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EDITORIAL

Comprehensive management of full-thickness luminal defects: The next frontier of gastrointestinal endoscopy

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Abstract

Full thickness gastrointestinal defects such as perforations, leaks, and fistulae are a relatively common result of many of the endoscopic and surgical procedures performed in modern health care. As the number of these procedures increases, so too will the number of resultant defects. Historically, these were all treated by open surgical means with the associated morbidity and mortality. With the recent advent of advanced endoscopic techniques, these defects can be treated definitively while avoiding an open surgical procedure. Here we explore the various techniques and tools that are currently available for the treatment of gastrointestinal defects including through the scope clips, endoscopic suturing devices, over the scope clips, sealants, endoluminal stents, endoscopic suction devices, and fistula plugs. As fistulae represent the most recalcitrant of defects, we focus this editorial on a multimodal approach of treatment. This includes optimization of nutrition, treatment of infection, ablation of tracts, removal of foreign bodies, and treatment of distal obstructions. We believe that by addressing all of these factors at the time of attempted closure, the patient is optimized and has the best chance at long-term closure. However, even with all of these factors addressed, failure does occur and in those cases, endoscopic therapies may still play a role in that they allow the patient to avoid a definitive surgical therapy for a time while nutrition is optimized, and infections are addressed.

Key words: Perforation; Fistula; Anastomotic leak; Over the scope clips; Overstitch; Stent; Endoscopic

Core tip: Endoscopic methods are replacing surgical options as the first line therapy for a wide array of gastrointestinal tract defects. Here we will review the available endoscopic modalities, their appropriate applications and their respective success rates. The fusion of standard surgical principles with flexible, intra-luminal modalities is likely to be the key to the successful endoscopic management of these challenging clinical problems.

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INTRODUCTION

Whether in the form acute perforations, acute or sub-acute anastomotic leaks or chronic fistulae, full-thickness gastrointestinal (GI) tract defects remain a challenging and highly morbid healthcare problem. According to the Center for Disease Control (CDC) over 6 million abdominal procedures (including upper and lower endoscopies) were performed in the United States in 2010[1]. As the number of abdominal procedures performed annually in the United States increases, the number of full thickness GI defects that occur as a result will also increase. Historically, full-thickness luminal defects mandated surgical exploration (with its associated high rates of morbidity and mortality)[2,3]. Recent advancements in the comprehensive endoscopic management of GI defects have yielded encouraging results.

In centers of expertise, endoscopic methods have begun to replace surgical options as the first line therapy for a wide array of GI tract defects[4-6]. Here we will review the available endoscopic modalities, their appropriate applications and their respective success rates. The fusion of standard surgical principles with flexible, intra-luminal modalities is likely to be the key to the successful endoscopic management of these challenging clinical problems. Much like polyp resection, gastrostomy tube insertion and GI bleeding, we believe that surgery for full-thickness luminal defects will shortly be relegated only to patients who fail endoscopic therapy in the majority of cases[7].

SCOPE OF THE PROBLEM

GI tract defects include perforations, anastomotic leaks and fistulae and occur with numerous disease states as well as following a wide array of endoscopic, surgical and radiologic procedures. They vary greatly in their presentation and in their associated morbidity and mortality; an acute esophageal perforation from an endoscope and a persistent gastro-cutaneous fistula following gastrostomy tube removal are clearly different clinical entities. Yet until recently, these processes were thought of similar when endoscopic modalities were considered. As the volume of cases within which endoscopic closure could be attempted increases, it becomes increasingly clear that a spectrum of endoscopic therapies is necessary.

Technical limitations are not the only hurdle to overcome in the complete endoscopic management of these conditions. Many surgeons are unaware of or unwilling to permit (and/or not able to perform themselves) the application of novel therapies to patients who have perforations, leaks or fistulae. Many endoscopists with the skill and expertise to manage full thickness perforations do not have access to the patients presenting with these problems (unless they are the result of an iatrogenic endoscopic injury). There is therefore a disconnect between those individuals with the knowledge and skill to manage full thickness perforations and those who are evaluating and caring for the patients. The volume of this patient population is not inconsequential. The spectrum of diseases to which endoscopic methods could be applied includes:

Esophageal

The incidence of acute perforations during esophagogastroduodenoscopy (EGD) is approximately 0.03%[8,9]. One series of 217, 507 EGD procedures had a perforation rate of 0.033% with the esophagus being injured most commonly (51%)[9]. That same series showed a mortality rate of 17% despite intervention. The CDC reported that the total number of upper endoscopies performed in the United States in 2010 (including both diagnostic and therapeutic) was 1.1 million[1]. With an average perforation rate of 0.03%, this would equal 330 perforations.

Anastomotic leaks after esophagectomy ranges from 8%-10%[10,11]. Furthermore, patients with esophageal leaks after surgical resection have an increased mortality rate ranging from 18%-35% compared to patients undergoing similar procedures without leaks[10,12-14].

Gastric

Postoperative gastric leaks range from 1.7%-2.5% after Roux-en-Y gastric bypass (RYGB) and 1.5%-7% after sleeve gastrectomy[5,15-17]. The mortality rate for patients who develop leak ranges from 0.6%-14%[18,19]. The American Society for Metabolic and Bariatric Surgery reported that the number of bariatric surgeries performed in the United States is steadily rising with 158000 cases in 2011 and 179000 cases in 2013.

Iatrogenic gastric perforations during upper endoscopy are rare, but it is the site of injury in 3% of all iatrogenic injuries during both diagnostic and therapeutic EGD[9].

Gastrogastric fistulae occur in patients who underwent Roux-en-Y gastric bypass and develop a fistulous connection between the gastric pouch and the native bypassed stomach that is left *in-situ*. In one series of 1292 patients who underwent Roux-en-Y gastric bypass, 1.2% developed gastrogastric fistulae[20].

Gastrocutaneous (GC) fistulae represent an abnormal connection between the stomach and the skin. GC fistulae can occur at the site of percutaneous endoscopic gastrostomy (PEG) tubes, which are subsequently removed. In the vast majority of cases, these fistulous tracts close spontaneously after the PEG tube is removed. However, in 1.1% of cases these fistulae persist[21,22]. Approximately 216000 PEG tubes

are placed each year[21].

Duodenal and small bowel

Worldwide, peptic ulcer disease affects 4 million people annually[23]. Between 2%-14% of those ulcers will perforate with mortality ranging from 10%-40%[24,25]. In the setting of acute perforation during upper endoscopy, the duodenum is the location of perforation in 32% of cases[9].

Enterocutaneous (EC) fistulae, or tracts from the small bowel to the skin, are a devastating complication of abdominal surgery with mortality rates approaching 20%[26]. Patients with EC fistulae suffer from malnutrition, dehydration, skin excoriation, infection and sepsis. Although the largest percentage of EC fistulae are in patients with Crohn's disease, other inflammatory processes, malignancy, abdominal surgery, trauma, and radiation are all well-known causes[27].

Colon

The incidence of acute colonic perforations during screening colonoscopies ranges from 0.07% to 0.082%[15,28]. These numbers are similar for both screening and therapeutic colonoscopies. In 2010 there were roughly 500000 colonoscopies performed in the United States which would mean that there were approximately 400 perforations[1].

Fistula formation from the colon to other structures or to the skin is most commonly due to diverticular disease, but may also occur in patients after surgical intervention. In one review from the Cleveland Clinic of all patients treated for diverticular disease from 1960 to 1986, 20.4% had internal fistulae with colovesicular fistulae being the most common (65%)[29]. In one series examining colocutaneous fistulae, 88 of 93 patients (94.6%) were following surgery[30].

The incidence of leaks after colorectal resection and anastomosis ranges from 2.6%-26.2%[31]. Many patients who develop an anastomotic leak and require reoperation ultimately receive a permanent stoma[32,33]. Historically, the majority of these cases were treated surgically with the associated morbidity and difficulty of caring for these patients who are often in extremis. The advent of multiple endoscopic techniques and modalities has provided a safe and effective alternative to open surgical management of these complex problems[34].

Other conditions

There are a myriad of other types and combinations of GI tract leaks that are potentially addressable endoscopically including those related to cancer, radiation therapy, urologic procedures and radiologic interventions. Radiation therapy to the abdomen for other reasons can result in abdominal pathology including perforation and fistulae in up to 5% of patients[35]. In one review of fluoroscopically placed intraperitoneal chemotherapy catheters 6 of 750 patients (0.8%) experienced bowel perforation at the time of catheter placement[36].

When one considers the total volume of patients who present with a full thickness GI tract defect, it becomes clear that endoscopic therapies have the ability to change the way we think about managing a wide array of complex disease states.

AVAILABLE ENDOSCOPIC THERAPIES IN THE ACUTE OR CHRONIC SETTING AND THEIR OUTCOMES

The majority of the published literature describing the success of endoscopic management of GI defects consists of small case series and retrospective reviews. To date, there have been no randomized trials to evaluate the efficacy of endoscopic management versus traditional surgical management. The small reported successes of endoscopic management compared to the increased morbidity and mortality associated with surgical management of these disease processes are pushing the use of endoscopic therapies forward and expanding their scope of application. Larger, randomized trials need to be performed to further establish the following endoscopic therapies as both effective and superior to open surgical techniques.

It should be emphasized that the chronicity of the defect has implications about its etiology. Csendes *et al*[37] defined defects appearing 1-4 d as acute, 5-9 d as intermediate, and 10 or more days as late. Leaks presenting less than 2 d from the procedure likely represent a technical error such as stapler misfire or tissue injury while leaks presenting 5-7 d after the procedure more often represent ischemia[38].

Acute GI perforations are those that are identified at the time of injury or immediately afterwards by the sequelae that most commonly accompany perforations including fever, tachycardia, elevated white blood cell count, abdominal pain, peritonitis, systemic inflammatory response syndrome, and sepsis[39]. Early diagnosis and treatment of the defect is essential for improved patient outcomes[37].

Chronic defects are evidenced by contained fluid collections, or established fistulae to the skin or other tubular structures. The success of endoscopic therapies in the setting of longstanding leaks and fistulae has been more limited with fistulae being particularly difficult to manage[40-43]. Our experience has been similar to what has previously been reported. Since 2012 we have endoscopically managed 14 patients with GI fistulae and 6 patients with leaks and achieved a long-term closure rate of 64% and 100% respectively[44]. We believe there are multiple factors affecting the outcome in more chronic GI defects that we will explore in more detail later.

Through the scope clips

Endoscopic clips that are passed through the endoscopic working channel and are deployed within the lumen of the GI tract were initially designed for hemostasis and endoluminal marking (Figure 1). They are also

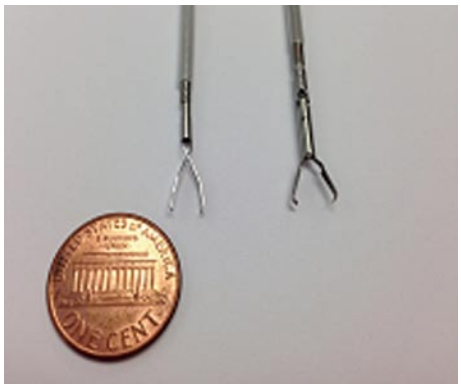

Figure 1 Examples of through the scope clips prior to deployment. Left: QuickClip 2 (Olympus Medical Systems Co., Tokyo, Japan); Right: Resolution Clip (Boston Scientific, Marlborough, MA).

referred to as through the scope clips (TTSC), hemoclips and endoclips. In the late 1990's, reports emerged describing their use as a method to close gastric and colonic perforations[45,46]. Although effective at closing smaller defects, the ability to close larger defects is quite poor due to the small size of the clips, the low grasping force that they generate and the inability to grasp deeper tissues[45]. They are more effective at closing surgically incised tissue with straight regular edges, as opposed to tissue that was bluntly perforated with irregular, striated or gaping edges. Their effectiveness at closing surgically incised mucosal edges has been well documented in the areas of submucosal dissection and POEM (Figure 2)[47-50].

TTSC have been shown to be successful in closing iatrogenic defects in the GI tract with clinical success rates ranging from 59%-83%[51,52]. It is felt that the limitation to their success is their small size, small closing force and mucosa-only tissue apposition, although in the right setting such as small defects that are not gaping, they can be quite effective.

These two factors about endoclip use have introduced bias into the initial clinical experience with acute GI tract perforations. Many acute defects are successfully closed with readily available endoscopic equipment and therefore escape the preview of surgical consultation. Larger defects are more likely to be unsuccessfully managed with TTSC clips and therefore surgeons receive a biased view of the true success rate of the most commonly applied endoscopic therapy.

Endoscopic suturing devices

The endoscopic suturing platform (Overstitch, Apollo Endosurgery, Austin, TX) is a disposable device that is attached to the end of a therapeutic double channel endoscope (Figure 3). It allows for placement of full-thickness absorbable or non-absorbable sutures. The device can be used multiple times without the need to remove the scope from the patient. The sutures can also be applied in a running or interrupted fashion (including simple and figure-of-8 sutures). Since its introduction, it has been successfully used in the closure of GI fistulae, acute perforations and at sites of endoscopic resection[53,54].

Endoscopic suturing devices have been found to provide safe and effective suturing. In one human *in-vivo* study, the Overstitch device was found to place sutures consistently at a subserosal depth in the colon without full thickness penetration or injury to adjacent structures[55]. It has been used successfully in the closure of staple-line leaks after sleeve gastrectomy, anchoring stents to help prevent migration, and closing gastrogastric fistulae[6,54,56,57]. However, the long-term success has been mixed with one study of 95 patients with gastrogastric fistulae achieving a 35% long-term closure rate[58].

Stents

The use of stents as a diversion method in full thickness GI defects is a non-FDA approved use that has been widely accepted by surgeons and endoscopists alike as a method for defect management. Stent deployment at the site of the defect helps by allowing diversion of enteric contents away from the defect. Multiple types of stent have been studied including metallic (partially or completely covered), plastic (covered, expandable), and biodegradable (Figure 4). Stent placement often permits continued enteral nutrition and can be used in cases of larger defect (> 1.5 cm)[59-61]. Although stents have been successful at treating GI defects, they are prone to migration in as much as 20%-30% of cases and require frequent observation with radiographic monitoring[61,62]. This has been addressed with techniques using TTSC and endoscopic suturing devices to anchor the stent in place. Stents also do not create a complete seal within the GI tract and, although variable in its amount, leak around stents is a near universal finding. Percutaneous placement of enteric stents have also been effective in patients with high-output EC fistulas by decreasing the output of the fistula, improving wound care, TPN requirements, and oral diet tolerance[63].

There is a large body of evidence supporting the use of stents in the treatment of GI defects. A recent meta-analysis of 7 studies of stent placement for acute leak after bariatric surgery showed a radiographically confirmed closure rate after stent removal of 87.8% (95%CI: 79.4%-94.2%)[64]. That same analysis showed a migration rate of 16.9% and only 9% of patients undergoing reoperation. Some authors advocate for clip placement to anchor the stents to help prevent migration. One study used 2 to 4 endoscopic clips to anchor the stent in 23 of 44 consecutive patients and found that stent migration occurred in 13% of patients with clips and 34% of patients without[65].

Sealants

Tissue adhesives and hemostatic agents, including fibrin sealant, have been used with varying degrees of success in the management of GI track defects. Fibrin sealant is composed of fibrinogen and thrombin, which are combined to make an acellular clot at the site of

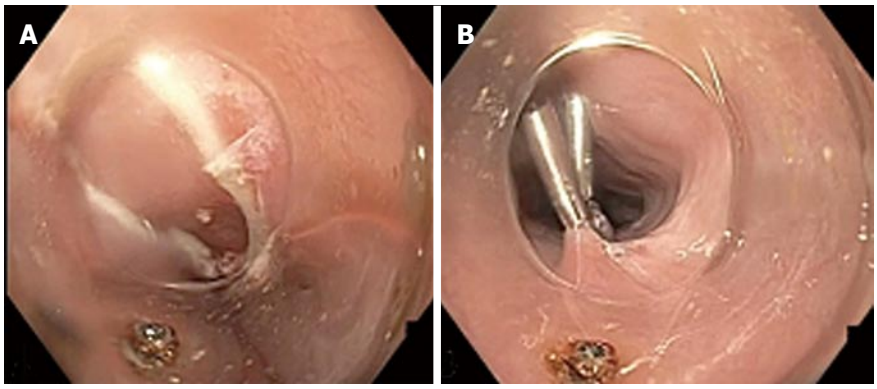

Figure 2 Endoscopic view of mucosotomy during peroral endoscopic myotomy. A: Esophageal mucosal defect after completion of peroral endoscopic myotomy; B: Defect closed with sequentially placed through the scope clips.

Figure 3 Endoscopic suturing device (Overstitch, Apollo Endosurgery, Austin, TX).

Figure 4 Examples of endoscopic stents. From Left: Fully covered plastic stent, fully covered metal stent, partially covered metal stent, larger diameter partially covered metal stent.

application. In one report fibrin glue was injected into the submucosa of a tracheoesophageal fistula causing a wheal and subsequent occlusion of the fistula in a pediatric patient[66]. In another series of 15 patients with persistent fistulae after conservative treatment, fibrin glue was used to occlude the fistula opening and resulted in long-term closure in 86.6% of patients after a mean of 2.5 sessions[67]. Tissue adhesives and sealants will likely be utilized primarily as an adjunct therapy to the definitive closure of leaks with an alternative method (such as a clip or suturing device).

Fistula plugs

SurgiSIS AFP plugs (Cook Biotech, West Lafayette, IN) were developed for the use in anal fistulae and have been used successfully in the treatment of GC fistulae after bariatric surgery[68]. Porcine small intestinal submucosa (SIS) is a bioprosthetic collagen material used in many settings including hernia repair, dressings for venous stasis ulcers, and anal fistulae. One group used SurgiSIS strips to endoscopically occlude GI fistulae in 25 patients with an 80% long-term closure rate[69].

Vacuum-assisted devices

Vacuum-assisted sponge closure has been used in the setting of esophageal and colorectal defects. Porous sponge foam is cut to be just smaller than the defect and sutured to the end of a nasogastric feeding tube (Figure 5). This is then grasped with endoscopic graspers and introduced into the defect. The nasogastric tube is then placed on continuous external suction. This suction minimizes secretions escaping through the defect while increasing blood flow to the area. Furthermore, the sponge induces granulation of the surrounding tissue and promotes healing[70]. Sponges need to be changed every 2-3 d. Small defects with adjacent fluid collections that aren't septated are more amenable to this therapy.

Vacuum-assisted sponge devices have been used successfully in small esophageal defects. In one series of five patients with fluid collections related to a leak at an esophageal anastomosis, all 5 patients resolved their leak with vacuum-assisted sponge therapy. The median length of therapy was 28 d with 9 sponge changes. Two of the patients developed stenosis at the anastomosis and one suffered from a fatal hemorrhage after a dilation procedure revealed an aortoanastomotic fistula[70].

Managing leaks with endoscopically placed tubes

Other strategies for managing leaks from the GI tract

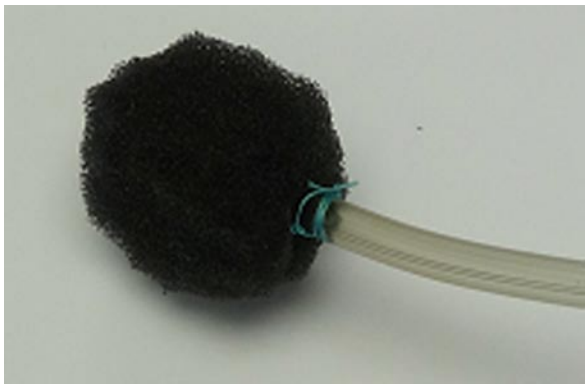

Figure 5 Vacuum-assisted closure device constructed of porous sponge and sutured to a nasogastric feeding tube.

Figure 6 Examples of the over the scope clips (Ovesco Endoscopy, Tubingen, Germany).

without repairing the defect include using the hole for other therapeutic modalities. Such "tube ostomy" formation is a standard surgical maneuver for difficult perforations in retroperitoneal organs like the colon and duodenum. In patients who presented with an acutely dislodged PEG tube and a leaking gastrotomy, the defect can be used to enter the abdominal cavity endoscopically, and replace the tube correctly, a so called "PEG rescue"[71]. We recently published a similar technique in a patient with a dislodged esophagostomy tube. By passing a wire from the cutaneous opening at the skin, securing this wire in the esophagus endoscopically, and drawing the wire out through the patients mouth, a new esophagostomy tube could be placed without any further surgical intervention[72]. Both of these examples illustrate the ability of the endoscopist to use established techniques to endoscopically manage what would traditionally be managed surgically.

Over the scope clips

Over the scope clips (OTSC) (Ovesco Endoscopy, Tubingen, Germany and Padlock, Aponos Medical, Kingston, NH) have gained popularity for the closure of GI track defects. Their ease of use, large capacity caps and short learning curve are the factors responsible for their surge in use.

Ovesco OTSC are made of elastic, biocompatible nitinol and are capable of full thickness closure of defects measuring 2 cm in diameter[73] (Figure 6). Two devices are available to use in conjunction with the OTSC to aid in apposition of the tissues prior to firing: a twin-grasper and a 3-pronged tissue anchor. Either device can be passed through the working channel and is used to secure the edges of the defect and draw them up into the cap prior to deployment of the OTSC. Because of the larger size of OTSC compared to TTSC they are able to close larger defects and take full-thickness bites of the tissue. They also provide a larger closure force due to their design. The Padlock device consists of a nitinol ring and a clear applicator cap that is placed on the end of the endoscope (Figure 7). Once deployed, the ring provides 360-degree tissue compression and approximation.

OTSC has been reported in many case series to be successful in closing acute perforations, leaks, and fistulae with long-term success rates ranging from 71%-100%[74-78]. A recent multi-centered international review examined 188 patients with acute perforations, leaks, and fistulae who were treated with OTSC and found that long-term closure rates were achieved in 90%, 73.3% and 42.9% respectively[79]. Since 2012 we have endoscopically treated 20 patients with the OTSC (6 with leaks and 14 with fistulae) resulting in a 100% and 64% closure rate respectively[44].

FACTORS LEADING TO SUCCESSFUL OUTCOMES

There are multiple factors that influence the ultimate closure rate in any endoscopic therapy, but common themes emerge in the literature in regards to closure rates. Defect size, that is the size of the luminal defect, not the length of the leak or fistula outside the GI tract, seems to play a role with smaller defects being easier to close than larger ones[58]. This is likely due to the technically difficult closure that larger defects present. Also, even though OTSC has been shown to close larger defects measuring up to 3 cm, in *ex-vivo* studies the bursting pressures have been much lower in repairs of larger defects compared to smaller ones[80]. Using the right tool for the type and location of the defect is crucial. Time from perforation to attempted closure certainly plays a role, with longer times being less successful[40-43]. Accurately measuring and appreciated the size of the defect and ensuring closure fluoroscopically at the time of attempted closure also play a role. Furthermore, the type of defect remains important, with acute perforations being more successfully closed than leaks or more chronic fistulae[41].

RECOMMENDATIONS FOR ENDOSCOPIC CLOSURE

When there is clinical suspicion for acute GI perforation, leak, or fistulae, at an area of the GI tract that is reachable by endoscopic means, we recommend prompt

Figure 7 Example of the Padlock over the scope clips (Aponos Medical, Kingston, NH).

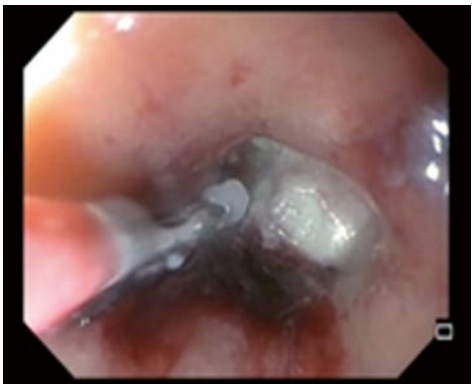

Figure 8 Endoscopic removal of suture foreign body at the opening of a rectal stump fistula.

endoscopic evaluation and treatment. The absolute contraindication to endoscopic therapy is evidence of peritonitis on abdominal exam[73]. Prompt endoscopic intervention provides two major benefits: Firstly, the endoscopist is able to provide a direct evaluation of the location and extent of the defect, and secondly, they are able to provide timely therapeutic attempts at closure for those lesions that are appropriate for endoscopic management.

The method of closure in acute full thickness GI defects will be dictated by three factors: the location, the size, and the operator's proficiency and familiarity with each therapy. Smaller defects may be amenable to TTSC, while larger ones may require one or more deployments of the OTSC. Very proximal perforations may not be amenable to stenting due to the foreign-body sensation that many patients experience with proximal stenting that approaches the upper esophageal sphincter. In many cases of initial failure, multiple attempts with various modalities are often required to ultimately obtain long-term closure[81]. We previously described the use of laparoscopy and endoscopic stent placement for management of leaks following bariatric surgery, but have since moved to definitive endoscopic closure of all leaks with endoscopic suturing or over the scope clips[5]. We now reserve stent use for leaks not amenable to or that have failed previous attempts at definitive closure.

We do not recommend any one type of endoscopic therapy for any specific location in the GI tract. Rather, we recommend that the endoscopist become familiar with all treatment modalities so as to use whichever method he/she deems appropriate based on clinical judgment. We reemphasize that often these defects require multiple attempts with varying modalities to achieve long-term closure, thus familiarity with all types of endoscopic therapies is strongly encouraged.

Because endoscopic closure of fistulae has routinely achieved the lowest long-term success rates, we recommend adopting traditional surgical fistula management techniques jointly with endoscopic attempts at closure[82-85]. Addressing the factors described by the classic acronym FRIENDS (foreign bodies, radiation, infection/inflammation, epithelialization, neoplasm, distal obstruction, and steroids) in the setting of fistula management is imperative to long-term success. It has been our experience that by addressing these issues on a case-by-case basis, we have achieved somewhat higher closure rates in patients with long-term fistulae. Since 2012 we have endoscopically treated 14 patients with GI fistulae with the OTSC resulting in a 64% closure rate[44].

Foreign bodies at the endoluminal opening of any fistula will contribute to its persistence by the foreign body reaction that they perpetuate. We routinely remove any suture, indigestible food matter, or other foreign bodies present within fistulous tract (Figures 8 and 9). Furthermore, once external drains have effectively treated the fluid collection for which they were placed, they should be removed in conjunction with the endoscopic treatment of the fistulous opening.

Infection must be treated with adequate source control in the form of external drainage for infected fluid collections and organism-specific antibiotic coverage. If the patient displays hemodynamic instability or sepsis due to uncontrolled infection, surgical intervention may be warranted as endoscopic management is typically reserved for the more stable patient.

Inflammation at the site of the fistulous opening is a commonly sited factor for failed closure. It is felt that closure rates are lower due to the difficulty in achieving adequate tissue apposition due to the fibrotic and inflamed edges that are present at the fistula opening[86]. Cauterization of the margins of chronic fistulae has been advocated to facilitate subsequent closure with the OTSC[87]. We routinely ablate the margins prior to clip placement in all chronic fistulae.

Epithelialization of the fistula tract can be addressed by both mechanical and ablative techniques. We frequently use argon plasma coagulation to ablate the epithelialized surface of the fistula tract to help prevent recurrence (Figure 10)[88]. Other authors have described mechanical debridement with biopsy forceps or brushes to disrupt the epithelial lining that may be present with more chronic tracts.

Distal obstruction or stenosis may precipitate the

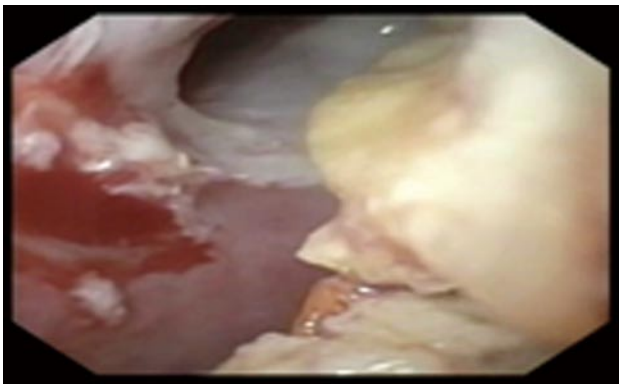

Figure 9 Undigested food within an esophago-cutaneous fistula tract.

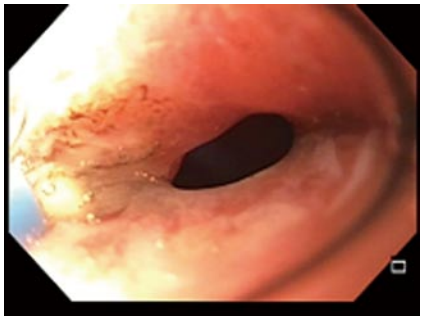

Figure 10 Circumferential argon plasma coagulation catheter ablating epithelialized fistula tract.

failure or breakdown of more proximal anastomoses or staple-lines[89]. When distal stenosis is discovered, this must be addressed concomitantly with any attempt to close proximal fistulae. Stenosis may be adequately treated with serial endoscopic dilations, though more recalcitrant strictures may require stenting (Figure 11)[90].

For the patient who is receiving steroid therapy for unrelated processes, coordination with the provider managing their steroids may provide a window where the steroid load can either be lessened or withheld for a period while endoscopic treatment is attempted. This may not be possible in all cases, but should be addressed on a case-by-case basis.

Maintaining adequate nutrition in these patients is imperative to promote healing. We recommend early enteral feeding in all cases possible. This may be achieved by obtaining feeding tube access distal to the site of the fistula such as a nasojejunal tube, or a percutaneous endoscopic jejunostomy tube. If this is not feasible, total parenteral nutrition may be initiated and continued until enteral feeding is tolerated.

In patients with acute perforations, endoscopic management alone may be sufficient for long-term success. In patients with chronic GI fistulae, all aspects of a patient's care must be optimized in order to achieve long-term success. Similar to the treatment of a patient with acute GI hemorrhage, multimodality endoscopic therapies may be required for more complex or chronic

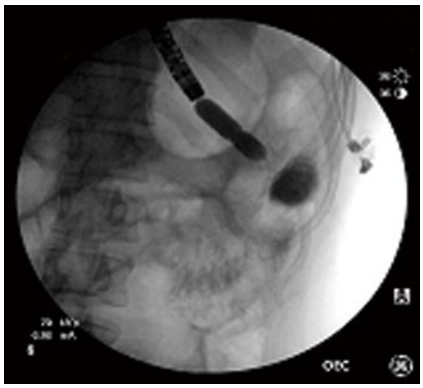

Figure 11 Endoscopic balloon-dilation of a stenotic gastrojejunostomy with adjacent jejunoanastomotic fistula.

GI tract perforation. A large gastro-gastric fistula after RYGB, for example, may require suture foreign body removal, argon plasma ablation of the epithelialized track, endoscopic suture closure of the largest portions of the defect, over the scope clip application to smaller portions and endoscopic dilation of a simultaneous gastro-jejunal anastomotic ulcer. Failure to address all of these issues will likely result in short term endoscopic failure.

Unfortunately, there will be patients who ultimately fail endoscopic therapy and will require surgical intervention. However, even in these patients, early endoscopic management can lessen the symptoms of high-output fistulae, enable patients to leave the hospital if even for a brief period, allow time for nutritional status to be improved, infections to be treated, and time for more in-depth operative planning that would otherwise not be available in the emergent setting.

CONCLUSION

There has been a great deal of advancement in the field of endoscopic treatment of full thickness GI defects with high rates of long-term closure. TTSCs, endoscopic suturing devices, stents, sealants, fistula plugs, vacuum-assisted devices, and OTSC have all been shown to be effective modalities. The treatment of acute perforations is generally more effective than the treatment of chronic fistulae. Because of this, we recommend a marriage of endoscopic therapies with classic fistula management to give the patient the best chance at long-term closure. Ultimately, even in the case of failure, endoscopic therapy can "buy time" for patient optimization prior to definitive surgical management.

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EDITORIAL

Registered nurse-administered sedation for gastrointestinal endoscopic procedure

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Abstract

The rising use of nonanesthesiologist-administered sedation for gastrointestinal endoscopy has clinical significances. Most endoscopic patients require some forms of sedation and/or anesthesia. The goals of this sedation are to guard the patient's safety, minimize physical discomfort, to control behavior and to diminish psychological responses. Generally, moderate sedation for these procedures has been offered by the non-anesthesiologist by using benzodiazepines and/or opioids. Anesthesiologists and non-anesthesiologist personnel will need to work together for these challenges and for safety of the patients. The sedation training courses including clinical skills and knowledge are necessary for the registered nurses to facilitate the patient safety and the successful procedure. However, appropriate patient selection and preparation, adequate monitoring and regular training will ensure that the use of nurse-administered sedation is a feasible and safe technique for gastrointestinal endoscopic procedures.

Key words: Registered nurse; Sedation; Gastrointestinal endoscopy; Safety; Complication

Core tip: The registered nurse-administered sedation for gastrointestinal endoscopy (GIE) procedures has clinical consequences. Generally, moderate (conscious) sedation for these procedures has been offered by the registered nurses by using benzodiazepines and/or opioids. Sedation training courses including clinical skills and knowledge are necessary for the registered nurses to facilitate the patient safety and the successful procedure. However, appropriate patient selection and preparation, adequate monitoring and regular training as well as anesthesiologist consultation in high risk cases and procedures will ensure the use of sedation by registered nurses is a safe and effective technique in GIE procedure.

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INTRODUCTION

Currently, gastrointestinal endoscopy (GIE) procedure is usually performed for diagnosis and treatment of gastrointestinal abnormalities. The need for sedation is depended on the patient physical status, degree of endoscopic difficulty and type of endoscopy, duration of procedure and physicians' preferences. The best methods for sedation during these GIE procedures are still controversial[1]. Endoscopic sedation can be administered by the trained nurse. However, the nurse administering sedation must be skilled to manage the oversedated patients[2,3]. The aim of the report is to present the current knowledge and the clinical application for routine clinical practice concerning the registered nurse-administered sedation for GIE procedures.

DEFINITIONS

Several guidelines created by the American Society of Anesthesiologists (ASA)[4] and the American Academy of Pediatrics[5] created the guidelines and definitions of procedural sedation.

Minimal (mild) sedation

Patient generally responds to the verbal command. Cardiorespiratory functions are unchanged. Minimal sedation does not invoke the monitoring requirements define in this policy. Although minimal sedation does not technically characterize the procedural sedation, the physicians should be aware that sedation can readily develop to the deeper level of sedation depth. The physicians and the registered nurses should be prepared to appropriately care for the patient in the event the level of sedation deepens.

Moderate (conscious) sedation

Patient responds persistently to the verbal command or light tactile stimulation. Additionally, the interventions are not needed to maintain the patent airway and the cardiorespiratory functions are sufficient and also usually preserved.

Deep sedation

Patient responds persistently to repeated or painful stimulation. The capacity to preserve respiratory function may be diminished. In addition, the patient may necessitate support in maintaining the airway and spontaneous respiration may be insufficient. However, the cardiovascular function is generally preserved.

General anesthesia

Patient does not response to the painful stimulus. The cardiorespiratory functions are usually reduced and the patients commonly demand the support in maintaining the airway. In addition, the positive pressure ventilations may be needed.

INDICATIONS

The two primary goals of suitable sedation for GIE procedures are to assist the procedures, and to reduce the anxiety and discomfort[6]. The optimal depth of sedation levels that registered nurses should be aiming for is minimal or moderate sedation depth[7].

LOCATIONS

Currently, endoscopic sedation can be performed in many units. The majority of practical locations of GIE procedures are endoscopy unit and operating room. Physicians who can facilitate the use of GIE sedation include the registered nurses, gastroenterologists, surgeon and anesthesiologists[8].

REQUIREMENTS

Personnel

A physician who continues current advanced life support qualification and who is familiar with endoscopic sedation, must be immediately available during the sedation and after the procedure. Resident and trainee may contribute in the GIE procedures by the supervision of staff physician. The physician is responsible for prescribing the medications including dose and type as well as also understanding pharmacology and the complications related with the sedative drugs. The physician will be in attendance throughout the procedure and will be responsible for managing the patient and must be able to manage the complications that may occur. In addition, the physicians performing the GIE procedure will maintain the responsibility and the competency for providing GIE sedation.

Consequently, an extra person is needed to establish an airway management. The registered nurses with appropriate competency can administer sedative medications with a written physician's order[9]. In addition, the registered nurse must be continuously monitored the patient and must be skilled to recognize clinical signs of hypoventilation and respiratory depression as well as abnormal vital signs and pulse oximetry readings. Importantly, the physician performing a GIE procedure can not be the person monitoring the patient.

Procedure room

The endoscopic room must be large sufficient to contain the operative personnel and monitoring equipments as well as permit an emergency cart to be brought into the room for emergency patient resuscitation. Additionally, the endoscopic room has adequate power outlets and adequate lighting to observe the patient and the monitoring equipments. The cart system with adequate space for the monitors, placed in a position where it is easily visible at all times for the personnel performing the procedural sedation.

Resuscitation equipment

The oxygen source, face mask and bag as well as suction equipments will be available in the endoscopic room. These equipments should be functional and checked before the start of GIE procedure. Moreover, the airway equipments including laryngoscope, endotracheal tubes and airways as well as an emergency cart will be available for the urgent use. This emergency cart must include the equipments for administering the resuscitate drugs and intravenous fluids including blood and blood components, as needed[1].

Monitoring

The patient undergoing sedation will be continuously monitored by the registered nurse with appropriate competency and knowledge. Consequently, vital signs, oxygen saturation and the responsiveness to a verbal stimulus will be documented before administration of sedative medications, 5 min during the endoscopic procedure and at least every 15 min in the recovery room. Electrocardiogram should be established in the high risk patients including elderly patients, patients with cardiac problems and ASA physical status $\geqslant$ Ⅲ[1].

PRE-SEDATION ASSESSMENT

Pre-procedural assessment and preparation part is very important. All patients scheduled for GIE sedation will have a pre-procedural assessment by a physician or registered nurse that includes the patient's medical condition, allergies, previous experience with sedation, drug use, alcohol and tobacco use, past medical history and current medications. A goal of physical exam including airway assessment and the major organ systems will be carried out. ASA physical classes of the patients should be documented before the procedure. A high ASA physical class is at increased risk for developing complications during sedation. Appropriate pre-procedure consultation with the proper specialists including an anesthesiologist is strongly recommended for the patients with severe underlying diseases.

The physician and the registered nurses are responsible for determining and documenting the patient's ASA physical class. If the provider determines that the patient is in an unstable condition or the GIE procedure is more invasive or complicated, sedation should not be considered by the registered nurses and an anesthesiologist consultation is recommended. Furthermore, the patients with ASA physical status IV or V are not the suitable cases in the absence of an anesthesiologist. Routine laboratory testing should not be carried out. However, the laboratory testing ought to depend on patients' physical status and underlying diseases.

Moreover, the informed consent must be completed before sedation is administered or the procedure is performed. All patients will be counseled on the risks, benefits, limitations and methods of sedation and also documented in the medical record before giving sedative drugs. Importantly, the patients can not drive home after sedation. A responsible adult person who will transport the patient should be confirmed before starting the GIE procedure. Fasting should be adhered to the guidelines except for necessary medications. All adult patients should be fasting for at least six hours before the procedural sedation. However, patients with normal gastric emptying time may have clear liquids in moderate amounts three hours prior to sedation. In addition, a time-out will be accomplished before the endoscopic procedure.

AMERICAN SOCIETY OF ASA CLASSIFICATION

The patient physical status is assessed from the ASA classification system. The ASA class should be determined by a person who will be performed GIE sedation: (1) ASA Ⅰ: Healthy patients; (2) ASA Ⅱ: Minimal systemic diseases, controlled on medications such as controlled hypertension, diabetes; (3) ASA Ⅲ: Severe systemic diseases with some limitations such as asthma, heavy smoking, obesity or multiple severe systemic illnesses all well controlled on medications, the patient with history of myocardial infarction or cerebrovascular accident; (4) ASA Ⅳ: Severe systemic diseases with severe limitations and life threatening such as poorly controlled hypertension, diabetes and coronary arterial disease; and (5) ASA Ⅴ: Not predicted to live 24 h regardless of any intervention.

PREPARATION OF SEDATION

The registered nurse who administered the sedative drugs should be considered monitoring equipments and availability of emergency medications and equipments during preparation of the procedure. The registered nurse may take the responsibility to monitor the patient during and after GIE sedation. In addition, the intravenous line must be continued all through the GIE sedation.

SUPPLEMENTAL OXYGEN

Several guidelines advise that oxygen supplementation should be performed during moderate and deep sedation[4]. However, oxygen supplementation will delay the finding of apnea by the pulse oximetry. The capnography can be a role for monitoring ventilation. Clinically, the incidence of desaturation will be reduced during the oxygen supplementation[10].

INTRAPROCEDURAL MANAGEMENT

Monitoring equipments during intraprocedural period should be included pulse oximetry, blood pressure monitor and ECG monitor. Resuscitation equipments and the reversal agents could be immediately accessed. Consequently, patients should receive supplemental

oxygen during the procedure when oxygen saturation reduces a 3% below their baseline saturation. An airway evaluation of the patient is continuously assessed. All evaluation and documentations are also noted. Accordingly, the consciousness should be reviewed frequently whenever sedative drugs are being titrated as well as also documented during sedation. Importantly, the patient is still remained responsive to a verbal stimulus and continued sufficient spontaneous ventilation. Ventilation should be continuously observed by clinical assessment. In patients where verbal response is not possible, search for other indications of consciousness.

A registered nurse experienced in moderate sedation can monitor and sedate the ASA physical status Ⅰ-Ⅱ patients. Generally, anesthesiologist should be consulted for the ASA physical status Ⅳ-Ⅴ patients and the deeply sedated patients as well as the high-risk patients. These patients need special care to make certain adequacy of pulmonary ventilation and to maintain hemodynamic parameters. In addition, the patient's airway must be supported and maintained.

SEDATIVES AND ANALGESIAS

Benzodiazepines

Benzodiazepines are widely used in procedural sedation even in GIE sedation because of their anxiolytic effects and dose-dependent anterograde amnesia[11]. Diazepam is not an ideal agent for short GIE procedures and in the outpatient cases because of its very long elimination half-life. In contrast, midazolam is the commonest premedication and sedative agent because of its pharmacokinetic properties[11]. Midazolam has a synergistic effect with anesthetic drugs. In that way, it can reduce the sedative medications[12]. Respiratory depression is the most important side effect of benzodiazepines when used in combination with opioids and/or sedative drugs. The standard dose is 0.03-0.1 mg/kg intravenously. The registered nurse can be safely used these dugs for GIE sedation.

Opioids

Opioids are usually used for the reduction of procedural pain and positional discomfort. Opioids are often used and carefully titrated with the combination of other sedative drugs[11]. The choice of which opioid should be used significantly depends on patients' physical status, the type and the duration of endoscopic procedure. Fentanyl and pethidine are widely used for GIE procedures. Similar to benzodiazepines, the registered nurses can be safely used the opiods for GIE sedation.

Pethidine

Pethidine (meperidine) is a synthetic opioid. Its onset and duration of action is longer than fentanyl. The standard dose of pethidine is 0.5-2 mg/kg intravenously. Its use in the renal insufficiency patients increases the potential for neurotoxicity. The patients taking monoamine oxidase inhibitors are contraindicated with pethidine[13]. Pethidine is commonly combined with midazolam for GIE procedure in the adult patients[14,15]. Pethidine and fentanyl are equally effective in providing analgesia for pediatric GIE procedures[16,17].

Fentanyl

Fentanyl has a rapid and short duration of action. It is also a synthetic opioid, and is the commonest opioid used for GIE sedation[11]. Normally, the dose of fentanyl is 0.5-2 mcg/kg intravenously. A previous study demonstrated that there were no significant differences in the recovery period, patient satisfaction, time to awake and sedation-related cardiorespiratory complications between the fentanyl-based sedation and the alfentanil-based sedation for esophagogastroduodenoscopy and colonoscopy. However, fentanyl is cheaper than alfentanil in each case[18].

Sufentanil

Sufentanil is also a synthetic opioid and is more potent than fentanyl. The standard dose of sufentanil is 0.1 mcg/kg intravenously[19]. Few studies have been evaluated the clinical efficacy of sufentanil in GIE procedure. In a previous study, the authors compared analgesia and sedation provided by one of four different opioids in combination with midazolam during GIE procedure. Patients were given 1-3 mg midazolam and sufentanil 5-10 mcg, meperidine 50-100 mg, fentanyl 50-100 mcg or alfentanil 150-300 mcg plus additional opioid and/or midazolam if needed. The study was concluded that sedation and analgesia were comparable in the upper gastrointestinal groups. Recovery time was shorter with sufentanil and alfentanil. However, analgesic properties of meperidine were significantly greater than sufentanil[20].

Alfentanil

Alfentanil also has a rapid and short duration of action. However, it is less potent than fentanyl. Donnelly and colleague studied the efficacy and cost of substituting sedation by using alfentanil and midazolam for the existing regimen of diazepam and meperidine in patients underwent upper GIE procedure. Their study demonstrated that the use of alfentanil for sedation in upper GIE procedure was safe and effective, and did not increase the total sedation cost[21]. Moreover, Liu *et al*[22] colleague demonstrated that the patient controlled analgesia with propofol and alfentanil offered greater sedation and patient satisfaction as well as a low complication rate compared with the combination of opioid and benzodiazepine.

Remifentanil

Remifentanil has an ultra-short action. It is a synthetic opioid. Importantly, the clearance of remifentanil is unchanged in the patients with hepatic and renal impairment[11,23]. Generally, remifentanil is given only by a continuous infusion technique. An analgesic dose of

remifentanil is 0.025-0.15 mcg/kg per min[24]. However, remifentanil is not extensively used for GIE procedure. Further studies should to be investigated.

REVERSAL AGENTS

Naloxone

Naloxone is an opioid antagonist. A dose ranges from 1-4 mcg/kg intravenously, and it may be repeated if required. The duration of action of naloxone is about 30-45 min[11]. Because of its short duration of action, an infusion dose of 3-5 mcg/kg per hour could be used after a bolus dose.

Flumazenil

Flumazenil is a benzodiazepine antagonist. It selectively binds to the GABAA receptor complex. The duration of action is approximately 1 h. The standard dose of flumazenil is 0.2 mg intravenously. It can be repeated if necessary. The maximum dose of flumazenil is 1 mg/dose and 3 mg/h[11]. Similar to naloxone, flumazenil can cause acute withdrawal syndrome in the patients who receive benzodiazepines chronically[11].

SAFETY OF NURSE-ADMINISTERED BENZODIAZEPINES AND OPIOIDS

Generally, the registered nurses can administer the benzodiazepines and opioids for moderate sedation in GIE procedures. Additionally, the registered nurse also can be administered the reversal agents by the order of a physician[25]. Consequently, the study of Yang *et al*[26] also investigated the nurse-administered moderate sedation by using the clinical criteria (Ramsay sedation scale, RSS) compared with using Bispectral Index values. They used midazolam and fentanyl or hydromorphone. The authors confirmed that the registered nurses could be safely and effectively performed moderate sedation by using benzodiazepine and opioid for GIE procedures.

However, the registered nurses should not to be sedated in the advanced GIE procedures such as ERCP and EUS procedures[27]. Guimaraes and colleagues assessed a cohort study of 9598 patients underwent ERCP and EUS procedures. The incidence of sedation and endoscopy-related complications as well as serious morbidity and mortality rates were compared. The study demonstrated that the anesthetic management for ERCP and EUS procedures in high-risk patients significantly decreased the incidence of sedation-related complications when compared with the registered-nurse care. However, endoscopy-related complications were unchanged[27].

PROPOFOL

Propofol is a phenol derivative with rapid and short duration of action. It has anxiolytic, hypnotic, anesthetic and antiemetic properties. The onset of action is about 30-60 s. The plasma half-life ranges from 1 to 4 min[28]. However, it does not have an analgesic effect. Propofol is commonly used for sedation in therapeutic GIE procedures[15]. It also potentiates the effects of other sedative drugs. The disadvantages of propofol are related with airway obstruction, apnea and hypotension as well as pain at the injection site.

NURSE-ADMINISTERED PROPOFOL

To date, propofol administration by nonanesthesiologists is controversial. Advocates of nurse-administered propofol sedation are due to the patient safety and the low cost[3,29,30]. American Society of Anesthesiologists guideline on sedation by nonanesthesiologists describes propofol as an anesthetic agent that is commonly related with deep sedation[4]. The use of propofol for routine GIE procedures also is not recommended by American Society of Gastrointestinal Endoscopy[31]. Generally, the registered nurses administered propofol sedation is cost-effective.

Several studies have been demonstrated the safety and efficacy of the registered nurses administered propofol sedation. For example, the study of Rex *et al*[32] demonstrated that the registered nurses and endoscopists could safely administer the propofol for GIE endoscopy[32]. Additionally, several data were also confirmed these in the invasive GIE procedures including ERCP, EUS and balloon endoscopy[33,34].

Moreover, the safety of nurse-administered propofol sedation in an ambulatory center also confirmed by the report of Walker and colleagues[35]. This report described the authors' experience in 9152 GIE procedures. The sedation-related adverse events were observed in seven patients including laryngospasm, apnea and pulmonary aspiration and all related with upper GIE procedures. However, tracheal intubation was not needed in all these cases.

To date, no clinical studies are directly compared between the registered nurse and gastroenterologist or endoscopist-administered sedation for GIE procedures. The administration of propofol by registered nurse is usually performed under direct supervision of the physician. The safety profiles of this sedation technique by the registered nurse for GIE procedures were evaluated in 27500 patients. Among these patients, 6.7% developed hypoxemia (SpO_2 < 90%) and 6.2% required oxygen supplementation. Severe hypoxemia (SpO_2 < 85%) was observed in 0.62% and 0.25% during upper GIE and colonoscopy, respectively. Bag mask ventilation or tracheal intubation was not required. Hypotension was observed in 1.2% and 3.5% during upper GIE and colonoscopy, respectively, and was immediately treated by using intravenous fluid administration. The mean recovery time was 14.6 min. This study demonstrated that propofol administration by the registered nurse was safe and effective[36].

Several studies have been confirmed that gastro-

enterologist or endoscopist can be safely and effectively performed GIE sedation in mild or moderate depth of sedation level. Redondo-Cerezo and colleagues assessed the efficacy and safety of endoscopist-administered propofol for GIE procedures[37]. They studied the propofol administration by gastroenterologist for sedation in EUS procedure. The induction time, duration of procedure, recovery time, patients' comfort and safety, hemodynamic profiles and complications as well as patient and endoscopist satisfaction were analyzed. Their study confirmed that propofol administration by gastroenterologist for EUS procedure in the elderly or the high-risk populations was safe and effective[38].

Recently, a tool for evaluation of the competency of the registered nurse-administered propofol has been developed by Jensen *et al*[39]. The study explored the reliability and validity of the nurse-administered propofol assessment tool. This study demonstrated that the assessment of sedation proficiencies could be performed by using a simulator. However, the video assessment required experienced physicians. Overall, this assessment tool demonstrated a good validity. Further investigations and controlled studies need to be confirmed.

POST-SEDATION CARE

Following the procedure, the registered nurse must continually monitor the patient until the patient ready to discharge. The patient also remains the responsibility of the registered nurse during the recovery period. Generally, the institutions would establish the recovery and discharge criteria for their patients. The recovery unit must have proper monitoring and resuscitation equipments.

The patients' vital parameters and the level of consciousness should be continuously observed in the post-sedation unit. The registered nurse is also required to manage the complications in this unit. The intravenous line and monitors should be utilized until the patient meets specific discharge criteria. If the reversal agents are used, the patients ought to be observed for $\geqslant$ 90 min after the administration of these drugs to assure they do not become re-sedated.

DISCHARGE CRITERIA

The registered nurses working in the post-procedural care use the discharge scoring system to assess the patient before discharge home or move to the ward. The discharge scoring systems such as the Aldrete score and the Post-Anesthesia Discharge Scoring System (PADSS) are commonly used for GIE procedures. The Aldrete and the PADSS scoring systems need continuous re-assessment of the patient. However, all discharge scoring systems have some disadvantages[40]. Importantly, the high-risk patients should be individually assessed. Currently, the reliability of these discharge scoring systems is clearly demonstrated. In the ambulatory setting, patients now accept the idea of going home only a few hours after diagnostic and/or therapeutic GIE procedures. The content and delivery of discharge instructions that outpatients receive from the registered nurse is very important. So far, the role of the registered nurse in providing patient education at the discharge process is becoming increasingly[41].

Importantly, the discharge criteria must be present before a patient can be discharged following GIE sedation. The following criteria suitable for the discharge are patient oriented to time, place and person or at pre-procedure status, vital signs within 20%-30% of pre-procedure values, unobstructed airway and sufficient ventilation, adequate oxygenation, easily and appropriately responsive to verbal commands, no severe pain and nausea/vomiting as well as the Aldrete score should be 9 or 10 in a total of 10. In the author's previous study, the periodic assessment of the home-readiness showed that most patients would complete an acceptable score on or before 1 h after GIE procedure. The time to complete an acceptable score associated with the type of GIE procedures. Consequently, most delayed recovery times after acceptable recovery scores were owing to the non-medical causes[42].

ANESTHESIOLOGIST CONSULTATION

The majority of sedation-related complications during and after GIE procedures are respiratory-related events such as pulmonary aspiration, hypoventilation, airway obstruction and apnea as well as the cardiovascular-related events such as hypotension and bradycardia[43]. Sedation-related adverse events are a risk to the success of the GIE procedure itself. Endoscopic sedation training is a very important issue. The registered nurses can learn about GIE sedation when to call for help and when to join the services of anesthesiologists. To date, the registered nurse should consult anesthesiologists for the patients with ASA physical status IV and V and the patients with known or suspected difficult airway management. In addition, anesthesiologists should be required for emergency or complicated GIE procedures such as ERCP, EUS and small bowel enteroscopy[44]. Moreover, anesthesiologist consultation is advocated for the patients with extremes of age or with significant renal or liver impairment, severe cardiorespiratory diseases, history of difficulty with moderate sedation, patients with previous inadequate response or adverse effect to moderate sedation, alcohol and drug abuse as well as patient or procedure needed at least deep sedation depth.

CONCLUSION

The use of registered nurse-administered sedation for GIE procedures has clinical significances. Most endoscopic patients require some forms of sedation and/or anesthesia. Generally, mild and moderate sedation for GIE procedures has been offered by the

nonanesthesiologist by using benzodiazepines and/or opioids. In contrast, the propofol sedation by the registered nurse is depended on the knowledge, skills and experience of individual nurse as well as the policy and the country guidelines. Importantly, the sedation training courses including clinical skills and knowledge as well as anesthesiologist consultation in high risk cases and procedures are necessary for the registered nurses to facilitate the patient safety and the successful GIE procedure. Additionally, appropriate patient selection and preparation, adequate monitoring and regular training will ensure that the use of registered nurse-administered sedation is also a practicable and safe technique for GIE procedures.

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REVIEW

Current applications of endoscopic suturing

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Abstract

Endoscopic suturing had previously been considered an experimental procedure only performed in a few centers and often by surgeons. Now, however, endoscopic suturing has evolved sufficiently to be easily implemented during procedures and is more commonly used by gastroenterologists. We have employed the Apollo OverStitch suturing device in a variety of ways including closure of perforations, closure of full thickness defects in the gastrointestinal wall created during endoscopic full thickness resection, closure of mucosotomies during peroral endoscopic myotomy, stent fixation, fistula closure, post endoscopic submucosal dissection, endoscopic mucosal resection and Natural Orifice Transluminal Endoscopic Surgery defect closures, post-bariatric surgery gastrojejunal anastomosis revision and primary sleeve gastroplasty.

Key words: Endoscopic suturing; Peroral endoscopic myotomy; Endoscopic full thickness resection; Natural Orifice Transluminal Endoscopic surgery; Endoscopic bariatric surgery; Endoscopic sleeve; Transoral outlet reduction

Core tip: The recent development of an endoscopic suturing platform, the only such device that is currently available in the United States, has led to a rapid expansion of endoscopic suturing applications ranging from simple procedures such as stent fixation to more complex ones such as closure of large full thickness defects and primary and revisional bariatric endoscopic surgery.

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INTRODUCTION

Endoscopic suturing devices have been used in a limited fashion for about a decade. Some of the known devices

Table 1 Advantages and disadvantages of different suturing patterns

Suturing Pattern	Pros	Cons
Interrupted/ simple	Less tissue drag during tightening of the suture compared to a running suture No risk of suture crossing and entanglement as described for running suture above Any failure during suturing would only involve the most recently placed interrupted suture rather than the entire suturing work up to that point as is the case with running sutures Suture failure after termination of the procedure would only involve a small segment of the closure without the risk of dehiscence of the entire closure that exists with running sutures	Approximation of the defect edges occurs as soon as the first interrupted suture is tightened and may limit good visualization and grasping of the edges of the nearly closed defect thus making placement of the subsequent interrupted sutures difficult or inaccurate Substantial increase in cost proportionate to the number of sutures used as discussed under running sutures above
Figure of 8	Specialized suture used to close small circular defect in a circular fashion with equal circumferential anisotropic compression towards the center of the defect. Thus, it may be the optimal suturing pattern for fistula closure or oversewing an ulcer containing large vessel(s) at risk for bleeding	Technically more challenging than interrupted sutures Risk of suture entanglement Any suture failure (*e.g.*, erosion through tissue, breakage) would result in slack along the entire suture and result in dehiscence of the entire closure
Running	Allows clear visibilty of the defect edges until the suturing is completed Less expensive as it uses only one suture and cinch (in the United States, for the OverStitch platform, each additional suture+cinch adds approximately $100)	Tissue drag caused by the suture going through multiple bites of tissue requires gentle slow careful technique during tightening of the suture prior to cinching Avoiding entanglement of the long suture leading to the start of the suture line during placement of the transverse sutures across the defect requires careful technique and experience Any error such as accidental drop of the needle, fraying and breakage of the suture or device failure results in loss of the entire work up to that point with the need to start the closure from the beginning Similarly, any suture failure after termination of the procedure (*e.g.*, suture eroding through tissue prematurely or breaking) would result in failure of the entire closure

include the Bard Endocinch (MA-US), T-bars (Wilson Cook-NC-US), NDO Plicator (MA-US-no longer available) and GERDX TM (G Surg Seeon, Germany)[1-3]. There are reports on limited preliminary data from experimental or limited-release devices[4-7]. The OverStitch endoscopic suturing system (Apollo Endosurgery, Austin, Texas) evolved from the previously developed Eagle Claw device[8] and is currently the only widely available suturing device, and only Food and Drug Administration approved commercially available device in the United States[9]. Since the other devices briefly mentioned are not available either because they have been withdrawn or because they are at early experimental stages of development, this review will focus on the rapidly emerging widespread applications of suturing enabled by the Overstitch platform. Figure 1 illustrates the use of the endoscopic suturing device. It is a disposable, single-use device that is mounted onto a double-channel gastroscope and it can enable interrupted or continuous suture application[10]. Table 1 and Figure 2 demonstrates the advantages and disadvantages of different suturing patterns. Full thickness suturing is possible for tissue approximation or plication in the gastrointestinal tract *via* use of a tissue anchor, curved suturing arm and a cinch. The current version was approved in 2011 and early use included oversewing a recurrent marginal ulceration, a fundic ulcer, stoma reduction after gastric bypass surgery, and closure of a post-operative rectovaginal fistula[11,12].

PERFORATION CLOSURE

Closure of iatrogenic inadvertent endoscopic perforations not associated with endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR) is largely confined to the animal model. Recently, three patients with iatrogenic esophageal perforation had apparent successful repair with the OverStitch device[13]. The OverStitch device was used to successfully close a full thickness gastric defect in the pig in a two week survival study[14]. An interesting study in humans assessed the depth of endoscopic suture placement in the colon. Test sutures were placed intraoperatively in patients undergoing partial colectomy in the portion of the colon to be resected. Examination of the resected colon demonstrated successful placement of full thickness transmural sutures[15]. Figure 3 demonstrates a case in which we performed successful closure of a very large perforation that occurred during a colonoscopy performed to evaluate Crohn's disease in a 35-year-old patient. The patient had a second perforation at the cecum that was not appreciated by the referring endoscopist and was discovered during surgical exploration performed due to persistent abdominal pain, fever and leukocytosis 24 h after the index colonoscopy. The surgeon discovered a second perforation in the cecum, which he successfully repaired surgically and confirmed successful endoscopic closure of the splenic perforation not requiring surgical intervention. He noted that the endoscopic sutures placed using the OverStitch

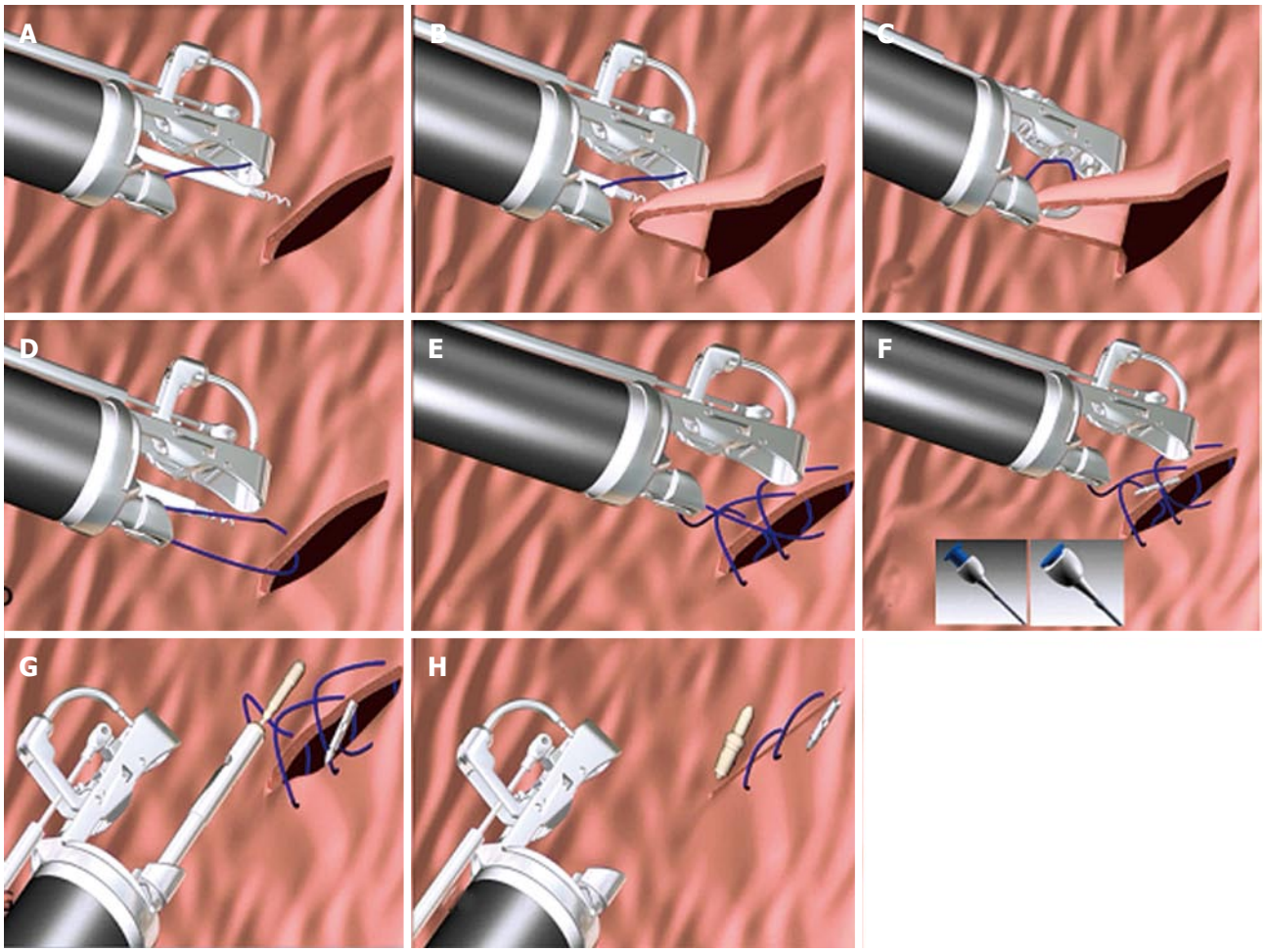

Figure 1 Steps involved in placing endoscopic sutures (Courtesy Apollo endosurgery Austin Texas). A: Grasp the tissue using the tissue helix; B: Retract the tissue into the needle path; C: Drive the needle through the tissue; D: Open the arm and release the tissue; E: Repeat stitched as desired; F: Press the blue button to release the needle (T-fastener); G: Tighten and cinch; H: Repeat as desired.

device had traversed the entire colonic wall, which is in accordance with the results of the colectomy study described above.

STENT FIXATION

Covered self-expanding metal stents have been employed in the treatment of perforations, strictures and fistulae/leaks. The covered feature allows subsequent removal but also predisposes to stent migration. Previously, endoscopic clips have been deployed to prevent stent migration with doubtful efficacy, but there is now an increasing experience with endoscopic suturing for this purpose. A porcine model study comparing clip *vs* suture fixation of esophageal stents favored suturing in terms of migration tendency and force needed to disrupt the stent fixation[16]. A study of esophageal fully covered self-expanding metal stents (FCSEMs) for leaks and strictures compared stenting with and without suturing, and the sutured stents migrated much less.(55% *vs* 35%)[17]. A case series featuring a variety of upper gastrointestinal issues (perforation, leaks, fistulae) necessitating stents had a similar migration of sutured stents (7 of 21 sutured SEM's)[18]. FCSEMs may have a role in treating post-bariatric leak/fistulae and our center and others have employed suturing for stent fixation and occasionally for primary defect closure[19].

FISTULA/LEAK CLOSURE

There is accruing experience with endoscopic suturing use in the treatment of gastrointestinal fistula/leak closure. These can be acute or chronic in nature and often result as complications from surgical anastomoses and stapled tissue divisions such as those of bariatric surgery (especially sleeve gastroplasty). As mentioned, suturing is often used in conjunction with other therapies including stents and glue[20]. The StomaphyX suturing system was used to treat gastric leaks in two bariatric patients[17]. The OverStitch device achieved closure in 3 of 7 patients with gastrogastric fistulae after gastric bypass[8]. This device has been used for a variety of fistulae[21,22]. One study demonstrated the superiority of the full-thickness OverStitch device compared to a superficial suction-based suturing system in the closure of gastrogastric fistulae[23]. The OverStitch device was used to close a persistent esophagopleural fistula[24].

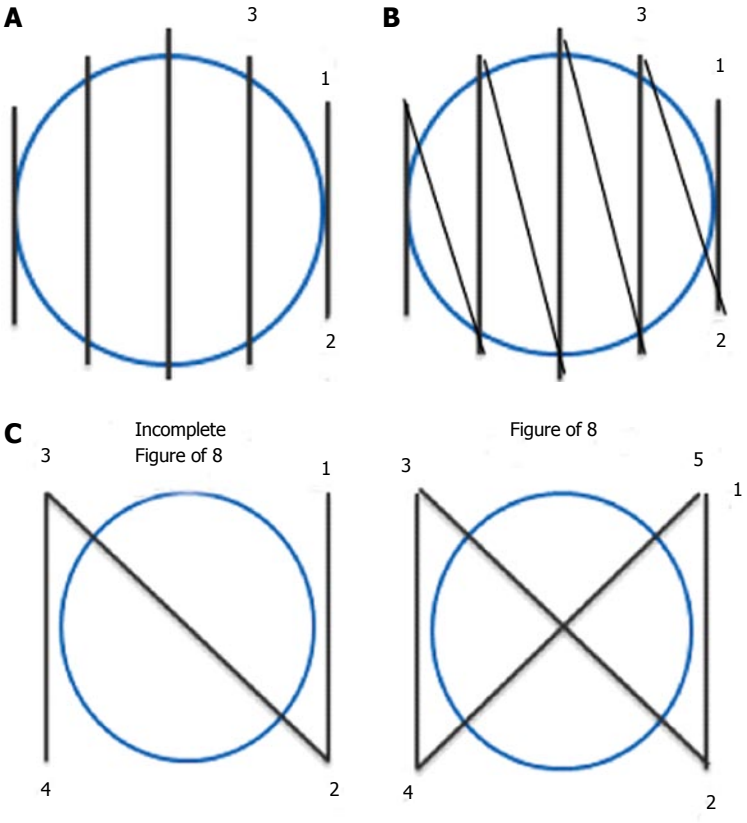

Figure 2 Types of suture pattern. A: Interrupted suture; B: Running suture; C: Figure of 8 suture.

Patients who are fortunate enough to have removal of their feeding tube after gastrostomy usually have wound closure, but occasionally there is a persistent gastrocutaneous fistula. There are a variety of closure techniques and endoscopic suturing may be employed as the sole intervention or in combination with other therapies (glue, clips, percutaneous suturing, *etc.*) Successful closure with the OverStitch device has been described[25,26].

ESD-EMR CLOSURE

There has been a veritable explosion of publications regarding endosurgical resection; predominantly ESD and related offshoots such as submucosal tunnel endoscopic resection (STER) and endoscopic full-thickness resection (EFTR). Endoscopic suturing has ensconced itself as an important if not indispensable component of advanced endoscopic resection. A porcine model study suggested quicker and more complete closure of ESD defects with sutures *vs* clips[27]. However, the efficacy of closure was somewhat subjective (visualization) and this comparison will need to be made in humans. The same group noted in another porcine study that effective suture closure after ESD can be done in a variety of ways and combined with clips[28]. In one study of 12 patients having ESD (4 gastric 8 colon), closure was made successfully with the OverStitch device and the patients were discharged home on the day of the procedure[29].

ESD has evolved such that large submucosal lesions and those with significant extraluminal extension can be resected with the technique known as EFTR. EFTR requires closure of potentially large defects (essentially intentional perforations) and endoscopic suturing is invaluable for this purpose. A porcine two-week survival study demonstrated the feasibility of suturing to close a full-thickness gastric defect (average size of gastric specimen 11 mm) without site ulceration[30]. Three patients with endoscopic perforation avoided surgery *via* OverStitch closure of the defect (all > 2 cm) in conjunction with catheter decompression of pneumoperitoneum, NGT insertion and Ⅳ antibiotics[31]. We employ the device after EFTR for gastric stromal tumors[32]. Without availability of the robust closure achievable with endoscopic suturing, closure of EFTR defects with endoscopic clips often requires specialized adjunctive techniques to achieve secure closure of these large perforations. We have demonstrated use of an omental patch to achieve secure closure with endoscopic clips of a large gastric EFTR one of our early cases prior to OverStitch availability[33]. In Asia, where OverStitch is not yet available, EFTR operators have largely converted to closures of EFTR defects with the endoloop and clips technique further emphasizing the inadequacy of clips for secure closure of these relatively large perforations[33-36]. Figure 4 demonstrates a few cases of EFTR defect closure with OverStitch. Kantsevoy

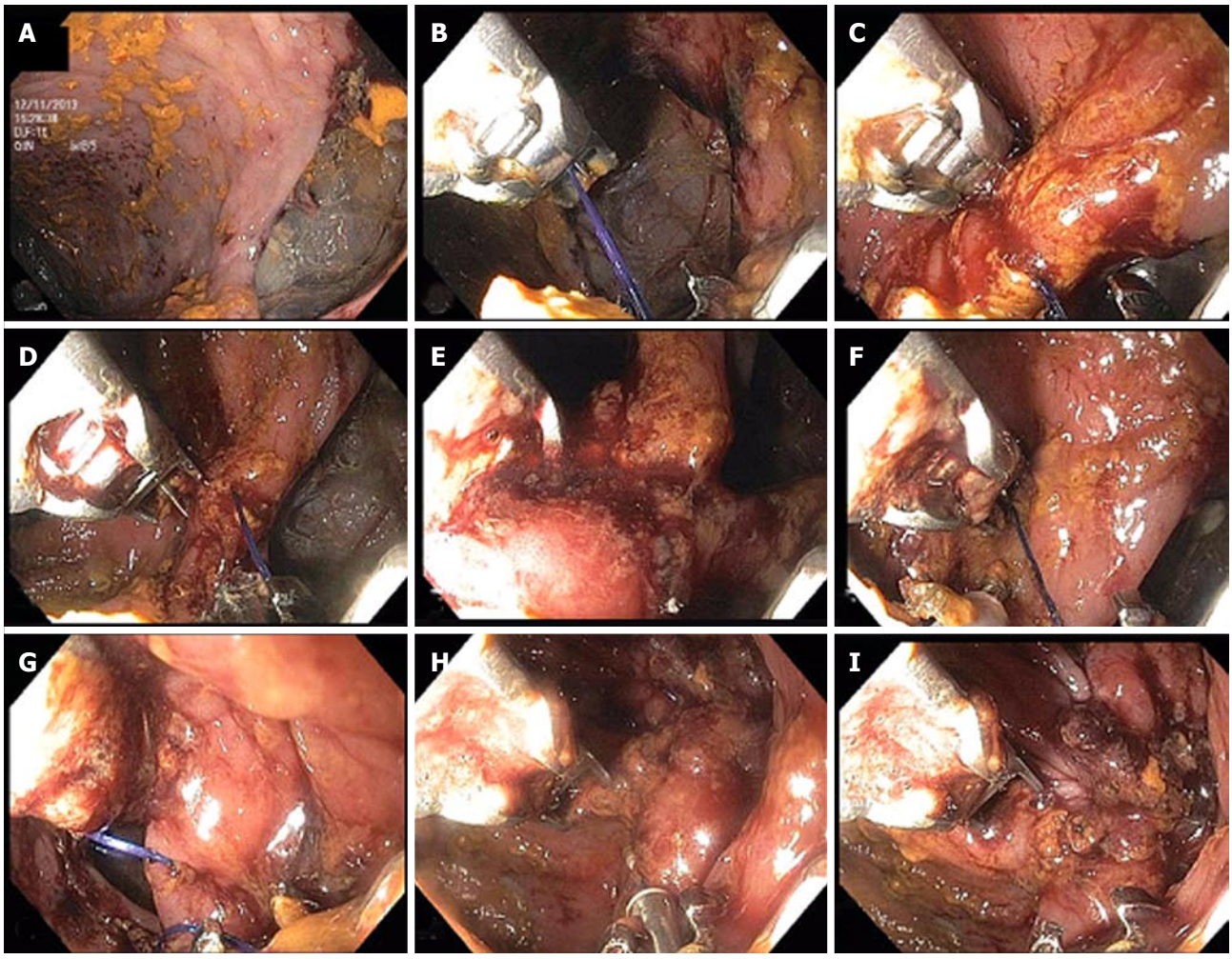

Figure 3 Closure of colonic perforation with endoscopic suturing device. A: Initial tissue bites forming a running suture (B-E) starting at the inferior edge of the perforation and progressing towards the center; F: Tissue helix retractor is used to ensure deep tissue bite along the distal, superior edge of the perforation; G: Suturing has reached the superior edge of the perforation the edges of which are now being pulled together by the sutures; H: After tightening of the sutures closure of the perforation has been achieved and the cinch device is seen being deployed at the 6 o' clock position of the image; I: Immediately after cinch deployment, the complete closure of the perforation is seen. Gastrografin was injected through the scope that confirmed absence of leak (not shown).

had successful OverStitch closure of two patients with one cm colon perforations after more extensive experience with closing two centimeter colon defects in pigs[36].

ESD is challenging for lesions in difficult locations where the endoscope cannot achieve a path tangential to the lesion such as the gastric lesser curvature. For such lesions, ESD can be facilitated by countertraction accomplished *via* use of the OverStitch device to create a "suture-pulley"[37].

A natural extension of EFTR is Natural Orifice Transluminal endoscopic surgery (NOTES) where the endoscopic intervention is done within the peritoneum and the trans-gastric entry site reliably closed. A suturing device was demonstrated to attain durable closure of gastric defects ranging to 18 mm in an animal model[38]. Closure success is similar for both continuous and interrupted suture application[39]. The OverStitch device was used in conjunction with a robotic device to remove a five cm diameter area of the gastric wall in two pigs, solely *via* endoscopic means[40].

PERORAL ENDOSCOPIC MYOTOMY MUCOSOTOMY CLOSURE

Per-oral endoscopic myotomy is a successful clinical application of NOTES. Endoscopic suturing has been utilized for closure of inadvertent mucosotomies and perforations during peroral endoscopic myotomy (POEM)[38-40]. Endoscopic suturing has also been shown to be useful in closing the mucosal entry point after the myotomy is performed (Figure 5)[41-43]. This is now our customary practice in POEM. During the first three years of our POEM experience (2009-2012), prior to the availability of endoscopic suturing, we performed closure of the tunnel entry site with clips. However, when endoscopic suturing with the OverStitch device became available, we converted to closure using suturing hoping for a more predictable and secure closure. We performed a retrospective comparison of clip closure *vs* OverStitch closure in our series of POEM procedures. We compared our initial 62 POEMs closed with a variety of endoscopic clips commonly available

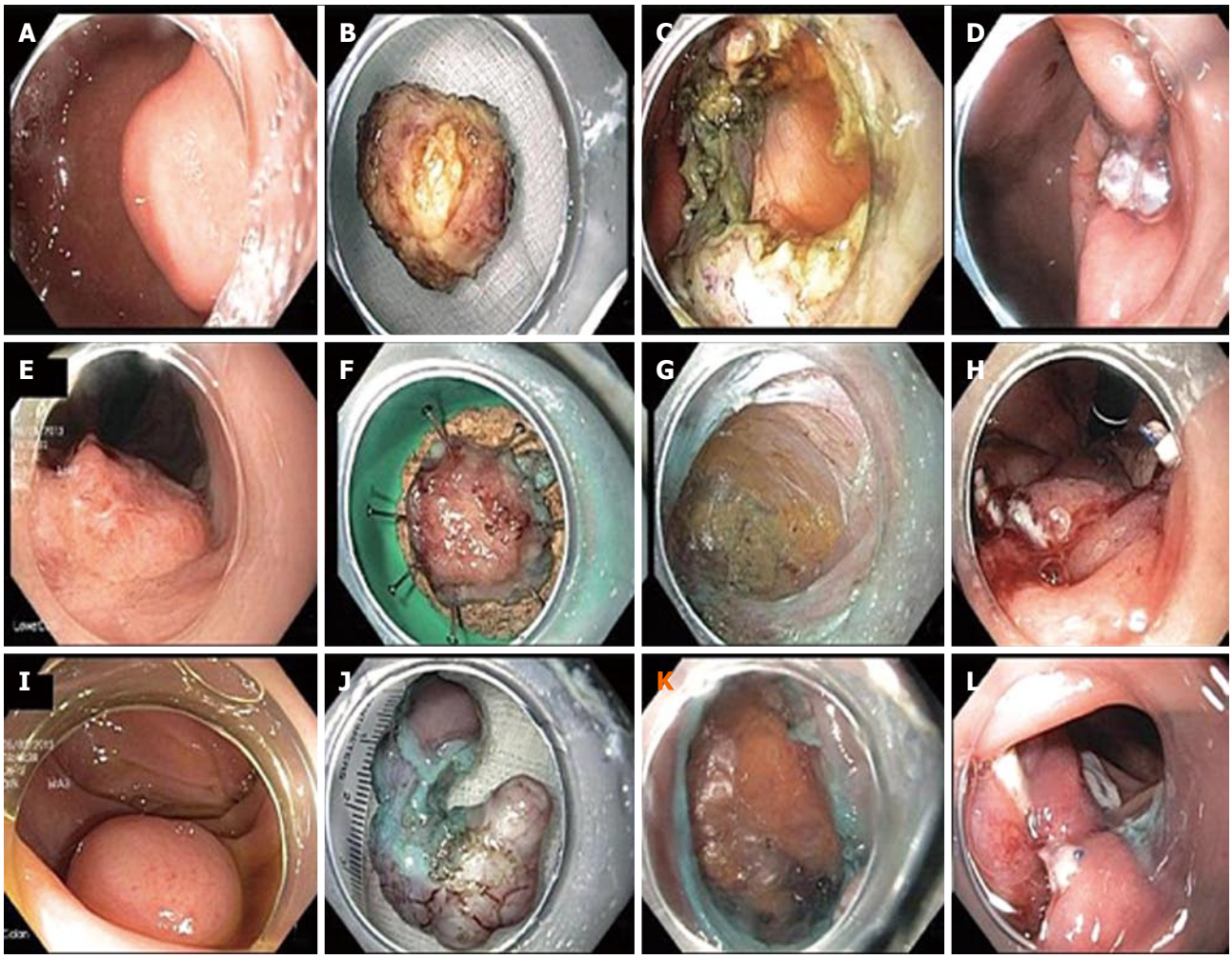

Figure 4 Closure of intentional full thickness perforations after subepithelial tumor removals with endoscopic suturing device. A: Endoscopic image of gastric muscularis propria based subepithelial tumor; B: 2.5 cm schwannoma; C: Resection crater revealing transmural fat; D: Endoscopic sutured closure of defect; E: Endoscopic image of rectal carcinoma superficially extending to muscularis propria; F: 1.3 cm rectal low-grade adenocarcinoma; G: Resection crater demonstrating perirectal fat, circular muscle layer and longitudinal muscle layers; H: Endoscopic sutured closure of defect; I: Endoscopic image of sigmoid muscularis propria based subepithelial tumor; J: 3cm leiomyosarcoma; K: Resection crater demonstrating peritoneal fat; L: Endoscopic sutured closure of defect.

in the United States with the subsequent 61 POEMS closed with endoscopic suturing (Table 2). We did not detect a significant difference in length of stay (1.9 *vs* 1.7 d) or complications (no significant complications in either group). There was one conversion to clips in the suturing group due to a superficial hypopharyngeal mucosal tear caused while attempting to insert the endoscopic suturing device in a patient with very narrow hypopharynx. Closure time and cost per closure was assessed for the most recent 25 cases where clips were used and the most recent 25 cases where suturing was used (after a plateau in the learning curve had been achieved by both techniques) and were found to be similar: mean closure time 8.8 (6-15) *vs* 10.1 (5-16) min and mean cost per closure $916 ($454-$2160) and $818 respectively, (cost based on the cost of these devices to our institution). We should note here, however, that endoscopic suturing device cost varies geographically with relatively small differences within the United States but significantly higher prices in Europe due to distribution costs there.

POST-BARIATRIC SURGERY ENDOSCOPIC STOMA REDUCTION

It is commonplace for patients with Roux-en-Y gastric biopsy to have dilation of both the gastric pouch and the gastrojejunal stoma. Endoscopic suturing lends itself well in reducing the gastric pouch and the stomal diameter, though most work to date centers on the latter. Endoscopic treatment of this condition avoids the need for revisional surgery which is technically challenging and carries significant morbidity. Twenty-five patients with dilated GJ anastomosis (mean 26 mm) had 100% technical success using the OverStitch device with marked reduction of the stoma diameter (mean 6 mm) and mean weight loss of 11 kg[44]. These results are concordant with the results of a multicenter randomized trial[45]. Weight loss was shown to be

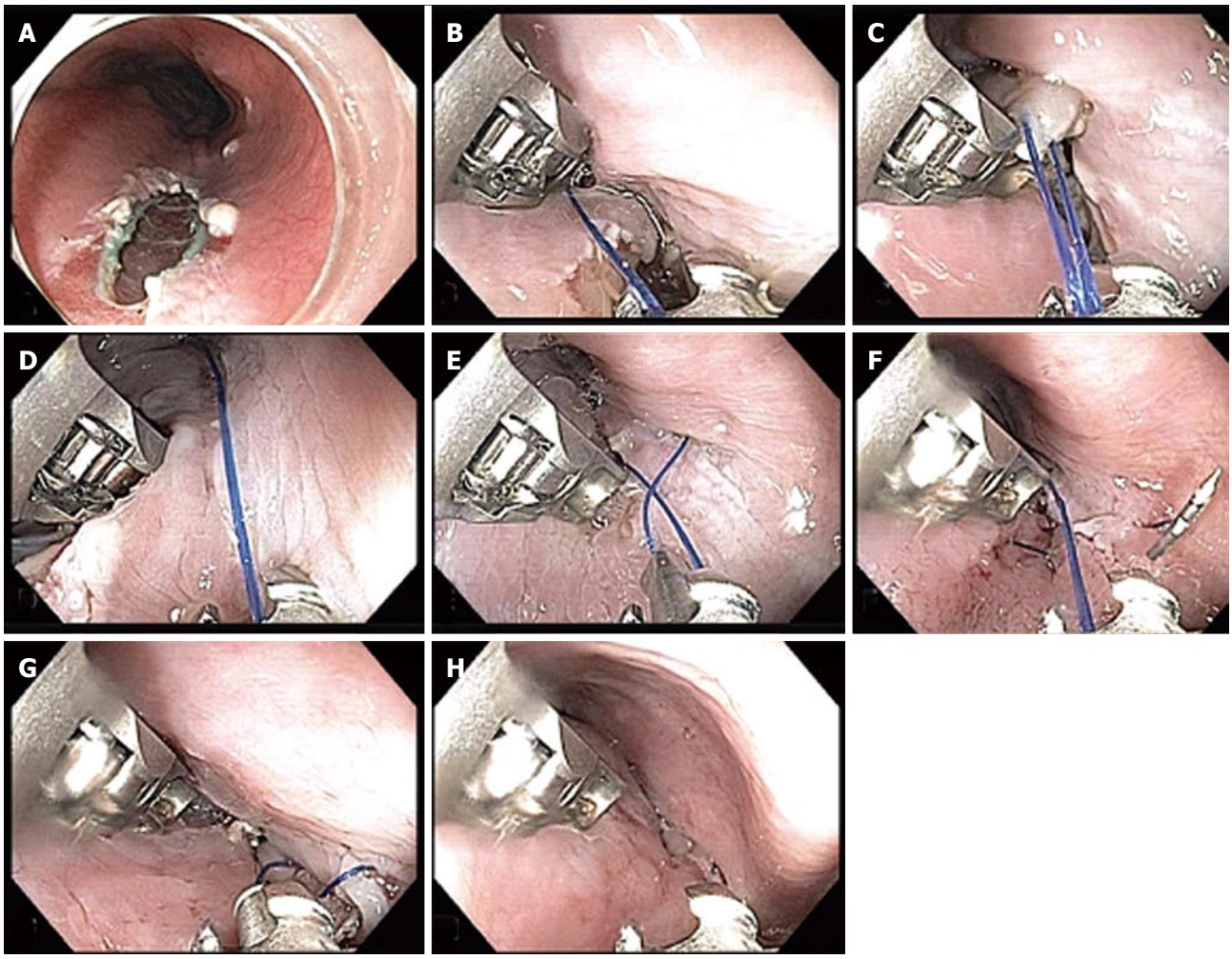

Figure 5 Closure of per oral endoscopic myotomy tunnel orifice with endoscopic suturing device. A: Closure of peroral endoscopic myotomy (POEM) tunnel orifice in a posterior POEM with the tunnel opening at the 5 o' clock position; B, C: We use a single running suture for closure starting at the distal, left margin of the defect as shown here. We attempt to penetrate mucosa and submucosa but not muscularis propria to avoid ischemia and pain or even possible injury to mediastinal structures; D: We proceed with suture placement through the right margin of the defect which is accomplished by torquing the endoscope as shown here; E: It is important to avoid having the running suture (here held by the needle onto the needle transfer catheter prior to loading it onto the needle driver) cross over the long suture leading to the start of the suture line which would then result in inability to properly deploy the cinch to the start or the suture line; F: The single running suture has been completed and has approximated the edges of the defect and the needle has been dropped in order to serve as a T-tag securing the suture at the proximal end of the defect; G, H: The cinch catheter is inserted over the long suture leading to the start of the running suture in the distal end of the defect, the suture is tightened and the cinch is deployed securing the suture at the start of the suture line in the distal end of the defect.

Table 2 Peroral endoscopic myotomy mucosal tunnel closure comparing endoclips and overstitch

	Endoclip	Overstitch
Total number of patients	62 patients	61 patients
Comparison of 25 consecutive closures		
Closure technique (mean number)	8 clips (5-14)	1 suture, 1 cinch, 1 device
Closure duration (mean minutes, $P = 0.1$)	8.8 min (6-15)	10.1 min (5-16)
Cost analysis (mean dollars, $P = 0.2$)	$915.84 ($453.81-$2160)	$818
Hospital Stay (mean days, $P = 0.1$)	1.9 d	1.7 d
Complications	No leaks Increased length of stay (4 d) in one patient with thick mucosal edges approximated with clips and endoloop	No leaks One aborted overstitch closure due to a mucosal tear in the hypopharynx during Overstitch insertion. Had mild sore throat for 4 d

inversely proportionate to stoma diameter[46]. Transoral outlet reduction (TORe) is most effective with a full thickness suturing device as compared to a superficial suturing device, even with similar stoma apertures[47].

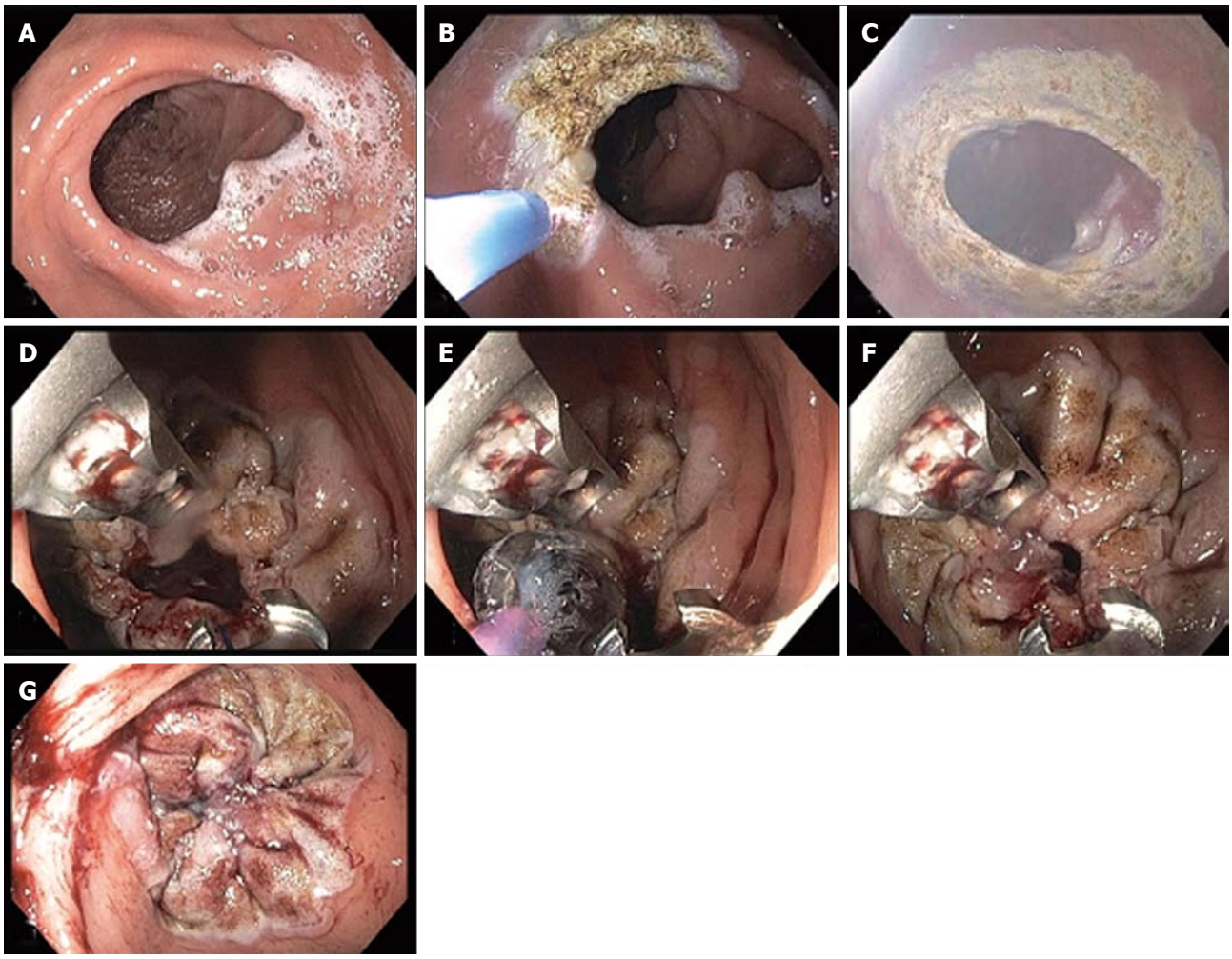

Figure 6 Endoscopic revision of gastrojejunal anastomosis in gastric bypass patient. A: An enlarged gastrojejunal anastomosis is noted; B and C: Argon plasma coagulation was used around the stoma to ablate the mucosa and facilitate tissue fusion during the healing process; D: Two sutures were used obtaining circumferential tissue bites to achieve a purse-like closure of the stoma; E: A 10 mm controlled radial expansion balloon was dilated and placed through the stoma opening via the second channel of the double-channel therapeutic endoscope and then the sutures were tightened so that the final stoma diameter was approximately 10 mm in size; F and G: The balloon was then deflated and removed. A markedly diminished stoma orifice is seen at the end of the procedure.

Preliminary TORe experience at our center in 10 patients is also favorable with mean weight loss of 19 lbs at mean follow-up of 34 wk. Figure 6 demonstrates TORe *via* endoscopic suturing in a 39-year-old woman who had roux en y gastric bypass 14 years ago. Longer term data concerning TORe is being accumulated.

PRIMARY ENDOSCOPIC OBESITY SURGERY

It appears that the restrictive anatomy after surgical sleeve gastroplasty can be duplicated by endoscopic plication of the gastric wall *via* endoscopic suturing. Two groups utilizing an older endoscopic suturing platform (Endocinch) performed gastric restriction in humans with excellent technical success rates and encouraging short term efficacy. Fogel utilized an early generation device of the Endocinch platform to reduce the gastric volume in 64 obese subjects from South America with no reported complications and an impressive 58% excess weight loss at 12 mo that has not been replicated however by other groups[48]. More recently another group used a second generation of the same device used by Fogel to reduce the gastric volume in 18 obese patients from the United States with no complications and a 27% (SD 22%) excess weight loss at 12 mo[49]. Preliminary encouraging data are emerging on endoscopic sleeve gastroplasty performed with the OverStitch device[50]. Under the current protocol followed at the Mayo Clinic, Brigham and Women's, our center and other centers investigating this technique in the United States, sutures are placed approximating the anterior wall, greater curvature and posterior wall of the stomach extending from the antrum to the fundus to achieve restriction similar to that of a surgical sleeve gastroplasty (Figures 7 and 8). The impressive restriction can be seen on the endoscopic images from a patient that underwent the procedure at our institution (Figure 9). Preliminary data indicate no significant morbidity with short-term weight loss similar

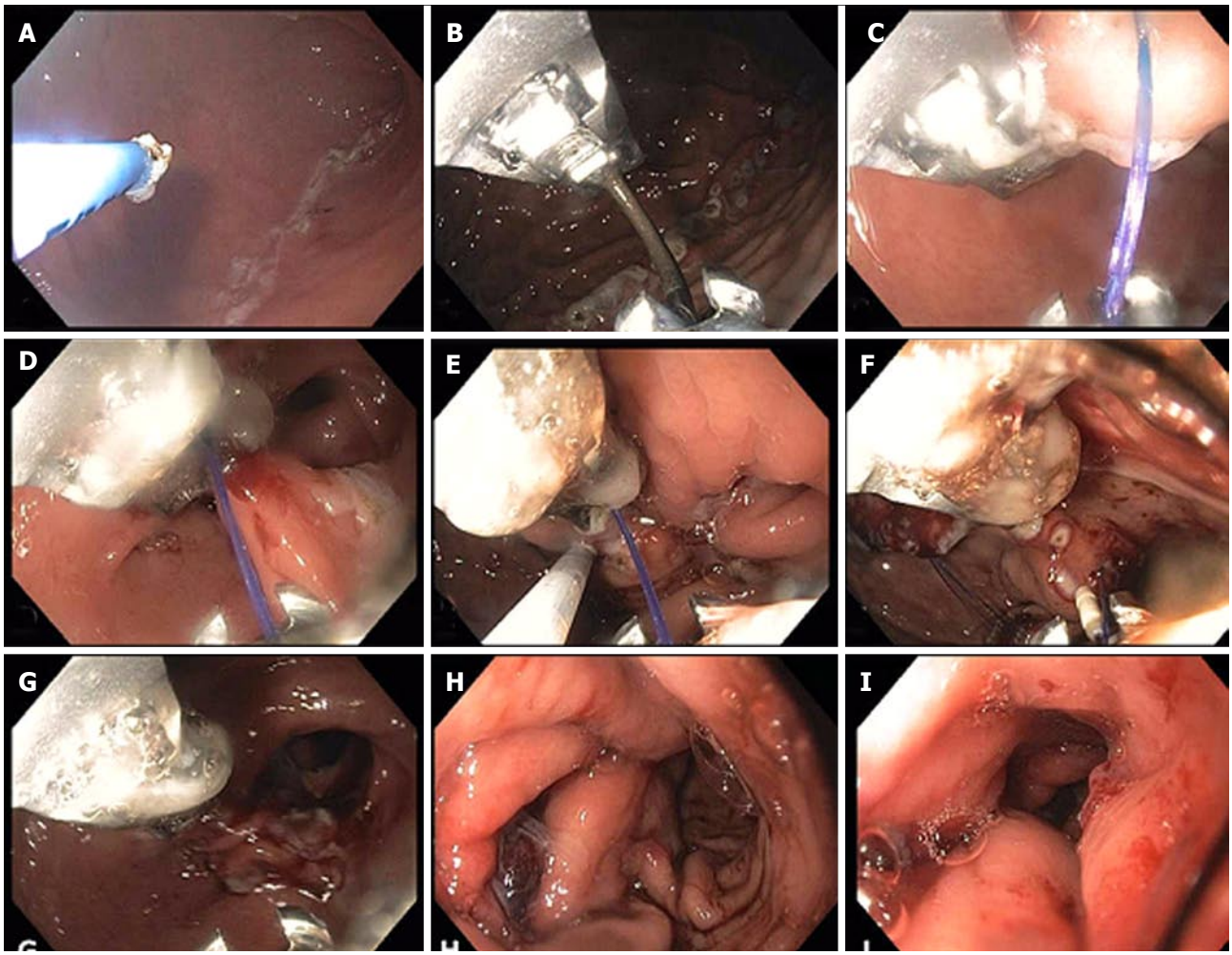

Figure 7 Endoscopic sleeve gastroplasty. A: Initially argon plasma coagulation is used at a setting of 0.8 L 30 W, forced coagulation to mark the anterior and posterior extents of a corridor that will contain the outer sutures to be placed (as shown in the attached schematic (bites along the anterior wall, greater curvature and posterior wall); B: The suturing device is inserted and placement of the first running outer suture is begun as shown in figures C and D reducing the lumen along the greater curvature of the antrum; E: The helical tissue retractor is used through the second channel of the endoscope as seen in figure E to achieve deep, transmural if possible placement of the sutures and to facilitate suture placement in difficult locations; F: Insertion of the cinch device shown at the 6 o'clock position. The running suture can be seen at 7 o'clock prior to tightening; G: After tightening and cinching of the suture the lumen reduction forming the beginning of the endoscopic sleeve can be seen; H: Completion of the outer sutures of the outer sutures showing marked lumen reduction; I: Completion of the inner row of sutures with final appearance of the endoscopic sleeve gastroplasty at the end of the procedure. A tight 3-4 cm tunnel is seen which extends from just distal to the fundus to approximately 3 cm proximal to the pylorus.

to that reported for laparoscopic band (Christopher Gostout personal communication). Thus this procedure may find a niche along with other minimally invasive interventions, such as intragastric balloons, in the treatment of patients with moderate obesity (BMI 30-35) for whom traditional bariatric surgery may represent overtreatment. We have entered an era of endoscopic management of obesity, and the huge economic burden associated with this entity will drive further studies and technological development.

WINTHROP ENDOSCOPIC SUTURING EXPERIENCE

At our institution, we employed the Overstitch endoscopic suturing device extensively and in a variety of ways[51] (Table 3). One hundred and seventy-seven procedures incorporated endoscopic suturing. Since this represents one of the 2 or 3 largest volume series worldwide and includes novel applications such as a large number of POEM tunnel closures, we briefly review these data that illustrate the broad range of applications of endoscopic suturing. We typically do not require an overtube for device insertion. The closure success was remarkable with all patients having suturing for POEM, STER, EFTR, ESD, accidental perforations and leak closures having complete closure. Of these 149 closure procedures, there were no episodes of leakage or wound dehiscence; only 2 minor adverse events including one patient with dysphagia due to stricture at site of tunnel closure requiring a single balloon dilation with total resolution of dysphagia and one superficial mucosal tear in the hypopharynx during OverStitch insertion, which was clinically insignificant except for transient sore throat. Table 2 presents comparative data on POEM closure with clips *vs* suturing. We used clips in the

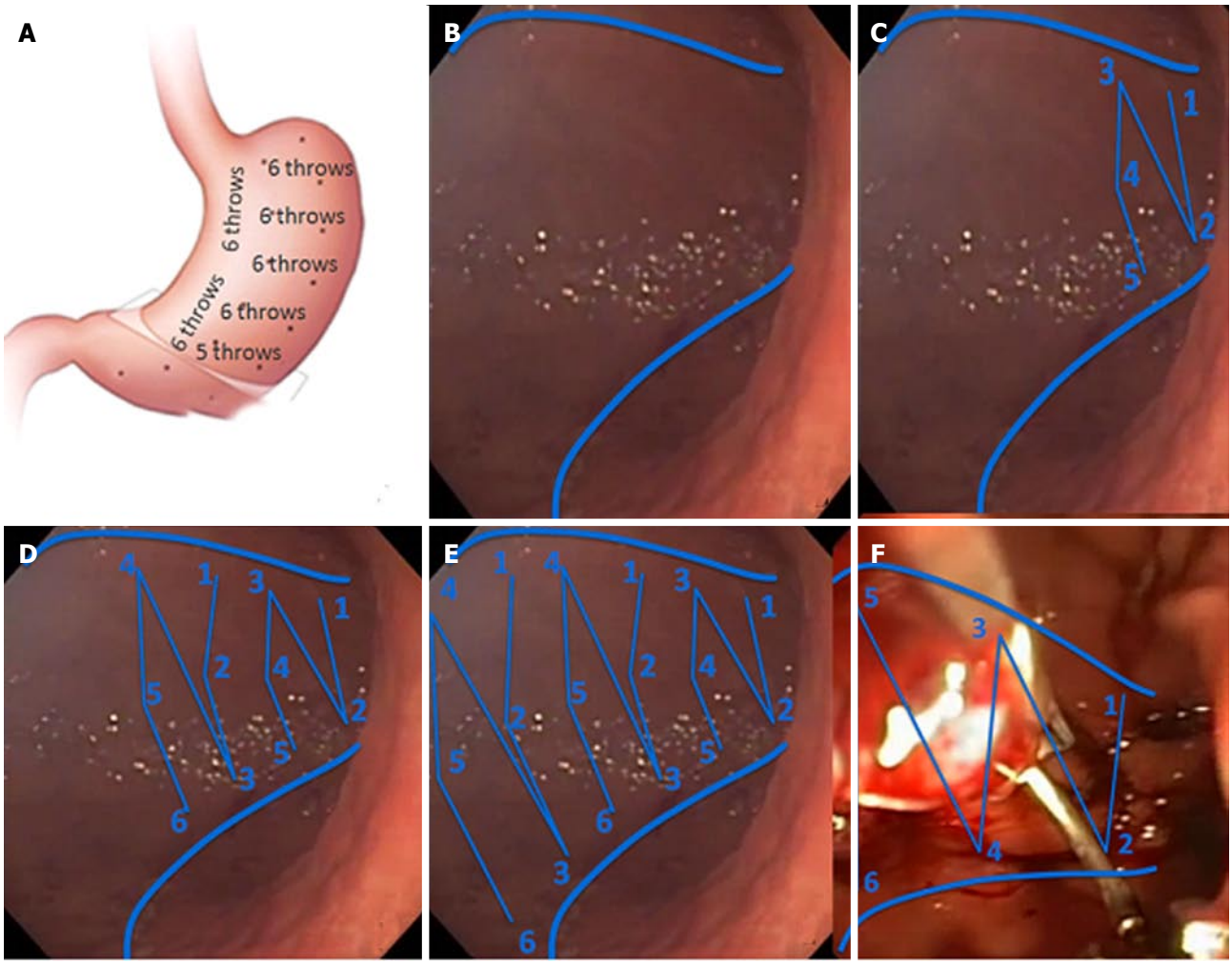

Figure 8 Suture placement needed to achieve endoscopic sleeve gastroplasty. A: Schematic of the configuration of sutures used to achieve endoscopic sleeve gastroplasty. Initially 5 to 8 plication sutures are placed along the greater curvature in a distal to proximal direction, followed by placement of an inner row of 2 to 3 short anterior/posterior "retention sutures" that take some of the tension off the plication sutures; B: Using APC ablation two lines are made along the anterior and posterior wall that mark the outer borders of the plication sutures; C: The first plication suture is placed within 3 cm of the pylorus where due to the narrowing of the lumen results in a modified 5-point suture with the first bites placed on the anterior and posterior wall of the antrum while the 3rd, 4th and 5th bites are placed on the anterior wall, greater curvature and posterior wall; D, E: Subsequent plication sutures all have the same 6 point configuration (anterior wall, greater curvature, posterior wall, anterior wall, greater curvature, posterior wall); F: The inner row of retention sutures consists of sutures of sutures between the anterior and posterior wall a shown (Courtesy Apollo Endosurgery Austin Texas).

Table 3 Winthrop University Hospital endoscopic suturing registry

Indication	Number of Cases	Comment
POEM submucosal tunnel entry closures	100	100% successful closure
EFTR of subepithelial tumor intentional defect closures	24	Mean closure time: POEM/STER -10 min for a mean 2 cm defect
STER submucosal tunnel entry closures	6	EFTR/ESD -13 min for mean 3 cm defect
ESD	22	Perforations/leaks-18 min for mean 1.8 cm defect
Accidental perforation	16	Complications: No episodes of leakage or wound dehiscence 2 minor adverse events
Transoral outlet reduction	7	At mean 34 wk follow-up, mean 19.1 lb weight loss (2-34 lbs)
Primary sleeve gastroplasty	1	At 32 wk follow-up pt lost 40 lbs
Ulcer oversew	1	Required surgical intervention 2 wk post procedure due to lack of response
Leak/fistulae closure	14	2 leaks and 12 fistulas (9 gastric sleeves, 2 roux en y gastric bypass, 1 post- PEG tube removal. 2/2 (100%) leaks and 10/12 (83%) fistulas were successfully closed
Stent anchoring	10	Mean time was 8 min. No episodes of stent migration at mean 8 wk

POEM: Per oral endoscopic myotomy; EFTR: Endoscopic full thickness resection; STER: Submucosal tunnel endoscopic resection; ESD: Endoscopic submucosal dissection.

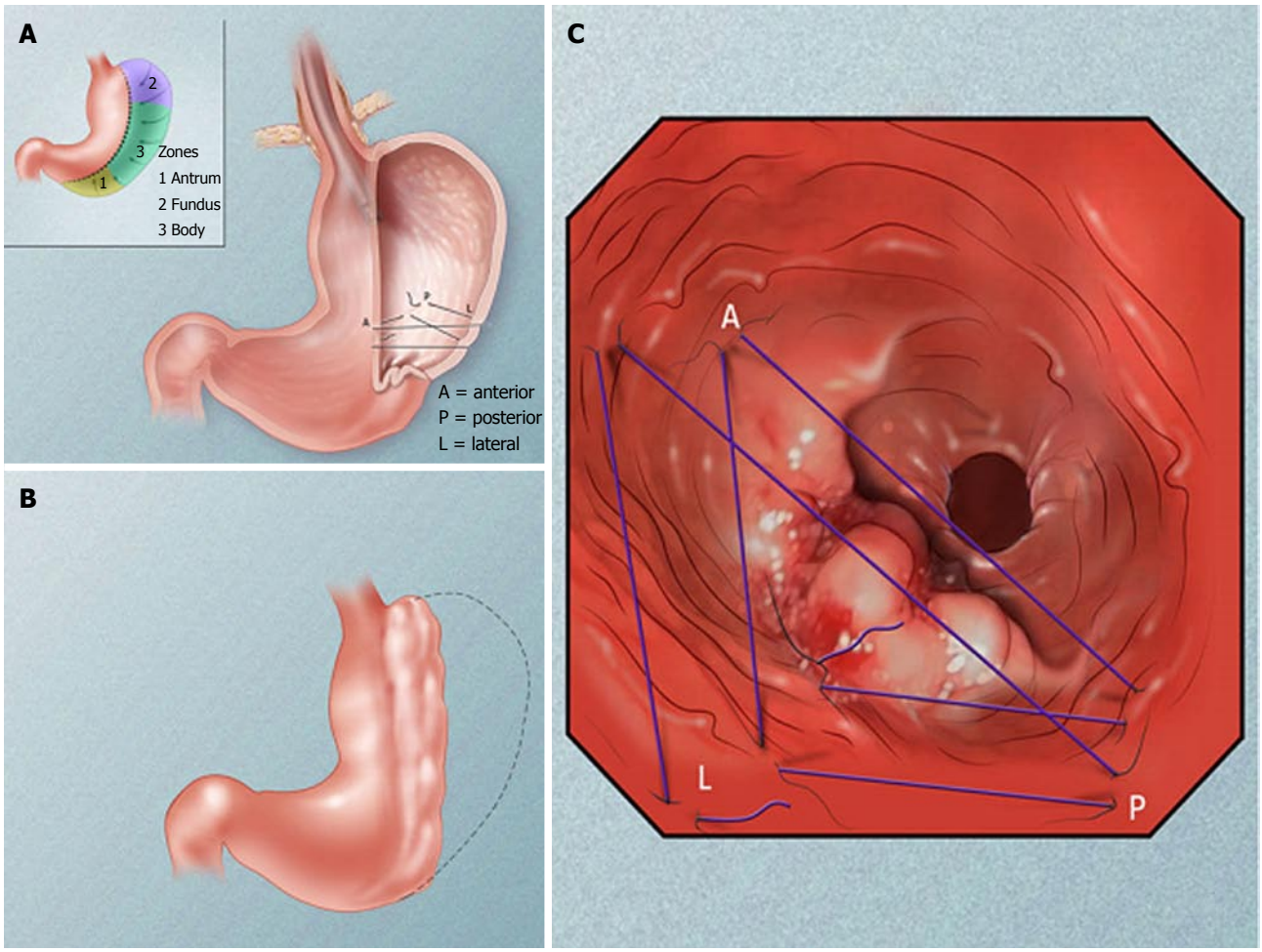

Figure 9 Illustration of the overall sleeve gastroplasty configuration achieved by placement of sutures as to achieve plication of the greater curvature of the stomach. A: Endoscopic gastroplication pattern; B: Plicated stomach; C: Schematic of suture pattern (Courtesy Apollo Endosurgery Austin Texas).

first half of our experience but switched to endoscopic suturing over the past two years. We selected the most recent 25 consecutive cases in each group (to eliminate any learning curve effects) to compare cost, closure time, length of stay and complications. There was no statistically significant difference between clips and suturing for POEM closure (however, regarding cost, it should be noted that this reflects costs of clips and the suturing device in the United States). All 10 sutured stents were in the same place at 8 wk. There was significant weight loss with both gastric outlet stomal reduction and the one primary sleeve gastroplasty. There were two fistula patients that required surgery and the single ulcer oversew patient required surgery for no evident healing at 2 wk.

FUTURE CONSIDERATIONS

The current version of the OverStitch, the dominant endoscopic suturing device requires a double channel gastroscope which limits flexibility and length of insertion thus making suturing in difficult locations such the gastric fundus or duodenum or in deep locations such as the right colon and small bowel difficult or impossible. Newer versions of the device are expected to address these issues. Looking further into the future, it is unclear what the impact of the development of flexible endoscopic staplers might have on endoscopic suturing. One would expect that selection of stapler *vs* suturing device would be guided by similar considerations as guide selection of hand-sewn *vs* stapled closures or anastomoses in surgery. However, unfortunately, this dilemma may not be a consideration for the near future given the expense and technical hurdles involved in developing flexible endoscopic staplers which likely resulted in two prior stapler devices having failed to become commercially viable[52,53]. Another device is in early trials but in its current version is restricted to a single indication, endoscopic fundoplication to treat GERD.

CONCLUSION

There has been a true revolution in gastrointestinal endoscopy with the evolution of endoscopic suturing to now be practically incorporated into clinical practice. As noted, there is a wide gamut of potential applications. There are issues including training and best imple-

mentation, but these should be clarified with time. The current instruments may be replaced or refined with technological developments and experience. Endoscopic suturing is here to stay!

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Endoscopic botox injections in therapy of refractory gastroparesis

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Abstract

Gastroparesis (GP) is a common disease seen in gastroenterology practice particularly in western countries, and it may be underdiagnosed. The available drug therapies for this condition are quite disappointing. Botulinum toxin type A (BT) has been found to be effective therapy in various spastic disorders of smooth muscle of gastrointestinal tract. However, the benefits of BT injections in GP have been unclear. Several retrospective and open label studies have shown clinical advantages of intrapyloric Botulinum toxin type A injections, while two small randomized trials did not show positive results. Therefore, the available published studies yielded conflicting results leading to fading out of botox therapy for GP. We recognize possible clinical benefit of BT injections without any disadvantages of this treatment. We are calling for revisiting the endoscopy guided botox therapy in refractory GP. In this review we discuss important features of these studies pointing out differences in results among them. Differences in patient selection, doses and method of administration of botox toxin in the prior studies may be the cause of conflicting results. The mechanism of action, indications, efficacy and side-effects of BT are reviewed. Finally, we recognize limited evidence to recommend BT in GP and calling attention for future research in this field since no advances in drug management had been made in the last two decades.

Key words: Gastroparesis; Delayed gastric emptying; Botox; Botulinum toxin; Refractory gastroparesis

Core tip: Refractory gastroparesis (GP) has been identified as a chronic debilitating disease. After failure of diet and prokinetic drugs for treatment of refractory GP only surgical options are left. Because of the limited available treatment options and frequent failure of medical therapy, botulinum toxin (BT) injection in the pylorus might offer clinical value in GP. Currently available evidence is not strong enough to support the recommendation of this procedure in all patients with

refractory GP; but promising results have been seen as most patients have noticed symptomatic improvement. Although BT injections were successful in some GP patients, the role of BT remains undetermined. We addressed the position of botulinum toxin in the spectrum of available treatments for refractory GP. Continuing other treatment modalities after BT may improve the results.

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INTRODUCTION

Refractory gastroparesis (GP) constitutes a major therapeutic challenge. Drug therapies are often found to be ineffective for a long term treatment. We found in our practice that some GP patients noticed significant improvement in symptoms and quality of life after botulinum toxin (BT) injections. Therefore, we question if there is a role for intrapyloric BT-A injections for treatment of GP. In this review article, the latest available literature (using Medline) and our own data on this topic will be summarized.

Epidemiology and types of GP

GP has been defined as a chronic disorder of impaired gastric motility in the absence of any mechanical obstruction of the upper gastrointestinal tract. Characteristic symptoms include early satiety, nausea, vomiting, bloating, postprandial fullness and upper abdominal pain[1]. The age adjusted prevalence of GP has been estimated to be 9.6 for men and 37.8 for women per 100000 by a community based study[2]. Most cases of GP have been found to be idiopathic or secondary to autonomic neuropathy associated with diabetes mellitus, surgery, Parkinson disease and collagen vascular diseases[3,4].

Idiopathic GP (IGP), the most common type of GP, is a result of viral or bacterial infection[5]. The underlying etiology of IGP is degeneration of myenteric plexus combined with loss of interstitial cells of Cajal[6]. In diabetic GP (DGP), many mechanisms are responsible for delayed gastric emptying (GE) including neuropathy which affects vagal nerve, reduction in the numbers of intrinsic inhibitory neurons responsible for motor coordination, and reduction in number of pacemaker cells. Acute hyperglycemia with serum glucose levels > 288 mg/dL significantly delays GE in diabetic patients when compared to euglycemia[7]. Post-surgical GP is less common type seen after surgery for peptic ulcer, fundoplication and bariatric surgery, pylorus-sparing pancreatoduodenectomy and heart and lung transplantation[8-10].

Pathophysiology and diagnosis of GP

Delayed GE as the major pathophysiological mechanism of GP is multifactorial, which includes impaired fundal tone, antral hypomotility, antroduodenal discoordination, gastric pacemaker dysrhythmias and excessive inhibitory feedback from the small bowel to the stomach[11]. It has been suggested that increased tone of the pylorus (pylorospasm) may contribute to delayed gastric emptying[12]. Therefore, reduction of pyloric pressure may facilitate improved GE and this can be achieved by botulinum toxin-A (BT-A) injection.

Diagnosis of GP is established based on the presence of clinical symptoms of GP, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying. It is also recommended to document delayed gastric emptying before starting drug therapy of gastroparesis[13].

Treatment of GP

Treatment options for GP include dietary changes, prokinetic drugs, antiemetics, correction of malnutrition and electrolyte disturbances, jejunal feeding, parenteral nutrition, gastric neurostimulation therapy and surgery. In refractory cases of GP, a total gastrectomy has been suggested[14]. Prokinetic agents are the mainstay of treatment in GP after diet failure. However, the side effects and lack of effectiveness limits the long-term use of prokinetics in GP. Because of limited medical options, botulinum toxin-A intrapyloric injections have been offered as a salvage therapy in cases of refractory GP.

Botulinum toxin: Mechanism of action and clinical uses

Botulinum toxin, a bacterial neurotoxin, is one of the most potent paralytic agents of skeletal muscle. In two (2) *in-vivo* studies on piglets evaluating effects of BT-A on smooth muscle, the basal sphincter of Oddi pressure decreased by 50%, and lower esophageal sphincter pressure decreased by 60% with BT-A injection when compared to saline injection[15,16]. An *in vitro* study done on pyloric muscle strips showed that BT-A injection was able to decrease contractions induced by acetylcholine (Ach), substance P and electric field stimulation[17]. Two underlying mechanisms have been proposed for the action of BT-A. At low doses, BT-A inhibits the calcium dependent release of acetylcholine from cholinergic nerve terminals, and at higher doses direct inhibition of smooth muscle contraction has been observed[17]. The effects of BT-A are time and concentration dependent as axonal sprouting and accumulation of extrajunctional Ach lead to slow reversal of denervation[18,19].

BT-A has been found to be effective in the treatment of spastic disorders of smooth muscle in the upper and lower gastrointestinal tract. Case reports and prospective trials have shown positive results with BT-A administration in treatment of diffuse esophageal spasm[20], achalasia[21], oropharyngeal dysphagia[22], anismus[23], anal fissures[24] and anterior rectocele[25]. Administration of BT-A has a very low rate of adverse reactions and complications. Several case reports and

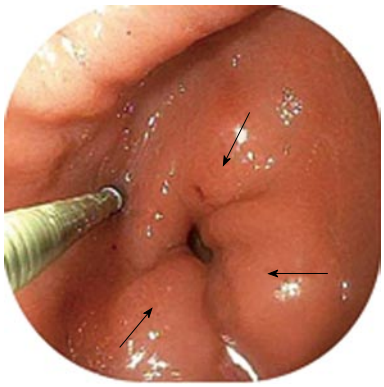

Figure 1 Endoscopic technique for botox injection in the pylorus (4 quadrants - see arrows).

trials of the effects of intrapyloric BT-A injection in GP have been published. Two small prospective studies suggested a limited value of endoscopic intrapyloric BT-A injections in GP[26,27].

There is conflicting data whether BT-A can effectively relieve the symptoms, improve quality of life and improve the rate of gastric emptying in GP patients.

Suggested technique of BT-A injection

The commercial preparation of BT-A in the United States is supplied in vials containing a 50 or 100 U of the lyophilized powder. The powder is diluted in 5 mL of normal saline to yield a solution containing 20-25 U/mL. After diagnostic upper endoscopy, the pyloric sphincter area is identified, and a sclerotherapy needle (23 or 25 gauge) is introduced through the biopsy channel. Aliquots of 1-1.5 mL (20-25 U botulinum toxin/mL) are injected into each of four quadrants of the pylorus, for a total of 100 U (See Figure 1). A total dose between 100 to 200 U can be injected. Patients go home after routine post-sedation criteria are met and they are allowed to eat light meal later on the same day.

CLINICAL STUDIES OF BT-A FOR TREATMENT OF GP

The first data on the intrapyloric application of botulinum toxin in patients with GP was published by Ezzeddine *et al*[28] in 2002. An open label trial included 6 males with diabetic GP, documented by solid phase gastric emptying study, and a mean age of 62 years. All patients had 100 U of botulinum toxin injected in the pyloric sphincter. A solid phase gastric emptying study was done before the BT-A injection, and then repeated at 48 h and 6 wk after the procedure. The mean solid phase gastric emptying at 90 min improved from 27.8% before BT-A injection to 44.4% at 2 wk, and 49% at 6 wk. Baseline clinical symptoms were recorded and the symptoms were reassessed at 2 wk and 6 wk interval after the BT-A injection to document improvement. A mean improvement of 55% was noticed at both 2 and 6 wk. No complications were seen after BT-A therapy. This study was very limited in terms of population and control group but it certainly demonstrated some clinical efficacy and immediate improvement in gastric emptying rate.

In an open label trial[29], eight patients (including 6 women) with type 1 diabetes and GP were studied. Mean age was 41 years. A control group consisted of asymptomatic non-diabetic patients matched for age and gender. A higher dose of BT-A 200 U was used. Clinical symptoms, antro-pyloric manometry, gastric emptying, weight and insulin use were measured at baseline and at 12 wk with follow up completed in 7 patients. Prokinetic drugs were not discontinued during the trial. Significant improvement in symptoms after the BT-A injection was reported in all the patients with the average symptom score reduction to 12 from 27.4 patients had improvement in the solid phase gastric emptying post therapy including 1 case of normal GE study. Three patients had no improvement in GE, and 1 patient had a worse gastric emptying rate when compared to the pre-procedural values. Radiologists reading the gastric emptying study were blinded to the trial protocol. Pylorospasm was demonstrated on antro-pyloric manometry in all patients with GP, but it was not seen in any of the controls. Significant reduction in pylorospasm was found after BT-A when compared to baseline. Insulin requirement was increased in 4 patients at 8 wk and remained increased in 3 of them at 12 wk follow up. Weight gain was noticed in all patients except one. Prokinetic drug use was reduced in 50% of the patients.

A retrospective study by Bromer *et al*[30] included 63 patients (53 women; 10 men) with average age 42 years. Most of the patients (44) received a dose of BT-A 200 U and 13 patients received 100 U. No dose was recorded for 6 cases. The outcomes in this study were assessed on the basis of improvement in major GP symptoms. Forty-three percent patients reported improvement in symptoms, and men had better response to BT-A therapy than women. The mean duration of response to BT-A therapy was 5.1 mo. Treatment with BT-A was repeated based on recurrence of symptoms. Apart from the small study population, the absence of any quantitative measure of improvement and no standardized scale of symptomatic relief limited the quality of this study.

A small retrospective analysis of 21 patients (15 females) with refractory GP was recently published from the United Kingdom[31]. The mean age of patients was 47.8 years and 81% of cases were secondary to DGP. A dose of 200 U of BT-A was used in all the patients. The mean follow up was 2 years. Sixty-two percent patients reported response to treatment compared to 19% non-responders. The mean response duration was 4.2 mo. Weight gain and increased insulin requirement was observed in the diabetic group. Greater effectiveness of BT-A therapy was found in the diabetic population compared to idiopathic GP cases.

In an open label trial[32] of 10 female patients with

IGP, a mean duration of symptoms of 4 years and prokinetics failure, BT-A in doses 80-100 U was used. Response was assessed on the basis of upper GI symptom improvement and 4-h solid phase gastric emptying study at 4 wk after the treatment compared to the baseline. Nine out of 10 patients reported improvement in symptom scores. An improvement in the gastric emptying rate was found in 7 of the 10 patients (70%), while 2 patients had no change and 1 case had worsening of gastric emptying rate. The patients were followed up for at least 6 mo. In 5 out of 10 patients repeat BT-A injections were required due to recurrent symptoms. All the patients reported improvement after the second BT-A injection. This study showed effectiveness of repeat BT-A injection but at the same time raised a question regarding long term outcomes of the procedure.

In another open label study[33], 20 patients with GP (17 women; 17 IGP) received 100 U of BT-A injections in the pylorus. An assessment of solid and liquid gastric emptying, and improvement in intensity of cardinal GP symptoms was performed at 4 wk. Significant improvement was found in solid phase gastric emptying and the symptom score compared to pre procedural numbers, but no improvement in liquid phase emptying was seen. No correlation was found between symptomatic improvement and the change in gastric emptying rate. This study had only a short follow up. The study raised an important question pertaining to the methods of measurement of improvement in GP patients. If we should assess the objective improvement based on the diagnostic test (GE study), a measurable standard, or the subjective improvement should be determined on the basis of their symptom scores as outcome measures.

Those promising results from the open label trials and observational studies prompted researchers to conduct randomized control trials. Two randomized, placebo controlled double blinded studies were published. In a trial by Friedenberg *et al*[26], a total of 32 patients were divided into two groups of 16, and randomized to receive either 200 U of botulinum toxin or saline injection in the pylorus. Each group contained 9 patients with diabetic GP. All patients had a symptom score $\geqslant$ 27. A decrease of 9 points or more in the symptom score at 1-mo follow up was considered as the primary endpoint. Only 6 patients in the botox group showed improvement compared to 9 patients in the saline injection group. Gastric emptying rate improved markedly in the BT-A group, but did not reach statistical significance when compared to the placebo group. Out of the 32 patients, 17 had no symptom improvement including 10 from the BT-A group. The study was based on an assumption of an efficacy of 80% for the BT-A injection which was relatively high and had a small population size and low statistical power. The second randomized controlled study by Arts *et al*[27] included 23 patients with GP (18 women, and 19 IGP). The mean age of the patients was 45 years. The study was double-blinded and patients received either BT-A injection at a dose of 100 U or saline injection in a cross-over pattern. Baseline gastric emptying and GP cardinal symptom index (GCSI) were recorded. In the first session, 12 patients received BT-A injections and 11 had saline injections. Both groups showed considerable improvement in the solid phase gastric emptying after the first injection. But no subsequent improvement was seen in either group after the second injection (cross-over). No statistically significant difference was seen when pooled data was compared from both groups after the two procedures. Both groups showed similar improvement in GCSI. Even though the pooled data analysis showed considerable improvement of post-prandial fullness and bloating in the BT-A group, it was not statistically different from the placebo group.

The largest study published up to date was a retrospective trial of 179 patients including 81 with DGP and 76 IGP cases[4]. The response was measured in terms of symptom improvement and change in body weight within 1 to 4 mo after BT-A injection. Almost 51% patients reported benefit and 32% of them had no benefit from the BT-A therapy. No record was available for the rest of the patients. BT-A was injected in doses ranging between 100-200 U. Patients who received higher doses reported better symptom control. Many patients (87) underwent repeat BT-A injections and received doses of 150 U or 200 U. Similar results were observed on repeat injections among first time responders and non-responders. This study results suggested a better response in women, younger patients (< 50 years old) and those with idiopathic GP.

Recently a case series[34] of 3 patients with diabetic GP and islet cell transplant between ages 42-55 years was published. They were treated with intrapyloric BT-A injections (2 patients received 200 U and one received 150 U). Symptomatic improvement was noticed in all the patients. The response lasted 6-8 wk in 2 patients who had BT-A 200 U injections and 8 mo in the patient who received lower dose 150 U. This result raised a question of the most effective dose to use for intrapyloric BT-A injections in GP.

The data on the use of BT-A in pediatric population with GP is even more scant. Only 1 study[35] has been published on BT-A in refractory GP. A retrospective review of 47 children including 23 girls was conducted with follow up available for 45 of them. The mean age of the patients was 9.8 years and mean follow up was 18 mo. The majority of the patients (66%) had idiopathic GP. Botulinum toxin was injected at a dose of 6 U/kg up to a maximum total dose of 100 U. The outcome was measured based on symptoms index as no response, mild, moderate or complete resolution of symptoms. At least mild improvement in symptoms was seen in 66.7% patients, with only 1 patient reporting worsening of symptoms. Repeat BT-A injections were required in 18 patients, out of which 8 showed response and 7 did not benefit from repeat treatment. Median duration of response to BT-A was 3 mo. The children older than 12

Table 1 Summary of the literature on use of botulinum toxin injection for gastroparesis in adults

Ref.	Number of patients	Study design	Botox dose (units)	Results (% of patients with symptomatic improvement)
Ezzeddine *et al*[28]	6	Prospective non-controlled	100	55
Lacy *et al*[29]	8	Prospective non-controlled	200	100
Bromer *et al*[30]	63	Retrospective	100 (n = 13) 200 (n = 44) Unknown (n = 6)	43
Rameshshanker *et al*[31]	21	Retrospective	200	62
Miller *et al*[32]	10	Prospective non-controlled	80-100	100
Arts *et al*[33]	20	Prospective non-controlled	100	100
Friedenberg *et al*[26]	32	RCT	200	37.5
Arts *et al*[27]	23	RCT	100	100[1]
Coleski *et al*[4]	179	Retrospective	100-200	51

[1]100% improvement was seen on botulinum toxin as well as normal saline so botox was not proved to be better than placebo. RCT: Randomized-controlled trial; n: Number of patients.

years showed better response when compared to those of < 12 years old. This study was important by showing that efficacy rates, duration of response and safety of botox in children were comparable to the results seen in adult population.

In a recent meta-analysis[36] of 15 studies, including single case reports of GP, almost all open label and retrospective studies showed a beneficial effect of BT-A treatment for GP, while 2 randomized control trials have shown no superiority of BT-A in comparison to placebo. Based on the meta-analysis, it has been suggested that the current evidence did not justify the use of BT-A in GP patients, but the analysis consisted of only a small population (186 patients). Across these studies, the 2 randomized control trials included in the meta-analysis were found to be significantly heterogeneous. Because of these limitations, the meta-analysis failed to add any useful knowledge for practical purposes in therapy of GP (Table 1).

DISCUSSION

Botulinum toxin has been widely used in the past as a treatment option for patients with refractory GP with clinically beneficial effects, mainly symptomatic improvement. All the open label trials have reported the intrapyloric BT-A injection to be useful therapy in GP[28-35]. However, two small prospective randomized control trials (RCT)[26,27] did not show positive response to botox injection in regards to symptomatic improvement and rate of gastric emptying. Both studies in different subgroups (DGP *vs* IGP) of patients have not proven BT-A to be superior to normal saline injection, and cast some doubts over its effectiveness. Based on results of those RCTs some GI societies do not recommend routine use of botox injections as a treatment option in GP.

Limitations of therapy for gastorparesis

It has been a major concern that currently available drug therapy for severe GP is very limited. Traditionally prokinetics, metoclopramide, domperidone and cisapride, have been widely used in the treatment of functional dyspepsia and GP[37]. These prokinetic agents work by increasing antral contractility and accelerating gastric emptying[38]. In a systematic analysis, prokinetics have been shown to be more effective than placebo in GP by improving the symptoms of postprandial fullness, nausea and vomiting[39-42]. However, available prokinetic drugs only modestly enhance gastric emptying and the evidence that their symptomatic improvement in GP is related to enhancement of gastric emptying is actually lacking. Serious side effects such as cardiac arrhythmias (QT prolongation) seen with cisapride (Propulsid; Janssen Pharmaceutica, Titusville, NJ) led to withdrawal of the drug from United States market in 2000[43]. Cisapride was also banned in India and Philippines in 2011, and its use in Europe has also been quite limited. Metoclopramide (Reglan; A. H. Robins, Richmond, Va) is the most commonly used drug for the treatment of GP. However, extrapyramidal symptoms and sedative effects of metoclopramide limited its usage in GP. Metoclopramide significantly increases the risk of tardive dyskinesia, drug-induced Parkinsonism, and subjective akathisia[44]. The severity of tardive dyskinesia was greater in diabetics when compared to non-diabetics[44]. A dramatic reduction in prescribing of metoclopramide by clinicians for GP has been seen after a black box warning was placed for the risk of tardive dyskinesia when used for prolonged period[45]. Side effects are a common reason for discontinuation of metoclopramide therapy. Erythromycin is the only other Food and Drug Administration (FDA) approved drug for use in GP. Studies have shown symptom improvement in only 43% of the patients taking

erythromycin[46]. The use of erythromycin is often limited by development of tachyphylaxis as a result of down regulation of motilin receptors, which develops days after initiating the treatment[47]. Other side effects of erythromycin such as nausea, vomiting, and abdominal pain seen more often with higher doses can result in discontinuation of therapy[48,49]. Domperidone (Motilium; Janssen) appears to be effective for treating symptoms of GP. However, it is not available for sale in the United States. Domperidone has not been approved by the FDA because of concerns regarding its cardiotoxicity, mainly QT prolongation seen especially in hypokalemic patients[50]. The hurdles in obtaining the drug have discouraged the physicians in United States regarding its applications in GP. Currently, domperidone can be prescribed in United States for GP patients 12 years of age and older through an expanded access investigational new drug application and local institutional review board (IRB) approval[51].

Hence, there is a clear need for new therapeutic approaches for the treatment of GP. Gastric electric stimulator (GES) has been shown in clinical studies to be effective to control nausea and vomiting in GP patients. Even though patients with refractory symptoms have embraced the availability of this device, the special status and certain requirements used by some third party insurance carriers may deny coverage. The GES device has a humanitarian device status. Therefore, the gastric electrical stimulator cannot be implanted at any center unless its placement has been approved by the local IRB. Candidates for this therapy are patients with diabetes and IGP with relentless nausea and vomiting, who have failed medical therapy. Conversely, patients without nausea and vomiting but with other manifestations such as fullness, early satiety, anorexia, and abdominal pain have not been shown to predictably respond to gastric stimulation[52].

General concerns regarding studies on botox in GP

Most published studies looked only at a total symptom score (GCSI) rather than selected symptoms of nausea and vomiting. From clinical standpoint improvement in symptoms appears to be the most important outcome when treating patients with GP. The most troublesome symptoms for patients are nausea and vomiting, which tremendously limit oral intake and may lead to progressive weight loss and malnutrition. Abdominal pain associated with GP is the most challenging symptom to treat since patients often request pain medications, especially narcotics, and those drugs can lead to further delay in gastric emptying and diffuse GI tract dysmotility. Chronic dependence on narcotics has to be recognized in patients with both IGP and DGP. Those patients are taking opioids for different reasons including abdominal pain, but often not related to GP. Narcotics use makes this condition more difficult to treat. For some patients discontinuation of pain medications is not a viable option because of their quality of life.

In patients with refractory GP, even a partial clinical response may provide significant improvement in quality of life and possibly reduce number of hospitalizations. On the other hand, improvement in GE has not been shown to correlate with symptom improvement in this patient population. Therefore assessing response to BT-A based on GE study only has its own limitations.

Patients with severe refractory GP often require frequent visits to emergency center (ER) and hospitalizations, which is also associated with higher cost of medical care. Because of above limitations and high prevalence of GP, other therapeutic options are needed to improve symptoms and quality of life in GP patients. With the limited availability of medical treatment options, side effects and drug failure, we believe that physicians may need to reconsider botox as a trial therapy before directing patient with refractory GP for more aggressive treatment such as surgical interventions including placement of jejunostomy tube or GES and gastrectomy.

Our limited experience with Botox therapy in GP

In our small retrospective unpublished study of patients with GP (confirmed by solid phase gastric emptying study) treated with intrapyloric BT-A injection, a survey was performed to assess symptoms, the overall improvement after procedure, and the number of visits to ER and hospitalizations[53]. Twenty-five patients (19 females; 6 males) were included in the analysis. The causes of GP were idiopathic 17, diabetes 6, and postsurgical 2. Mean follow up was 31 mo. Seventy-two percent of our patients noticed significant (> 50%) symptom improvement. The patients who benefited the most from BT-A injection were males and those with IGP. Twenty-eight percent of patients (7/25), non-responders to botox therapy underwent laparoscopic GES placement. Reduction in number of ER visits and hospitalizations was reported by 24% of patients.

Role of botox in treatment of GP

The results of available literature are quite controversial to determine the clinical effects of botox therapy in GP. Some patients clearly reported symptomatic improvement with botox therapy. In refractory GP cases it is quite difficult to reject this therapeutic option especially as it is very safe.

For example, there is also controversy on effectiveness of botox in patients with anismus, but it has been often used since no other therapies offer benefits in this condition. We have solid data available on use of botox in achalasia, including safety and need for repeat injections. Despite more effective and permanent solutions available including Heller myotomy and peroral endoscopic myotomy, BT-A injections are still in the armamentarium for achalasia[54,55].

Several questions need to be further addressed regarding botox application in refractory GP. First, it is unclear, which patients with GP benefit the most from botox therapy. Some studies have suggested better results in patients with IGP including our own data[4,53].

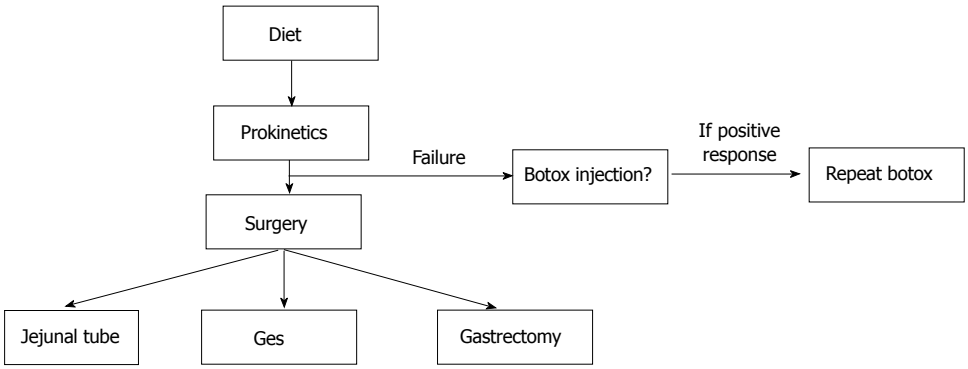

Figure 2 Summary of therapeutic options for gastroparesis. GES: Gastric electric stimulation.

There may be also a sex difference in response to BT-A injections. In a one retrospective study men had superior response[30], while the other large study showed the opposite results[4]. The effects of patient age on outcomes also need to be evaluated further. In pediatric population, older children appeared to have better results to BT-A injection[35]. There is a concern regarding safety of multiple BT-A injections into pylorus which could lead to local scarring as documented for comparison in achalasia patients[56,57].

Another issue that requires further study is to evaluate if the effect of botox injection may be dose dependent? Is a higher dose of botox more beneficial in GP? There is no clear answer to this question. In the RCTs botox was mainly used in two different dosages of 100 U or 200 U, and both showed negative outcomes[26,27]. Question has been raised about the effectiveness of higher dose of botox and the length of the response[34]. For example, in achalasia, no data exist to support that higher dose of botox is more effective and has longer lasting beneficial effect. One of the concerns is rather a short lasting effect of BT-A injections in GP. Based on the available studies the beneficial effects of Botox lasted between 3-8 mo[32,34]. Therefore, patients may require additional BT-A injections. The results on the duration of response to BT-A injection appear to be similar to published data in patients with achalasia. Often retreatment may be needed.

When to repeat BT-A injection? Should botox be used if there is no prior response or only if previously there was a good response to it? Should a higher dose of botox be injected next time if no response is found to the first treatment? Should the dose of botox be selected based on the severity of delayed gastric emptying?

Based on the prior studies, patients who had a positive response to the first dose continued to respond to repeat BT-A injections[4,32]. The studies do not provide an answer in which setting to use repeat botox. In our practice we use a standard dose of 100 U in each case. From personal experience we repeat BT-A injection only if there is an initial symptomatic improvement after first injection. The BT-A injections are repeated based on duration of response typically every 6 mo if needed. In patients with IGP spontaneous improvement in symptoms over time can be expected. Therefore botox injection may be used as a bridging therapy during a period of severe symptoms before the condition can be managed by diet and prokinetic drugs only.

To our knowledge no studies evaluated quality of life in patients with GP after BT-A injections. This issue may also be evaluated in further studies. If lower number of ER visits or hospitalizations can be documented with Botox therapy this could have an impact on cost of care in GP patients. Finally, we recognize that patients after BT-A injection need to continue to follow the diet and drug therapy. Diet and prokinetics adjustments should be done gradually as patients report symptomatic improvement. In only one study a reduction in prokinetic medication use has been addressed as an outcome measure[29].

There may still be a role for Botox use when patients fail diet modification, prokinetics or when the promotility drugs are not available. (See our proposed algorithm (Figure 2). At present there is no clear answer which patients benefit the most from botox injection. In general, patients have no contraindications for BT-A injection unless they face major cardiopulmonary issues not allowing for a safe endoscopy. Studies suggest that GP patients with pylorospasm have the best response to BT-A injections. However, in clinical practice, no easy access to gastroduodenal motility testing is available. Therefore, a decision to use botox has to be individualized in GP. Botox injections should not be used routinely in all GP cases.

CONCLUSION

Pyloric injection with botulinum toxin is an easy to perform procedure with minimal risk and negligible side effects compared to other available treatments for refractory GP. Although, the lack of convincing evidence has limited the use of botox in clinical practice, most uncontrolled studies have shown symptomatic improvement in the GP patients. Other concern regarding botox use is that, the dose and most effective site of BT-A injection for optimal response has not been standardized. Misplaced injections and skills of the endoscopist should also be taken into account

when determining the effectiveness of treatment with botox injection. If botox therapy is effective, the results of this treatment have not been long lasting and repeat procedures may be necessary. The long-term effects with repeat procedures have not been well studied. Further large population randomized studies are required to justify the use of botox for refractory GP. There may be a role for BT-A therapy in properly selected GP patients. With limited treatment options, we believe that botox injections can still be considered as treatment option for refractory GP when drug therapy failed.

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Endoscopic ultrasound in common bile duct dilatation with normal liver enzymes

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Abstract

In recent years, the description of isolated bile duct dilatation has been increasingly observed in subjects with normal liver function tests and nonspecific abdominal symptoms, probably due to the widespread use of high-resolution imaging techniques. However, there is scant literature about the evolution of this condition and the impact of endoscopic ultrasound (EUS) in the diagnostic work up. When noninvasive imaging tests (transabdominal ultrasound, computed tomography or magnetic resonance cholangiopancreatography) fail to identify the cause of dilatation and clinical or biochemical alarm signs are absent, the probability of having biliary disease is considered low. In this setting, using EUS, the presence of pathologic findings (choledocholithiasis, strictures, chronic pancreatitis, ampullary or pancreatic tumors, cholangiocarcinoma), not always with a benign course, has been observed. The aim of this review has been to evaluate the prevalence of disease among non-jaundiced patients without signs of cytolysis and/or cholestasis and the assessment of EUS yield. Data point out to a promising role of EUS in the identification of a potential biliary pathology. EUS is a low invasive technique, with high accuracy, that could play a double cost-effective role: identifying pathologic conditions with dismal prognosis, in asymptomatic patients with negative prior imaging tests, and excluding pathologic conditions and further follow-up in healthy subjects.

Key words: Unexplained common bile duct dilatation; Endoscopic ultrasound; Normal liver enzymes

Core tip: Common bile duct dilatation, often without identified causes, in subjects with normal liver function tests and nonspecific abdominal symptoms, and absence of lesions on prior noninvasive imaging tests, is increasingly found in the clinical practice. Since the clinical suspicion for biliary pathology in that setting is usually low, and there are limited literature data, this condition is ignored. However, recent evidences show the existence of pathologies among these patients, often with a non-benign course. In this scenario, endoscopic

ultrasound may have a role in the identification of the etiology of dilatation.

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INTRODUCTION

The biliary system plays a central role in digestive pathophysiology, since it allows bile sterile flow from hepatocytes, through intra- and extra-hepatic ducts, Oddi's sphincter and Vater's ampulla, to the duodenum determining lipids absorption and excretion of metabolites and toxins in the small bowel[1]. In case of obstruction of these structures (as observed in choledocholithiasis, Mirizzi's syndrome, neoplastic or flogistic papillary strictures, parasitic infection, cholangiocellular or pancreatic adenocarcinoma), liver biochemical abnormalities and jaundice, sometimes in association with fever or abdominal pain, usually appear[1].

In recent years, due to the widespread use of high-resolution imaging techniques in order to investigate the causes of nonspecific abdominal symptoms, isolated bile duct dilatation in non-jaundiced patients with normal liver function tests has been increasingly reported. There is scant literature about the diagnostic impact of endoscopic ultrasound (EUS) in this setting and not much is known about the natural evolution of this condition. The aim of this review has been to analyze EUS accuracy in this scenario.

CAUSES OF BILIARY DILATATION

There are controversies regarding the upper normal diameter of the common bile duct (CBD) but it is conventionally accepted to be 7 mm[2-6]. A variety of factors can influence bile duct size, prominently imaging modality, age[7-10] and prior cholecystectomy. In transabdominal ultrasound (TUS), distal CBD may be difficult to visualize because of bowel gas, thus resulting in underestimation of duct size compared to other imaging techniques as computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC)[11]. On CT and MRCP imaging, bile duct wall is included in the measurement and, because of its oblique course and the difficulty to separate a possible low cystic duct insertion, result on the axial source may be inaccurate[8]. Finally, magnification and duct distension by contrast, used in ERCP and transhepatic cholangiography, may overestimate duct size[8].

Several studies in the last 20 years reported an increase in the CBD diameter in older patients, even if with consistent variability[6,7,9,10,12]. Based on autoptic observations, some authors identified loss of elastic fibers and proximal compensatory dilatation due to distal sclerosis as potential causes of the phenomenon[13]. Moreover, the fragmentation of the longitudinal smooth myocyte bands in elderly subjects and use of drugs such as calcium antagonists and nitroglycerine, may reduce contractility and cause hypotonus of the duct[12,14]. Finally, prior cholecystectomy seems to influence CBD diameter since gallbladder physiologically plays a role in accommodation of pressure fluctuation in biliary system which, after surgery, could be transferred to bile duct causing dilatation[11,15-17].

Among non-obstructive etiologies of CBD dilatation, opioids consumption has been described. Opiates may cause an increase in the basic pressure and in frequency of phasic contractions of the Oddi's sphincter leading to biliary dilatation[18,19]. In a study performed by Farahmand *et al*[20], the authors showed an association between increased biliary diameter, evaluated on TUS, and addiction to opioids in asymptomatic patients, with normal levels of serum bilirubin and alkaline phosphatase tests and absence of obstructive factors on TUS. In a recent study, opium addicts, symptomatic for abdominal pain were subjected to EUS. The authors observed CBD dilatation, especially in the extra hepatic tract, in all 15 patients included and increased surface area of Vater's papilla in 12 of them, after a mean of 20 years of opium addiction[21].

Pathologic conditions are also able to induce isolated bile duct dilatations with non-specific symptoms or biochemical abnormalities. Choledocholithiasis, which develops in about 10%-20% of patients with gallbladder stones, may be asymptomatic in half of cases and CBD stones cannot always be identified by traditional non invasive imaging techniques[22]. Reported sensitivity in detection of CBD stones is 18%-74% for TUS and 50%-90% for CT[23-25]. Recently developed imaging modalities, such as MRCP and helical computed tomographic cholangiography (HCT-C) have shown higher sensitivity than TUS and conventional CT, and remain less invasive than ERCP[26]. However, EUS is considered more accurate in detecting CBD stones, especially if smaller than 5 mm in diameter, which are sometimes not identified by MRCP and HCT-C[26]. When choledocholithiasis is suspected, sensitivity of EUS reaches 90% for the detection of CBD stones[27-29]. In a prospective study, performed by Fernández-Esparrach *et al*[30] on patients with dilatated biliary tree, EUS increased the pretest probability of accurately diagnosing choledocholithiasis as the cause of obstruction from 49% to 84%. On the contrary, this probability decreased from 49% to 0% if EUS ruled out lithiasis as the cause of obstruction[30].

In a meta-analysis published in 2008, on EUS perfor-

mance in detecting choledocholithiasis, the authors proposed EUS as a less low invasive technique to be incorporated into the diagnostic algorithm of patients with suspected CBD stones, in order to confirm the pathological condition before proceeding with therapeutic ERCP, when indicated[31]. Scheiman *et al*[32], in a prospective study and cost analysis performed on a cohort of patients referred to ERCP, defined EUS the preferred initial diagnostic test, compared with MRCP, for the evaluation of biliary system and identification of extrahepatic disease.

After excluding tumors, stones, flogistic strictures, a rare cause of CBD dilatation may be identified in choledochal cysts, a heterogeneous group of congenital focal or multiple anomalous dilatations of the biliary tree, usually diagnosed in childhood but remaining undetected until adulthood in 25% of cases[33,34]. Although abdominal pain is the most frequent symptom in adult patients, non-specific symptoms are also reported and the cyst may be incidentally identified in patients undergoing radiologic evaluation for other clinical suspicions[35,36].

IMPACT OF EUS IN THE DIAGNOSTIC WORK UP OF CBD DILATATION

In the presence of CBD dilatation without symptoms or clinical and laboratory alarm signs, when non-invasive imaging test (TUS, CT or MRCP) fail to indentify the etiology, clinical suspicion for biliary pathology is low, thus making further investigations unwarranted[2,8]. In this setting, despite negative results of previous imaging tests, diagnostic EUS could have a role in the identification of the etiology of dilatation (Figure 1) with a very low complication rate[37]. EUS combines endoscopy with real-time and high-resolution ultrasound providing excellent sonographic visualization of the extrahepatic biliary tree without interference of bowel gas, due to its ability to place the transducer in close proximity to the extrahepatic bile duct. Additionally, EUS permits the accurate and systematic visualization of the wall of the duodenum, including the papillary region[38].

Several authors compared MRCP and EUS in detecting choledocholithiasis showing cost-effectiveness and higher accuracy of EUS in detecting distal small stones in non-dilated ducts[26,32,39]. De Lédinghen *et al*[39] reported a 100% negative predictive value of EUS in the diagnosis of lithiasis, thus excluding the needing for further investigation and limiting unnecessary surgery. In the previously mentioned study by Scheiman *et al*[32], EUS was the most useful test for confirming a normal biliary tree, and the initial EUS strategy had the greatest cost-utility by avoiding unnecessary ERCPs and preventing ERCP-related complications[40].

In 2001, a prospective study performed by Kim *et al*[41] showed the existence of pathological conditions in subjects with dilatated CBD, despite the lack of symptoms, jaundice or causative lesions in TUS. Among the 49 patients who underwent ERCP, a significant prevalence of abnormal findings likely causative of dilatation (periampullary duodenal diverticula, benign strictures, choledochal cysts, anomalous pancreaticobiliary ductal anatomy and distal CBD masses), associated with both normal or altered liver chemistry tests, was found.

In 2007, Malik *et al*[3] retrospectively evaluated a cohort of patients with CBD dilatation and non-diagnostic imaging (TUS, CT or MRCP), previously performed for abdominal pain, weight loss or elevated liver enzymes in serum. These patients underwent EUS, being divided into two groups based on the level of clinical suspicion for biliary pathology (32 patients with normal liver chemistry tests and 15 patients with elevated enzymes)[3]. In the first group, the authors identified two findings on EUS (6%) potentially causative of biliary dilatation, a 7-mm stone of the CBD and a periampullary diverticulum. In the second group, 8 significant findings (53%) were observed: 4 periampullary diverticula, 3 choledocholithiasis and 1 ampullary tumor, not previously detected by TUS and CT.

As expected, the prevalence of biliary pathology is significantly higher in the case of elevated liver chemistry tests; however, despite the lack of pathological findings with non-invasive imaging techniques and normal liver biochemistry, biliary abnormalities may still be present and EUS is recommended for further evaluation.

A study by Carriere *et al*[42] showed a EUS yield of 28.7% in a cohort of 94 patients with unexplained isolated CBD dilatation, although an undetermined number of subjects of the group underwent endoscopy because of abdominal pain and/or abnormal liver function tests, thus suggesting a higher pre-test probability of pathological findings.

In an abstract published in 2009, based on a retrospective study, 30 patients with biliary dilatation and no evident causes on prior imaging underwent EUS[43]. Four patients had normal biliary system on EUS, 15 patients presented a dilatation of unknown etiology while pathology accounting for CBD dilatation was demonstrated in 11 of them (choledocholithiasis, ampullary adenoma, chronic pancreatitis or cholangiocarcinoma). Similarly to other studies, prevalence of abnormal findings during EUS examination was different between the patients with abnormal and those with normal liver chemistry tests (55% and 33% respectively). Conversely, the number of pathological findings in the latter group differed from percentages reported by other authors[2,3], probably because no details were specified in this study, about clinical presentation and previously used imaging techniques. Notably, none of the patients with unexplained CBD dilatation on EUS was found to have causative lesions after a mean follow-up of 16 mo.

Similarly, Bruno *et al*[2] studied 57 patients with normal liver enzymes (aminotransferases, gamma glutamyltranspeptidase and bilirubin) referred to EUS at our centre after prior negative imaging studies, excluding previous

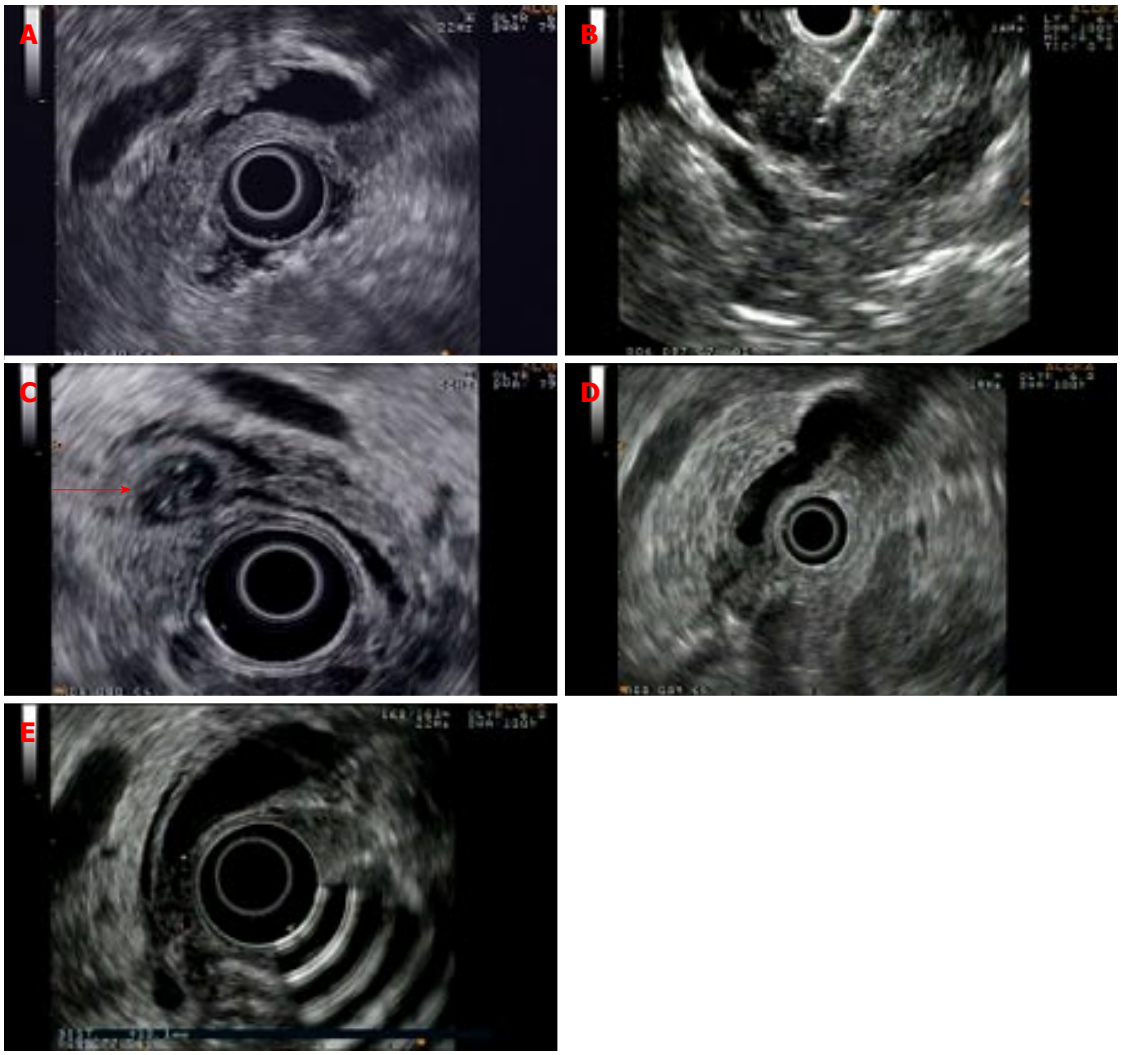

Figure 1 Examples of pathologic findings identified on endoscopic ultrasound in patients with negative prior imaging tests. A: Choledocholithiasis: Small stones in the common bile duct; B: Small pancreatic cancer; C: Small duodenal diverticulum with bile duct indentation (see arrow); D: Ampullary carcinoma with pancreas invasion; E: Inflammatory thickening of the distal common bile duct.

ERCP or history of biliary obstruction, pancreatitis or jaundice. Reasons for initial investigations were unspecific abdominal pain, dyspepsia, weight loss or pancreatic enzymes elevation in 49.2% of patients but in the majority of them biliary dilatation was an incidental finding. Employed imaging techniques, some of which performed in other centers, were TUS (7%), TUS and MRCP (63.1%), TUS and CT (10.5%) or TUS, MRCP and CT (19.3%). Abnormal EUS findings were observed in 12 patients (21%). As already described by other authors, causative identified lesions were periampullary diverticula, although a true compression on the CBD was rare (2/6), 2 ampullary adenoma, chronic pancreatitis according to predefined criteria[44] in 2 cases, a 7-mm biliary stone and one pancreatic cancer; 66.7% of patients were completely asymptomatic while unspecific abdominal pain or dyspepsia had been reported by the others. As suggested by the authors, a 21% prevalence of pathologic findings among patients with the aforementioned features, is probably overestimated since chronic pancreatitis and periampullary diverticula without bile duct indentation are not sure causes of biliary dilatation. Excluding these cases, the percentage is lower (10.5%) and comparable with Malik's findings[3].

Recently, a retrospective study was performed by Rana *et al*[45] about EUS diagnostic accuracy in patients with unexplained dilatation of CBD on MRCP, in order to establish EUS yield in the clinical practice. Among the 40 selected patients, 10 subjects had elevated serum alkaline phosphatase while the others presented normal liver function tests: in the former group, EUS detected a pathological condition causing dilatation of CBD (stones, cholangiocarcinoma, benign strictures) compared to a minority of significant findings identified in patients with normal liver tests (33.3% received diagnosis for stones or chronic pancreatitis). The remnant 20 patients with dilatated biliary system and normal liver function had regular EUS findings. There was no difference in the mean duct diameter in subjects presenting elevated serum alkaline phosphatase compared to patients with normal liver function tests nor between groups with identified pathology or not. The authors concluded, as

reported by previous scientific literature, that abnormal liver function tests are useful to identify patients with high pre-test probability of pathological findings underlying however that normal biochemistry does not exclude the existence of biliary ducts abnormalities.

Finally, Oppong *et al*[46] presented data retrospectively collected from a cohort of patients referred for EUS evaluation to a tertiary center. By excluding subjects with jaundice, liver function tests abnormalities, evidence of mass, stricture or ductal filling defect on pre-EUS imaging or symptoms suggestive of sphincter of Oddi dysfunction or chronic pancreatitis, they selected 40 patients with isolated dilatation of CBD. New findings on EUS were identified in 8 patients (20%). In 7 the following was considered as cause of dilatation: 3 had biliary polyps (not confirmed in 2 patients who later underwent ERCP), 3 had biliary stones and 1 had portal vein compression on the CBD. Microlithiasis, identified in the eighth subject, was assessed as a secondary event. Prior cholecystectomy was significantly more frequent in patients with no new findings on EUS, although CBD diameter did not differ among patients with prior surgery or not.

CONCLUSION

Changes in bile duct anatomy and adaptation of biliary system to normal or pathological processes, impose an accurate analysis of the patient anamnesis, liver biochemical parameters, clinical context in order to differentiate subjects with higher probability of biliary pathology from those with low index of suspicion. In recent years, the availability of a low-invasive modality, without post-procedural risk of pancreatitis, led to an increasing use of EUS in the investigation of biliary dilatation, even when symptoms or signs typically suggestive of obstruction were absent. On the other hand, the use of high-resolution cross-sectional imaging to investigate abdominal symptoms commonly results in increasing findings of dilatated biliary ducts in patients with normal liver tests. Currently, EUS program presents an increasing number of referrals in this setting and evidences in literature suggest a promising role for this technique in the identification of a potential biliary pathology, despite a low pre-test clinical suspicion. Firstly, in a small subset of patients, although asymptomatic or with vague symptoms, it can underlie pathologic conditions with dismal prognosis even with negative prior imaging tests. Secondly, according to the known high negative predictive value of EUS[47,48], if EUS evaluation does not identify the cause of biliary dilatation, the patient should be reassured and no further follow-up is recommended, since no pathologic conditions emerged during follow-up period in the aforementioned studies.

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Endoscopic management of hilar biliary strictures

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Abstract

Hilar biliary strictures are caused by various benign and malignant conditions. It is difficult to differentiate benign and malignant strictures. Postcholecystectomy benign biliary strictures are frequently encountered. Endoscopic management of these strictures is challenging. An endoscopic method has been advocated that involves placement of increasing number of stents at regular intervals to resolve the stricture. Malignant hilar strictures are mostly unresectable at the time of diagnosis and only palliation is possible.Endoscopic palliation is preferred over surgery or radiological intervention. Magnetic resonance cholangiopancreaticography is quite important in the management of these strictures. Metal stents are superior to plastic stents. The opinion is divided over the issue of unilateral or bilateral stenting.Minimal contrast or no contrast technique has been advocated during endoscopic retrograde cholangiopancreatography of these patients. The role of intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy, and endoscopic ultrasound still remains to be defined.

Key words: Biliary strictures; Malignant; Benign; Endoscopy; Endoscopic retrograde cholangiopancreatography

Core tip: Management of benign or malignant hilar biliary strictures is difficult. Surgery is technically demanding for benign hilar biliary strictures and results of endoscopic management are not very satisfactory. Endoscopic palliation is preferred modality of managing malignant hilar strictures. However, it is still controversial to drain unilaterally or bilaterally. Use of contrast during endoscopic retrograde cholangiopancreatography and leaving some ducts undrained is a major problem in these patients. We have reviewed the literature on all these aspects of hilar biliary strictures.

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INTRODUCTION

Biliary strictures at hepatic hilum are not uncommon and present a difficult diagnostic and therapeutic

Table 1 Etiology of benign and malignant hilar strictures[1]

Malignant hilar strictures
Primary tumors (cholangiocarcinoma)
Local extension (gallbladder cancer, hepatocellular carcinoma, and pancreatic cancer)
Lymph node metastases (Breast, colon, stomach, ovaries, lymphoma, and melanoma)
Benign hilar strictures
Postoperative injuries (cholecystectomy, liver transplantation, liver resection, and biliodigestive anastomosis)
Primary sclerosing cholangitis
Others (stone disease, follicular cholangitis, parasite infection, granular cell tumor, chronic fibroinflammatory process, compression from portal cavernomatosis, granulomatous process, and lymphoplasmacyticscleros ingpancreatitis/cholangitis)

problem. Hilar strictures can be benign or malignant which are often difficult to differentiate. Various modalities as surgery, endoscopy and radiology have been used in the management of these strictures with variable results. The role of some newer modalities, *e.g.*, intraluminal brachytherapy, intraductal ablation devices, photodynamic therapy (PDT), still remain investigational.

Etiology

Etiologically, these strictures can be divided into benign or malignant causes[1] (Table 1). The differentiation of benign from malignant hilar strictures is difficult.

Diagnosis

The alkaline phosphatase isoenzyme and CA19-9 have been used to discriminate benign from malignant strictures with variable sensitivity and specificity[2-4]. Radiologic evaluation of patients with hilar strictures can be done with ultrasonography, contrast-enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreaticography (MRCP). These modalities can help to delineate the level of bilary obstruction along with the extent of biliary dilatation. Any mass lesion or distant metastasis can also be detected with these methods[5-9]. Increased alkaline phosphatase and CA19-9 levels, increased thickness of bile duct wall to ⩾ 5 mm and regional lymphadenopathy (> 1 cm) on CT scan, and cholangiographic appearance of abrupt cutoff and separation of biliary ductal system suggest a malignant etiology of hilar obstruction[10]. Another study showed an association of raised bilirubin levels of > 8.4 mg% and CA19-9 level > 100 U/L with malignant etiologies of biliary obstruction[11]. MRI/MRCP performed better than CT to differentiate benign and malignant causes of biliary obstruction[11]. However, in a study of 49 patients with mass lesion at hilum on abdominal ultrasonography or CT scan, raised CEA and CA 19-9 levels, and presence of irregular, eccentric strictures with abrupt cutoff suggesting malignancy on cholangiography, benign diseases was documented in 24% of cases on surgical histopathology[12]. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) provide a better assessment of the biliary tree. It also enables brush biopsy and cytology studies providing a histological diagnosis in these patients. However, these procedures carry a significant risk of complications[13,14]. Various studies have shown a variable sensitivity (37%-70%) and high specificity (> 95%) for biopsies or brush cytology (Table 2)[15-18].

Table 2 Brush cytology in malignant biliary obstuction

No.	Ref.	No. of patients	Sensitivity (%)	Specificity (%)
1	Venu *et al*[15]	53	70	100
2	Foutch *et al*[16]	24	60	100
3	Ferrari Júnior *et al*[17]	70	56	100
5	Singh *et al*[18]	30	37	100

Table 3 Bismuth-lazorthes Classification of postsurgical benign biliary strictures

Type I: Common hepatic or main bile duct stump ⩾ 2 cm
Type II: Common hepatic duct stump < 2 cm
Type III: Hilar stricture- ceiling of the biliary confluence is intact, right and left ductal system communicate
Type IV: Ceiling of the confluence is destroyed, bile ducts are separated
Type V: Type I, II or III plus stricture of an isolated right duct

Endoscopic ultrasound (EUS) has shown promising results for the diagnosis of hilar strictures. In a study of 24 patients with negative or unsuccessful brush cytology results in cases of proximal bile duct obstruction, EUS revealed a mass lesion in 23 patients (96%)[19]. EUS-FNA in these patients provided a sensitivity of 77% and accuracy of 79%. However, the negative predictive value was quite low (29%). In another study of 44 patients with negative brush cytology in cases of suspected hilarcholangiocarcinoma, EUS-FNA had an accuracy of 91% with 89% sensitivity and 100% specificity[20]. Intraductal ultrasonography enhances the diagnostic accuracy of ERC (88%) as compared to MRC (58%) or ERC alone (76%)[21].

MANAGEMENT

Benign biliary strictures

Benign biliary strictures at the hepatic hilum most commonly result from surgical injuries, most often after cholecystectomy. Post-cholecystectomy strictures develop in 0.2%-0.5% of patients undergoing surgery and account for 80% of benign hilar strictures[22]. Post-liver transplant strictures develop in 5.9% of patients[23].

The management and outcome of postsurgical strictures depends on the type of stricture. Bismuth and Lazorthes classified postsurgical biliary strictures based on the level of healthy biliary mucosa suitable for anastomosis (Table 3)[24,25].

Surgical management of postsurgical benign biliary strictures carries a morbidity of 18%-51%, mortality

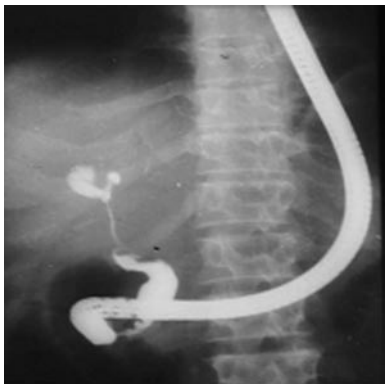

Figure 1 Postoperative type 3 hilarstricture with patent confluence.

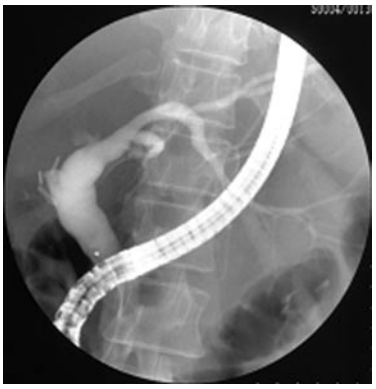

Figure 2 Postoperative type 5 hilarstricture involving right hepatic duct.

Table 4 Bismuth classification of malignant hilar block[31]

Type I: Obstruction within 1 cm of bifurcation but confluence patent
Type II: Obstruction limited to confluence
Type III: Obstruction at confluence with proximal extension to right or left side
Type IV: Obstruction involving bilateral secondary or tertiary branches or multifocal strictures

of 4%-13%, and recurrence rate of 10%-30%[22]. It, therefore, requires specific skills and expertise. The management of hilar postsurgical strictures (types III, IV, and V) is more challenging and results in worse outcomes (Figures 1 and 2)[1]. A retrospective study of 57 patients surgically treated for cicatricial biliary strictures showed a higher rate (14%) of stricture recurrence and cholangitis in patients with hilar obstruction compared to none in patient with lesions below the hilum[26]. A recent study reported the safety and efficacy of right hemihepatectomy with cholangiojejunostomy in patients with strictures involving secondary bile duct branches associated with vascular injuries. The study showed 100% survival without stricture recurrence after a mean follow up of 80 mo. No major postoperative complications were documented[27].

Endoscopic management of postsurgical strictures is more safe and efficacious. Two 10F plastic stents are placed in for a maximum duration of 12 mo. Stent exchange is done at 3 mo interval to reduce the risk of stent blockage and cholangitis (classical approach)[28,29]. Endoscopic management is feasible in 80% of cases. Stricture recurrence occurs in 20% of patients after stent removal over a period of 9.1 years. All the instances of restenosis were noted within 2 years of stent removal. Mean time from stent removal to symptom onset was 2.6 mo (range 1 wk–2 year)[29].

An aggressive approach involves insertion of an increasing number of plastic stents until resolution of stricture, with stent exchange performed at 3-5 mo interval[30]. In a study of 40 patients with 18 hilar strictures, overall success rate with this approach was 89%. Recurrence occurred in only one patient after a mean follow up of 48.8 mo (range 2-11.3 years). Mean number of stents used was 3.2 ± 1.3 (range 1-6) over a period of 12.1 ± 5.3 mo (range 2-24 mo)[30].

Malignant biliary strictures

Cholangiocarcinoma, carcinoma gall bladder (GB) and secondaries account for majority of malignant hilar biliary strictures. Malignant hilar biliary strictures are classified as per the Bismuth Classification (Table 4)[31]. It carries a poor prognosis with 5 year survival of < 10%. Curative resection is feasible in < 10%. Palliation remains the mainstay of therapy. However, surgical palliation is associated with an unacceptable 33% mortality[31,32].

Current options for palliation include surgical bypass, percutaneous drainage and endoscopic stenting.Endoscopic drainage is safer and more successful with a lower propensity to bile leak, infection and haemorrhage. However, a recent randomized controlled study of 54 patients with unresectable carcinoma GB with Bismuth type 2 (Figure 3) or 3 hilar block showed better drainage (89% *vs* 41%) and lower complication rate (cholangitis 48% *vs* 11%) with percutaneous approach[33]. Both the groups had similar procedure-related mortality (4% *vs* 8%), 30-d mortality (4% *vs* 8%) and median survival (60 d in both; P = 0.71). Percutaneous drainage resulted in a significantly better quality of life, as assessed at 3 mo after the procedure[33]. This study used plastic stents instead of metal stents in unresectable carcinoma GB with Bismuth type 2 or 3 hilar block and biliary ducts were left opacified and undrained after contrast injection which could be responsible for higher rates of complication with endoscopic approach. Hence, the results need to be interpreted with caution.

Endoscopic stenting in hilar obstructions can be done with plastic or metal stents (Figures 4-7). Plastic stents are less expensive, have technically easy insertion with relatively easy removal and exchange. But, they have limited stent patency. Metal stents have prolonged stent patency, do not occlude side branches and have easier passage across biliary strictures due to relatively smaller delivery system. But, greater cost and difficulty

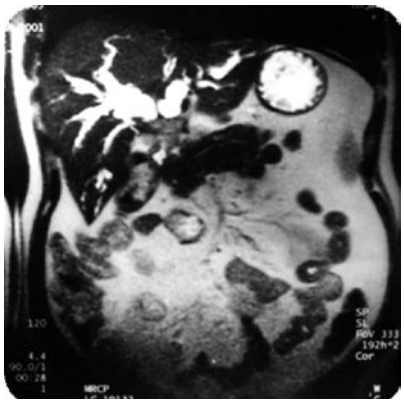

Figure 3 Magnetic resonance cholangiopancreaticography showing type 2 malignant hilarstricture.

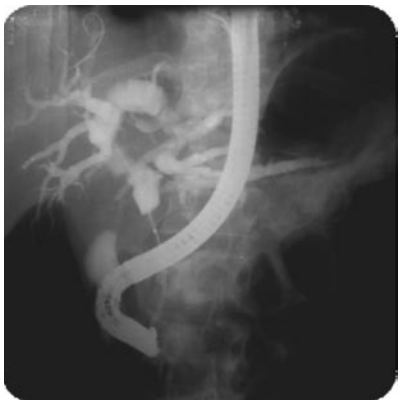

Figure 4 Type 1 malignant hilar stricture.

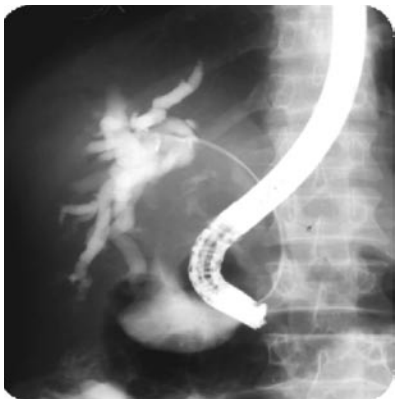

Figure 5 Type 2 malignant hilarstricture.

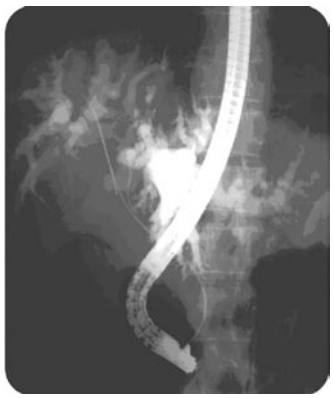

Figure 6 Type 2 malignant hilarstricture with bilateral guide wires.

in removal once blocked are the limitations[34].

Metal stents have been shown to perform better than even large bore plastic endoprostheses. A prospective randomized trial of 20 patients with Bismuth type Ⅱ-Ⅳ hilar obstruction compared 14 French plastic stents with 24 French metal endoprostheses in the management of malignant hilar obstructions with obstructive jaundice[35]. Metal stents insertion was associated with greater success as well as patency rates compared to placement of plastic stent. It was also cost-effective due to lower number of re-interventions required in these patients. Another randomized controlled trial of 108 patients with Bismuth type Ⅱ-Ⅳ unresectable hilarcholangiocarcinoma demonstrated better drainage and more prolonged survival with self-expandable metal stents compared to plastic stents[36]. A meta-analysis of 10 trials showed a significantly higher successful drainage rate [odds ratio (OR) = 0.26; 95%CI: 0.16-0.42; I^2 = 40.3%], lower early complication rate (OR = 2.92; 95%CI: 1.65-5.17; I^2 = 0%), longer stent patency [hazard ratio (HR) 0.43; 95%CI: 0.30-0.61; I^2 = 57.6%], and longer patient survival (HR = 0.73; 95%CI: 0.56-0.96; I^2 = 56.9%) with metal stents in comparison with plastic stents[37].

There is much controversy regarding the placement of unilateral or bilateral stents for hilar strictures. In a study of 190 patients with Bismuth type Ⅰ-Ⅲ hilar strictures, successful drainage after single stent was achieved in 80% of patients[38]. The placement of a second stent was considered only in patients with new onset cholangitis or incomplete resolution of cholestatic symptoms. Early complications were observed in 7%, 14% and 31% patients with type Ⅰ, Ⅱ and Ⅲ strictures, respectively. De Palma *et al*[39,40] showed that unilateral stenting is feasible, safe and effective. In a prospective study of 61 patients with hilar malignancy, the placement of a single metal stent across the stricture into duct easier to access achieved successful stent insertion in 96.7% and successful drainage in 96.7% patients. Median survival of these patients was 140 d with median stent patency of 169 d. Stent malfunction was seen in 4.9%[40]. A recent meta-analysis also revealed that unilateral and bilateral biliary drainage may have equivalent efficacy in hilar biliary obstruction with a higher success rate for unilateral stent placement[37]. A case series of 151 patients with unresectable Bismuth type Ⅱ and Ⅲ hilar biliary obstruction revealed similar successful drainage rate, complications, 30-d mortality, number of re-interventions and survival based on whether right or left biliary ductal system was drained[41]. However, in patients with bilobar opacification of biliary ductal system, bilateral drainage should be obtained to reduce the risk of cholangitis[42].

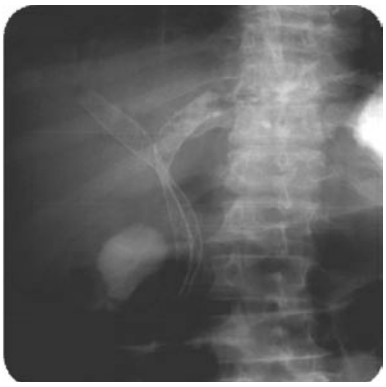

Figure 7 Bilateral metal stents in type 2 malignant hilar stricture.

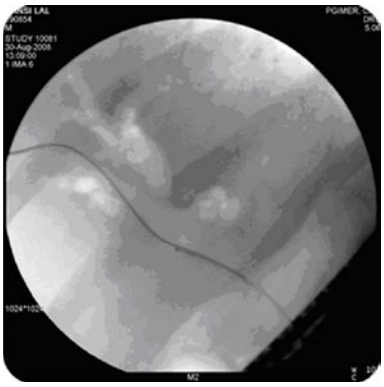

Figure 8 Air cholangiogram showing type 2 malignant hilar stricture.

It was widely held that draining 25% of liver volume provides adequate palliation of obstructive jaundice with biochemical improvement in these patients[43]. However, a recent study of 107 patients with Bismuth type Ⅱ-Ⅳ hilar strictures concluded that drainage of more than 50% of liver volume predicts efficacy of drainage and translates into longer survival (119 d *vs* 59 d, P = 0.005),especially in Bismuth type Ⅲ hilar strictures[44]. Bilateral stent insertion is often required to achieve more than 50% drainage. The study, however, has several drawbacks. The study had a retrospective design, most of the patients underwent plastic instead of metal stenting in hilar biliary obstruction and majority of the patients had cholangiocarcinoma which has relatively prolonged survival and can confound the results.

Failure to drain the hepatic lobes or segments after contrast injection is responsible for most of the cases of post procedure early cholangitis and mortality[42]. It brought to the fore the concept of contrast free stenting[45,46]. To avoid bilateral contrast injection and stent placement in Bismuth-type III and IV Klatskin tumors, Hintze *et al*[47] used MRCP in 35 patients for ERC and unilateral stent insertion. The placement of stents under MRCP guidance reduced incidence of post-ERC bacterial cholangitis. A prospective study of 18 patients with Bismuth type Ⅱ malignant hilar biliary obstruction demonstrated successful endoscopic drainage in all the patients and no cholangitis or 30-d mortality with MRCP guided contrast-free unilateral metal stenting[45]. Another study of 15 patients with Bismuth type Ⅱ malignant hilar strictures used contrast-free balloon-assisted unilateral plastic stenting with 100% successful drainage and no cholangitis or 30-d mortality[48]. Comparison of air and iodine contrast cholangiography in hilar strictures in a retrospective study showed less cholangitis with air contrast in Bismuth type Ⅱ-Ⅳ strictures[49]. Subsequently, two studies showed 100% successful stent placement and drainage with no cholangitis and 30 d mortality with contrast-free air cholangiography-assisted (Figure 8) unilateral stent deployment[50,51]. A recent randomized controlled study compared CO_2 cholangiography with iodine contrast cholangiography in 36 patients with Bismuth type Ⅱ-Ⅳ malignant hilar obstruction and revealed lower incidence of cholangitis in CO_2 group (5.6% *vs* 33.3%, P = 0.04)[52].

NEWER APPROACHES

Novel approaches including drug eluting stents, EUS guided biliary drainage, intraluminal brachytherapy, intraductal ablation devices and PDT have recently been used with variable results.

External beam irradiation therapy in malignant biliary strictures is limited by radiation tolerance of liver, bowel and kidneys. Intraluminal brachytherapy allows greater radiation dose locally administered to predefined volume of tissue. It can be administered *via* endoscopic or percutaneous route. A few recent studies have documented the safety and efficacy of intraluminal brachytherapy in association with stent placement in unresectable, malignant hilar strictures. This new method resulted in prolonged survival in these patients[53-56].

PDT is a promising mode of therapy for unresectable cholangiocarcinoma. It uses a combination of photosensitising chemical and light of appropriate wavelength to generate cytotoxic reactive oxygen species culminating in tumour cell death by necrosis or apoptosis. Continuous biliary drainage is achieved by stent implantation after the procedure. A randomized controlled study of 39 patients with histologically confirmed unresectable cholangiocarcinoma was terminated prematurely due to prolongation of survival (median 493 d *vs* 98 d; P < 0.0001), more effective biliary drainage and improved quality of life with stenting and PDT in comparison with stenting alone[57]. In a recent retrospective study of 184 patients with hilar cholangiocarcinoma managed with either surgery (60), stenting (56) or stenting with PDT (68); PDT had a longer survival compared to stenting (12.0 mo *vs* 6.4 mo, P < 0.01) and comparable survival to R1/R2 resection (12.2 mo)[58]. In conclusion,management of hilar biliary strictures is a difficult problem. Surgical, endoscopic and percutaneous approaches have been

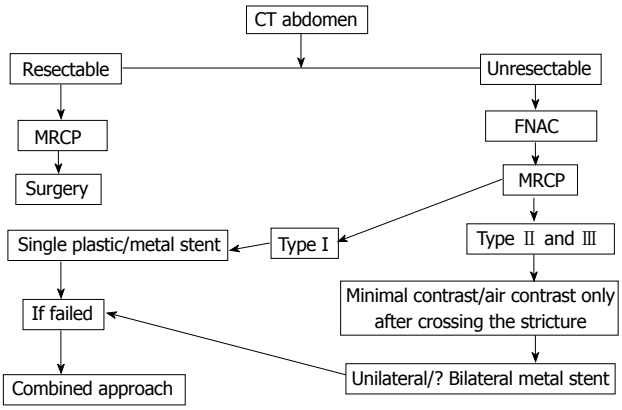

Figure 9 Approach to malignant hilar biliary strictures. CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreaticography; FNAC: Fine needle aspiration cytology.

used in the management of these strictures with variable results. However, the appropriate management also depends on expertise available at that centre. Endoscopic management with increasing number of plastic stents and surgery for failed cases in benign biliary strictures is a reasonable approach. Appropriate management algorithm for malignant hilar strictures is given in Figure 9.

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MINIREVIEWS

Towards the Holy Grail: What can we do for truly scarless surgery?

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Abstract

The work of Muhe and Mouret in the late 1980s, paved the way for mainstream laparoscopic procedures and it rapidly became the mainstream method for many intra-abdominal procedures. Natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) are very exciting new modalities in the field of minimally invasive surgery which work for further reducing the scars of standard laparoscopy and towards scarless surgery. However, according to objective assessment of the literatures, there is no clearly demonstrated benefit of NOTES (LESS), even cosmesis is poorly supported and had mixed results in the available data. NOTES (LESS) is far from the truly scarless surgery. Towards the Holy Grail, we have developed several techniques of creating nonvisible scar and named them as "Scar-hidden Endoscopic Surgery". With the rapid development of science and technology, we believe that minimally invasive surgery over the next 2 decades will continue to bring remarkable change and realize truly scarless surgery even we may not be able to imagine what lies ahead.

Key words: Minimally invasive surgery; Scarless surgery; Laparo-endoscopic single-site surgery; Natural orifice transluminal endoscopic surgery; Scar-hidden endoscopic surgery

Core tip: Natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) are very exciting new modalities in the field of minimally invasive surgery which towards scarless surgery. However, according to objective assessment, NOTES (LESS) is far from the truly scarless surgery. Towards the Holy Grail, we have developed several techniques of creating nonvisible scar and named them as "Scar-hidden endoscopic surgery". With the rapid development of science and technology, we believe that minimally invasive surgery over the next 2 decades will continue to bring remarkable change and realize truly scarless surgery.

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INTRODUCTION

The past thirty years has witnessed the infancy and rapid development of minimally invasive surgery (MIS). From the early multiple small incisions laparoscopic surgery to the single incision laparoscopic surgery nowadays, minimally invasive surgery has come a long way from its initial stage and scarless surgery has been the Holy Grail.

EVOLUTION OF SCARLESS SURGERY

Phillipe Mouret performed the first laparoscopic cholecystectomy in 1987[1]. Since then, laparoscopic approach has been used to many disease processes and gradually become the mainstream procedure for many intra-abdominal surgeries. Compared with open procedures, laparoscopic surgery has shown to decrease postoperative morbidity, shorten hospitalization and convalescence, and improve cosmesis for many applications[2,3]. Therefore laparoscopic surgery has been a well-established and commonplace technique worldwide in the past century. However, there were still 3-6 small incisions post-operation, which not only cosmetically unappealing, but also increase the wound pain and potential wound morbidity, such as abdominal wall bleeding and hernia, and intra-abdominal organ damage[4].

The quest for scar reduction and the increasing recognition of patient's satisfaction has led to the innovation of conventional laparoscopic surgery. In the last decade, natural orifice transluminal surgery (NOTES) and Laparo-endoscopic single-site surgery (LESS) have been considered as the most advanced representative "evolution" of minimally invasive surgery. NOTES was first descripted by Kalloo *et al*[5] in 2004 and developed towards the scarless surgery, but did not gain popularity due to a variety of reasons including difficulty in accessing anatomical sites, lack of appropriate devices and sterility. The lack of success of NOTES has prompted the interest in LESS which also aimed to "scarless" effect. Compared with NOTES, LESS offers an advantage to surgeons with its similar performance used in traditional laparoscopy. However, LESS is also more technically difficult than traditional laparoscopic surgery, due to the challenges included loss of triangulation, external an internal conflict[6]. What's more is that while laparoscopic literature sought to demonstrate superiority of the technique over that of open surgery, the publications on LESS generally seem to seek to demonstrate equivalence with laparoscopy, with the major focus being on cosmesis[7]. LESS still has far a long way to go before becomes the mainstream approach for truly scarless surgery as it remains an evolving technique.

WHAT'S TRULY SCARLESS SURGERY?

With the rapid development of science and technology, scarless surgery has been the Holy Grail of MIS. However, what's MIS? Indeed, the term "minimally invasive surgery" has often been bastardized to imply a specific access strategy such as laparoscopy, robotic surgery or endoscopy, but the true definition of minimally invasive surgery may have been created by Sir William Osler over a century ago when he said that, "Diseases that harm call for treatments that harm less". More specifically, minimally invasive surgery should meet the following factors. The first and foremost factor is curing the pathology[8]. When approach and technique are considered, the most important question that mandates answer is will the pathology be appropriately treated with the absolute best safety profile possible. Secondary to surgical efficacy is decrease blood loss, postoperative pain, postoperative complications, surgical time (not by itself an absolute goal), convalescence and length of hospital stay. Thirdly, and the least important are surgical cosmesis and cost-effectiveness ratios. Based on the above, when define the truly scarless surgery, not only do these procedures should provide equivalent outcomes to traditional laparoscopic surgery, but also offer significant benefits as quicker recovery, shorter hospital stays, less scarring, less pain, lower morbidity and less surgical time (not an absolute goal).

Towards to the scarless surgery, NOTES and LESS have been developed and aimed to reducing the incisions of conventional laparoscopy. Surgeon's interest was focused on reducing or eliminating the incisions caused by the procedure. The hope is that reduced access points will ultimately decrease pain, morbidity, convalescence, and improve cosmesis. However, according to objective assessment of the literature which compared current standard laparoscopic techniques with NOTES (LESS), there is no clearly demonstrated benefit of NOTES (LESS), even cosmesis is poorly supported and had mixed results in the available data[9,10]. In patient polls, surgical success, risk, pain, convalescence and cost all ranked higher than cosmesis. NOTES and LESS were far from the truly scarless surgery.

WHAT WE HAVE DONE FOR SCARLESS SURGERY?

As already mentioned, scarless surgery has been the Holy Grail of minimally invasive surgery. However, as it is difficult, if not impossible, to achieve truly scarless in current days, several techniques of creating nonvisible scar have been developed, which we named as "Scar-hidden endoscopic surgery (SHES)". SHES include 2 broad categories of those techniques performed by obtaining new access to peritoneal cavity and those by hiding scar in the anterior abdominal wall.

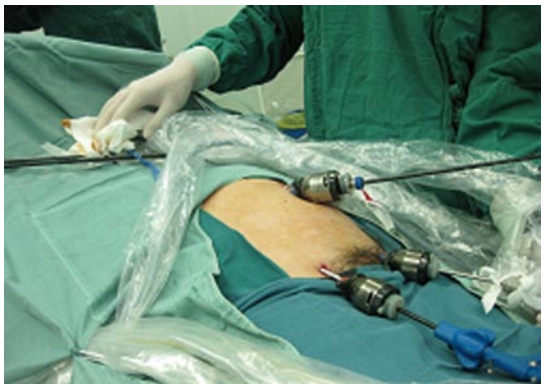

Figure 1 Ports position of approach 1.

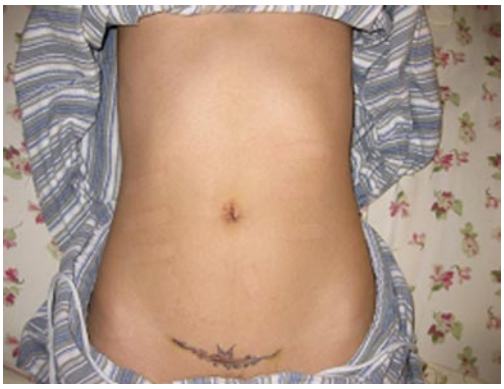

Figure 2 Scars are hidden in the tattoo.

Obtain new access to peritoneal cavity

The use of first category was represented by NOTES. In its purest form, NOTES does not use any transabdominal ports therefore decreased pain and eliminated the abdominal wound morbidity. However, NOTES was hampered by difficulty in accessing anatomical sites, lack of appropriate devices and sterility, thus far been successfully performed in patients and not a truly scarless surgery.

Hide the scar in the anterior abdominal wall

The limitations of NOTES led to the concept of LESS which also produced nonvisible scar as it hidden easily in umbilical plica. However, LESS is also more technically difficult than traditional laparoscopic surgery, due to the inherent challenges. As techniques mentioned above were fraught with problems, we attempted other approaches.

Approach 1: Transfer the incision to the superior margin of suprapubic hair

Surgical technique: A10-mm trocar was placed through an umbilical incision. After establishment of a pneumo-peritoneum, a 5-mm 30° laparoscope was introduced through the trocar. Two 5-mm suprapubic trocars were placed near the right and left ends of the superior margin of suprapubic hair under the guidance of the laparoscope. The laparoscope was then moved to the left side trocar. The instruments were introduced through the umbilical and the right side ports (Figure 1).

Advantages: Our research indicated that, compared with LESS, this approach characterized by no visible scar, a shorter operation time, minimal bleeding, *etc.*, but longer instruments should be used[11].

Approach 2: Transfer the incision to the tattoo (Figure 2) or previous operation scar (Figure 3)

The surgical technique and advantages of this approach were the same as described in approach above. What' s different is that the two 5-mm trocars were placed near the right and left ends of the tattoo or previous operation scar.

Approach 3: Transfer the incision to the linea alba (the transxiphoid-umbilical laparoscopic approach)

Surgical technique: A 15-mm incision was made at the right side of the umbilicus; a 10-mm trocar for the optic unit and another 5-mm trocar for the grasper were inserted side by side into the incision; a 5-mm trocar for instruments (ultrasonic scalpel, grasper, electrosurgical hook knife and hem-o-lok clips) was placed 20 mm inferior to the xiphoid (Figure 4).

Advantages: In our opinion, the transxiphoid-umbilical laparoscopic approach for laparoscopic cholecystectomy is as comfortable as the conventional techniques for laparoscopic cholecystectomy and allows the use of normal laparoscopic instruments. It has an advantage over conventional three-port laparoscopic cholecystectomy in both postoperative pain and, more importantly, cosmetic outcome, without a significant learning curve or increase in operative time. It offers a realistic better approach to conventional LC for chronic benign gallbladder disease.

Approach 4: Reduce the size of incision.

According to a previous study of us, the Optimized two-trocar LESS technique (a 2-mm trocar inserted for a grasper in the right upper abdomen) was found to be faster and less painful than the LESS approach and the 2-mm incision was almost nonvisible post-operation[12]. Under the guidance of this technique, we proposed another novel SHES as described below.

Surgical technique: A 15-mm incision was made at the right side of the umbilicus; a 10-mm trocar for the optic unit and another 5-mm trocar for an ultrasonic scalpel or clips were inserted side by side into the incision. Under laparoscopy, a 2-mm needle-shape grasper was placed direct through the abdominal wall in the midclavicular line 20 mm inferior to the costal margin, and electrocautery placed 20 mm inferior toxiphoid (Figure 5).

Advantages: Using the 2-mm needle-shape instruments, the new technique has following advantages: (1)

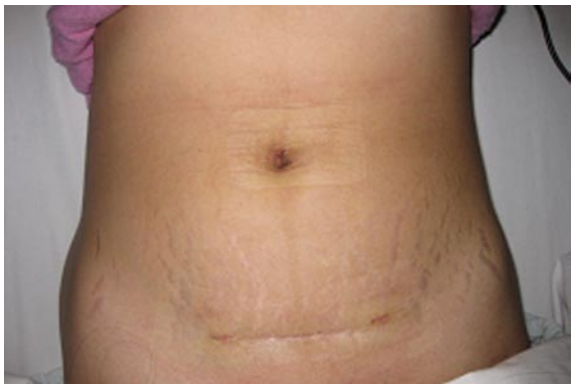

Figure 3 Scars are hidden in previous operation scar.

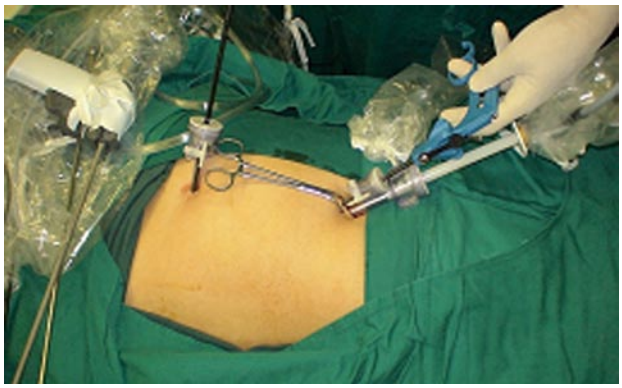

Figure 4 Ports position of the transxiphoid-umbilical laparoscopic approach.

The 2-mm grasper and electrocautery are at the normal location as the same as the traditional laparoscopic surgery. It helps to regain manipulate triangulation which not only enable performing sufficient traction of the gallbladder but also allow good mobilization of the gallbladder in order to dissect the calot's triangle safely; (2) compared with LESS, the novel SHES was performed more feasibly and safely, with significantly shorter operation time and higher satisfactory score. Cosmesis, safety, and economy were balanced better in this new technique; and (3) the scars of the new technique were hidden in the natural folds of the skin around the navel and were too small to affect cosmesis when the 2-mm puncture hole on the upper abdomen healing. Compared with conventional laparoscopic surgery, it produced better cosmetic results while the operative time was almost equal according to our data[13].

WAY TO TRULY SCARLESS SURGERY

According to the above analysis, NOTES or LESS is far from the truly scarless surgery as there were no longer follow-up, controlled and randomized studies which supported the touted benefits. There is no doubt that NOTES or LESS will be spurred on by rapid advances in technology and better instrumentation. However,

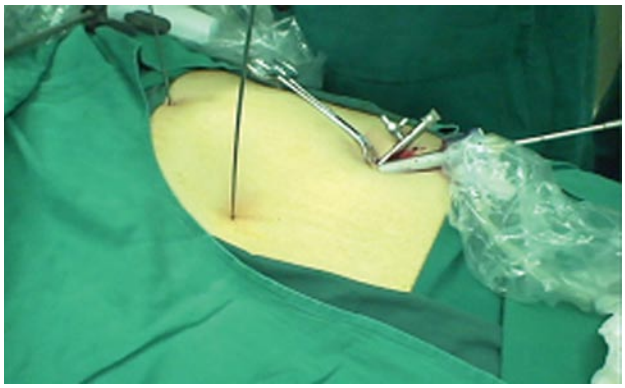

Figure 5 Laparoscopic cholecystectomy by using 2-mm needle-shape instruments without trocar.

when offering conventional *vs* investigational treatment options for patients, surgeons should be honest and balanced the safety and efficacy in their decision making.

In a word, what we believe is that, with the rapid development of science and technology, such as the use of da Vinci Surgical System, minimally invasive surgery in the nearly future will continue to bring remarkable changes and realize the truly scarless surgery.

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Management of iatrogenic colorectal perforation: From surgery to endoscopy

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Abstract

Iatrogenic colon perforation is one the most pernicious complications for patients undergoing endoscopic screening or therapy. It is a serious but rare complication of colonoscopy. However, with the expansion of the indications for endoscopic therapies for gastrointestinal diseases, the frequency of colorectal perforation has increased. The management of iatrogenic colorectal perforation is still a challenge for many endoscopists. The methods for treating this complication vary, including conservative treatment, surgical treatment, laparoscopy and endoscopy. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation. Specifically, we shed light on the endoscopic management of this rare complication.

Key words: Iatrogenic perforation; Colorectum; Surgery; Laparoscopy; Endoscopy

Core tip: Iatrogenic colorectal perforation is one of the most pernicious complications for patients who undergo endoscopic screening or therapy. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation, including conservative treatment, surgical treatment and laparoscopy. The flying development of the endoscope and its surgical assistant accessories have improved the endoscopic clip closure procedure. It can remarkably decrease the rate of surgical reparation following iatrogenic perforation of the colon.

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INTRODUCTION

Iatrogenic perforation of the colon and rectum is an avoidable complication of diagnostic tests or an unavoidable procedure of endoscopic treatment. In the past, the causes of iatrogenic perforation were

barium enema and diagnostic endoscopy. Recently, due to the expanded indications for endoscopic resection lesions, more colon perforation occurs after colonoscopy therapy. As a major cause, it is estimated that the frequency of iatrogenic perforation is 0.019%-0.8% and 0.10%-3% for diagnostic and therapeutic colonoscopy, respectively[1-4]. Perforation located at the colon can rapidly cause peritonitis and even sepsis. These complications imply high morbidity and mortality. Therefore, all endoscopists should pay more attention to prevent this kind of perforation and immediate treatment is needed once colon perforations occur. In this review, we highlight the etiology, recognition and treatment of colorectal iatrogenic perforation. Specifically, we shed light on the endoscopic management of this rare complication.

ETIOLOGY

Colonoscopy is widely used during diagnosis and therapy in endoscopy. There has been an increasing number of patients undergoing this procedure. Consequently, the number of associated complications has also risen. In addition, older and less appropriate patients are receiving colonoscopies who are more vulnerable to iatrogenic colonoscopic injury. In the Iqbal *et al*[5] study, the perforation rates were higher at the rectosigmoid junction and the sigmoid colon (52%). The perforation rates in other sites of the colon were 17% (cecum), 14% (ascending colon), 7% (transverse colon), 8% (descending colon) and 1% (rectum), respectively. The perforation size was between 0.1 and 6.0 cm (average, 1.7 cm). Mechanical injury leads to the largest perforations, while electrocautery injury causes the smallest perforations. The patient risk factors were state of anticoagulation, extensive contamination, active malignancy, prior hospitalization history, delayed diagnosis and steroid usage. Electrocautery, polypectomy and mechanical injury caused the postoperative morbidity. Other factors which pose difficulty in colonoscopy and likely cause perforations include the existence of dense or wide-mouthed diverticula, incomplete bowel preparation, active hemorrhage and, the most important, the experience of endoscopists.

DIAGNOSIS

With the different causes, sizes and sites of perforation, there are various complaints from patients, including non-pain, only localized instantaneous pain which happens suddenly, severe cramp-like pain and distension of the abdomen[5,6]. If there was a tiny perforation caused by snaring or the endoscopic knife application, the patient would not have symptoms or only local pain. In general, the frequency of these kinds of abdominal pain is remarkably higher in perforation caused by diagnostic endoscopy than surgical endoscopy. Abdominal roentgenogram provides a quick sign. Cho *et al*[3] reported a lot of subdiaphragmatic free air in all cases of perforation caused by diagnostic endoscopy and in almost 45% of therapeutic perforation cases. Thus, abdominal roentgenogram is a cost-effective and useful method to detect the presence of subdiaphragmatic free air, with a positive predictive value of 92%[5]. However, sometimes subdiaphragmatic free air cannot be detected by abdominal roentgenogram. In this setting, computed tomography can offer great help in diagnosing the free air, micro-perforations and/or abscess. Patients who are clinically unstable or who exhibit peritonitis on physical examination warrant immediate exploration.

MANAGEMENT

Conservative management

If a patient presents as subdiaphragmatic free air alone, it is not an indication for surgical reparation. Most patients who do not show signs of peritoneal irritation or abdominal sepsis have an ideal prognosis after being given intravenous antibiotic therapy, bowel rest and serial abdominal examinations[7]. Conservative management in appropriate patients results in a shorter length of hospitalization and lower morbidity. Iqbal *et al*[5] reported only one death among patients undergoing conservative treatment, a patient in the intensive care unit whose family refused surgery.

Surgical management

Prompt abdominal surgery is usually recommended once perforation has occurred[8,9]. Immediate surgical intervention is not compulsory. Intraoperative findings determine the surgical management. Surgery may be primary closure or resection with primary anastomosis in cases of intra-abdominal contamination accompanied by normal tissues in order to limit the comorbidity. Due to the extensive contamination, poor tissue situation and a higher complication rate, stoma or fecal diversion after reparation is chosen. Iqbal *et al*[5] indicated that only two preoperative factors determined the type of procedure, the time after the perforation and mechanical injuries. Comparing patients who were diagnosed with perforation after 24 h, those within 24 h were more suitable for a primary closure because the latter was more likely to have extensive fecal contamination. Moreover, mechanical injury always induced larger perforations (average, 1.9 cm) which needs fecal diversion after resection. However, this type of injury cannot always be ascertained before surgery.

Laparoscopic management

With the emergence and development of minimally invasive surgery over the last few decades, laparoscopic colonic repair has been increasingly adopted for colorectal perforation repair[10-12]. In the past, laparotomy was usually selected as the treatment approach for iatrogenic colon perforation and most patients under-

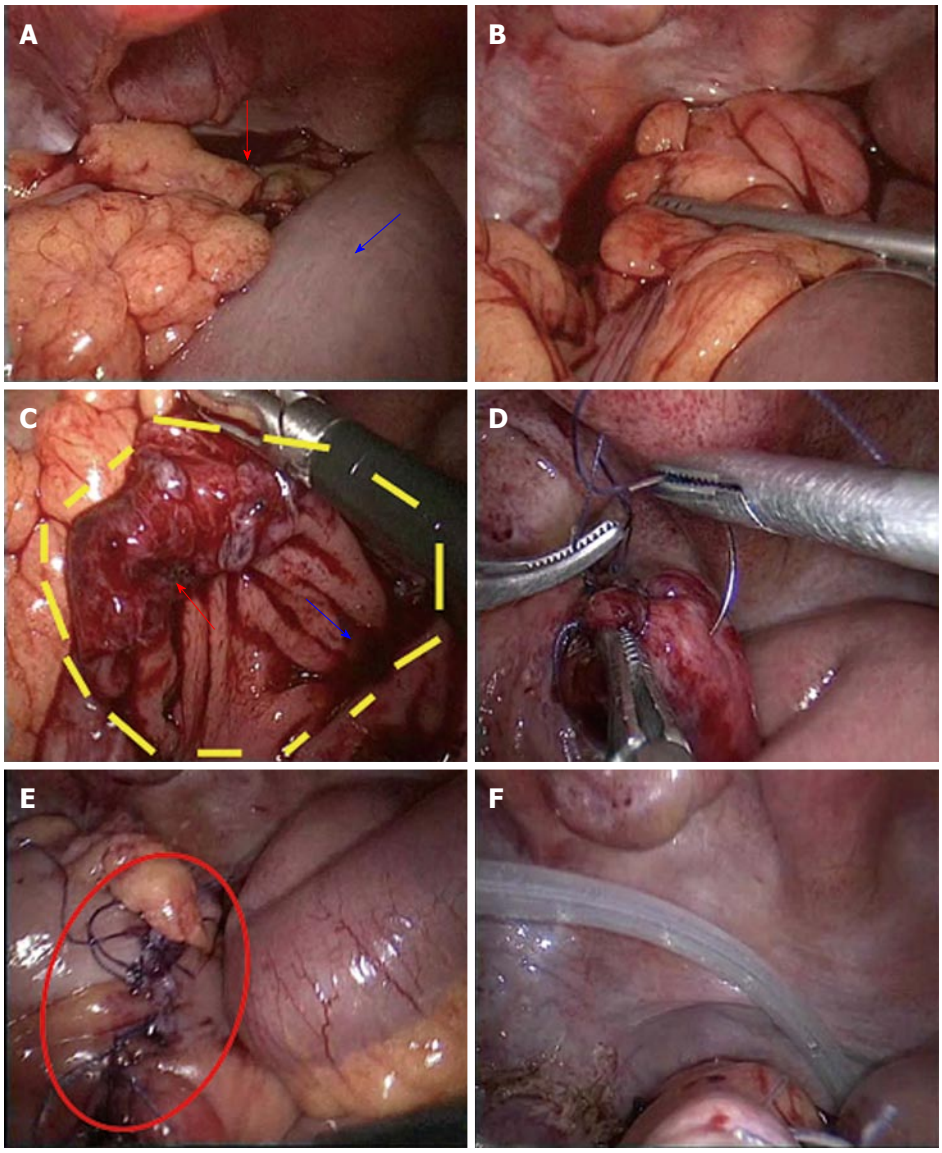

Figure 1 Laparoscopic management of iatrogenic colorectal perforation with endoscopic assistance. A: Laparoscopic examination of iatrogenic colorectal perforation: blue arrow, small bowel dilation; red arrow, perforation location; B: Explore and make sure of the perforation location; C: Expose the perforation: blue arrow, anal side; red arrow, opposite side; D: Suture the perforation; E: Effective closure of the perforation; F: Place a drainage tube.

went colostomy[13,14]. Unfortunately, ileostomy and colostomy are associated with a significant decrease in patient quality of life and require another operation to restore intestinal continuity[15]. Several doctors have therefore proposed either a primary repair of the colorectal perforation or a segmental colectomy with primary anastomosis. The improvement of laparoscopic techniques boosts the practice of laparoscopic repair for colon perforations more widely[16]. In the Zhang *et al*[4] study, their experience in laparoscopic direct suturing of colon perforations indicated that laparoscopic primary perforation repair was a safe and feasible repair method. Compared to an open method, patients who underwent laparoscopic repair had a significantly shorter total incision length (16 ± 15 mm *vs* 163 ± 54 mm), shorter overall length of stay (5.1 ± 1.7 d *vs* 9.2 ± 3.1 d) and fewer perioperative complications (two *vs* five)[17]. Thus, their data suggest it is rational to regard laparoscopic therapy as the initial approach for repairing iatrogenic colorectal perforation.

Endoscopic management

Despite the fact that laparoscopy is effective in resolving colorectal iatrogenic perforation, recent advances of endoscopic techniques have made it possible to handle iatrogenic perforations by applying mini-invasive procedures. Endoscopy can assist laparoscopy to close the perforation (Figure 1). Repairing the perforation alone with endoclips has been well described in related studies since 1997[18]. In addition, large or difficult intestinal perforations can be treated with a combined application of endoclips and endoloops[19]. In the recent study by Kim *et al*[20], 115285 diagnostic colonoscopies were performed with a total of 27 iatrogenic colon

perforations (incidence of 0.02%). Endoscopic closure of the perforation site was attempted in 16 patients, with success in 13 patients. This suggests that immediate endoscopic closure with clips can be performed for diagnostic perforations as well as therapeutic colonoscopy-associated perforations.

Jovanovic *et al*[21] reported that endoscopic closure of colonic perforations could be performed when the perforation is < 1 cm. Few authors[22,23] have used the endoclips to treat perforations > 1 cm. Trecca *et al*[22] reported 2 perforations > 3 cm that were managed by using endoclips successfully. In the Velchuru *et al*[24] case report, the perforation was 3 cm in size and 7 clips were used to close the defect. The patient was discharged on the second day. The number of clips used depends on the size of the perforation. Endoscopic closure of an iatrogenic colonic perforation at colonoscopy is feasible as the prepped colon contains minimal contamination. Considering the technical challenge of endoclip application, an experienced endoscopist is the most important factor, as well as the site and size of the perforation. Clip closure was reported to be successful in 69.2% to 92.6% of cases[25,26].

However, there have also been some limitations in the treatment of colorectal perforation by endoscopic clips. It is hard to evaluate the degree of closure after an endoscopic clip reparation. If the endoscopic clip closure is incomplete, it would develop to limited leakage, which may result in the abdominal symptoms again. In these cases, minor symptoms make it difficult to decide whether or not to operate. The proper management may be delayed until the optimal period. Moreover, delayed complications can develop due to extra-luminal contaminants or intermittent minor leakage. The Cho *et al*[3] study indicates that peritoneal abscess formation developed in 50% of cases after a large perforation repaired by endoscopic clips. After colorectal perforation, the decision to perform surgery or endoscopic closure should be made promptly, within 24 h. The high risk clinical factors within 24 h after a colon perforation include a large perforation, leukocytosis, fever, severe abdominal pain and large peritoneal free gas and these should also be identified within 24 h.

CONCLUSION

In conclusion, iatrogenic colorectal perforation is one of the most pernicious complications for patients undergoing endoscopic screening or therapy. Its management is still a challenge for many endoscopists. The methods of treating this complication are varied and include conservative treatment, surgical treatment and laparoscopy. With the development of endoscopy and its assistant accessories, using endoscopic clips to repair the iatrogenic perforation could remarkably decrease the possibility of undergoing additional surgery. For patients with a high risk of complications after endoscopic clip reparation, an early decision regarding additional surgery such as laparoscopy is also significant.

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ORIGINAL ARTICLE

Retrospective Study

Accuracy of endoscopists' estimate of polyp size: A continuous dilemma

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Author contributions: Izzy M and Virk MA contributed equally to this article; Izzy M made substantial contributions to conception and design of the study, drafting the article, making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published; Virk MA made substantial contributions to conception and design of the study, making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published; Saund A contributed to acquisition of the data and drafting the article; Tejada J contributed to acquisition of the data and making critical revisions related to important intellectual content of the manuscript; Kargoli F contributed to data analysis and interpretation; Anand S contributed to critical revisions related to important intellectual content of the manuscript and final approval of the version of the article to be published.

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Abstract

AIM: To examine the discrepancy, if any, between the endoscopist's estimate and pathologist's measurement of colonic polyp size.

METHODS: We retrospectively studied 88 patients who underwent colonoscopy with a clear unequivocal documentation of polyp size by both the endoscopist and pathologist. Endoscopist measurements were based on the visual estimate of polyp size seen on high definition screens. The measurement was done by our pathologists after formalin fixation. We compared the endoscopist estimate of the polyp size to the pathologist measurement in order to explore the discordance between the two readings. Data regarding demographics and method of polypectomy (snare polypectomy *vs* excisional biopsy) was collected, as well. Statistical analysis software statistical software was used to analyze the data.

RESULTS: Our cohort included 88 patients from which 111 polyps were removed. Fifty-two (46.8%) of the 111 polyps were excised using biopsy forceps and fifty-nine (53.2%) were removed by snare. In the biopsy forceps group, the mean polyp size documented by the pathologist was 0.38 ± 0.19 cm and the mean polyp size documented by the endoscopist was 0.54 ± 0.16

cm. The mean difference was 0.15 cm (P < 0.001). In the snare group, the mean polyp size documented by the pathologist was 0.54 ± 0.24 cm and the mean polyp size documented by the endoscopist 0.97 ± 0.34 cm. The mean difference was 0.42 cm (P < 0.001). Combining both groups, the mean size documented by pathologist was 0.46 ± 0.23 cm compared to 0.76 ± 0.35 cm documented by the endoscopist. The mean difference was 0.3 cm (95%CI: 0.23-0.36).

CONCLUSION: Post polypectomy measurement by the pathologist are generally smaller than the endoscopist's estimate.

Key words: Polyp size estimate; Colonic polyps; Endoscopist estimate

Core tip: Our results suggest wide variance in polyp size documentation. Neither endoscopist estimate nor pathologist measurement accurately reflects colonic polyp size. Inaccurate determination of polyp size can negatively impact advanced adenoma detection. Using a screen cursor like that used in ultrasound and computed tomography scanners may serve as a standardized, accurate technique to solve this issue.

Izzy M, Virk MA, Saund A, Tejada J, Kargoli F, Anand S. Accuracy of endoscopists' estimate of polyp size: A continuous dilemma. *World J Gastrointest Endosc* 2015; 7(8): 824-829 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i8/824.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i8.824

INTRODUCTION

The incidence of colorectal cancer continues to rise to make it the fourth most common cancer in men and third most common cancer in women[1]. The concept of adenoma-carcinoma sequence has been already established by several studies[2-4]. The various characteristics that need to be considered upon evaluating the malignant potential of an adenomatous polyp are size, villous components and dysplasia[2,5]. These factors significantly impact the decision regarding follow up surveillance studies. While an experienced pathologist can precisely recognize the villous component or dysplastic changes in the polyp, achieving an accurate estimate of the polyp actual size remains challenging for the endoscopist as well as the pathologist.

With the growing importance on early detection of premalignant colonic polyps, accurate determination of polyp size becomes critical to recognize patients with potential to develop colon cancer. National and international guidelines consider polyp size as a key factor in determining follow up intervals with 10 mm cutoff as an important threshold for closer monitoring and surveillance[6,7]. Polyps less than 5 mm rarely show pre malignant histological features while a size over 10 mm has a 33% potential of pre malignant characteristics[8-10]. Polyp size is visually estimated during endoscopy. This is an approximate determination with variability between observers. Pathological measurements are made after excision using the untreated sample or after treatment with formaldehyde[11]. There is a possibility of incomplete estimation because some polyps are submitted piecemeal or fragmented. In addition, visual estimation is 2 dimensional while pathologic measurement is 3 dimensional[12]. Accurate estimation of polyp size also appears to be critical based on its location. Gupta *et al*[13] have reported advanced adenomas are more likely with a smaller size estimate on the right side of the colon. In this study, we aim to investigate examine the inconsistency, if any between the endoscopist's estimate and pathologist's measurement of polyp size hoping to find a way to standardize the polyp size measurement.

MATERIALS AND METHODS

Eighty-eight subjects who underwent endoscopic polypectomy over a two-year period were studied retrospectively. Data was collected on 111 excised polyps. Visual estimation by the endoscopist was recorded to the nearest millimeter. Pathological estimation after fixation with formaldehyde was obtained from biopsy pathology reports. Data regarding the method of polypectomy being biopsy forceps *vs* snare was collected from the each procedure report and analyzed accordingly. Demographic data was collected, as well. We only included patients with clear numerical documentation of the polyp size by the pathologist and the endoscopist and clear documentation of method of polypectomy in the endoscopy report. Subjects with incomplete data or missing parameters were not included. Only cases that were cared for by the teaching consult service were included. From the entire cohort, a random selection of 88 cases that fulfill these criteria was made by our GI pathologist. In order to get a wide representation of all endoscopists and fellows rotating through our service, an average of 3-4 cases from each month over the course of 2 years was maintained.

Visual estimates were obtained using Olympus Evis Exera 111 (CF-HQ190L/I and PCF-HQ190L/I) colonovideoscopes with dual focus optical system and Narrow Band Imaging. Visual estimation was done by the endoscopists for snared polyps and in reference to open forceps for excisional biopsies. The method of polypectomy was determined based on the size of the polyp and type of its attachment, *i.e.*, sessile or pedunculated. All study colonoscopies were performed by our 9 gastroenterology fellows under the supervision of 4 experienced faculty members. The documented

Table 1 Discrepancy in reporting polyp size between endoscopists and pathologists based on the method of excision

Method of excision	Number of polyps	Mean endoscopist's estimate	Mean pathologist's measurement	Mean difference	Overestimate	*P* value
Biopsy excision	52	0.54 (± 0.16) cm	0.38 (± 0.19) cm	0.15 cm	39%	< 0.001
Snare polypectomy	59	0.97 (± 0.34) cm	0.54 (± 0.24) cm	0.43 cm	77%	< 0.001
Total	111	0.76 (± 0.35) cm	0.46 (± 0.23) cm	0.3 cm	65%	< 0.001

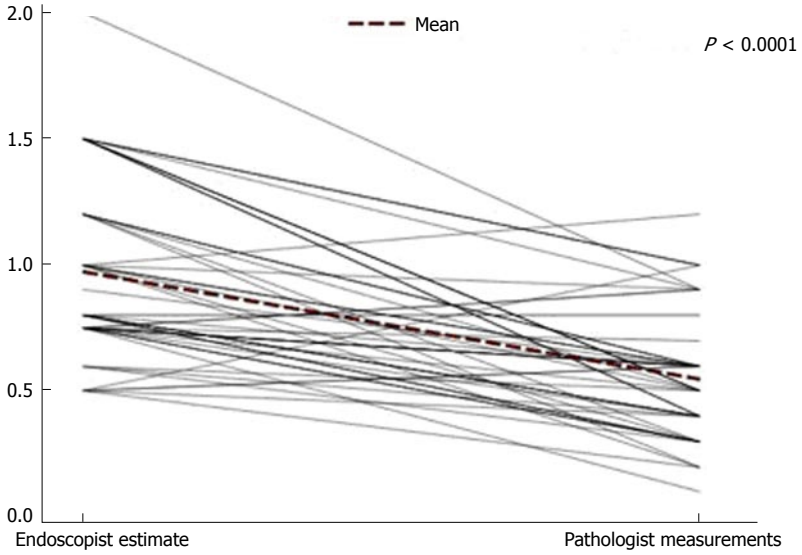

Figure 1 Snared polyp overestimate by endoscopist. Dotted line is the mean difference (Measurements in centimeters).

size was agreed upon by the performing fellow and supervising faculty.

The pathological estimate was blinded to the visual estimate. The macroscopic measurement was done at the cut-up bench.

Statistical analysis

Retrospective analysis was performed comparing visual polyp size and pathological measurement. Continuous and categorical data were presented using means (± SD) and frequencies, respectively. Student *t* test was used to measure the difference of the means between different polypectomy techniques (snare *vs* excisional biopsy). Paired *t*-test was used to estimate the difference of the means between the visual and the pathological polyp size estimates. Linear regression model was used to determine the predictors of the difference of the means between the two estimates (visual *vs* pathological). All statistical analysis was done using statistical analysis software (9.2, South Carolina).

RESULTS

As seen in Table 1, 37% were men and 63% were women with 75% African American, 21% Hispanic, 3% Caucasian and 1% Asian American. Fifty-two (46.8%) of the polyps were excised using biopsy forceps and 59 (53.2%) of the polyps were removed by snare polypectomy. In the biopsy excision group the mean visual size reported by the endoscopist was 0.54 ± 0.16 cm *vs* a mean polyp size of 0.38 ± 0.19 reported during pathological exam. The mean difference was 0.15 (95%CI: 0.09-0.215) (Figure 1). The location of the polyp did not have any impact on the reported measurements. In the snare polypectomy group the mean visual size reported by the endoscopist was 0.97 ± 0.34 cm *vs* a mean polyp size of 0.54 ± 0.24 reported during pathological exam. The mean difference was 0.42 cm (95%CI: 0.33-0.52) (Figure 2). Visual overestimation in the biopsy excision group was 39% in comparison 77% in the snare polypectomy group.

Combining both groups, the mean visual size was 0.76 ± 0.35 cm compared to 0.46 ± 0.23 cm by pathology. The mean difference was 0.3 cm (95%CI: 0.23-0.36). Visual estimates during endoscopy were within 1mm of the pathological measurement in 28 polyps (25%) and were within 2 mm in 52 polyps (46%) (Figure 3).

DISCUSSION

To date, our study is the largest in the field with special emphasis on the method of polypectomy as a factor affecting the endoscopist visual estimate. It also clearly shows that endoscopists tend to overestimate the polyp size; a fact that was previously considered a controversial concept. This study showed that endoscopists tend to overestimate the polyp size by 65% in comparison to the measurements reported by pathologists. This difference between polyp size

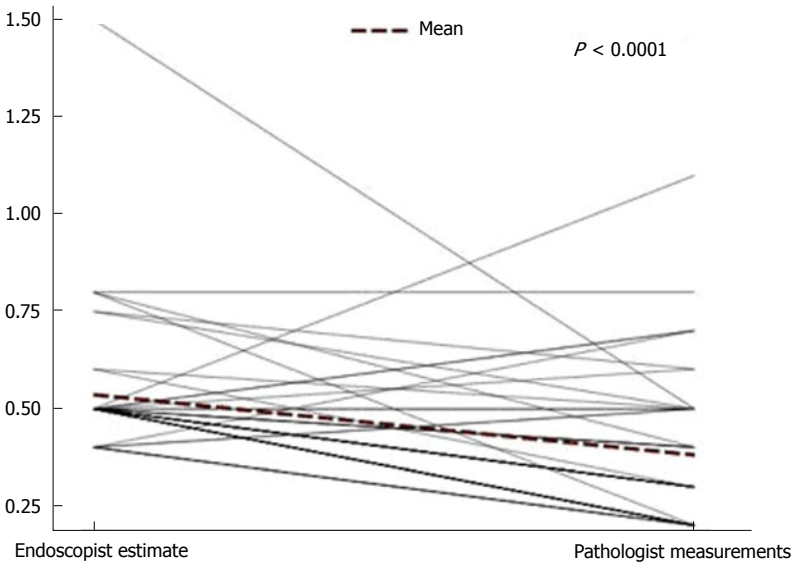

Figure 2 Forceps-excised polyp overestimate by the endoscopist. Dotted line is the mean difference (Measurements in centimeters).

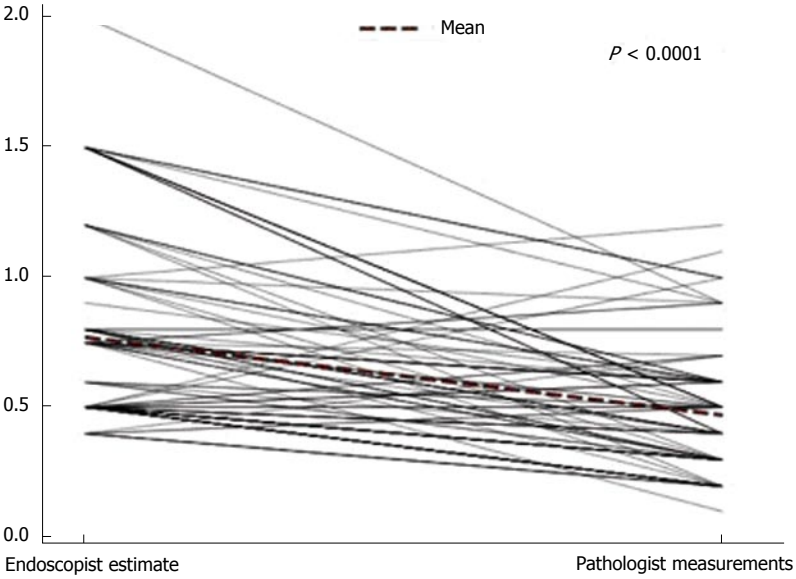

Figure 3 All polyps overestimate by endoscopist. Dotted line is the mean difference (Measurements in centimeters).

measurement that was noted between the endoscopists and pathologists may be attributed to the physical damage of the specimen. The polyp may be damaged in situ during excision or the endoscopist may not remove the polyp in its entirety. This will result in a specimen being sent to the pathologist that is actually smaller than it was *in situ*. Another factor that could be considered is the formalin fixation effect on size shrinkage. However, previous studies have shown that there was no significant difference between post excision polyp size and post fixation measurement, which strongly argues against formalin impact on polyp size[14,15]. Piecemeal submission of polyp tissue for pathological exam can be a factor that results in discrepancies in size too. Furthermore, a study by Schoen *et al*[14] determined that the type of polyp had an impact on the estimated size. In their measurement of 61 polyps, of which, 44 were pedunculated, the size was overestimated by the endoscopist 55% of the time. The stalk on pedunculated polyps may cause the polyp to sit on an angle which makes it more difficult for the endoscopist to accurately estimate its size. In our study, no such observation was noted.

In the current study, only 46% of the endoscopists estimations were within 2 mm of the pathologic measurements. There appears to be a wide variance in the remaining 54% of the measurements. Several published studies support our conclusion that endoscopists overestimate polyp size. A study of 61 polyps concluded that endoscopists overestimated polyp size by greater than 3 mm in 20% of the cases[14]. Morales *et al*[15] determined that in a sample of 31 polyps the endoscopists' estimates were on average 1.6 mm greater than the postpolypectomy measurement.

Other studies contradict our findings by asserting that endoscopists underestimate polyp size. A study of 107 polyps conducted by Turner *et al*[16] concluded that on average both colonoscopists and pathologists significantly underestimate polyp size in comparison to the prefixation measurement. Another recent study on 35 polyps also concluded that colonoscopists underestimate polyp size in 74% of the cases[11]. However, this study of 35 polyps presents a potential bias due to its small sample size.

It is noteworthy that, in our study, endoscopists showed greater overestimation of size in the polyps that were removed by snare biopsy *vs* removal using biopsy forceps (39% *vs* 77%). This can suggest that larger polyps are likely to be overestimated than smaller ones.

One possible limitation of this study is the retrospective model rather than a prospective one. This makes the study rely on the merit of record keeping by the endoscopists and pathologists. Moreover, we also looked only at post fixation size and did not have adequate data on prefixation measurements. However, the latter factor is unlikely to impact our findings in view of previously published studies about the effect of formalin fixation.

In conclusion, this study determined that endoscopists tend to overestimate the size of colonic polyps. This was more pronounced in case of snared polyps in comparison to polyps excised by forceps. Considering the major importance of accurate polyp size estimation on detecting advanced adenoma, visual estimates provided in a non-standardized manner can result in significant observer (endoscopist) variations. Pathology reports for the size are not reliable either considering that most polyps get some degree of physical damage upon removal, which directly affects the size. Use of measurement cursors is a standard practice during imaging studies and sonography. We suggest that the addition of a measurement cursor to video endoscopes can standardize the visual estimates and provide accurate information to determine appropriate surveillance intervals allowing for better management and ultimately a decreased mortality rate from colon cancer.

COMMENTS

Background

Colonic polyp size is critical in determining the significance of the polyp and thus the colonoscopy surveillance interval. The inaccuracy in determining the size can have remarkable consequences represented by repeating colonoscopy earlier than needed in case of overestimating the actual polyp size or delaying a necessary procedure which might result in development of colorectal cancer in case of underestimating the polyp size.

Research frontiers

There have been only few small studies that attempted to address the issue of estimating polyp size by the endoscopists. Those studies have shown inconsistent results in terms of endoscopists' tendency to overestimate *vs* underestimate polyp size.

Innovations and breakthroughs

This study is, to date, the largest of its kind and it clearly shows that endoscopists tend to generally overestimate polyp size with wide variance in the overestimate. On the other hand, the pathologist's measurement cannot be considered reliable given the possibility of physical damage or shrinkage of the polyp.

Applications

This study highlights the desperate need for an accurate standardized method of measuring colonic polyp size. To solve this issue, the authors suggest using cursors for colonoscopy screens like those used in ultrasound and computed tomography scanners.

Peer-review

This is a well-written manuscript. The retrospective nature of the study may actually be a plus as it gives a true representation of the endoscopists estimation of size as they would normally do in their routine practice.

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Toward an easier indigocarmine chromoendoscopy

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Author contributions: Barret M drafted the manuscript; Camus M, Leblanc S and Coriat R performed the endoscopic procedures; Prat F corrected the manuscript; Chaussade S performed the endoscopic procedures and designed the study; all authors approved the final version of the manuscript.

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Abstract

Indigocarmine chromoendoscopy has been proven to improve the detection of colonic lesions during screening colonoscopy, and is associated with increased adenoma detection rates. Furthermore, it is commonly used to help in the delineation and characterization of colorectal neoplasms. However, it usually requires the use of a spraying catheter that decreases the suction capacity of the endoscope, and is time- consuming. Herein, we report on the feasibility of indigo carmine chromoendoscopy during colonoscopy without using a spraying catheter, with the dye being administered through the air/water channel of the endoscope. Since the suction channel remains free, the air can be exsufflated and the staining then applies uniformly onto the colonic walls with the excess indigocarmine dye being immediately eliminated. In our experience with various types of colonoscopes and cap-assisted colonoscopy, this procedure makes indigocarmine chromoendoscopy much easier and quicker to perform, and might save the use of a spray catheter.

Key words: Indigocarmine; Chromoendoscopy; Colonoscopy; Adenoma detection rate; Colorectal cancer screening

Core tip: We report on the feasibility of indigocarmine chromoendoscopy during colonoscopy without using a spraying catheter, with the dye being administered through the air/water channel of the endoscope.

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TO THE EDITOR

Indigocarmine chromoendoscopy has proven useful in increasing the overall diagnostic yield of colonoscopy and the adenoma detection rate[1]. This technique is currently recommended in routine colorectal cancer

Figure 1 0.2% indigocarmine solution prepared in the water bottle.

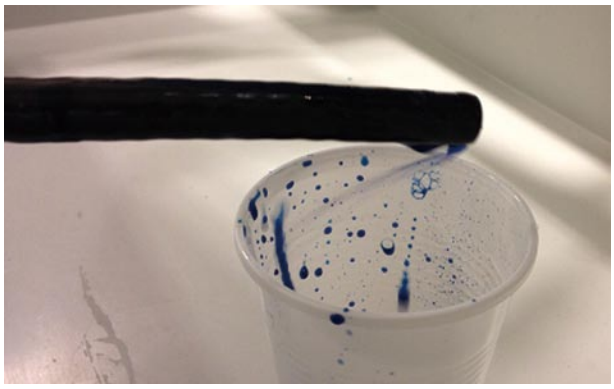

Figure 2 Indigocarmine dye application through the air/water channel of the endoscope.

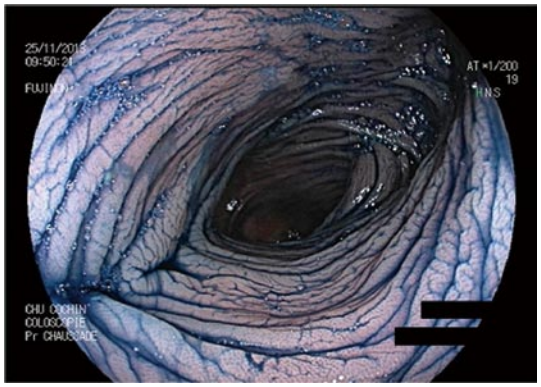

Figure 3 Endoscopic view of the colonic mucosa after indigocarmine staining using a Fujifilm® colonoscope.

screening in patients with long-standing inflammatory colitis or hereditary nonpolyposis colorectal cancer[2]. The standard technique implies pancolonic spraying with 0.2% indigocarmine delivered through a spraying catheter inserted in the accessory channel of the colonoscope. Spraying is performed segmentally during withdrawal of the endoscope and excess dye is suctioned before mucosal examination.

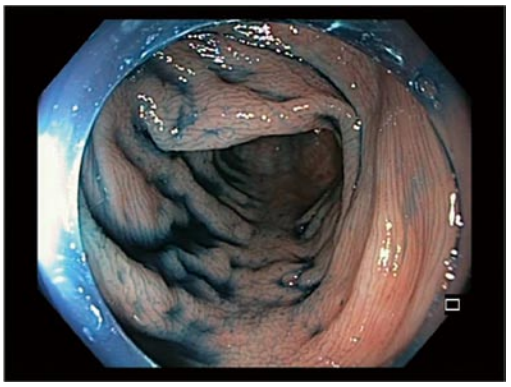

Figure 4 Endoscopic view of the colonic mucosa after indigocarmine staining using an Olympus® colonoscope and a cap.

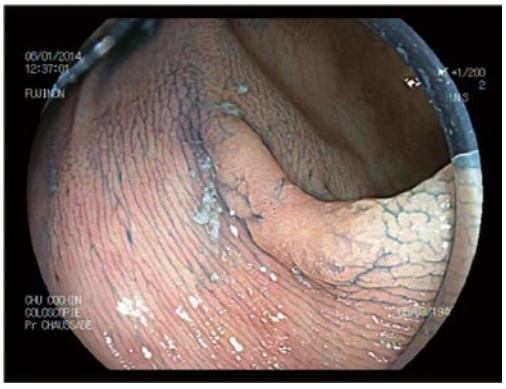

Figure 5 Endoscopic view of a sessile serrated adenoma after indigocarmine staining.

However, the use of a spray catheter has a certain cost, limits the suction capacity of the endoscope and often requires several passages with the endoscope, which can sometimes be difficult in some patients. We report on the feasibility of the indigocarmine dye application directly through the colonoscope air/water channel. Upon cecal intubation, the indigo carmine solution is prepared in the water bottle, using two 10 mL vials of 1% indigocarmine diluted in 80 mL of water, in order to obtain the 0.2% concentration (Figure 1). The indigo carmine dye is delivered by pressing on the air/water valve while orienting the head of the endoscope against the colonic walls and withdrawing the colonoscope. The indigocamine dye application is shown on Figure 2. It should be noted that the indigocarmine stained water does not remain on the objective lens of the endoscope rendering clear water unnecessary for the cleaning of the tip of the endoscope during the chromoendoscopy procedure. Once the end of a colonic segment has been reached, suction of the air allows uniform application of the dye on the mucosa and elimination of excess fluid. New air insufflation is then needed for the colonic mucosal examination.

Immediately after the procedure, the air/water channel of the endoscope is flushed with water from another water bottle until the outflow is clear, to make sure that no indigocarmine dye remains inside the channel. After standard washing, we did not observe any residual staining in the water bottles. Our preliminary experience with 15 patients suggests that this simplified indigocarmine chromoendoscopic technique is feasible with Olympus® or Fujifilm® colonoscopes, with or without a cap (Figures 3-5) and with a median withdrawal time of 21 ± 12 min.

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