Endoscopic Treatment Options for Gastro-oesophageal Reflux Disease

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The incidence of gastro-oesophageal reflux disease (GORD) is on increasing trend in last decade. The true incidence of GORD may be underestimated because of the use of over-the-counter medications, such as antacids and proton pump inhibitors (PPIs). GORD not only adversely affects the patient's quality of life, but it is also a potential risk factor for the development of Barrett's oesophagus and oesophageal adenocarcinoma.[1]

PPIs have been the mainstay of medical management of GORD. However, about 20% to 30% of patients with erosive reflux disease and 40% of patients with non-erosive reflux disease do not respond to PPIs. Moreover, no significant improvement is observed in symptoms with doubling the dose of PPIs.[2] The potential adverse effects of using PPIs for long term are also a matter of concern. These adverse effects include Clostridium difficile infection, bone fractures, hypomagnesaemia, and higher incidence of chronic kidney disease in susceptible populations.[3-5]

Anti-reflux surgery (ARS) has been the mainstay of treatment for patients not responsive to PPIs and documented reflux on pH-impedance analysis. However, a quarter of patients restart PPIs on long-term follow-up. Moreover, a requirement of re-intervention exists in about 15% and 30% patients after laparoscopic or conventional fundoplication, respectively.[6] Other adverse events known to occur with ARS include dysphagia, gas bloating, and inability to belch.[7] Patients with refractory GORD may not agree to ARS due to its invasive nature and possible adverse events as mentioned above. In a randomised controlled trial (RCT) comparing ARS with PPIs, the remission rates were similar in both arms at 5-year follow-up. However, adverse events, including gas bloating, dysphagia, and flatulence, were significantly higher in the ARS arm.[8]

Laparoscopic fundoplication was the only surgical option for GORD until recently. The introduction of magnetic sphincter augmentation (MSA) has marked the beginning of a new era in the surgical management of these patients. MSA device consists of a small flexible band of interlinked titanium beads with magnetic cores. It is placed laparoscopically around the lower oesophageal sphincter (LES) without altering hiatal or gastric anatomy. The beads separate during swallowing as well as during belching or vomiting.[9] Therefore, adverse events, such as dysphagia, inability to belch, and vomiting, are less frequent as compared to the traditional ARS. A published literature suggests that

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MSA is equally effective with less procedure duration as compared to ARS.[10] The most common adverse event with MSA procedure is dysphagia for which the device may have to be removed in some patients. Recently, a case of endoluminal perforation has been reported with MSA resulting in severe dysphagia.[11]

With the increasing prevalence of GORD, there is an unmet need for minimally invasive treatment modalities for patients who do not respond to PPIs and are unwilling for ARS. Minimally invasive endoscopic options for GORD have been in place for more than a decade now. Some of these have not stood the test of time either due to inefficacy, non-durable response, or safety issues. These include implantation and injection devices. The currently available endoscopic anti-reflux modalities (EARMs) include radiofrequency ablation (RFA), transoral incisionless fundoplication (TIF), medigus ultrasonic surgical endostapler (MUSE), Endoscopic full thickness plication (GERx) anti-reflux mucosectomy (ARMS).

RadioFrequency Ablation

The Stretta system uses application of radiofrequency energy via a needle balloon catheter system to the LES muscle and gastric cardia. Multiple applications (up to 14) are given by changing the position of the balloon catheter assembly using catheter rotation and by changing its linear position in relation to the Z line. The system typically delivers low power (5 W) energy with a thermocouple that ensures avoidance of high temperatures at muscularis (>85°C) and mucosal levels (>50°C). In addition, regular irrigation prevents any injury to the mucosa.

The mechanism of action is not completely elucidated. The proposed mechanisms include hypertrophy of the muscularis propria and reduced transient LES relaxations after RFA.[12,13] Fibrosis at the gastro-oesophageal junction (GOJ) was considered as one of the modes of action. However, in a recent study, reduced GOJ compliance was found after RFA, which normalised on administration of sildenafil (smooth muscle relaxant), suggesting against the development of GOJ fibrosis after RFA.[14] The efficacy and durability of response with RFA in patients with GORD are evident by multiple RCTs and a systemic review.[15-20]

Transoral Incisionless Fundoplication

The TIF procedure is a minimally invasive treatment for GORD and follows the principles of ARS, i.e., by reducing a hiatal hernia (≤2 cm) and creating a valve 2 to 4 cm in length and greater than 270° circumferential wrap. It is performed in the outpatient setting under general anaesthesia. The TIF procedure has undergone several modifications since its introduction about a decade ago. In this procedure, a fundoplication device (EsophyX) is used with a flexible endoscope and gently introduced into the stomach under visualisation. The endoscope along with the device is retroflexed, and a helical retractor is engaged into the tissue slightly distal to the Z line. The fundus of the stomach is folded up and around the distal oesophagus utilising the tissue mold and chassis of the device. Subsequently, an

integrated suction apparatus grasps the distal oesophagus and positions it below the diaphragm. H-shaped fasteners, made of polypropylene, are then delivered through apposed layers of oesophageal and fundus tissue to anchor the repair. This process is repeated to create a full thickness, partial circumference, and gastro-oesophageal fundoplication. Approximately 20 fasteners are implanted during the procedure to create fusion of the oesophageal and fundus tissues and form the valve. The advantages of TIF are that it is less invasive than ARS, is performed in outpatient settings, has fewer adverse effects, and does not preclude the chances of revision ARS, if required. Serious adverse events reported with TIF are rare and include perforation, pneumothorax, and bleeding.[21]

Medigus Ultrasonic Surgical Endostapler (MUSE)

The MUSE is an endoscopic stapling device for transoral partial fundoplication. The complete device consists of a flexible endoscope, an endostapler, a video camera, and an ultrasound transducer. After inserting the device, retroflexion is performed in the stomach, and the device is withdrawn until the chosen stapling level (usually 3 cm above the Z line). Subsequently, the stapler is fired under the guidance of ultrasonic gap finder. The process is repeated to form a flap akin to laparoscopic fundoplication.[22]

Endoscopic Full Thickness Plication (GERx)

The procedure of EFTP itself has undergone several modifications since its initial introduction for GORD. A single suture was initially placed below GOJ. However, the results were not impressive as a single suture could not create an effective anti-reflux barrier. Subsequently, the technique was modified, and multiple plication implants were placed to achieve a robust antireflux valve. In a prospective study including 36 patients, symptoms improved in 92% and 89% of patients were off PPIs at 1-year follow-up after EFTP with one or more plication implants. Post-procedure adverse events were minor and included pain in the abdomen, shoulder, and chest. There were no long-term adverse events.[23]

Anti Reflux Mucosectomy (ARMS)

The ARMS procedure is based on the principle that after mucosal resection, the mucosal healing results in scar formation. This in turn results in shrinkage and remodeling of gastric cardia flap valve; thereby, reducing reflux events. Although the first case was performed more than a decade ago, the results of the first series were published recently. The advantages of ARMS include no requirement of any propriety devices and no endoprostheses are left in situ. However, no randomised studies have been conducted, and durability of response is unknown. In addition, the amount of mucosa to be resected for optimal results is not known and needs further evaluation. As with other EARMs, patients with large hiatal hernia are not suitable candidates for ARMS procedure.[24]

Conclusion

PPIs remain the cornerstone of medical management of GORD, and EARMs are not meant to replace PPIs altogether. They

may bridge the unmet gap between PPIs and ARS. However, more studies with long-term follow-up and randomised comparisons are required to establish the role of EARMs in the management of GORD. Studies assessing the predictive factors for response or non-response to EARMs will help in minimising failures and maximising efficacy.

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Progress in Nonmetastatic Prostate Cancer

Since 2010, the Food and Drug Administration (FDA) has approved five new drugs for the treatment of metastatic, castration-resistant prostate cancer on the basis of a primary end point of overall survival. Progress in the treatment of nonmetastatic prostate cancer has been slower.

However, an Oncology Drugs Advisory Committee of the FDA voted not to approve denosumab for the prevention of metastasis because the prolongation in median bone metastasis-free survival was small, no benefits were noted with regard to progression-free or overall survival, and denosumab was associated with osteonecrosis of the jaw. Although unsuccessful, these trials served to better characterize the natural history of nonmetstatic, castration-resistant prostate cancer and to inform the design of subsequent phase 3 clinical trials.

The FDA granted priority review for a supplemental new drug application for enzalutamide in nonmetastatic, castration-resistant prostate cancer.

The distinction between nonmetastatic and metastatic depends on the type of imaging used.

Newer imaging tests, including positron-emission tomography with choline or fluciclovine or the targeting of prostate-specific membrane antigen, are substantially more sensitive for metastasis detection.

The FDA approval of apalutamide for nonmetastatic prostate cancer and the anticipated approval of enzalutamide in the same context represent important steps forward for men with rising PSA levels during androgen-deprivation therapy. The benefit-risk evaluation suggests that treatment with either drug is better than waiting until the appearance of metastases.

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