon injection, the solution spreads circularly into the esophageal wall. Because of the rapid diffusion of the solvent, in-situ precipitation of the polymer takes place,giving rise to a spongy, non-shrinking non-migrating implant ring within the muscle of the LESphincter. By 3 months after injection, mature well-delinated fibrous capsules surround the implant and separate it from the esophageal muscle. It is postulated that the ensuing "thickening" of the LES augments its action and prevents reflux. Injection of Enteryx has been successfully accomplished in 15 patients with GERD and hiatal hernia <3cm. With a follow-up period from 1 to 13.5 months, 90% of the evaluated patients demonstrated symptomatic improvement and 80% eliminated daily PPI usage. The LES pressure and total exposure time in pH<4 were improved after Enteryx injection and except for moderate retrosternal discomfort no serious adverse events were recorded.

CONCLUSIONS

The results of the recent studies of endoscopic treatment of GERD are promising in the short-term but serious issues are raised regarding protocol designs, application of technologies and long-term out-comes.

A randomized control group is missing in all studies, and the variance in GERD severity, degree of esophagitis and response to medical therapy before embarking on endoscopic treatment, is obvious among the three reports. The presence of a hiatal hernia larger than 3cm excludes the majority of patients with severe GERD from being candidates for any of the three endoscopic means. Furthermore, the methods of precise definition of the length of hernia, a confusing issue in gastrointestinal endoscopy, is not clarified. Gastroplication, the most complex procedure of all, demands the highest level of skill, lasts one hour and a repeat session may be needed. Its performance requires the positioning of an oropharyngeal esophageal tube to fascilitate the multiple scope insertions required for the achievement of two knots. Some steps of the procedure are essentially blind and a variety of procedure-associated adverse effects may occur, complicating performance. Rfe delivery, though lasting as long as Gastroplicaiton, is less demanding in terms of required depth of sedation and skills. These advantages fade when taking into consideration that direct vision control of each of the six levels of Rfe delivery is impossible, and thermal lesions more than 2cm above the SCJ are considered a risk factor for the development of serious complications. Injection of Enteryx in the muscle layer of OGJ requires continous x-ray control since the depth of implantation can not be otherwise defined. Submucosal injection of PMMA, the easiest and demanding of all endoscopic modalities, carries the inherent disadvantage of the substance used as a PMMA carrier. Collagen, although a BSE–free solution, should be changed for a different carrier before PMMA implantation becomes widely accepted in humans.

Regarding the long term results of endoscopic means of GERD treatment, it is beyond argument that nerve pathways may regenerate, stiches may fall apart and implants may migrate away from LES. It is obvious that multicentral longer-term trials should be conducted before any endoscopic modality can find a place in the armamentum of GERD treatment.

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