New Frontiers in Small Bowel Endoscopy

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Background

Endoscopic accessibility to the small intestine has been a challenge to the gastroenterologist for decades. The length of the small intestine, in addition to its free intra-peritoneal location, vigorous contractility, and overlying loops, confound standard endoscopic techniques. Sonde enteroscopy was introduced in 1986, but was eventually abandoned as it was labor-intensive for the gastroenterologist and uncomfortable for the patient.[1] The small thin Sonde scope was passed through the nose and then into the stomach. Another endoscope was then passed through the mouth and the Sonde enteroscope was introduced into the small bowel using the larger endoscope that had been passed through the mouth. A balloon was then inflated; with the help of peristalsis and the patient who was advancing the enteroscope, the apparatus was eventually advanced to the distal jejunum and/or ileum over a 6-10 hour period. At the end of the advancement period, the gastroenterologist slowly removed the Sonde enteroscope and was able to visualize pathologic findings, but was unable to perform any therapeutic manuevers.

Push enteroscopy, using a pediatric colonoscope or a dedicated small bowel enteroscope ranging in length between 200 and 260 centimeters, remains

the most commonly performed endoscopic procedure for the small intestine.[2, 3] The endoscope is passed through the mouth with or without an overtube, and external compression is used in an attempt to pass the enteroscope 50-150 cm distal to the ligament of Treitz. While the procedure is helpful for identification and treatment of proximal causes of small bowel bleeding or pathology, the exam is limited by looping of the enteroscope, causing patient discomfort and preventing further advancement of the enteroscope into the mid-jejunum or ileum.

Intra-operative enteroscopy (IOE) was traditionally the gold standard for small bowel imaging, but has largely been replaced by the advent of balloon-assisted enteroscopy.[4] While IOE traditionally had the highest diagnostic yield, disadvantages included a high complication rate, need for a surgeon as well as an endoscopist, and post-procedural hospital stay. Intra-operative enteroscopy was initially performed in the 1950s with a sterile rigid sigmoidoscope passed through an operative colotomy or enterotomy.[5] By the 1970s, fiberoptic endoscopes were used for IOE.[6] In 1980, Bowden and colleagues performed intra-operative enteroscopy by passing a fiberoptic colonoscope first orally and then anally while the surgeon manually telescoped the bowel over the tip of the endoscope.[7] The terminal ileum was intubated in over 90% of patients using this technique, while minimizing the mortality and morbidity associated with enterotomy for earlier intraoperative enteroscopy procedures. Currently IOE is reserved for patients with small bowel lesions that are not accessible by balloon-assisted enteroscopy due to the presence of adhesions, or may remain an option

for patients with multiple lesions requiring endoscopic resection, for example in patients with familial polyposis syndromes.

The concept of double-balloon enteroscopy (DBE), also known as "push-and-pull" enteroscopy, was initially conceptualized by Dr. Hinori Yamamoto of Jichi Medical University in 1997.[8] Dr. Yamamoto based the development of DBE on the concept that stretching of the small intestine prevents advancement, (Figure 1) and that the usage of a balloon-attached flexible overtube and a second balloon attached to the endoscope tip would permit deep examination of the small bowel. Latex balloons at the tip of the enteroscope and the overtube are inflated and deflated with air from a pressure-controlled pump system. By inflating the overtube balloon enough to grip the intestinal wall (which can occur at a balloon pressure of 45 mmHg), the endoscope can be inserted further without forming redundant loops in the small intestine. The overtube can then be inserted while the endoscope balloon is inflated. This method allows for insertion of the endoscope deep into the small intestine. With the development of a 200 cm enteroscope that had an outer diameter of 8.5 mm equipped with a 140 cm overtube with an outer diameter of 12 mm, total enteroscopy was completed with the endoscope tip advanced into the cecum in a reported case.[9] The current DBE system was developed and marketed by Fujinon, Inc in November 2003.[10] (Figure 2)

The single-balloon enteroscope (SBE) system (Olympus Corporation, Tokyo, Japan) was developed in 2006 and was introduced into the commercial

market on May 19, 2007.[11] The rationale behind development of the Olympus Single Balloon Enteroscope System was to reduce the learning curve for balloon-assisted enteroscopy, avoid the difficulty of attaching the enteroscope balloon to the distal tip of the scope encountered in DBE, and eliminate the requirement of inflating and deflating two balloons in multiple steps with the current DBE insertion technique. (Figure 3)

Indications for Balloon-Assisted Enteroscopy (BAE)

The major indication for BAE remains obscure GI bleeding, including patients with obscure overt bleeding or iron-deficiency anemia with no source detected on conventional upper endoscopy and colonoscopy. Other indications include small bowel evaluation for abnormalities detected on prior radiographic examinations including polyps, strictures, neoplasms, or changes consistent with inflammatory bowel disease. BAE may be indicated for further evaluation and management of abnormal findings on capsule endoscopy including arteriovenous malformations, ulcerations, neoplasms, or other findings. BAE may be useful in the management of refractory sprue, or in the evaluation of patients with unexplained diarrhea and suspected small bowel pathology. In patients with genetic syndromes including familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome, BAE offers an opportunity to diagnose polyps and perform polypectomy. Other less common indications for DBE might include placement of percutaneous jejunostomy tubes, evaluation of the bypassed stomach in patients after gastric bypass, foreign body removal (most commonly swallowed dentures or retained capsule endoscopes) or to perform ERCP in

patients with Roux-en-Y anatomy. Retrograde BAE may be an alternative in patients with failed conventional colonoscopy.

Approximately 5% of patients presenting with gastrointestinal hemorrhage have no source found by upper endoscopy and colonoscopy.[12] In approximately 75% of these patients, responsible lesions can be detected in the small bowel.[13-15] Small bowel arteriovenous malformations (AVMs) are the most common finding in 20-40% of patients presenting with obscure overt bleeding.[16] Other potential causes of bleeding in order of frequency include ulcerations (found in approximately 20% of examinations), primary or metastatic tumors (prevalence 5%), and/or vascular lesions including Dieulafoy's lesions or hemorrhage associated with portal hypertension.

The natural history of bleeding from AVMs remains poorly understood. There appears to be a spontaneous cessation rate from AVMs of approximately 40% per year.[17, 18] Outcomes after endoscopic therapy for AVMs have not been well studied, In a 1996 retrospective study,[19] 83 patients who had demonstrated gastrointestinal bleeding from small bowel AVMs demonstrated on both push and Sonde enteroscopy were followed for outcomes after their examinations. Fifty-five (66%) patients underwent electrocautery of their AVMs while 28 (34%) patients received only medical therapy. Follow-up assessments of these patients revealed that over a mean of 26 months, the non-cauterized group continued to bleed, requiring 2.2 $\pm$ 3.9 units of packed red blood cells per month which did not change significantly after diagnosis, while the cauterized group significantly improved

from 2.4 ± 3 units per month pre-treatment to 0.32 ± 0.91 units/month after cauterization ($p<0.001$). Further studies examining the impact of endoscopic therapy on the natural history of AVMs are warranted.

Efficacy of Balloon-Assisted Enteroscopy

Published studies examining outcomes associated with DBE are shown in Table 1. Single balloon enteroscopy (SBE) was introduced in 2007 and limited publications on efficacy are described below.

Summary statistics based on the 1221 patients in Table 1 who have undergone 2400 DBE examinations demonstrated a mean (± SD) diagnostic yield of 63% ± 18% (range 16-81%) and diagnostic or treatment success of 62% ± 13% (range 42-84%). Total enteroscopy was achieved in 34% ± 23% (range 0-86%) and appeared to increase with operator experience. Obscure bleeding was the indication for the DBE in approximately 36-100% of examinations, and the overall diagnostic yield from DBE ranged from 43-80%. The data suggest higher diagnostic yields with increasing operator experience, as the U.S. data was based on the first 40 DBE examinations at each participating institution, which might partially explain the low diagnostic rate in that series.[20] Patients with obscure bleeding as an indication for DBE had higher pathology detection rates compared to other indications. A recent meta-analysis comparing capsule endoscopy (CE) to DBE enrolling 11 comparative studies found that the pooled overall yield for CE and DBE was 60% (n = 397) and 57% (n = 360), respectively.[21] Ten studies reported vascular findings; the pooled yield for CE and DBE was 24% (n = 371) and 24% (n = 364), respectively. (weighted

incremental yield of CE – DBE of 0%; 95% CI, -5% to 6%; P = 0.9). Nine studies reported inflammatory findings; the pooled yield for CE and DBE was 18% (n = 343) and 16% (n = 336), respectively (p=NS). Nine studies reported polyps/tumors; the pooled yield for CE and DBE was 11% (n = 343) and 11% (n = 336), respectively (p=NS). The authors concluded that CE should be the initial diagnostic test because of its noninvasive quality, tolerance, ability to view the entire SB, and for determining the initial route of DBE. However, because of its therapeutic capabilities, DBE may be indicated in patients with a positive finding on CE requiring a biopsy or therapeutic intervention, if suspicion for a SB lesion is high despite a negative CE, and in patients with active bleeding. A recent cost-effectiveness model suggested that initial DBE was a cost-effective approach for patients presenting with obscure bleeding who most likely had AVMs present in the small bowel that would be accessible via an empiric anterograde approach.[22]

As single balloon enteroscopy (SBE) was introduced in 2007, there is currently limited literature on its efficacy. In a prospective Japanese study by Tsujikawa and colleagues in 78 patients undergoing SBE, the overall diagnostic yield was 54%, treatment success 58%, and total enteroscopy was performed in 6/24 (25%) of attempted examinations.[23] The mean $\pm$ SD examination time was 63 $\pm$ 20 minutes for the anterograde approach and 70 $\pm$ 19 minutes for the retrograde approach. Further studies are warranted examining the efficacy of SBE compared to DBE examinations.

Complications

Potential complications after BAE can include complications common to all endoscopic procedures including aspiration, infection, and sedation-related issues. The most common reported problem secondary to DBE has been the presence of abdominal cramping, present after 2-20% of examinations. The cramping is usually temporary and has been decreased due to the usage of carbon dioxide rather than room air for the enteroscope.[24] Potential reasons for the pain include trapped gas, intestinal spasm, transient intussusception, and/or bowel wall hemorrhage.[25]

Complications that appear to be increased post-DBE include pancreatitis, gastrointestinal hemorrhage, and perforation. Summarizing the DBE cases listed in Table 1, small intestinal perforation occurred in 5 of 2400 (0.2%) procedures. A recent multicenter survey study including 2367 DBE procedures from 10 centers demonstrated that the overall perforation rate was 0.3%.[26] Perforations were more likely to occur in patients undergoing stricture dilation or argon plasma coagulation for arteriovenous malformations. Perforations may be more likely in patients with pre-existing weakened intestinal walls which are then subjected to distension and traction from the DBE procedure. The prior literature has suggested increased risk of perforation in patients with lymphoma undergoing chemotherapy,[27] patients with inflammatory bowel disease with or without stricture dilation, recently created intestinal anastomoses,[20] and altered surgical anatomy, particularly the presence of an ileoanal anastomosis.[28] Caution should be exercised in situations of extensive diverticulosis or other conditions associated with bowel wall fragility including Ehlers-Danlos syndrome. In patients

with fixed small intestine from prior radiation or extensive abdominal surgery, alternative methods of investigation of the small bowel are advised. Polypectomy of large polyps has also been associated with increased risk of performation: In a series of 178 patients in Germany undergoing therapeutic DBEs, 3 (1.7%) patients experienced perforation after polypectomy of large polyps > 3 cm in size.[29]

Pancreatitis has also shown to be increased post-DBE, ranging in frequency from 0.1%-1% of the patients. Potential mechanisms for post-DBE pancreatitis include pancreatic duct obstruction by direct oppression of the papilla with the inflated balloon, increase in duodenal intraluminal pressure caused by the overtube and gastrointestinal shortening technique, reflux of duodenal contents into the pancreatic duct due to intraluminal hypertension caused by the inflated balloon, and/or injury or ischemia due stretching and shortening of the proximal small bowel. Elevation of amylase levels have been noted in up to 45% of patients post-DBE, although clinical pancreatitis occurred in only 17% of these patients in one study.[30] Although the occurrence of pancreatitis is not well understood, it is recommended to avoid initial balloon inflation in the duodenum.

Conclusions

The introduction of balloon-assisted enteroscopy has opened up opportunities for the endoscopist to diagnose and manage small bowel disorders that remained previously untreated or required intraoperative enteroscopy. Efficacy of DBE has been shown to be equivalent to that of capsule endoscopy. CE remains preferred as the third line test after negative endoscopy and

colonoscopy in patients with obscure bleeding due to its ability to visualize the entire small bowel, ease of administration, and decreased potential for complications. DBE may be the preferred initial test in patients with a high likelihood of actively bleeding vascular lesions of the small bowel requiring endoscopic intervention, or in patients with prior imaging modalities demonstrating lesions requiring endoscopic therapy or biopsy. Single balloon enteroscopy and spiral enteroscopy are new imaging modalities for the small bowel currently undergoing investigation and comparison to DBE.

Table 1. Published Studies of DBE in Patients with Obscure GI Bleeding

Author	Patients with Bleeding/ DBE exams	Diagnostic Yield	Diagnostic or Treatment Success	Total DBE*	Rebleed Rate	Complications
Yamamoto 2004 [27]	66/178 (37%)	76%	61%	86%	N/A	Perforation – 1 (0.6%)
May 2005 [31]	90/248 (36%)	80%	76%	35%	N/A	None
Ell 2005 [32]	64/147 (44%)	72%	62%	16%	N/A	None
Di Caro 2005 [33]	33/89 (37%)	80%	42%	44%	N/A	None
Mehdizadeh 2006 [69]	130/237 (55%)	43%	60%	0%	N/A	Perforation – 1 (0.4%)
Hadithi 2006 [34]	35/35 (100%)	60%	77%	20%	20%	None
Heine 2006 [35]	168/275 (61%)	73%	55%	42%	N/A	Pancreatitis – 3 (1%)
Kaffes 2006 [36]	32/40 (80%)	48%	75%	0%	N/A	Perforation – 1 (2.5%)
Monkemuller 2006 [37]	29/70 (41%)	67%	57%	30%	0%	Polypectomy bleed – 1 (1.4%)
Manabe 2006[38]	31/31 (100%)	74%	74%	29%	0%	None
Nakamura 2006[39]	28/28 (100%)	41%	43%	63%	6%	Perforation – 1 (3.6%)
Akahoshi 2006[40]	20/103 (19%)	43%	43%	40%	N/A	None
Barreto 2007[41]	40/86 (47%)	73.5%	50%	20%	3.5%	None
Cazzato 2007[42]	71/100 (71%)	69%	65%	N/A	N/A	None
Zhong 2007[43]	191/378 (51%)	65%	84%	56%	N/A	Polypectomy bleed – 1 (0.3%)
Zhi 2007[44]	92/155 (59%)	81%	61%	N/A	N/A	Perforation – 1 (0.65%)
Stark 2008[45]	101/200 (50%)	80%	72%	25%	N/A	None
Totals**	1221 patients 2400 exams	63%	62%	34%		Perforation – 5 (0.2%) Pancreatitis – 3 (0.1%)

* Defined as initial DBE in one direction with tattoo at most distal insertion point followed by DBE from opposite direction with prior tattoo site identified
** Calculated mean averages for diagnostic yield, treatment success and total DBE rates

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