Innovation and Best Practices in Endoscopy

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THESIS

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Introduction and outline of thesis

INTRODUCTION

Advances in gastrointestinal (GI) endoscopy have played an important role in improving the diagnostic and therapeutic options for physicians treating patients with GI diseases. Indeed, the advent of endoscopy transformed the field of Gastroenterology and contributed significantly to its emergence as a specialty separate from Internal Medicine and General Surgery. As the pace of technological progress has quickened, innovation in GI endoscopy has only accelerated, expanding the tools available to the practicing gastroenterologist. However, it remains essential that physicians examine technology with a critical eye to ensure that new devices or techniques are truly an improvement for patient care, both in terms of efficacy and safety. In addition, it is important that existing practices are frequently examined and critically reevaluated in order to deliver clinical care at the highest level of quality. For this reason, clinical research is a necessary component of the modern practice of medicine, a maxim that holds true for GI endoscopy as much as for any other field.

The practice of endoscopy can be traced back to the development of an early gastroscope by Rudolf Schindler and George Wolf of Germany in the early 1920's.[1] However, this device relied on a series of optical lenses and prisms that made it rather cumbersome to use. It wasn't until the innovation of fiberoptics, bundles of fine glass fibers capable of conducting light over distances, that flexible endoscopy became a clinically useful proposition.[2] Basil Hirschowitz was a major pioneer in this area and introduced the first fully flexible gastroscope to the world in the 1950's.[3] These advances were then incorporated into lower GI endoscopy in the form of the first flexible sigmoidoscope by Bergein Overholt in 1963.[4] Soon thereafter, longer versions were developed into colonoscopes and by the 1970's, colonoscopy was being rapidly adopted by gastroenterologists. The 1970's also heralded the advent of biliary endoscopy, first in Japan and then most prominently by Peter Cotton in Britain who coined the term endoscopic retrograde cholangiopancreatography (ERCP).[5] In the ensuing decades, GI endoscopy in the form of gastroscopy, colonoscopy and ERCP became cornerstones in the practice of gastroenterology. The field has been further expanded by the development of endoscopic ultrasound (EUS),[6] which enables ultrasound images to be obtained from within the lumen of the GI tract, and most recently by small bowel endoscopy,[7,8] which has placed the small intestine within the diagnostic and therapeutic reach of gastroenterologists.

This paper will focus on innovation and best practices in endoscopy, first with respect to colonoscopy, and second in regards to small bowel endoscopy.

Colonoscopy

In current practice, one of the most common reasons that patients undergo colonoscopy is colon cancer screening and polyp surveillance. Indeed, colonoscopy is the preferred colon cancer screening modality by the American College of Gastroenterology[9] and the American Gastroenterological Association.[10] This is important because colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality.[11] In the vast majority of cases, colon cancers develop from a prolonged adenoma-to-carcinoma sequence, which given sufficient time and accumulation of enough genetic mutations, enable polyps to transform and grow into cancer.[12] Considerable efforts within the field of Gastroenterology have been devoted to the use of colonoscopy for the detection and removal of potentially pre-cancerous polyps, with the aim of preventing colon cancer, and for the diagnosis of early stage disease that is more likely to be treatable and result in long-term survival. Indeed, colonoscopy has been shown to decrease the likelihood of developing colon cancer as well as CRC-related mortality.[12-15] However, recent evidence suggests that colonoscopy has not been as universally protective against CRC as had been previously hoped, particularly for proximal cancers located in the right colon.[16,17] Theories as to why this might be the case include speculation about altered biology of cancers that develop in the proximal colon and technical issues relating to the performance of colonoscopy itself.[18] In particular, one of the problems is incomplete colonoscopy that fails to examine the entire colon to the cecum, which may occur in more than 10-20% of cases.[19,20] Furthermore, wide variability in detection rates of neoplastic lesions, with inadequately low rates by many practitioners, demonstrates that colonoscopy technique plays an important role in the cancer prevention properties of the test.[21] In particular, longer colonoscope withdrawal times have been clearly linked to significantly greater adenoma detection rates and to an increased mean number of polyps detected per patient, with a minimum withdrawal time of 6 minutes established as a necessary threshold.[22] In addition, from a public health standpoint, a considerable proportion of the population remain averse to undergoing colonoscopy, particularly because of fears of procedure discomfort,[23,24] decreasing the potential impact for overall CRC reduction. Thus, optimizing the technical performance of colonoscopy and improving its acceptance among patients is important for maximizing the possible benefits to society.

The most common reasons for a technically challenging colonoscopy include a narrowed, angulated sigmoid colon and a long, redundant colon in which the endoscopist "runs out of scope" before reaching the cecum,[25] of which the latter is usually due to excessive looping of the endoscope. Furthermore, while the physiology of pain experienced during colonoscopy is caused by stretching of the mesentery attached to the bowel, a study with "on demand" patient-controlled analgesia showed that 79% of pain-

ful episodes were caused by endoscope looping, primarily when the scope tip was in the sigmoid colon.[26] Experts agree that colonoscopy is most successful at reaching the cecum and most comfortable for patients when the endoscope is kept in a straight position by minimizing loop formation and reducing loops once they have formed.[25,27] Thus, identification and reduction of endoscope loops is critically important for the successful and comfortable completion of colonoscopy. Over the years, many techniques have emerged to overcome loop formation and assist the performance of colonoscopy, including withdrawal of the endoscope with torque, abdominal wall pressure and patient position changes. A study that examined colonoscopy while using external magnetic imaging identified loop formation in 91% of cases, but found that conventional maneuvers to overcome loops such as abdominal compression and position changes were only successful in 52% of attempts.[28] This is not surprising given that 69% of loops were incorrectly diagnosed, an important consideration given that understanding of loop shape is necessary to determine the type of maneuver needed to overcome it. Despite these limitations, these maneuvers form the cornerstones of current colonoscopy technique. Technological innovations such as smaller caliber "pediatric" colonoscopes and "variable stiffness" colonoscopes with adjustable rigidity have been introduced that have had moderate success in diminishing patient discomfort, reducing sedation requirements and increasing rates of cecal intubation.[29-32] Yet despite these efforts to improve colonoscopy practice, the reality is that many procedures are still done poorly. An audit of all colonoscopies performed in Winnipeg, Manitoba from 2004 to 2006 demonstrated a dismal completion rate of only 65%.[33] Thus, greater improvements are clearly needed to bring the performance of colonoscopy up to an excellent standard.

Part of achieving high standards in the delivery of colonoscopy requires that endocopists receive sufficient training to ensure that they possess the necessary skills to reach those targets. Unfortunately, a clear consensus is lacking as to the nature and extent of training required to accomplish these aims, and whether additional measures are necessary to ensure ongoing quality and competency in endoscopy for those already in clinical practice. While the skillset necessary to effectively perform colonoscopy has been clearly defined by the American Society of Gastrointestinal Endoscopy (ASGE),[34] there are discrepancies regarding the minimum number of procedures required to meet the threshold for competency, with the traditional ASGE guideline of 140 procedures differing significantly from the 50 procedures mandated by general surgery and family medicine societies.[35] Furthermore, a substantial learning curve has been demonstrated that suggests a far higher minimum threshold of 275 procedures is needed to achieve a reasonable standard of quality metrics.[36] Thus, the true training needs of colonoscopy learners remains uncertain. Recently, attention has turned to incorporating technological innovations such as computerized endoscopy simulation[37,38] and magnetic imaging

systems[39] to facilitate the learning process, particularly at earlier stages of training. Whether this will translate into improved performance of colonoscopy in subsequent clinical practice has yet to be determined.

Small Bowel Endoscopy

For several decades after the widespread adoption of gastroscopy and colonoscopy into clinical practice, the small intestine remained a "black box" that was for the most part inaccessible to endoscopists. Access to the small bowel was either limited in scope (push enteroscopy), highly invasive (intra-operative enteroscopy) or consisted of relatively crude radiologic studies (small bowel barium X-ray and enteroclysis). This all changed with two dramatic technological innovations that occurred at the start of the last decade. Capsule endoscopy (CE) was approved for use in Europe and the United States in 2001[7] and later in Japan in 2007, and has quickly become part of standard-of-care in the investigation of small bowel diseases.[40] Around the same time, Hironori Yamamoto introduced double balloon endoscopy (DBE) as the first type of overtube-assisted device that enabled direct endoscopic access to the entire GI tract.[41] Together, CE and DBE have revolutionized the approach to small bowel diseases in general and to obscure GI bleeding in particular.

CE consists of a pill camera that is swallowed by the patient and then moves passively through the GI tract by persistalsis, taking thousands of images that are wirelessly transmitted by radio waves to sensors placed on the patient's abdomen, which are themselves connected to a special data recorder.[42] Once the study is completed, the data recorder is docked to a computer workstation and the endoscopic images are reformatted into a video file that can then be viewed for analysis. CE is appealing for patients since it is relatively non-invasive and is performed in an outpatient setting with virtually no discomfort, and is attractive to physicians since it is a safe, reliable and effective method for visualizing the entire small bowel. However, the disadvantages of CE are that it is a purely diagnostic test without therapeutic capabilities, there is no means to facilitate tissue biopsy, and accurate localization of findings can be difficult.[43] Furthermore, it does not provide a real-time examination and cannot be steered back toward a suspected area of pathology to allow for further inspection. The main indications for CE are obscure GI bleeding, unexplained iron-deficiency anemia, known or suspected non-stricturing small bowel Crohn's disease, refractory Celiac disease, hereditary polyposis syndromes, and suspected small bowel tumors.[44]

Overtube-assisted enteroscopy is both a diagnostic and therapeutic procedure with the potential for navigation of the entire small intestine by combining sequential oral and anal approaches.[45] The major advantage over CE is the ability to obtain tissue biopsies,

as well as to perform therapeutic interventions such as hemostasis for bleeding, polypectomy, balloon dilation or placing ink tattoo at the site of pathologic findings to direct subsequent surgery.[46] However, it is an invasive and lengthy procedure that requires deep sedation, typically with propofol, and has an increased risk for potentially serious complications, including intestinal perforation, bleeding and acute pancreatitis.[47-49] DBE was the first type of overtube-assisted enteroscopy and is the technique that has been adopted most widely. It consists of a 200 cm endoscope and a 140 cm flexible, polyurethane overtube, both of which are fitted at the distal tip with an inflatable latex balloon. The overtube balloon is inflated to grip the intestinal wall and hold it in place, preventing stretching of the intestine and allowing advancement of the endoscope without the formation of redundant loops of bowel. After advancement of the overtube to the distal tip of the endoscope, both balloons are simultaneously inflated while the endoscope and overtube are pulled back together in a shortening maneuver pleating the intestine back over the scope. This cycle is successively repeated as the endoscope is advanced through the small intestine. Single balloon endoscopy (SBE) is another form of overtube-assisted balloon enteroscopy that was introduced more recently in 2008.[50] SBE works in a similar manner as DBE, but there is a balloon only on the overtube and not on the endoscope, meaning that endoscope tip deflection combined with suction is used to "hook" the bowel wall to enable shortening, whereas this is accomplished more reliably by inflating the endoscope balloon with DBE. An even newer and entirely different overtube-assisted technique is spiral enteroscopy, which utilizes a unique overtube that has raised helices at its distal end, a locking device to fix the overtube to the enteroscope, and two foam handles at its proximal end that are twisted to cause the overtube to rotate.[51,52] Clockwise rotation of the spiral overtube acts in a manner similar to that of a screw, advancing the endoscope while pleating the bowel onto its surface. The spiral overtube can be used with either a DBE or a SBE endoscope (without balloon overtube) and enables rapid advancement deep into the small bowel. DBE, SBE and spiral enteroscopy may be performed via an anterograde approach through the mouth or via a retrograde approach through the anus. The majority of the research literature and the bulk of clinical experience involves DBE, whereas SBE and spiral enteroscopy remain more emerging technologies.[43]

Given the highly invasive nature of overtube-assisted enteroscopy, perhaps it should not be surprising to find complication rates for DBE that far exceed those for colonoscopy, with an overall adverse event rate of more than 1%.[49] Indeed, the three most common, serious complications include bleeding (0.6%), intestinal perforation (0.3%) and acute pancreatitis (0.3%).[47,48] The development of acute pancreatitis post-DBE was a surprising finding and its cause remains unclear. Multiple theories have been proposed and the technique for the initial advancement of the enteroscope has been accordingly modi-

fied,[53] yet hyperamylasemia and acute pancreatitis remains a concern for both DBE[54] and SBE.[55]

AIM OF THESIS

As outlined above, substantial innovation and significant improvements have been made in the field of GI endoscopy, but many challenges remain. Ongoing, continuous efforts are needed to help achieve the best possible practice of endoscopy, in terms of optimizing technical performance, clinical outcomes and patient safety. New ways of doing things and new solutions to longstanding challenges need to be considered, while new technologies must be critically evaluated to ensure that they are better and not simply newer. In this paper, these questions are asked first with respect to colonoscopy and secondly with respect to small bowel endoscopy.

Despite more than four-decades experience with colonoscopy, clinically relevant limitations persist, not least being difficulties with incomplete procedures that result in suboptimal examinations, and challenges regarding procedural discomfort and safety that may affect patient willingness to undergo these tests. Therefore, techniques or strategies that improve the completion rate and/or comfort of colonoscopy are needed. In **Chapter 2**, a prospective, randomized controlled trial is presented that compared magnetic imaging-assisted colonoscopy to conventional colonoscopy with respect to patient comfort as well as procedural metrics such as cecal intubation rate and time-to-cecum. It was hypothesized that magnetic imaging would improve the performance of colonoscopy by enabling visualization of endoscope position and loop formation.

Recognizing that a proportion of colonoscopy procedures will invariably be incomplete, attention was next directed toward potential solutions to address this problem. A number of different strategies have been used in the past to overcome colonoscopy cases that are previously incomplete.[56-59] Recently, techniques from small bowel endoscopy have been borrowed with the demonstration that DBE may successfully enable completion of previously failed cases.[60-62] However, it was unclear if SBE, a newer method of overtube-assisted enteroscopy, was also a feasible and effective strategy for overcoming incomplete colon examinations. This study is presented in **Chapter 3**.

In **Chapter 4**, the new small bowel endoscopy techniques are further explored, focusing on the best strategy for evaluating patients with obscure GI bleeding (OGIB), the most common indication for small bowel investigations. OGIB is defined by the American

Gastroenterological Association as bleeding that persists or recurs without identification of its source after negative esophagogastroduodenoscopy and colonoscopy.[63] It is classified as "overt" when patients present with clinically evident manifestations such as hematemesis, hematochezia or melena, and "occult" when patients have iron-deficiency anemia or positive fecal occult blood testing. Approximately 5% of GI bleeds are thought to remain "obscure" after initial conventional work-up, with a presumed source of bleeding attributed to the small intestine.[63] Consequently, OGIB is the predominant reason why small bowel endoscopy is performed. However, it has remained unclear whether CE or DBE is the preferred first-line small bowel investigation for GI bleeding patients. Arguments can be made for why each test can justifiably be performed first,[43] but the general consensus, although not uniformly shared, has been to begin with CE,[64] particularly because CE is less invasive, has a reasonably good negative predictive value for rebleeding, and helps guide the route of insertion (oral vs. anal) of subsequent DBE if a culprit lesion is found.[65-68] However, because CE is a purely diagnostic test, DBE is often still required to treat a bleeding source, which has provided the rationale for beginning with DBE in the first place.[69] Added to this confusion is the persistent uncertainty as to whether a higher diagnostic yield is obtained by performing CE or DBE. In fact, there are no prospective, randomized controlled trials comparing CE and DBE that can answer this question. Two meta-analyses were previously performed that compared the diagnostic yields of CE and DBE, but these included all small bowel indications and were not restricted to bleeding patients.[70,71] In order to address this question, a new meta-analysis was conducted that compared CE and DBE specifically in OGIB (**Chapter 4**).

When performing DBE, there are many factors that should be considered that may affect success in terms of insertion depth into the small bowel, clinical efficacy and patient comfort. Some of these variables include the prior use of purgative bowel prep, type of sedation, and use of CO2 rather than air for insufflation of the bowel.[72-74] Creating the optimal conditions for success is important, particularly because DBE is highly invasive for patients, and very time consuming and labor intensive for endoscopists. In order to visualize most of the small intestine, DBE usually needs to be performed in two directions, in an anterograde fashion via the mouth and separately in a retrograde fashion via the anus. Typically, at least in Europe and North America, most endoscopists begin with the anterograde approach, progressing to the more technically challenging retrograde procedure[75] only if the first approach does not yield the diagnosis or provide opportunity for necessary therapeutic interventions. However, there is uncertainty whether distal DBE should be performed immediately following an anterograde approach as a single bi-directional procedure, or whether doing so compromises the success of the retrograde DBE. To address this question, the technical success of retrograde DBE was examined between bi-directional cases, in which retrograde DBE immediately followed

an anterograde DBE, and uni-directional cases, in which retrograde DBE was performed on its own (**Chapter 5**).

One of the unexpected complications of DBE, as discussed previously, was the development of acute pancreatitis in some patients post-procedure.[76] Much more common than acute pancreatitis was the incidence of significant elevations of serum amylase, which were most often interpreted as evidence of subclinical pancreatic injury.[77,78] In fact, multiple studies have characterized this phenomenon with DBE, despite modification of the enteroscopy technique to delay balloon inflation until distal to the major papilla.[53,79,80] Similar findings with respect to post-procedure hyperamylasemia have been observed with SBE, but without associated acute pancreatitis.[81,82] However, it is unclear whether spiral enteroscopy, which involves rotation of a spiral overtube rather than inflation of balloons, may also be complicated by acute pancreatitis or hyperamylasemia. This question was addressed by the final study included in this paper that is presented in **Chapter 6**.

REFERENCES

1. Haubrich WS. The centennial year: the development of important ideas during the last 100 years. The advent and evolution of endoscopy. Gastroenterology 1997;112:591–3.
2. Hirschowitz BI. A personal history of the fiberscope. Gastroenterology1979;76:864–9.
3. Hirschowitz BI, Curtiss LE, Peters CW, Pollard HM. Demonstration of a new gastroscope, the fiberscope. Gastroenterology 1958;35:50;discussion51–3.
4. Overholt BF. Clinical experience with the fibersigmoidoscope. Gastrointest Endosc 1968;15:27.
5. Cotton PB. Cannulation of the papilla of Vater by endoscopy and retrograde cholangiopancreatography (ERCP). Gut 1972;13:1014–25.
6. Fukuda M. History and future of endoscopic ultrasonography. Endoscopy 1998;30 Suppl 1:A2.
7. Swain P. Wireless capsule endoscopy. Gut 2003;52(Suppl 4):48–50.
8. Yamamoto H, Kita H, Sunada K, Hayashi Y, Sato H, Yano T, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clinical Gastroenterology & Hepatology 2004;2:1010–6.
9. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739–50.
10. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844–57.
11. Leddin DJ, Enns R, Hilsden R, Plourde V, Rabeneck L, Sadowski DC, et al. Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. Can J Gastroenterol 2010;24:705–14.
12. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–81.
13. Müller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. Arch Intern Med 1995;155:1741–8.
14. Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006;295:2366–73.
15. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1–8.
16. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin Gastroenterol Hepatol 2008; 6:1117–21.
17. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010;102:89–95.
18. Rex DK. Preventing colorectal cancer and cancer mortality with colonoscopy: what we know and what we don't know. Endoscopy 2010;42:320–3.

19. Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology 2007;132:2297–303.

20. Loffeld RJLF, van der Putten ABMM. The completion rate of colonoscopy in normal daily practice: factors associated with failure. Digestion 2009;80:267–70.

21. Rex DK. Maximizing detection of adenomas and cancers during colonoscopy. Am J Gastroenterol 2006;101:2866–77.

22. Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533–41.

23. Ling BS, Moskowitz MA, Wachs D, Pearson B, Schroy PC. Attitudes toward colorectal cancer screening tests. J Gen Intern Med 2001;16:822–30.

24. DeBourcy AC, Lichtenberger S, Felton S, Butterfield KT, Ahnen DJ, Denberg TD. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J Gen Intern Med 2008;23:169–74.

25. Rex DK. Achieving cecal intubation in the very difficult colon. Gastrointest Endosc 2008;67: 938–44.

26. Shah SG, Brooker JC, Thapar C, Williams CB, Saunders BP. Patient pain during colonoscopy: an analysis using real-time magnetic endoscope imaging. Endoscopy 2002;34:435–40.

27. Waye JD. The best way to painless colonoscopy. Endoscopy 2002;34:489–91.

28. Shah SG, Brooker JC, Williams CB, Thapar C, Saunders BP. Effect of magnetic endoscope imaging on colonoscopy performance: a randomised controlled trial. Lancet 2000;356:1718–22.

29. Yoshikawa I, Honda H, Nagata K, Kanda K, Yamasaki T, Kume K, et al. Variable stiffness colonoscopes are associated with less pain during colonoscopy in unsedated patients. Am J Gastroenterol 2002; 97:3052–5.

30. Lee DWH, Li ACN, Ko C-W, Chu DW, Chan K-C, Poon C-M, et al. Use of a variable-stiffness colonoscope decreases the dose of patient-controlled sedation during colonoscopy: a randomized comparison of 3 colonoscopes. Gastrointest Endosc 2007;65:424–9.

31. Chen P-J, Shih Y-L, Chu H-C, Chang W-K, Hsieh T-Y, Chao Y-C. A prospective trial of variable stiffness colonoscopes with different tip diameters in unsedated patients. Am J Gastroenterol 2008; 103:1365–71.

32. Othman MO, Bradley AG, Choudhary A, Hoffman RM, Roy PK. Variable stiffness colonoscope versus regular adult colonoscope: meta-analysis of randomized controlled trials. Endoscopy 2009; 41:17–24.

33. Singh H, Penfold RB, DeCoster C, Kaita L, Proulx C, Taylor G, et al. Colonoscopy and its complications across a Canadian regional health authority. Gastrointest Endosc 2009;69:665–71.

34. Training Committee 2010-2011, Sedlack RE, Shami VM, Adler DG, Coyle WJ, DeGregorio B, et al. Colonoscopy core curriculum. Gastrointest Endosc 2012;76:482–90.

35. Gómez V, Wallace MB. Training and Teaching Innovations in Colonoscopy. Gastroenterol Clin North Am 2013;42:659–70.

36. Sedlack RE. Training to competency in colonoscopy: assessing and defining competency standards. Gastrointest Endosc 2011;74:355–366.e1–2.

37. Cohen J, Cohen SA, Vora KC, Xue X, Burdick JS, Bank S, et al. Multicenter, randomized, controlled trial of virtual-reality simulator training in acquisition of competency in colonoscopy. Gastrointest Endosc 2006;64:361–8.
38. Haycock A, Koch AD, Familiari P, van Delft F, Dekker E, Petruzziello L, et al. Training and transfer of colonoscopy skills: a multinational, randomized, blinded, controlled trial of simulator versus bedside training. Gastrointest Endosc 2010;71:298–307.
39. Coderre S, Anderson J, Rikers R, Dunckley P, Holbrook K, McLaughlin K. Early use of magnetic endoscopic imaging by novice colonoscopists: improved performance without increase in workload. Can J Gastroenterol 2010;24:727–32.
40. Nakamura T, Terano A. Capsule endoscopy: past, present, and future. Journal of Gastroenterology 2008;43:93–9.
41. Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001;53:216–20.
42. Eliakim AR. Video capsule endoscopy of the small bowel (PillCam SB). Current opinion in gastroenterology 2006;22:124–7.
43. Teshima CW. Small bowel endoscopy for obscure GI bleeding. Best practice & research Clinical gastroenterology 2012;26:247–61.
44. Ladas SD, Triantafyllou K, Spada C, Riccioni ME, Rey J-F, Niv Y, et al. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. Endoscopy 2010;42:220–7.
45. Yano T, Yamamoto H. Current state of double balloon endoscopy: the latest approach to small intestinal diseases. J Gastroenterol Hepatol 2009;24:185–92.
46. May A, Nachbar L, Pohl J, Ell C. Endoscopic interventions in the small bowel using double balloon enteroscopy: feasibility and limitations. Am J Gastroenterol 2007;102:527–35.
47. Mensink PBF, Haringsma J, Kucharzik T, Cellier C, Pérez-Cuadrado E, Mönkemüller K, et al. Complications of double balloon enteroscopy: a multicenter survey. Endoscopy 2007;39:613–5.
48. Gerson LB, Tokar J, Chiorean M, Lo S, Decker GA, Cave D, et al. Complications associated with double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol 2009;7:1177–82, 1182.e1–3.
49. Möschler O, May A, Müller MK, Ell C, German DBE Study Group. Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. Endoscopy 2011;43:484–9.
50. Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy 2008;40:11–5.
51. Akerman PA, Agrawal D, Cantero D, Pangtay J. Spiral enteroscopy with the new DSB overtube: a novel technique for deep peroral small-bowel intubation. Endoscopy 2008;40:974–8.
52. Akerman PA, Agrawal D, Chen W, Cantero D, Avila J, Pangtay J. Spiral enteroscopy: a novel method of enteroscopy by using the Endo-Ease Discovery SB overtube and a pediatric colonoscope. Gastrointest Endosc 2009;69:327–32.
53. Aktas H, Mensink PBF, Haringsma J, Kuipers EJ. Low incidence of hyperamylasemia after proximal double-balloon enteroscopy: has the insertion technique improved? Endoscopy 2009;41:670–3.

54. Zepeda-Gómez S, Barreto-Zuñiga R, Ponce-de-León S, Meixueiro-Daza A, Herrera-López JA, Camacho J, et al. Risk of hyperamylasemia and acute pancreatitis after double-balloon enteroscopy: a prospective study. Endoscopy 2011;43:766–70.

55. Sharma MK, Sharma P, Garg H, Sehgal L, Bhatia V. Clinical acute pancreatitis following anterograde single balloon enteroscopy. Endoscopy 2011;43(Suppl 2) UCTN:E20–1.

56. Shumaker DA, Zaman A, Katon RM. Use of a variable-stiffness colonoscope allows completion of colonoscopy after failure with the standard adult colonoscope. Endoscopy 2002;34:711–4.

57. Chong A, Shah JN, Levine MS, Rubesin SE, Laufer I, Ginsberg GG, et al. Diagnostic yield of barium enema examination after incomplete colonoscopy. Radiology 2002;223:620–4.

58. Rex DK, Goodwine BW. Method of colonoscopy in 42 consecutive patients presenting after prior incomplete colonoscopy. Am J Gastroenterol 2002;97:1148–51.

59. Copel L, Sosna J, Kruskal JB, Raptopoulos V, Farrell RJ, Morrin MM. CT colonography in 546 patients with incomplete colonoscopy. Radiology 2007;244:471–8.

60. Pasha S, Harrison M, Das A, Corrado C, Arnell K, Leighton J. Utility of double-balloon colonoscopy for completion of colon examination after incomplete colonoscopy with conventional colonoscope. Gastrointest Endosc 2007;65:848–53.

61. Gay G, Delvaux M. Double-balloon colonoscopy after failed conventional colonoscopy: a pilot series with a new instrument. Endoscopy 2007;39:788–92.

62. Moreels T, Macken E, Roth B, Van Outryve M, Pelckmans P. Cecal intubation rate with the double-balloon endoscope after incomplete conventional colonoscopy: A study in 45 patients. J Gastroenterol Hepatol 2010;25:80–3.

63. Raju GS, Gerson L, Das A, Lewis B, American Gastroenterological Association. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. Gastroenterology 2007;133:1697–717.

64. Delvaux M, Gay G. International Conference on Capsule and Double-Balloon Endoscopy (ICCD). Endoscopy 2011;43:533–9.

65. Lai LH, Wong GLH, Chow DKL, Lau JYW, Sung JJY, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. Am J Gastroenterol 2006; 101:1224–8.

66. Gay G, Delvaux M, Fassler I. Outcome of capsule endoscopy in determining indication and route for push-and-pull enteroscopy. Endoscopy 2006;38:49–58.

67. Li X, Chen H, Dai J, Gao Y, Ge Z. Predictive role of capsule endoscopy on the insertion route of double-balloon enteroscopy. Endoscopy 2009;41:762–6.

68. Nakamura M, Ohmiya N, Shirai O, Takenaka H, Morishima K, Miyahara R, et al. Route selection for double-balloon endoscopy, based on capsule transit time, in obscure gastrointestinal bleeding. Journal of Gastroenterology 2010;45:592–9.

69. Rondonotti E, Sunada K, Yano T, Paggi S, Yamamoto H. Double-balloon endoscopy in clinical practice: Where are we now? Digestive Endoscopy 2012;24:209–19.

70. Chen X, Ran Z-H, Tong J-L. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. World J Gastroenterol 2007; 13:4372–8.

71. Pasha SF, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2008;6:671–6.

72. Gerson LB, Flodin JT, Miyabayashi K. Balloon-assisted enteroscopy: technology and troubleshooting. Gastrointest Endosc 2008;68:1158–67.

73. Lo SK. Techniques, tricks, and complications of enteroscopy. Gastrointestinal endoscopy clinics of North America 2009;19:381–8.

74. Domagk D, Bretthauer M, Lenz P, Aabakken L, Ullerich H, Maaser C, et al. Carbon dioxide insufflation improves intubation depth in double-balloon enteroscopy: a randomized, controlled, double-blind trial. Endoscopy 2007;39:1064–7.

75. Mehdizadeh S, Han NJ, Cheng DW, Chen GC, Lo SK. Success rate of retrograde double-balloon enteroscopy. Gastrointest Endosc 2007;65:633–9.

76. Groenen MJ, Moreels TG, Orlent H, Haringsma J, Kuipers EJ. Acute pancreatitis after double-balloon enteroscopy: an old pathogenetic theory revisited as a result of using a new endoscopic tool. Endoscopy 2006;38:82–5.

77. Honda K, Itaba S, Mizutani T, Sumida Y, Kanayama K, Higuchi N, et al. An increase in the serum amylase level in patients after peroral double-balloon enteroscopy: an association with the development of pancreatitis. Endoscopy 2006;38:1040–3.

78. Kopacova M, Rejchrt S, Tacheci I, Bures J. Hyperamylasemia of uncertain significance associated with oral double-balloon enteroscopy. Gastrointest Endosc 2007;66:1133–8.

79. Pata C, Akyüz U. New modification of double-balloon endoscopy to reduce complications. Am J Gastroenterol 2007;102:2860–1.

80. Pata C, Akyüz U, Erzin Y, Mutlu N, Mercan A, Dirican A. Post-procedure elevated amylase and lipase levels after double-balloon enteroscopy: relations with the double-balloon technique. Dig Dis Sci 2010;55:1982–8.

81. Aktas H, de Ridder L, Haringsma J, Kuipers EJ, Mensink PB. Complications of single-balloon enteroscopy: a prospective evaluation of 166 procedures. Endoscopy 2010;42:365–8.

82. Manno M, Barbera C, Dabizzi E, Mussetto A, Conigliaro R. Safety of single-balloon enteroscopy: our experience of 72 procedures. Endoscopy 2010;42:773; authorreply774.

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Magnetic imaging-assisted colonoscopy vs. conventional colonoscopy: a randomized controlled trial.

Submitted for publication.

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ABSTRACT

Background and Aim: Optimizing performance of colonoscopy and improving its tolerability for patients is important. Magnetic imaging technology may improve performance by enabling visualization of loop formation and endoscope position. The purpose of this study was to compare magnetic imaging-assisted colonoscopy (MIC) with conventional colonoscopy (CC).

Methods: A prospective randomized trial was performed involving patients undergoing elective outpatient colonoscopy with randomization to MIC or CC. The primary outcome was patient comfort expressed by a visual analogue pain scale and by a sedation score. Secondary outcomes included endoscopic procedural metrics.

Results: Two hundred fifty-three patients were randomized and underwent MIC or CC. There were no differences in cecal intubation rates (100 vs. 99%), insertion distance-to-cecum (82 vs. 83 cm), time-to-cecum (6.5 vs. 7.2 minutes), or polyp detection rate (47 vs. 52%) between the MIC and CC groups. The primary outcomes of mean pain score (1.0 vs. 0.9 out of 10; p=0.41) and sedation score (8.2 vs. 8.5; p=0.34) also did not differ between MIC and CC. Within a subgroup of cases considered more challenging or difficult, time-to-cecum was significantly faster with MIC compared to CC, 10.1 vs. 13.4 minutes respectively (p=0.01). Sensitivity analyses confirmed a similar pattern of overall findings when each endoscopist was considered separately.

Conclusions: The latest version of MIC was no better than CC in terms of endoscopic procedural metrics and patient experience outcomes, when performed in experienced hands. However, within a subgroup of more challenging cases, MIC produced faster times-to-cecum.

INTRODUCTION

Colonoscopy decreases the likelihood of developing colorectal cancer (CRC) and CRC-related mortality[1-5] and is the CRC screening modality of choice.[6] However, incomplete colonoscopy that fails to reach the cecum remains an important limitation, occurring in 10-20% of cases.[7,8] Furthermore, a considerable proportion of the population remain averse to undergoing colonoscopy, particularly because of fears of procedure discomfort,[9,10] decreasing the potential impact for overall CRC reduction. Thus, optimizing performance of colonoscopy and improving its tolerability for patients is important.

Colonoscopy is most successful at reaching the cecum and most comfortable for patients when the endoscope is kept in a straight position, achieved by minimizing loop formation and reducing loops once they have formed.[11,12] To help overcome these challenges, real-time magnetic imaging-assisted colonoscopy (MIC) was developed that consisted of electromagnetic generator coils contained within a catheter inserted into the instrument channel of the colonoscope.[13] The coils produce a magnetic field detected by a series of sensors external to the patient, which triangulate the coil position in three-dimensional (3D) space, giving rise to a computer-generated image of the shape of the endoscope on a monitor. The initial studies using this catheter-based magnetic imaging system demonstrated significant improvements in cecal intubation rates, time-to-cecum, duration of time spent managing loops, and success of straightening attempts when colonoscopy was performed by trainees but not by experienced endoscopists.[14] Consequently, magnetic imaging technology has been generally regarded as a learning tool with limited clinical uptake outside of a training setting.

Recently, an updated version of MIC (ScopeGuide,™ Olympus America, Center Valley, PA) was developed that includes built-in electromagnetic coils embedded within the endoscope rather than in an inserted catheter, a thin and compact receiver dish mounted on a roll stand for convenient positioning during the procedure, integration of the 3D representation of the scope on the same screen as the endoscopic image, and an external hand-held coil used to identify the optimal location for abdominal pressure relative to the endoscope. It is hoped that these features will make the second-generation of ScopeGuide more user friendly, while facilitating a more comfortable patient experience and technically successful procedure when being performed by endoscopists in clinical practice.

The purpose of this prospective, randomized trial was to determine if real time visualization of the colonoscope using the new, second-generation ScopeGuide system is superior to conventional colonoscopy for improving patient experience in terms of re-

duced discomfort and decreased sedation requirements, and for improving endoscopic procedural outcomes.

METHODS

Study design

Consecutive, adult patients (18 years or older) referred for elective, outpatient colonoscopy at the University of Alberta Hospital (Edmonton, Canada) were considered for enrollment. Patients were excluded if they were admitted to hospital or if they had active, ongoing lower GI bleeding, if they were undergoing colonoscopy without prior purgative bowel preparation or if they required anesthetist-administered propofol, if they had a history of previous colonic surgery, cardiac pacemaker or implantable cardioverter-defibrillator, or if the colonoscopy was to be performed by a trainee under staff supervision. Eligible patients who provided informed consent were then randomized to undergo conventional colonoscopy (CC) or MIC using the second-generation ScopeGuide system, with patients, but not endoscopists, blinded to the randomization status. Simple, non-restricted randomization was performed using a computerized random-number generator immediately prior to the procedure. The study protocol was approved by the Health Research Ethics Board of the University of Alberta (effective 08/09/2011) and registered with Clinicaltrials.gov (registered 09/18/2011; NCT01438645).

Colonoscopy procedure

Colonoscopy was performed by one of three experienced endoscopists as clinically indicated. The control group underwent conventional colonoscopy using CF-H180AL variable-stiffness colonoscopes (Olympus America). The investigational group underwent magnetic imaging-assisted colonoscopy using Olympus CF-H180DL variable-stiffness colonoscopes, which differ only by the incorporation of the ScopeGuide system that generates a 3D image on the monitor depicting the shape of the colonoscope inside the patient's body (see Figure 1). Beyond the inclusion of ScopeGuide, the colonoscopy procedure did not differ between groups.

All patients received a purgative bowel preparation consisting of 4 L of a polyethylene glycol solution followed by an overnight fast (for morning procedures) or a 2 L/2 L split preparation (for afternoon procedures) according to the standard clinical practice at our center. Prior to the procedure, patients completed a visual analogue scale (VAS) reflecting their predictions for expected discomfort. All procedures were then performed using conscious sedation consisting of a benzodiazepine and an opioid analgesic. Initially, all patients received standardized doses of midazolam 2 mg IV and fentanyl 25

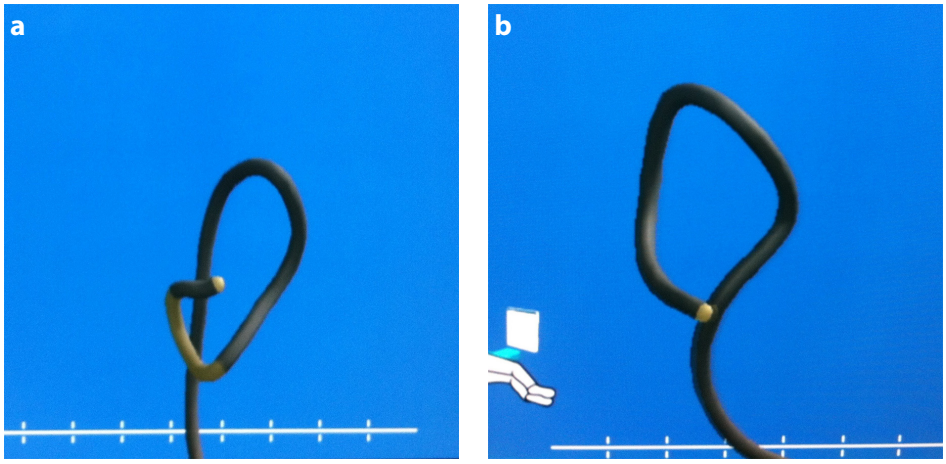

Figure 1. ScopeGuide image of endoscope forming a reversed alpha loop in the sigmoid (a) and straight in the cecum (b).

mcg IV. Additional doses were then provided when the nurse or physician believed that the patient was becoming uncomfortable. Insufflation of the colon was accomplished using room air, and alternative methods such as CO2 were not permitted. In all cases, the endoscopist attempted to minimize the formation of loops within the colon and reduced any loops whenever possible according to standard clinical practice, using the additional guidance from the ScopeGuide image in the investigational group. The use of technical maneuvers to facilitate completion of the procedure were permitted, including external abdominal pressure, repositioning of the patient, or tightening of the variable-stiffness setting on the colonoscope. Any abnormalities or polyps detected during insertion were more closely inspected, biopsied or removed during subsequent colonoscope withdrawal. Any additional diagnostic or therapeutic applications were permitted as clinically indicated. During the case, the nurse documented all procedural data using a standardized reporting form. At the conclusion of the colonoscopy, the endoscopist rated the procedural difficulty as "usual" or "difficult" based on the procedure characteristics described above. Patients completed another VAS reflecting their actual degree of discomfort experienced once they were completely awake after spending more than one hour in the recovery area.

Outcome measurements

The primary outcome measure was the patient experience during colonoscopy, defined by patient comfort as expressed on a visual analogue pain scale and sedation requirements. Since the conscious sedation consisted of two different drugs, the doses of these drugs were converted into a single numerical score. By convention, typical dose increments of midazolam consist of 1 mg units whereas those of fentanyl consist of 25 mcg

units, and each was assigned a numerical score of '1.' These were then added together to generate a unified *sedation score* for each patient. Patient comfort was then determined from the post-procedure VAS, which consisted of a 10 cm linear scale ranging from '0' at its extreme left representing "no pain" to '10' on its extreme right representing "unbearably severe pain." The *pain score* was rated between 0.1 and 10.0, with a lower value representing a more comfortable procedure. Secondary outcome measures consisted of endoscopic procedural outcomes such as time-to-cecum, cecal intubation rate, polyp detection rate, and insertion distance of the colonoscope to the cecal pole. As part of a secondary analysis to account for patient expectations regarding procedural discomfort that might modify their actual perception of pain during colonoscopy, the VAS was also measured pre-procedure, and the *pain difference* was determined by subtracting the pre-procedure from the post-procedure pain score. Finally, sensitivity analyses were performed to determine if the findings were consistent across all three endoscopists, and within the subgroup of self-rated "difficult" procedures.

Statistical analysis

The statistical software Stata 10.1 (Stata Corp, College Station, TX) was used to analyze the data. Means and ranges were used to summarize data for continuous variables and percentages were used for categorical variables. Student's t-test was used to compare the primary outcome of the *composite* score between the two groups, as well as for other continuous data. The Chi^2 test was used to compare proportions for categorical data. A two-sided $p \leq 0.05$ with 80% power was considered statistically significant (after correction for multiple comparisons). Multivariate regression was used to perform the sensitivity analyses. A sample size calculation was performed to detect a difference of 0.5 (out of the 10 point VAS scale) in the mean pain scores between the CC and MIC groups. Based on a predicted pain score of 1.5 in the CC group and 1.0 in the MIC group, it was estimated that 126 patients (63 in each group) would be required to demonstrate a statistically significant difference.

RESULTS

Between September 2011 and October 2012, 253 patients participated in the study; mean age 58 years (range: 18–86); 52% male. The indications for colonoscopy and other patient characteristics are shown in Table 1. One hundred twenty-two patients (48%) underwent CC and 131 (52%) had MIC. Complete colonoscopy was accomplished in 121 cases (99%) in the CC group and 131 cases (100%) in the MIC group. Incomplete colonoscopy occurred in one case due to a failed bowel preparation that left formed stool obstructing the mid-transverse colon. The mean endoscope insertion distance was 83

Table 1. Patient characteristics

	Conventional colonoscopy (n = 122)	Magnetic imaging colonoscopy (n = 131)	Total (n = 253)
Age	58.2 (18 – 82)	57.7 (19 – 86)	57.9 (18 – 86)
Gender – male (%)	63 (51.6%)	68 (51.9%)	131 (51.8%)
Previous colonoscopy	77 (63.1%)	66 (50.4%)	143 (56.5%)
Prior abdo or pelvic surgery	19 (15.6%)	26 (19.9%)	45 (17.8%)
Indication			
a) Screening or polyp follow-up	71 (58.2%)	79 (60.3%)	150 (59.3%)
b) GI bleeding	13 (10.7%)	23 (17.6%)	36 (14.2%)
c) Anemia or FOBT+	7 (5.7%)	10 (7.6%)	17 (6.7%)
d) Diarrhea	5 (4.1%)	11 (8.4%)	16 (6.3%)
e) IBD	8 (6.6%)	4 (3.1%)	12 (4.7%)
f) Other	18 (14.8%)	4 (3.1%)	22 (8.7%)

Table 2. Endoscopic outcomes

	Conventional colonoscopy (n = 122)	Magnetic imaging colonoscopy (n = 131)	Total (n = 253)	p
Cecal intubation	121 (99.2%)	131 (100%)	252 (99.6%)	0.30
TI intubation	42 (34.4%)	46 (35.1%)	88 (34.8%)	0.91
Distance to cecum (cm)	83.0 (53 – 130)	82.4 (49 – 150)	82.7 (49 – 150)	0.71
Time-to-cecum (min)	7.2 (2 – 29.5)	6.5 (1.2 – 28)	6.9 (1.2 – 29.5)	0.18
Total procedure time (min)	16.7 (8.1 – 36)	15.7 (5.7 – 40)	16.2 (5.7 – 40)	0.19
Polyp detection rate	51.6% (0.43, 0.61)	46.6% (0.38, 0.55)	49.0%	0.42
Mean # polyps (range)	1.7 (1 – 7)	1.9 (1 – 8)	1.8 (1 – 8)	0.36
Quality of bowel prep				
a) excellent	21.3%	29.8%	25.7%	
b) acceptable	49.2%	43.5%	46.3%	
c) fair	25.4%	24.4%	24.9%	
d) poor	4.1%	2.3%	3.2%	
Procedures self-rated as "difficult"	25 (20.5%)	36 (27.5%)	61 (24.1%)	0.19
Sedation, mean doses (range)				
Midazolam (mg)	5.8 (3 – 15)	5.5 (2 – 15)	5.7 (2 – 15)	0.31
Fentanyl (mcg)	86.3 (50 – 150)	83.2 (50 – 150)	84.7 (50 – 150)	0.29

Table 3. Patient experience outcomes

	Conventional colonoscopy (n = 122)	Magnetic imaging colonoscopy (n = 131)	Total (n = 253)	p
Sedation score	8.5 (4.5 – 17)	8.2 (4 – 21)	8.3 (4 – 21)	0.34
Pretest Pain score	2.2 (0.1 – 8.5)	2.9 (0.1 – 9)	2.5 (0.1 – 9)	**0.02**
Post pain score	0.85 (0.1 – 8.4)	1.03 (0.1 – 10)	0.94 (0.1 – 10)	0.41
Pain difference	- 1.3	- 1.8	- 1.6	0.14

Table 4. Subgroup of self-rated "difficult" colonoscopy procedures

	Conventional colonoscopy (n = 25)	Magnetic imaging colonoscopy (n = 36)	Total (n = 61)	p
Time-to-cecum (min)	13.4 (6.7 – 29.5)	10.1 (3.8 – 28)	11.5 (3.8 – 29.5)	**0.01**
Distance to cecum (cm)	91.2 (68 – 130)	85.7 (49 – 150)	88.0 (49 – 150)	0.30
Sedation score	9.54 (5 – 17)	9.08 (5 – 21)	9.27 (5 – 21)	0.61
Post pain score	1.48 (0.1 – 8.4)	1.15 (0.1 – 7.9)	1.28 (0.1 – 8.4)	0.53
Pain difference	- 1.05 (-6.8 – 3.3)	- 1.50 (-7.8 – 4.9)	- 1.32 (-7.8 – 4.9)	0.54

cm (range, 53-130) in the CC group and 82 cm (range, 49-150) in the MIC group (p=0.71), with a mean time-to-cecum of 7.2 minutes (range, 2-30) and 6.5 minutes (range, 1-28) respectively (p=0.18). Polyps were detected in 52% of cases in the CC group and in 47% of cases in the MIC group (p=0.42), with a mean of 1.7 (range, 1-7) and 1.9 (range, 1-8) polyps, respectively. No adverse events were recorded. See Table 2 for endoscopic procedural metrics.

The outcomes regarding patient comfort and sedation are shown in Table 3. The primary endpoints of *pain score* (0.9 vs. 1.0; p=0.41) and *sedation score* (8.5 vs. 8.2; p=0.34) did not differ between the CC and MIC groups, nor did the secondary endpoint *pain difference* (-1.3 vs. -1.8; p=0.14). A similar pattern was observed in the subgroup of 61 procedures (24%) self-rated by the endoscopist as being "difficult" (see Table 4), in which there were no significant differences between the CC and MIC groups with respect to these patient comfort metrics, However, time-to-cecum was significantly shorter with MIC compared to CC among this subgroup of "difficult" cases, with mean times of 10.1 minutes (range, 3.8-28) and 13.4 minutes (range, 6.7-29.5), respectively (p=0.01).

When sensitivity analyses were performed to determine if the same pattern of findings were observed for each endoscopist when considered separately, no differences emerged between the CC and MIC groups with respect to endoscopic procedural metrics such as cecal intubation rate, time-to-cecum, insertion distance to cecum or polyp detection rate.

DISCUSSION

Optimizing the technical performance of colonoscopy and its tolerability for patients is important. The development of magnetic imaging technology that enables real time visualization of the shape of the entire endoscope within the patient's body was anticipated to help achieve that aim. In this randomized trial, MIC using the latest generation of ScopeGuide was compared to CC with regards to patient comfort based on a post-procedure VAS pain score and a sedation score derived from standard dose increments of conscious sedation medications. However, MIC did not prove to be superior to CC for this primary outcome, nor for any of the secondary outcomes such as cecal intubation rate, time-to-cecum, endoscope insertion distance-to-cecum, or polyp detection rate. Thus, it appears that in general, MIC does not improve the technical performance of colonoscopy or the overall patient experience. Only within the subgroup of cases self-rated by the endoscopist as "difficult" did any differences emerge, with MIC achieving significantly faster times-to-cecum compared to CC, but with no differences in patient experience outcomes.

This study has several limitations that may affect the generalizability of the results. Firstly, the primary outcome of pain score and sedation score contain inherent biases, chiefly that increased sedation could be used to overcome greater procedural discomfort, potentially creating an apparent, but false, difference in pain score modified by the amount of sedation used. The most effective means to compare patient tolerability between MIC and CC would have been to perform unsedated colonoscopy, using the VAS to compare patient comfort between the techniques. Such strategies have been used in previous studies that evaluated the use of variable-stiffness colonoscopes.[15,16] However, our local patient population is generally resistant to the concept of unsedated procedures and this was deemed to not be viable. In any event, neither the visual analogue pain score nor the sedation score differed between groups, indicating that this potential for bias did not lead to confounding of the overall results. A second limitation was the performance of all procedures by individuals who have undergone advanced fellowship training in therapeutic endoscopy, for whom magnetic imaging assistance for routine colonoscopy was perhaps less likely to be of value. In hindsight, it would have been more informative

to include all endoscopists performing colonoscopy at our center, which would have provided a more diverse range of levels of experience and expertise that may have led to the identification of individuals for whom MIC was truly beneficial. Finally, the classification of procedural difficulty based on the subjective self-rating of the endoscopist was prone to bias, and the lack of objective criteria for classifying cases as challenging limits the generalizability of the finding that faster times-to-cecum were achieved with MIC within the subgroup of these difficult cases. However, since the classification of cases as "difficult" was done quite liberally (one-fourth were considered as such), there were likely sufficient numbers in this subgroup to provide a meaningful comparison, even though the study was not powered for subgroup analysis. Nevertheless, the demonstration of a significant difference in time-to-cecum for difficult cases between MIC and CC is at least hypothesis generating.

The main benefit derived from magnetic imaging assistance is the accurate identification and proper straightening of endoscope loops,[17] as well as visualization of the endoscope position within the different regions of the colon, which conceivably should facilitate faster and more comfortable procedures, while enabling the accurate localization of polyps or other pathology. While our study suggests MIC is unnecessary in most cases when colonoscopy is performed in experienced hands, there is good reason to speculate that magnetic endoscope imaging may benefit less experienced endoscopists and trainees. The cecal intubation rate in this trial was 99.6%, whereas large database studies of real life clinical outcomes reveal rates of incomplete colonoscopy ranging from 13-35%,[7,8,18] demonstrating the likely need for additional tools to facilitate the performance of colonoscopy in non-expert settings. Whether MIC can help improve these rates of complete colonoscopy, and whether it would be cost effective to do so given the added expense of ScopeGuide, remains unclear and requires further study. Regarding the likely benefit of magnetic imaging assistance during training, the initial study that evaluated the previous version of MIC demonstrated significant improvements in procedural metrics in cases performed by trainees.[14] More recently, a one-day training program at Stanford that used the older version of ScopeGuide as part of a simulator consisting of a soft plastic colon model mounted within a real-shaped body torso, led to significant improvements in subsequent colonoscopy performed on live patients without magnetic imaging assistance.[19] The trainees demonstrated improvements in their overall performance, as well as in cecal intubation rates, time-to-cecum and sedation requirements following the ScopeGuide training intervention. Thus, there is reason to speculate that magnetic endoscope imaging could become an essential training tool, forming the basis of a graduated process that transitions learners from computer simulation to unassisted colonoscopy. However, further study will be needed to verify this recommendation.

In summary, the latest version of magnetic imaging-assisted colonoscopy (ScopeGuide) performed no better than conventional colonoscopy in terms of endoscopic procedural metrics and patient experience outcomes, when performed in experienced hands. However, within a subgroup of more challenging cases, MIC may result in faster times-to-cecum. Nevertheless, the greatest utility of MIC may exist as a graduated training tool or to assist non-expert endoscopists, although this requires further study.

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REFERENCES

1. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N. Engl. J. Med. 1993; 329: 1977–81.
2. Müller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. Arch. Intern. Med. 1995; 155: 1741–8.
3. Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006; 295: 2366–73.
4. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann. Intern. Med. 2009; 150: 1–8.
5. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N. Engl. J. Med. 2012; 366: 687–96.
6. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am. J. Gastroenterol. 2009; 104: 739–50.
7. Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology 2007; 132: 2297–303.
8. Loffeld RJLF, van der Putten ABMM. The completion rate of colonoscopy in normal daily practice: factors associated with failure. Digestion 2009; 80: 267–70.
9. Ling BS, Moskowitz MA, Wachs D, Pearson B, Schroy PC. Attitudes toward colorectal cancer screening tests. J. Gen. Intern. Med. 2001; 16: 822–30.
10. DeBourcy AC, Lichtenberger S, Felton S, Butterfield KT, Ahnen DJ, Denberg TD. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J. Gen. Intern. Med. 2008; 23: 169–74.
11. Waye JD. The best way to painless colonoscopy. Endoscopy 2002; 34: 489–91.
12. Rex DK. Achieving cecal intubation in the very difficult colon. Gastrointest. Endosc. 2008; 67: 938–44.
13. Shah SG, Saunders BP, Brooker JC, Williams CB. Magnetic imaging of colonoscopy: an audit of looping, accuracy and ancillary maneuvers. Gastrointest. Endosc. 2000; 52: 1–8.
14. Shah SG, Brooker JC, Williams CB, Thapar C, Saunders BP. Effect of magnetic endoscope imaging on colonoscopy performance: a randomised controlled trial. Lancet 2000; 356: 1718–22.
15. Yoshikawa I, Honda H, Nagata K, Kanda K, Yamasaki T, Kume K, et al. Variable stiffness colonoscopes are associated with less pain during colonoscopy in unsedated patients. Am. J. Gastroenterol. 2002; 97: 3052–5.
16. Chen P-J, Shih Y-L, Chu H-C, Chang W-K, Hsieh T-Y, Chao Y-C. A prospective trial of variable stiffness colonoscopes with different tip diameters in unsedated patients. Am. J. Gastroenterol. 2008; 103: 1365–71.

17. Shah SG, Brooker JC, Thapar C, Suzuki N, Williams CB, Saunders BP. Effect of magnetic endoscope imaging on patient tolerance and sedation requirements during colonoscopy: a randomized controlled trial. Gastrointest. Endosc. 2002; 55: 832–7.

18. Singh H, Penfold RB, DeCoster C, Kaita L, Proulx C, Taylor G, et al. Colonoscopy and its complications across a Canadian regional health authority. Gastrointest. Endosc. 2009; 69: 665–71.

19. Kaltenbach T, Leung C, Wu K, Yan K, Friedland S, Soetikno R. Use of the colonoscope training model with the colonoscope 3D imaging probe improved trainee colonoscopy performance: a pilot study. Dig. Dis. Sci. 2011; 56: 1496–502.

3

Single-balloon assisted colonoscopy in patients with previously failed colonoscopy

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ABSTRACT

Background: Despite advances in training and equipment, complete colonoscopy fails even in experienced hands in up to 10% of cases. Double balloon endoscopy (DBE) has been successfully used to complete colonoscopy in these patients. Single balloon endoscopy (SBE) has become established for small bowel enteroscopy. However, it has yet to be studied for use in colonoscopy.
Objective: To assess the efficacy, performance and safety of single-balloon colonoscopy.
Design: Prospective cohort study.
Setting: Academic tertiary referral center.
Patients: Patients with previously failed conventional colonoscopy.
Results: 23 single-balloon colonoscopy procedures were performed in 22 patients: median age 53 (range 19-75) years; 14 females, 8 males. SBE colonoscopy succeeded in cecal intubation in 22 (96%) procedures, with a median total procedure time of 30 (range 20-60) minutes. SBE colonoscopy was normal in 9 cases but resulted in a positive diagnosis in 13 (57%) procedures, including polyps (n=6), active Crohn's disease (n=4), Crohn's-related stricture (n=1), and diverticulosis (n=2). Seven (30%) procedures were therapeutic including 1 case with balloon dilation and 6 cases with polypectomy. No complications were encountered.
Limitations: Limited sample size, no direct comparison with double-balloon endoscopy.
Conclusions: Single-balloon assisted colonoscopy seems a safe and effective method for completing colonoscopy in patients with previously failed or difficult colonoscopy. The outcomes are similar compared to previous studies with DBE colonoscopy in this patient group.

INTRODUCTION

Colonoscopy is the gold standard examination of the colon, and complete inspection to the cecum is important for all patients who undergo the procedure, particularly for the detection and removal of adenomatous polyps and colorectal cancer.[1] The U.S. Multi-Society Task Force on Colorectal Cancer has established target cecal intubation rates of 90% for all colonoscopies and greater than 95% for colonoscopies performed for colorectal cancer screening.[2] However, a population-based study from Canada that examined the records from over 330,000 colonoscopy procedures found that 13% of these studies failed to reach the cecum.[3] Furthermore, a recent large single-center series from the Netherlands demonstrated an 83% completion rate.[4] Multiple patient factors have been identified that increase the difficulty of colonoscopy and make successful cecal intubation more unlikely, including older patient age, female gender, diverticular disease, a low body mass index, prior abdominal or pelvic surgery, insufficient colon cleansing, long redundant colon loops, and a fixed, angulated sigmoid colon.[3-9] In recent years, the relatively new technique of double-balloon endoscopy (DBE) has been successfully applied to enable complete colon inspection in patients with previously incomplete colonoscopies.[10] Since the advent of DBE, single-balloon endoscopy (SBE) has become established as an alternative method of small bowel endoscopy, for both anterograde procedures via the mouth and retrograde procedures via the colon.[11-13] However, SBE has yet to be studied specifically for the completion of previously failed conventional colonoscopy. We report here our early experience using SBE to perform colonoscopy in patients in whom previous conventional colonoscopy was unsuccessful.

METHODS

Patients in whom a previous attempt with conventional colonoscopy failed to reach the cecum were prospectively enrolled for inclusion in the present study. The study was performed in a single, tertiary referral university hospital. Patients who had undergone a failed colonoscopy at our own institution proceeded directly to single-balloon assisted colonoscopy. Patients referred from other hospitals first underwent repeat colonoscopy at our center prior to being enrolled for single-balloon colonoscopy, unless a second, repeat colonoscopy had already been attempted at the referring center. Patients provided informed consent prior to undergoing single-balloon colonoscopy. The study was approved by the institutional review board of Erasmus MC University Medical Center.

Single-balloon assisted colonoscopy procedure

All patients underwent the standard colonoscopy bowel preparation used at our institution, which consists of 4 L of a polyethylene glycol solution and an overnight fast from midnight. Single-balloon colonoscopy was performed using the Olympus SIF-Q160Y endoscope (Olympus Optical Co., Tokyo, Japan), ST-SB-1 overtube with balloon, and balloon control unit. The technical specifications of the Olympus single-balloon endoscope and overtube have previously been described in detail, as has the technique of performing SBE.[11, 12, 14, 15] The single-balloon colonoscopy technique employed was identical to the colonic portion of retrograde SBE. In detail, the endoscope was inserted via the anus in a similar fashion as when performing conventional colonoscopy, with the overtube pulled back to the proximal end of the shaft of the endoscope. Once sufficient length of the endoscope had been inserted such that the distal end of the overtube was brought forward to the anus, the overtube was then slid over the endoscope with its balloon deflated. Once the overtube had been advanced, its balloon was inflated to anchor the bowel wall, and the endoscope was inserted further. At the point of maximal insertion, the balloon was deflated and the overtube was re-advanced over the endoscope. Once fully inserted, the balloon on the overtube was inflated while the scope tip was angled toward the bowel wall to "hook" the bowel, and both scope and overtube were pulled back together in order to pleat the bowel over the overtube and reduce any colonic loops. This cycle of advancing the endoscope, deflating the balloon, advancing the overtube, inflating the balloon, hooking the bowel and then pulling both the overtube and endoscope back together was repeated until the endoscope had successfully entered and inspected the cecum. The withdrawal process was simply the reverse of the insertion cycle. All procedures were performed by a single endoscopist (P.M.) with extensive experience with both DBE and SBE, together with an endoscopy nurse assistant.

Conscious sedation was used in the majority of procedures, using a combination of midazolam and fentanyl intravenously. In selected cases propofol sedation was administered.

The primary endpoint of the study was the rate of complete colonoscopy, defined as successful cecal intubation with photo-documentation of recognized cecal landmarks. Secondary outcomes included endoscopic procedural data such as diagnostic yield, therapeutic benefit, procedure time, rate and extent of terminal ileum intubation, complications, and patient demographic data.

RESULTS

Twenty-three single-balloon colonoscopy procedures were performed in 22 patients between January 2008 and November 2009. All patients were referred for single-balloon colonoscopy because of previously failed conventional colonoscopy: 14 (64%) females; median age 53 (19 – 75) years; 7 (32%) patients were referred from other hospitals for balloon-assisted colonoscopy at our center; 3 of these patients first underwent a repeat colonoscopy attempt at our center that was unsuccessful before proceeding to single-balloon colonoscopy, while the remaining 4 patients had already undergone a failed second colonoscopy at the referring center. The main indications for colonoscopy were the evaluation of Crohn's disease activity or investigation of suspected inflammatory bowel disease (43%), polyp(s) seen on radiology studies or on prior colonoscopy that could not be reached by the endoscope for removal (17%), and iron-deficiency anemia (13%); ***see Table 1***.

Table 1: Individual data of patients, findings and therapy.

Patient	Sex	Age	Indication	Cecum intubation	Total procedure time (min)	Diagnosis	Intervention
1	F	26	Suspected IBD	Yes	35	Normal	
2	F	74	Polyp seen on previous colonoscopy; unable to reach the polyp	Yes	32	Polyp in R colon (10 mm)	Polypectomy
3	M	70	Anemia	Yes	35	Normal	
4	F	75	Polyp on barium enema	Yes	60	Polyp in cecum (15 mm)	Polypectomy
5	M	61	Anemia	Yes	30	Diverticulosis	
6	M	74	Polyp on barium enema	Yes	35	Multiple polyps (5 – 15 mm)	Polypectomy
7	M	52	Anemia	Yes	30	Normal	
8	F	38	Evaluation of CD activity	Yes	36	Mildly active CD in TI	Step-up medical therapy
9	F	62	CRC family history	Yes	30	Polyp in left colon (10 mm)	Polypectomy
10	F	51	Abdominal pain	Yes	30	Normal	
11	M	36	Suspected IBD	Yes	20	Polyp in rectum (15 mm)	Polypectomy
12	F	74	Abdominal pain	Yes	30	Diverticulosis	
13	F	62	Rising CEA post-treatment for colon CA	Yes	20	Normal	
14	F	48	Suspected IBD	Yes	20	Normal	

Table 1: Individual data of patients, findings and therapy. (continued)

Patient	Sex	Age	Indication	Cecum intubation	Total procedure time (min)	Diagnosis	Intervention
15	F	47	Evaluation of CD activity	Yes	20	Mod-severely active CD in neo-terminal ileum	Surgical resection
16	F	52	CRC family history	Yes	30	Normal	
17	F	44	Obstructive complaints	Yes	20	Normal	
18	F	39	Evaluation of CD activity	No	60	Failed procedure	
19	F	40	Evaluation of CD activity	Yes	20	Mildly active CD in colon	Step-up medical treatment
20	M	44	Evaluation of CD activity	Yes	30	Normal	
21	M	67	Polyp seen on previous colonoscopy; unable to reach the polyp	Yes	30	Polyp in cecum (sessile, 25 mm)	EMR
22-1	M	19	Evaluation of CD activity	Yes	30	Stricture in transverse colon; unable to pass scope	Balloon dilation to 18 mm. Able to pass stenosis after dilation, subsequently started on adalimumab
22-2	M	19	Evaluation of CD activity	Yes	30	Improved stenosis; minimal CD activity	

Single-balloon colonoscopy resulted in successful cecal intubation in 22 (96%) procedures, with a median total procedure time of 30 (range 20-60) minutes. No external abdominal compression or fluoroscopic guidance was employed during the procedures. One procedure failed at the hepatic flexure due to the accumulation of solid colonic debris within the overtube because of a poorly prepped colon, leading to impaired smooth movement of the endoscope within the overtube, which made advancement difficult. In 12 (53%) procedures the terminal ileum was intubated and was inspected for a median length of 28 (range 5-80) cm. However, this was only attempted in patients for whom it was thought to be clinically relevant. The single-balloon colonoscopy provided a diagnosis in 13 (57%) cases, including polyps (n=6), active Crohn's disease (n=4), Crohn's-related stricture (n=1), and diverticulosis (n=2). Therapeutic interventions were performed in 7 (30%) procedures: polypectomy in 6 and 1 balloon dilation. Polypectomy yielded 2 tubulovillous adenomas with high-grade dysplasia, 2 tubulovillous adenomas with low-grade dysplasia, 1 tubular adenoma, and 1 juvenile polyp. Four small (< 5 mm) polyps were removed, but not retrieved for histology.

Twenty-one (91%) procedures were performed under conscious sedation. Propofol sedation was used in the remaining two (9%) procedures. Patients received conscious sedation consisting of midazolam and fentanyl, with median doses of 5.0 mg and 0.075 mg respectively during single-balloon colonoscopy, compared to median doses of 5.0 mg and 0.05 mg during the previous, failed colonoscopy. There was no statistical difference in the doses of midazolam (p=0.99) or fentanyl (p=0.34) given during conventional colonoscopy or single-balloon colonoscopy. However, sedation data from the previously failed colonoscopy were only available for 16 patients. There were no complications with any procedure.

DISCUSSION

This study demonstrates the viability of using the single-balloon endoscope system for colonoscopy in patients with previously failed conventional colonoscopy. In our cohort of patients among whom prior attempts at complete colonoscopy had failed, single-balloon colonoscopy proved to be an effective and safe method for completing colonic examination with a 96% success rate and no complications, yielding a positive diagnosis in over half of the procedures and endoscopic therapeutics in 30% of cases, with a median total procedure time of 30 minutes. The major limitation of this study is its lack of an active comparison with other endoscopic methods such as repeating conventional colonoscopy or other overtube-assisted modalities. Our results are similar to those achieved in studies using DBE to complete previously failed colonoscopy, in which successful cecal intubation was achieved in 88-100% of patients.[16-21] In the largest such study,[21] successful DBE colonoscopy was achieved in 93% of patients, with a mean time-to-cecum of 19 minutes. A further limitation of our study is that 'time-to-cecum' was not recorded and only 'total procedure time' was available for comparison. However, other studies of DBE colonoscopy have illustrated procedure times that are no faster than those in this study, with mean time-to-cecum of 28 minutes in one study[16] and mean total procedure time of 51 minutes in another.[20] Certainly there is no evidence to suggest that SBE colonoscopy is a slower method than DBE colonoscopy.

When the relative merits of SBE and DBE for small bowel enteroscopy are considered, there are some advantages of SBE that may also hold true for single-balloon colonoscopy. In particular, SBE may be easier to learn and more intuitive to perform for the practicing gastroenterologist,[11, 12, 14, 22] SBE may be faster to perform because of having only one balloon cycle as opposed to two with DBE, and the Olympus single-balloon endoscope is stiffer than the Fujinon double-balloon endoscope, which may be particularly helpful when maneuvering through redundant loops of bowel. We believe the

particular advantages of SBE may be especially useful when using the SBE endoscope to examine the colon, and that its potential disadvantage when compared to DBE, possible inferior insertion depth into the small intestine, is not an important factor when considering the use of SBE for colonoscopy.

In conclusion, single-balloon assisted colonoscopy seems a safe and effective method for completing colonoscopy in patients with previously failed or difficult colonoscopy. The outcomes are similar compared to previous studies with DBE colonoscopy in this patient group. As clinical experience with DBE and SBE has accumulated, it has become clear that both techniques offer an effective solution for completing difficult colonoscopy in patients with previously failed attempts.

REFERENCES

1. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003;124:544-60.
2. Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002;97:1296-308.
3. Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology 2007;132:2297-303.
4. Loffeld RJLF, van der Putten ABMM. The completion rate of colonoscopy in normal daily practice: factors associated with failure. Digestion 2009;80:267-70.
5. Hull T, Church JM. Colonoscopy--how difficult, how painful? Surgical endoscopy 1994;8:784-7.
6. Cirocco WC, Rusin LC. Factors that predict incomplete colonoscopy. Dis Colon Rectum 1995;38: 964-8.
7. Anderson JC, Gonzalez JD, Messina CR, Pollack BJ. Factors that predict incomplete colonoscopy: thinner is not always better. Am J Gastroenterol 2000;95:2784-7.
8. Anderson JC, Messina CR, Cohn W, Gottfried E, Ingber S, Bernstein G, et al. Factors predictive of difficult colonoscopy. Gastrointest Endosc 2001;54:558-62.
9. Takahashi Y, Tanaka H, Kinjo M, Sakumoto K. Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. Dis Colon Rectum 2005;48:1295-300.
10. Delvaux M, Gay G. Novel applications of balloon endoscopy [review article]. Gastrointestinal endoscopy clinics of North America 2009;19:509-18.
11. Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy 2008;40:11-5.
12. Kawamura T, Yasuda K, Tanaka K, Uno K, Ueda M, Sanada K, et al. Clinical evaluation of a newly developed single-balloon enteroscope. Gastrointest Endosc 2008;68:1112-6.
13. Ramchandani M, Reddy D, Gupta R, Lakhtakia S, Tandan M, Rao G, et al. Diagnostic yield and therapeutic impact of single-balloon enteroscopy: Series of 106 cases. Journal of Gastroenterology and Hepatology 2009.
14. Upchurch BR, Vargo JJ. Single-balloon enteroscopy [review article]. Gastrointestinal endoscopy clinics of North America 2009;19:335-47.
15. Lo SK. Techniques, tricks, and complications of enteroscopy [review article]. Gastrointestinal endoscopy clinics of North America 2009;19:381-8.
16. Kaltenbach T, Soetikno R, Friedland S. Use of a double balloon enteroscope facilitates caecal intubation after incomplete colonoscopy with a standard colonoscope. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2006;38:921-5.
17. Gay G, Delvaux M. Double-balloon colonoscopy after failed conventional colonoscopy: a pilot series with a new instrument. Endoscopy 2007;39:788-92.

18. Kita H, Yamamoto H. New indications of double balloon endoscopy. Gastrointest Endosc 2007;66: S57-9.

19. Mönkemüller K, Knippig C, Rickes S, Fry LC, Schulze A, Malfertheiner P. Usefulness of the double-balloon enteroscope in colonoscopies performed in patients with previously failed colonoscopy. Scandinavian journal of gastroenterology 2007;42:277-8.

20. Pasha SF, Harrison ME, Das A, Corrado CM, Arnell KN, Leighton JA. Utility of double-balloon colonoscopy for completion of colon examination after incomplete colonoscopy with conventional colonoscope. Gastrointest Endosc 2007;65:848-53.

21. Moreels T, Macken E, Roth B, Van Outryve M, Pelckmans P. Cecal intubation rate with the double-balloon endoscope after incomplete conventional colonoscopy: A study in 45 patients. Journal of Gastroenterology and Hepatology 2009.

22. Lo SK. Technical matters in double balloon enteroscopy [review article]. Gastrointest Endosc 2007;66:S15-8.

4

Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis

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ABSTRACT

Background and Aim: Uncertainty remains about the best test to evaluate patients with obscure gastrointestinal bleeding (OGIB). Previous meta-analyses demonstrated similar diagnostic yields with capsule endoscopy (CE) and double balloon enteroscopy (DBE) but relied primarily on data from abstracts and were not limited to bleeding patients. Many studies have since been published. Therefore, we performed a new meta-analysis comparing CE and DBE focused specifically on OGIB.

Methods: A comprehensive literature search was performed of comparative studies using both CE and DBE in patients with OGIB. Data were extracted and analyzed to determine the weighted pooled diagnostic yields of each method and the odds ratio for the successful localization of a bleeding source.

Results: Ten eligible studies were identified. The pooled diagnostic yield for CE was 62% (95% CI 47.3-76.1) and for DBE was 56% (95% CI 48.9-62.1), with an odds ratio for CE compared to DBE of 1.39 (95% CI 0.88-2.20; p=0.16). Subgroup analysis demonstrated the yield for DBE performed after a previously positive CE was 75.0% (95% CI 60.1-90.0), with the odds ratio for successful diagnosis with DBE after a positive CE compared to DBE in all patients of 1.79 (95% CI 1.09-2.96; p=0.02). In contrast, the yield for DBE after a previously negative CE was only 27.5% (95% CI 16.7-37.8).

Conclusions: CE and DBE provide similar diagnostic yields in patients with OGIB. However, the diagnostic yield of DBE is significantly higher when performed in patients with a positive CE.

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is the clinical condition in which patients with hemorrhage from the gastrointestinal tract have no source of bleeding identified after conventional upper endoscopy and ileocolonoscopy.[1] In the past decade, capsule endoscopy (CE)[2] and double balloon enteroscopy (DBE)[3] have revolutionized the approach to OGIB. No randomized, controlled trials exist comparing CE and DBE in OGIB, giving rise to uncertainty as to the best initial test to perform. Currently, the prevailing opinion is that patients should be investigated first by CE,[4] although two economic analyses[5, 6] have found that initial DBE is a more cost-effective strategy. Two meta-analyses comparing CE and DBE have previously been published, both finding similar overall diagnostic yields between the two modalities.[7, 8] However, these analyses relied on a small number of observational studies that were predominantly reported only in abstract form. In addition, the relative yields of CE and DBE were compared for the investigation of *small bowel diseases*, and were not specifically restricted to patients with OGIB. Furthermore, many new studies comparing CE and DBE have been published since these 2 systematic reviews were performed, greatly expanding the published literature on this topic. Thus, we chose to perform a new meta-analysis focused on the diagnostic yield of CE and DBE specifically in OGIB, in order to assess whether the accumulation of new data provide a more definitive answer for what is the best management strategy in these patients.

METHODS

Search strategy and selection of studies

A comprehensive literature search was performed to identify all published articles that presented original data from a comparative study examining the combined use of both balloon assisted enteroscopy (BAE), either DBE or single balloon enteroscopy (SBE), and CE in patients with OGIB. The search was performed using the PubMed, MEDLINE, EMBASE, and the Cochrane Library electronic databases through to January 1, 2010. Also, abstracts were searched from the conference proceedings of Digestive Diseases Week 2007, 2008 and 2009. The criteria for inclusion were published studies of any design that compared BAE and CE in the same patients with OGIB (both overt and occult). Studies that examined a broader population of patients with other indications for small bowel investigations were only included if the specific results for the subgroup of patients with GI bleeding could be discerned or were provided upon request by the study's authors. Non-comparative studies that utilized only CE or only BAE but not both procedures were

excluded. Abstracts older than 3 years not subsequently published as full articles were also excluded. The following MeSH headings and keywords were used in the search strategy: capsule endoscopy, wireless capsule endoscopy, video capsule endoscopy, double balloon endoscopy, double balloon enteroscopy, single balloon endoscopy, single balloon enteroscopy, push-and-pull endoscopy, push-and-pull enteroscopy, and balloon assisted endoscopy. The search was not limited to 'obscure GI bleeding' so that potentially relevant papers would not be excluded. The search was restricted to studies performed in humans and published in English. Finally, a manual hand-search of the reference lists from all retrieved original studies was performed.

The selection of studies took place in two phases. Initially, one reviewer (C.T.) screened the titles and abstracts of all unique references identified from the search for broad relevance, excluding those studies that clearly did not meet inclusion criteria, and selecting the remainder for closer scrutiny. These studies were then retrieved as full texts and independently assessed by two reviewers (P.M. and C.T) for relevance based on the inclusion and exclusion criteria. Where disagreement arose with respect to inclusion of a study, resolution was reached through discussion between the two reviewers.

Assessment of study quality

The quality of the studies was assessed using the STARD (STandards for the Reporting of Diagnostic accuracy studies) statement,[9-11] which is a validated checklist consisting of 25 items designed to improve the quality of reporting in diagnostic accuracy studies (see http://www.stard-statement.org) that has recently been applied to endoscopy.[12] The STARD checklist, modified by the removal of 4 items (#7, #13, #22, #24; giving a total possible score of 21) that we considered to not be applicable to studies comparing BAE and CE, was used to evaluate the quality of reporting in each of the included studies. The assessment of study quality were independently performed by two reviewers (P.M. and C.T.) after consensus was first agreed upon as to what was required to satisfy each of the STARD criteria. Studies with modified STARD scores of 17-21 were classified as "excellent quality," 12-16 "good quality," 7-11 "moderate quality," and < 7 "poor quality." Interobserver agreement was calculated and the strength of agreement (κ coefficient) classified according to standard definitions.[13]

Data extraction and analysis

Data were extracted on the diagnostic yield of DBE (as there were no SBE studies) and CE for identifying the source of bleeding, and were then entered into Review Manager (Cochrane Collaboration, Version 5.0) and pooled using weights derived from Mantel-Haenszel inverse variance. Heterogeneity was tested using a chi-square method and a

p-value of less than 0.1 was considered to reflect significant heterogeneity. Risk of bias was assessed using funnel plot analysis. Meta-analysis was performed using a random effects model to determine the odds ratio with 95% confidence intervals for the successful localization of the source of obscure GI bleeding comparing CE and DBE. In addition, pooled diagnostic yields for CE and for DBE were separately calculated using weightings based on Mantel-Haenszel inverse variance. Subgroup analyses of the diagnostic yields of DBE performed after a previously positive CE or a previously negative CE were conducted. Tests of statistical significance were performed using the paired and unpaired t-test with Stata 10.1 (Stata Corp, College Station, Texas) and with the Cochrane Collaboration Review Manager.

RESULTS

Description of studies

A flow diagram illustrating the study selection process is shown in Figure 1. One hundred forty-seven unique references were initially identified by the search, of which ten studies met all inclusion criteria.[14-23] In fact, fourteen studies met the criteria for inclusion in the systematic review, but 4 of these papers[24-27] were ultimately excluded from the meta-analysis because in these studies DBE was only performed in patients with a previously positive CE, which represents a selected patient population compared to patients with OGIB undergoing both CE and DBE.

A summary of the ten selected studies is provided in Table 1. No randomized-controlled trials were identified. DBE was used to perform balloon-assisted endoscopy in all included studies, with no study comparing SBE and CE. There were 651 patients who underwent CE and 642 patients who underwent DBE. This discrepancy in the number of patients who had CE and DBE exists because in the study by Fujimori *et al*.,[15] nine patients underwent CE but not subsequent DBE, without separate results being reported. In nearly all cases CE preceded DBE, except for one study[18] in which patients underwent DBE prior to CE, and a second study[21] in which CE was not uniformally performed before or after DBE. With only two exceptions,[14, 18] all studies examined a mixed population of OGIB patients, reporting combined results for both those with overt and occult manifestations of GI bleeding.

The assessments of study quality using the STARD statement criteria are presented in Table 1. The mean score was 16.1 (range 10 – 20; out of a possible score of 21). Five studies were considered to be of excellent quality,[14, 17, 19, 22, 23] four of good quality,[15, 16, 18, 21]

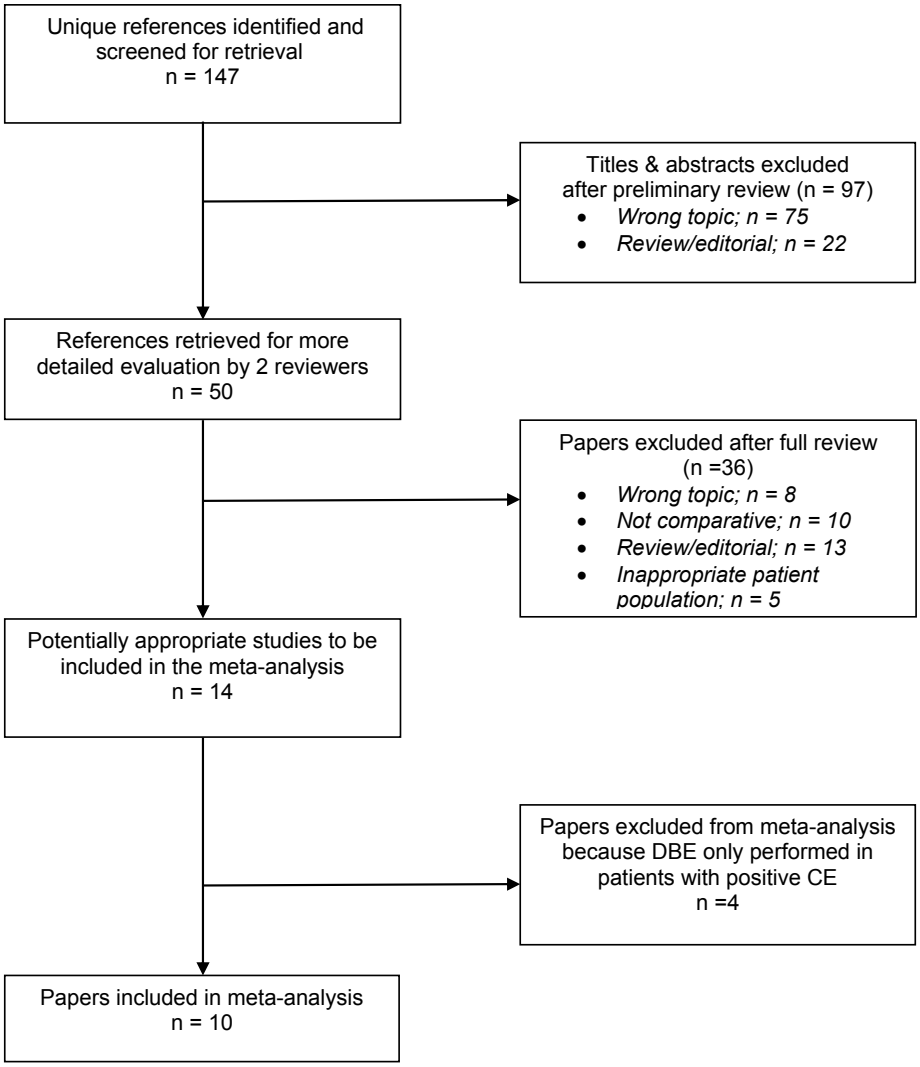

Figure 1. Flow diagram of studies identified in the meta-analysis

and one study as moderate quality.[20] The overall interobserver agreement was 86.2% giving a kappa of 0.62, indicating substantial agreement.

Diagnostic yields of CE and DBE

The efficacy outcomes from the studies included in the meta-analysis are presented in Table 2. The pooled diagnostic yield for CE was 61.7% (95% CI 47.3-76.1) and for DBE

Table 1. Summary of studies included in meta-analysis

Study	Country	Design	Total patients	OGIB patients examined with CE and DBE	Study quality (mean STARD score)
Matsumoto 2005	Japan	Prospective, blinded	13	13	Good (15.5)
Hadithi 2006	Netherlands	Prospective nonblinded	35	35	Excellent (18)
Mehdizadeh 2006	U.S.A.	Retrospective, nonblinded	188	115	Moderate (10)
Nakamura 2006	Japan	Prospective, blinded	32	28	Excellent (17.5)
Fujimori 2007	Japan	Prospective, nonblinded	45	45, 36[†]	Good (14.5)
Ohmiya 2007	Japan	Retrospective, nonblinded	479	74	Good (14.5)
Kameda 2008	Japan	Prospective, blinded	32	32	Good (16)
Arakawa 2009	Japan	Retrospective, nonblinded	162	74	Excellent (17)
Fukumoto 2009	Japan	Prospective, nonblinded	76	42[‡]	Excellent (17.5)
Marmo 2009	Italy	Prospective, nonblinded	193	193	Excellent (20)

OGIB obscure GI bleeding, *CE* capsule endoscopy, *DBE* double balloon enteroscopy, *STARD* STandards for the Reporting of Diagnostic accuracy studies

[†]45 patients had CE but only 36 patients underwent DBE in the study by Fujimori *et al*.

[‡]Unpublished data from subgroup of patients with OGIB, provided by personal communication with study author Akira Fukumoto, MD PhD, Onomichi, Japan

was 55.5% (95% CI 48.9-62.1). Meta-analysis comparing the successful localization of the bleeding source in each study revealed that the pooled odds ratio for the diagnostic yield for CE compared to DBE was 1.39 (95% CI 0.88, 2.20; p=0.16) (Figure 2). Visual inspection of funnel plots revealed no evidence of publication bias.

Subgroup analysis of the diagnostic yield of DBE performed after a previously positive CE was calculated only from those studies that provided sufficient data (Table 2). Among these studies,[14-17, 19, 20, 22] the pooled diagnostic yield was 75.0% (95% CI 60.1-90.0) and the odds ratio for the yield of DBE performed after a previously positive CE compared to that of DBE performed in all patients was 1.79 (95% CI 1.09-2.96; p=0.02) (Figure 3). A separate subgroup analysis revealed that the pooled diagnostic yield of DBE performed after a previously negative CE was 27.5% (95% CI 16.7-37.8).

Table 2. Summary of diagnostic yields

Study	n	Positive CE	Positive DBE	Reclassify Positive CE	Reclassify Positive DBE	DBE yield after prior (+) ve CE	DBE yield after prior (-) ve CE
Matsumoto 2005	13	10 (76.9%)	6 (53.8%)	8 (61.5%)	5 (38.5%)	-	-
Hadithi 2006	35	28 (80%)	21 (60%)	-	-	20/28 (71.4%)	1/7 (14.3%)
Mehdizadeh 2006	115	63 (54.8%)	57 (49.6%)	-	-	41/63 (65.1%)	16/52 (30.8%)
Nakamura 2006	28	17 (60.7%)	12 (42.9%)	14 (50%)	12 (42.9%)	9/17 (52.9%)	3/11 (27.3%)
Fujimori 2007	45 (36†)	18 (40%)	18 (50%)	18 (40%)	23 (63.9%)	16/16 (100%)	2/20 (10%)
Ohmiya 2007	74	37 (50%)	39 (52.7%)	48 (64.9%)	39 (52.7%)	-	-
Kameda 2008	32	23 (71.9%)	21 (65.6%)	29 (90.6%)	21 (65.6%)	15/23 (65.2%)	2/3 (66.7%)
Arakawa 2009	74	40 (54.1%)	74 (63.5%)	-	-	36/40 (90%)	11/34 (32.4%)
Fukumoto 2009‡	42	16 (38.1%)	18 (42.9%)	-	-	-	-
Marmo 2009	193	174 (90.2%)	132 (68.4%)	174 (90.2%)	132 (68.4%)	124/174 (71.3%)	8/19 (42.1%)

CE capsule endoscopy, *DBE* double balloon enteroscopy

†45 patients had CE but only 36 patients underwent DBE in the study by Fujimori *et al*.

‡Unpublished data from subgroup of patients with OGIB, provided by personal communication with study author Akira Fukumoto, MD PhD, Onomichi, Japan

- fields left blank where reclassification or subgroup results could not be discerned from the data

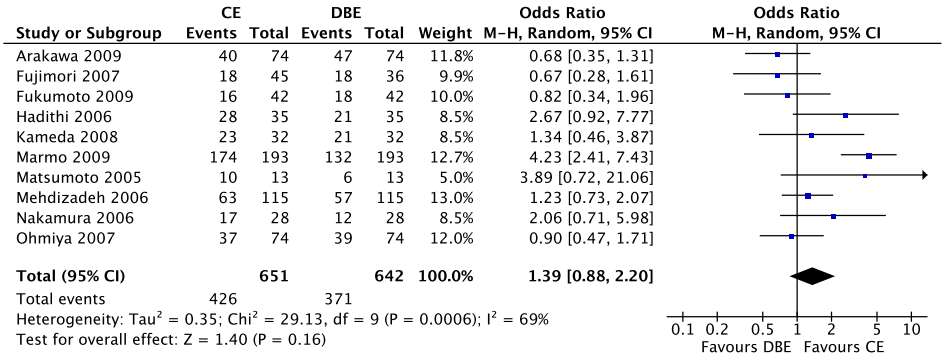

Figure 2. Relative diagnostic yield of CE compared to DBE

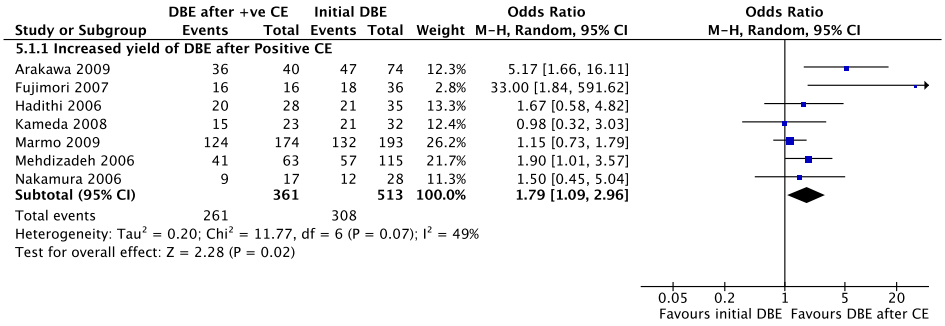

Figure 3. Increased diagnostic yield of DBE performed after positive CE

DISCUSSION

Two previous meta-analyses[7, 8] performed prior to our study both found similar diagnostic yields between CE and DBE (overall yield 60% for CE, 57% for DBE;[7] odds ratio 1.21 [95% CI: 0.64-2.29][8]). However, these studies were not restricted to patients with OGIB, relied primarily on data presented in abstract form, and involved a relatively small numbers of subjects: 375 patients in the study by Pasha *et al*.[7] and 277 in that by Chen *et al*.[5] Our updated meta-analysis focused exclusively on patients with OGIB, and examined ten published studies involving 651 patients. However, despite the increased sample size, no statistically significant difference in diagnostic yield was found when CE and DBE were compared: 62% for CE and 56% for DBE, giving a non-significant odds ratio of 1.39 for identifying the source of bleeding.

Despite the focus on OGIB patients unique to this study, our results replicated those of the previous meta-analyses.[7, 8] Nevertheless, an interesting new finding from our study is the subgroup analysis revealing that the diagnostic yield of DBE performed after a previously positive CE is 75%, notably higher than the diagnostic yield of 56% when DBE is performed in all patients, giving a statistically significant odds ratio of 1.79. Similar results were obtained in the four studies that were identified by our search for this systematic review but were excluded from the meta-analysis because DBE was only performed in patients with a previously positive CE.[24-27] The pooled diagnostic yield for DBE in these four studies was 81.1% (95% CI 75.1-87.1), Together, these data suggest that the yield from DBE is considerably enhanced when directed by findings from prior capsule endoscopy, an intuitive observation but one that has not been formally characterized previously.

A limitation of this comparative analysis is that in most studies, CE was performed prior to DBE and the endoscopist performing DBE was not blinded to the CE results. Since

there is a significantly increased diagnostic yield when DBE is performed after a positive CE, having the results from capsule endoscopy available may create detection bias in the yield of DBE. Only the studies by Nakamura *et al.*[14] and Kameda *et al*.[16] blinded the DBE endoscopist to the results of CE, and one study performed DBE prior to CE, which in effect is equivalent to blinding.[18] The combined diagnostic yields from these studies showed a non-significant difference in favor of CE: 69.2% (95% CI 58.7-79.7) for CE and 52.9% (95% CI 37.3-68.4) for DBE, (p=0.06) However, the combined sample size to make this comparison was small (n=73).

A further limitation of this meta-analysis is that the included studies examined patients both with overt OGIB and with occult OGIB and did not separately report results for these different groups. In fact, only two studies[14, 18] involving a total of 45 patients focused exclusively on overt OGIB, too small a number from which to draw any meaningful conclusions. It is very likely that patients with overt bleeding signs such as hematochezia or melena should be evaluated differently than patients with occult OGIB who present with fecal occult blood positivity or iron deficiency anemia. Indeed, a small retrospective case series by Mönkemüller *et al.*[28] that examined the use of emergency DBE (defined as performance within 24 hours of clinical presentation) for overt obscure GI bleeding patients demonstrated the feasibility of such an approach. In this study, the putative bleeding source was identified, and endoscopic therapy applied, in nine out of ten patients during 17 emergency DBE procedures performed following negative gastroscopy and colonoscopy. Furthermore, it is already known that the diagnostic yields of both CE[29-31] and DBE[32] are highest when performed within a short interval of an overt bleeding episode. What remains unanswered by the existing literature and could not be addressed by this meta-analysis, are the comparative yields of CE and DBE specifically within this overt bleeding population, and whether the prior performance of CE leads to any clinically meaningful subsequent increased yield of DBE after overt bleeding, as our study has shown it to do within a mixed group that included both occult and overt OGIB patients.

In summary, the results from this meta-analysis demonstrate that CE and DBE have similar diagnostic yields for the evaluation of obscure GI bleeding, albeit within a cohort that included both occult and overt OGIB patients. This confirms that the diagnostic algorithm for OGIB should in most cases begin with CE, especially among patients with occult bleeding, in particular because of the relatively non-invasive nature of CE in comparison to enteroscopy and because the yield of DBE is significantly enhanced when guided by a previously positive capsule study. However, the best strategy for the evaluation of overt OGIB patients remains unanswered and further prospective studies are needed to compare CE and DBE in this group.

REFERENCES

1. Raju GS, Gerson L, Das A, Lewis B, Association AG. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007; **133**: 1697-717.
2. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature* 2000; **405**: 417.
3. Yamamoto H, Sekine Y, Sato Y, *et al.* Total enteroscopy with a nonsurgical steerable double-balloon method. *Gastrointest. Endosc.* 2001; **53**: 216-20.
4. Ladas SD, Triantafyllou K, Spada C, *et al.* European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-7.
5. Gerson L, Kamal A. Cost-effectiveness analysis of management strategies for obscure GI bleeding. *Gastrointest. Endosc.* 2008; **68**: 920-36.
6. Somsouk M, Gralnek IM, Inadomi JM. Management of obscure occult gastrointestinal bleeding: a cost-minimization analysis. *Clin. Gastroenterol. Hepatol*. 2008; **6**: 661-70.
7. Pasha SF, Leighton JA, Das A, *et al.* Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. *Clin. Gastroenterol. Hepatol*. 2008; **6**: 671-6.
8. Chen X, Ran Z-H, Tong J-L. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. *World J. Gastroenterol*. 2007; **13**: 4372-8.
9. Bossuyt PM, Reitsma JB, Bruns DE, *et al.* Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. *Ann. Intern. Med*. 2003; **138**: 40-4.
10. Bossuyt PM, Reitsma JB, Bruns DE, *et al.* The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann. Intern. Med*. 2003; **138**: W1-12.
11. Smidt N, Rutjes AWS, van der Windt DAWM, *et al.* Reproducibility of the STARD checklist: an instrument to assess the quality of reporting of diagnostic accuracy studies. *BMC Med. Res. Methodol*. 2006; **6**: 12.
12. Areia M, Soares M, Dinis-Ribeiro M. Quality reporting of endoscopic diagnostic studies in gastrointestinal journals: where do we stand on the use of the STARD and CONSORT statements? *Endoscopy* 2010; **42**: 138-47.
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307-10.
14. Nakamura M, Niwa Y, Ohmiya N, *et al.* Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in patients with suspected small-bowel bleeding. *Endoscopy* 2006; **38**: 59-66.
15. Fujimori S, Seo T, Gudis K, *et al.* Diagnosis and treatment of obscure gastrointestinal bleeding using combined capsule endoscopy and double balloon endoscopy: 1-year follow-up study. *Endoscopy* 2007; **39**: 1053-8.
16. Kameda N, Higuchi K, Shiba M, *et al.* A prospective, single-blind trial comparing wireless capsule endoscopy and double-balloon enteroscopy in patients with obscure gastrointestinal bleeding. *J. Gastroenterol*. 2008; **43**: 434-40.

17. Marmo R, Rotondano G, Casetti T, *et al.* Degree of concordance between double-balloon enteroscopy and capsule endoscopy in obscure gastrointestinal bleeding: a multicenter study. *Endoscopy* 2009; **41**: 587-92.

18. Matsumoto T, Esaki M, Moriyama T, Nakamura S, Iida M. Comparison of capsule endoscopy and enteroscopy with the double-balloon method in patients with obscure bleeding and polyposis. *Endoscopy* 2005; **37**: 827-32.

19. Hadithi M, Heine GDN, Jacobs MAJM, van Bodegraven AA, V Bodegraven AA, Mulder CJJ. A prospective study comparing video capsule endoscopy with double-balloon enteroscopy in patients with obscure gastrointestinal bleeding. *Am. J. Gastroenterol*. 2006; **101**: 52-7.

20. Mehdizadeh S, Ross A, Gerson L, *et al.* What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. *Gastrointest. Endosc*. 2006; **64**: 740-50.

21. Ohmiya N, Yano T, Yamamoto H, *et al.* Diagnosis and treatment of obscure GI bleeding at double balloon endoscopy. *Gastrointest. Endosc*. 2007; **66**: S72-7.

22. Arakawa D, Ohmiya N, Nakamura M, *et al.* Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. *Gastrointest. Endosc*. 2009; **69**: 866-74.

23. Fukumoto A, Tanaka S, Shishido T, Takemura Y, Oka S, Chayama K. Comparison of detectability of small-bowel lesions between capsule endoscopy and double-balloon endoscopy for patients with suspected small-bowel disease. *Gastrointest. Endosc*. 2009; **69**: 857-65.

24. Kaffes AJ, Siah C, Koo JH. Clinical outcomes after double-balloon enteroscopy in patients with obscure GI bleeding and a positive capsule endoscopy. *Gastrointest. Endosc*. 2007; **66**: 304-9.

25. Li X-B, Ge Z-Z, Dai J, *et al.* The role of capsule endoscopy combined with double-balloon enteroscopy in diagnosis of small bowel diseases. *Chin. Med. J*. 2007; **120**: 30-5.

26. Hendel J, Vilmann P, Jensen T. Double-balloon endoscopy: who needs it? *Scand. J. Gastroenterol*. 2008; **43**: 363-7.

27. Kamalaporn P, Cho S, Basset N, *et al.* Double-balloon enteroscopy following capsule endoscopy in the management of obscure gastrointestinal bleeding: outcome of a combined approach. *Can. J. Gastroenterol*. 2008; **22**: 491-5.

28. Mönkemüller K, Neumann H, Meyer F, Kuhn R, Malfertheiner P, Fry LC. A retrospective analysis of emergency double-balloon enteroscopy for small-bowel bleeding. *Endoscopy* 2009; **41**: 715-7.

29. Pennazio M, Santucci R, Rondonotti E, *et al.* Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology* 2004; **126**: 643-53.

30. Apostolopoulos P, Liatsos C, Gralnek IM, *et al.* Evaluation of capsule endoscopy in active, mild-to-moderate, overt, obscure GI bleeding. *Gastrointest. Endosc*. 2007; **66**: 1174-81.

31. Bresci G, Parisi G, Bertoni M, Tumino E, Capria A. The role of video capsule endoscopy for evaluating obscure gastrointestinal bleeding: usefulness of early use. *J. Gastroenterol*. 2005; **40**: 256-9.

32. Tanaka S, Mitsui K, Yamada Y, *et al.* Diagnostic yield of double-balloon endoscopy in patients with obscure GI bleeding. *Gastrointest. Endosc*. 2008; **68**: 683-91.

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Retrograde double balloon enteroscopy: comparing performance of solely retrograde vs. combined same-day anterograde and retrograde procedure.

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ABSTRACT

Objective: Retrograde double balloon enteroscopy (DBE) is important for evaluating the distal small bowel but is more challenging compared to the oral route. Optimizing small bowel insertion may enhance the diagnostic utility of the examination. We sought to determine if insertion depths achieved with retrograde DBE when performed as an isolated procedure differed significantly from when performed immediately following anterograde DBE.

Materials and Methods: A retrospective analysis was conducted of all retrograde DBE procedures performed at our center with comparisons made between 'distal-only' DBE without preceding anterograde DBE, and 'combined' DBE after a prior same day anterograde DBE.

Results: Two hundred ninety retrograde DBE procedures were performed in 264 patients over 5 years. Success of terminal ileal intubation exceeded 95%. The mean insertion depth into the distal small bowel differed significantly with 112 cm (95% CI 95-129) in the 'distal-only' group and 92 cm (95% CI 85-98) in the 'combined' group (p=0.01), with a trend toward a corresponding increased diagnostic yield of 48% vs. 37% respectively (p=0.15). Multivariate regression analysis identified both insertion route strategy ('distal-only' > 'combined'; p=0.01) and type of DBE endoscope (diagnostic > therapeutic; p=0.02) as significant predictors of retrograde insertion depth.

Conclusions: The insertion depth of retrograde DBE is significantly greater when carried out as a separate distal procedure and not in combination with a preceding anterograde DBE, and when performed using a diagnostic as opposed to the therapeutic DBE endoscope. This increased retrograde depth of insertion may be associated with an increased diagnostic yield.

INTRODUCTION

The introduction of double balloon enteroscopy (DBE) over the past decade revolutionized our ability to visualize, sample histology, and provide therapeutics in the small bowel. While complete visualization of the small intestine is desirable, it is infrequently achieved in most centers with some exceptions(1, 2) and is most often not clinically necessary.(3) Nevertheless, optimizing the depths of the small bowel explored by DBE correlates with an increased frequency of identified abnormalities(4) and is important both to detect the presence and to confirm the absence of important pathology. The most commonly used approach is the combination of an anterograde procedure via the mouth, followed by a retrograde procedure via the anus if complete small bowel visualization is not achieved. The actual timing of this retrograde procedure is not well established: in some centers the retrograde procedure is performed at another scheduled appointment, while others perform a retrograde procedure immediately following the incomplete anterograde one.

Retrograde DBE enables the inspection of the distal small intestine and is usually indicated when small bowel disease is suspected but anterograde DBE fails to identify responsible pathology, when capsule endoscopy or radiographic imaging suggests the presence of distal small bowel abnormalities,(5, 6) and when Crohn's disease patients require evaluation beyond conventional ileo-colonoscopy.(7) However, the retrograde procedure is recognized as more technically challenging, with failure of terminal ileum (TI) intubation occurring in up to 21% of DBE cases.(8) Furthermore, once stable ileal intubation is achieved, depths of insertion from retrograde DBE and single balloon enteroscopy (SBE) are consistently much less than those achieved with anterograde DBE and SBE, ranging from 124 – 199 cm and 220 – 360 cm respectively.(9-15) Thus, identifying factors that may improve the insertion depth of retrograde DBE is important. One of the factors that may influence the performance of retrograde DBE is the timing of the procedure. Combining anterograde and retrograde DBE into a joint same-day procedure may be of increased efficiency for patients who only have to undergo a single bowel preparation and make only one hospital visit, and for the physician who can complete the endoscopic evaluation more immediately. However, we suspect that combining the procedure may compromise the insertion depth of the retrograde DBE, possibly because of air insufflation during the anterograde portion or because of increased patient intolerance during the longer combined procedure.

The aim of this study was to determine if the depth of insertion of retrograde DBE was significantly affected by whether the distal procedure was performed by itself or in combination with a preceding anterograde DBE on the same day.

METHODS

A retrospective analysis was performed of all retrograde DBE procedures performed at Erasmus MC University Medical Center, a tertiary referral university hospital in Rotterdam, The Netherlands. Procedure-related data were collected in a standardized, prospective fashion. All retrograde procedures were included in the analysis regardless of the indication for the investigation. SBE and spiral enteroscopy were excluded due to relatively low procedure numbers in comparison to DBE. The procedures were performed by three endoscopists with extensive accumulated experience in DBE, with the assistance of a trained enteroscopy nurse.

Double balloon enteroscopy procedure

DBE was performed with the Fujinon double-balloon enteroscopy system (Fujinon Inc., Saitama, Japan) using the diagnostic EN-450P5 endoscope prior to December 2006 and both the diagnostic and therapeutic EN-450T5 DBE endoscopes as clinically indicated after December 2006. DBE was performed according to the standard technique as described by Yamamoto et al.(1) All patients received a standardized bowel preparation consisting of 4 L of a polyethylene glycol solution the evening prior to the procedure and an overnight fast from midnight. Conscious sedation was used in the majority of procedures, using a combination of midazolam and fentanyl intravenously. In selected cases propofol sedation or general anaesthesia was administered. All cases were performed using standard air insufflation until September 2009, after which CO2 insufflation was used instead. Fluoroscopy was not routinely used to assist any of the DBE procedures except in selected cases (i.e. for dilation of stenotic lesions).

The clinical algorithm at our institution for patients with suspected small bowel pathology was to begin with an anterograde DBE. When the anterograde DBE provided a diagnosis that was sufficient explanation for the patient's presentation, no subsequent retrograde DBE was performed unless clinically required. However, when the anterograde DBE was non-diagnostic or if the abnormalities identified were thought to be too minor to account for the patient's symptoms, a subsequent retrograde DBE was performed, either on the same day immediately following the anterograde procedure or at a later date. The exception was Crohn's disease patients undergoing enteroscopy to evaluate the extent of disease involvement or to assess disease activity, in whom bi-directional DBE was routinely performed.

Part of the reasoning behind our policy for a same day combined oral/anal DBE procedure was that our hospital is a referral center for a significant portion of The Netherlands, with many patients having to travel from other cities to come for their small bowel investigations.

'Combined' or 'distal-only' procedure

The retrograde DBE procedures were classified as '*distal-only*' when performed in isolation without a preceding anterograde procedure. In contrast, when a retrograde procedure was performed following a prior anterograde DBE on the same day, it was classified as a '*combined*' case. Clinical and demographic data were identified and endoscopic outcomes determined for all patients who underwent a retrograde DBE. The primary outcome of interest was the depth of insertion into the small bowel proximal to the ileocecal valve, as calculated using the standard method of counting push-and-pull insertion cycles minus any endoscope slippage to estimate insertion depth.(16) Secondary outcomes included the diagnostic yield of the retrograde DBE procedures as well as subgroup analyses. For 'combined' cases the diagnostic yield was only calculated based on the results of the retrograde procedure and did not include any findings from the preceding anterograde DBE. Also, abnormalities identified in the colon during retrograde DBE were, for the purposes of this study, not considered positive findings contributing to the diagnostic yield of the enteroscopy, which was exclusively based on the diagnosis of small bowel lesions.

Statistical Analysis

The statistical software Stata 10.1 (Stata Corp, College Station, Texas) was used to analyze the data. Means and ranges were used to summarize data for continuous variables and percentages were used to summarize data for categorical variables. Student's t-test was used to compare the primary outcome of the retrograde depth of insertion for '*distal-only*' DBE with that for '*combined*' DBE. The Chi^2 test was used to compare proportions for categorical variables, including the secondary outcome of diagnostic yield. Two-sided p-values were used at 80% power to define a statistically significant result with a $p \leq 0.05$. Univariate and multivariate regression analysis was then performed using ANOVA to identify variables that may have been predictive of the primary outcome of small bowel insertion depth.

RESULTS

During the study period between July 2004 and January 2010, 290 retrograde DBE procedures were performed in 267 patients, including 140 (52%) females, mean age 47 (11 – 86) years. The most common indications for retrograde DBE were the evaluation of Crohn's disease (34%), iron-deficiency anemia or obscure GI bleeding (29%), and obstructive symptoms or abdominal pain (18%). Most retrograde DBE procedures were done as part of a 'combined' case (78%), whereas a minority were 'distal-only' cases (22%). Two-thirds of procedures were performed using the diagnostic EN-450P5

Table I. Clinical features

	Entire cohort	Combined route	Distal-only route	p-value
Number (n)	290	227 (78.3%)	63 (21.7%)	
Sex				
Male	142 (49.0%)	115 (50.7%)	27 (42.9%)	
Female	148 (51.0%)	112 (49.3%)	36 (57.1%)	0.27
Age (mean yrs; range)	46.7 (11-86)	47.2 (11-86)	44.9 (18-83)	0.35
Indications				
Anemia	85 (29.3%)	63 (27.8%)	22 (34.9%)	0.27
Crohn's disease	98 (33.8%)	79 (34.8%)	19 (30.2%)	0.49
Suspected Crohn's	12 (4.1%)	11 (4.9%)	1 (1.6%)	0.25
Abdominal complaints∞	53 (18.3%)	40 (17.6%)	13 (20.6%)	0.58
Chronic diarrhea	21 (7.2%)	17 (7.5%)	4 (6.4%)	0.76
Other§	21 (7.2%)	17 (7.5%)	4 (6.4%)	0.76
Endoscopic DBE Modality				
Diagnostic endoscope	194 (66.9%)	156 (68.7%)	38 (60.3%)	0.21
Therapeutic endoscope	96 (33.1%)	71 (31.3%)	25 (39.7%)	0.21

∞ Obstructive symptoms or abdominal pain

§ Includes refractory Celiac (n=2); Behcet's disease (n=11); Peutz-Jeghers (n=6); Capsule retention (n=2)

endoscope and one-third were performed with the therapeutic EN-450T5 endoscope. No significant differences in clinical features existed between patients in the 'combined' route group and patients in the 'distal-only' route group; see Table 1.

Conscious sedation was used in the majority of procedures: in 91% of 'combined' cases and 92% of 'distal-only' cases. Propofol was used for 8 (4%) procedures in the 'combined' group and for 5 (8%) procedures in the 'distal-only' group, whereas general anaesthesia was used in 12 (5%) cases in the 'combined' group and zero cases in the 'distal-only' group. Insufflation was achieved by using room air in 95% of retrograde DBE procedures since we have only recently adopted the use of CO2.

The success of terminal ileal intubation exceeded 95% and did not differ between the 'combined' and 'distal-only' groups. There was a significant difference in the primary endpoint of the depth of insertion into the distal small bowel between the two groups, with a mean insertion of 92 cm (95% CI 85 – 98) in the 'combined' group and of 112 cm (95% CI 95 - 129) in the 'distal-only' group (p=0.01). This corresponded to a trend toward an increased diagnostic yield of 48% in the 'distal-only' group compared to 37% in the 'combined' group that failed to reach statistical significance (p=0.15). There was a statistically significant increase in insertion depth in the 'distal-only' cohort compared to the 'combined' cohort for the anemia indication subgroup, for the non-Crohn's disease

Table II. Endoscopic outcomes

	Entire cohort	Combined route	Distal only	p-value
Procedures (n)	290	227	63	
Terminal ileum intubation (%)	277/290 (95.5%)	218/227 (96.0%)	59/63 (93.7%)	0.42
Mean depth of insertion into terminal ileum (95% CI; cm)	95.9 (89.5-102.4)	91.6 (84.8-98.3)	112.0 (95.2-128.9)	**0.01**
Diagnostic yield (%) (95% CI)	39.4% (33.6-45.1)	37.2% (30.7-43.6)	47.5% (34.7-60.2)	0.15
Indication				
Established CD (n)	98	79	19	
Insertion depth (95% CI; cm)	79.3 (70.2-88.5)	76.4 (66.4-86.4)	92.4 (68.2-116.5)	0.18
Diagnostic yield	54.3% (50/92)	54.7% (41/75)	52.9% (9/17)	0.90
Anemia (n)	85	63	22	
Insertion depth (95% CI; cm)	103.0 (90.5-115.6)	94.4 (81.0-107.8)	130.0 (100.7-159.3)	**0.01**
Diagnostic yield	28.0% (23/82)	22.6% (14/62)	45.0% (9/20)	**0.05**
Endoscope				
Diagnostic DBE (n)	194	156	38	
Insertion depth (95% CI; cm)	102.2 (94.3-110.1)	98.9 (90.8-107.0)	116.3 (92.3-140.2)	0.09
Diagnostic yield	34.7% (66/190)	31.8% (49/154)	47.2% (17/36)	0.08
Therapeutic DBE (n)	96	71	25	
Insertion depth (95% CI; cm)	82.2 (71.6-92.9)	73.9 (62.5-85.3)	105.4 (81.6-129.3)	**0.01**
Diagnostic yield	49.4% (43/87)	50.0% (32/64)	47.8% (11/23)	0.86

indication subgroup, and for procedures performed using the therapeutic DBE endoscope (see Table 2 for a summary of the endoscopic outcomes).

The mean total procedure time (exclusive of endoscope set-up time) was 82 (range 30 – 155) minutes for the 'combined' group and 59 (range 30 – 100) minutes for the 'distal-only' group. Unfortunately, this procedure time for the 'combined' group includes both the anterograde and retrograde procedures, as these were not separately recorded. The presence of positive findings on the preceding anterograde procedure did not influence the time spent on the retrograde portion, as the mean 'combined' total procedure times was 79 (95% CI 72.5 – 85.2) minutes when the anterograde DBE had yielded positive findings and was 83 (79.9 – 86.3) minutes when the anterograde DBE had been negative (p=0.26).

Simple linear regression and multiple regression methods were used to identify variables that were predictive of the primary outcome of small bowel insertion depth. On univariate analysis, the significant variables were the route of insertion (i.e. 'combined' route or 'distal-only' route) (p=0.01), the type of endoscope (p=0.005), and the indication for the examination (p=0.007). The age or sex of the patient and the use of CO2 for insufflation did not significantly affect the insertion depth outcome. With multivariate regression, only the route of insertion and the type of endoscope remained significant, with the 'distal-only' group having insertion depths 21 cm (95% CI 6 - 36) further on average than the 'combined' group (p=0.008), and the diagnostic DBE endoscope 17 cm (95% CI 3 - 30) greater on average than the therapeutic DBE endoscope (p=0.02), after controlling for the other variables.

The most common endoscopic findings were ulcerative, inflammatory lesions found in 29% of procedures, followed by vascular lesions (such as angiodysplasia) in 3%, polyps in 3%, and various other findings in 4% of cases. There were no statistically significant differences between the 'combined' or 'distal-only' groups with respect to the type of findings. Among patients who underwent retrograde DBE for the assessment of anemia, 28% had positive findings, including 15% with ulcerative, inflammatory lesions, 5% with vascular lesions, 1% with polyps, and 7% with other findings; overall this includes 9 'distal-only' procedures with positive findings (4 ulcers, 3 vascular, 2 other) and 14 'combined' procedures with positive findings (8 ulcers, 1 vascular, 1 polyp, 1 Meckel's diverticulum, 3 other). Again, there were no significant differences between the 'combined' or 'distal-only' groups.

The rate of total enteroscopy with complete visual inspection of the small bowel was 11% among the 'combined' group and 2% for the 'distal-only' group, but the latter only considered the retrograde DBE procedure by itself and not in combination with the previously performed anterograde DBE. This is because we tended to not make permanent ink markings of the most distal point reached during anterograde insertion, but rather used metal clips or took biopsies to create mucosal injury that would be recognized during an immediate retrograde procedure but would typically not be identifiable when the retrograde DBE was performed at a later date.

Three major complications (1%) occurred among our cohort: one episode of pancreatitis and two small bowel perforations. The acute pancreatitis occurred after a combined anterograde/retrograde procedure, but the patient recovered after conservative therapy during a short hospital stay. Both cases of perforation occurred after endoscopic balloon dilation of small bowel strictures (one radiation-induced, one Crohn's disease) during the retrograde procedure. Both perforation patients went to surgery and recovered well post-operatively.

DISCUSSION

While considerable research has been published describing the performance characteristics of DBE, very little attention has been directed specifically to the retrograde procedure. To our knowledge, this is only the second study to have this focus and represents the largest cohort of retrograde DBE procedures yet described. This study demonstrates that for patients undergoing retrograde DBE at our center, insertion depths into the distal small bowel were significantly greater when the procedure was performed in isolation rather than in combination with a preceding anterograde DBE on the same day. This superior insertion depth corresponded to a non-significant trend toward a superior diagnostic yield with retrograde DBE in patients who only had the retrograde procedure. Furthermore, multivariate analysis demonstrated that in addition to the route of insertion strategy, the type of DBE endoscope used significantly affected the depth of insertion into the small bowel, favoring the diagnostic over the therapeutic DBE endoscope. Conversely, success of terminal ileal intubation seemed unaffected by the route of insertion or the type of endoscope, with excellent intubation rates (≥ 94%) in all subgroups of our cohort.

While the depth of insertion for retrograde DBE was significantly greater with the 'distal-only' procedure compared to that with the 'combined' procedure, the insertion depths themselves achieved in this cohort, i.e. an overall mean insertion of 96 cm, appear inferior to those that have been reported in the literature. Indeed, early DBE case-series that included both anterograde and retrograde DBE outcomes reported superior insertion depths from the retrograde procedure, ranging from 120 - 130 cm by the Wiesbaden group (n=122),(3, 9) to 182 cm by early U.S. expert centers (albeit in a cohort in which intubation of the TI failed in over 30% of cases; n = 77),(12) to advancement to "one-third to two-thirds of the length of the entire small intestine" with no failures of TI intubation by Yamamoto et al. (n=89)(1) In contrast, more recent reports from experienced endoscopy centers in Indianapolis (n=31) and Mayo Jacksonville (n=85) report more similar retrograde insertion depths of 116 cm and 124 cm respectively.(13, 17) The cause of this variability in retrograde insertion depths remains unclear. The imprecise nature of the method for the estimation of insertion depth may be partly responsible, which remains based on a subjective assessment by the endoscopist. Comparisons of reported insertion depths between institutions should therefore be interpretated with caution. Furthermore, there may be other variables involved, including factors relating to endoscopist experience, patient population factors, or procedural factors such as those identified in this study. Indeed, in the only other published study focusing on retrograde DBE (n=59), increased balloon enteroscopy experience was associated with superior TI intubation rates and increasing depths of small bowel insertion, with the learning

curve improving after 20 distal procedures.(8) However, lack of experience would not account for the inferior insertion depths achieved in our cohort as the DBE procedures were performed by 3 endoscopists with considerable enteroscopy experience. The small number of endoscopists performing the procedures in our cohort also strengthens the internal validity of our insertion depth estimation technique. A notable patient population factor that may have had a negative impact on the depth of insertion is the high proportion of our cohort with Crohn's disease (34%), which is a feature unique to our small bowel endoscopy population. The mean insertion depth for Crohn's patients was 79 cm, significantly less than the mean insertion of 104 cm for the rest of the cohort ($p<0.001$). That said, indication for the DBE was not an overall predictor of insertion depth in the multivariate analysis, and the apparent difference described above may in fact be due to confounding by route of insertion or type of endoscope. Furthermore, even when the Crohn's patients are removed from our analysis, the depth of insertion among the remaining patients (104 cm) remains notably less than previous reports.

Another apparent discrepancy between this study and the existing literature is the relatively lower overall diagnostic yield of 39%. In contrast, in a meta-analysis that compared DBE with capsule endoscopy, the pooled diagnostic yield for DBE was 57%.(18) However, the diagnostic yields for the studies included in this meta-analysis and nearly all the case-series reported in the literature consist of findings from the combination of both the anterograde and retrograde DBE procedures. In this study, the diagnostic yield was only determined from the small bowel findings identified during the retrograde procedure, regardless of what may have been identified by a previous anterograde examination. This means that our diagnostic yield of 39% actually represents the *additive* diagnostic value of performing the distal procedure, which would likely be of clinical relevance to many patients. In comparison, the only other study to describe outcomes separately for retrograde DBE (n=59) had a diagnostic rate of 47%.(8) Additional possible reasons for why our rate remains lower is that colonic findings did not contribute to the diagnostic yield in our study, whereas it has been shown previously that nearly 10% of abnormal findings detected by DBE in the work-up of OGIB are found in the colon.(19) Finally, we do not perform capsule endoscopy at our centre, and as such, this was an unselected population less likely to have abnormalities than a pre-selected cohort with abnormal capsule findings.

What remains to be explained is why the insertion depth with retrograde DBE was significantly greater when performed as an isolated procedure as in the 'distal-only' group compared to when performed in conjunction with an immediately preceding anterograde DBE as in the 'combined' group. It is likely that air insufflation during the anterograde procedure plays a major role by distending the small bowel lumen and

thereby compromising the ability of the balloons to grip the intestinal wall. However, it is interesting that the use of CO2, which would be expected to overcome this factor, was not associated with greater insertion depths in the multivariate analysis, although perhaps the number of CO2 cases was insufficient to have enough statistical power to illustrate a difference. Endoscopist fatigue would not be a confounding factor as our total procedure times are relatively short, nor would there be a greater inclination for the endoscopist to prematurely stop the retrograde DBE in 'combined' cases because of the presence of sufficient explanatory findings on the anterograde procedure, as our clinical protocol dictated that we only proceeded to retrograde DBE when the anterograde portion was negative or yielded insufficient findings. However, it is possible that the endoscopist was more likely to terminate the retrograde procedure during 'combined' cases because of increasing patient intolerance caused by the increased duration of the 'combined' procedure in the setting of conscious sedation, which was used in over 95% of cases. Indeed, the total procedure time for both anterograde and retrograde DBE in 'combined' cases was 82 minutes compared to 59 minutes for 'distal-only' retrograde procedures. This suggests that the time devoted to the retrograde DBE during combined cases was likely less than that in 'distal-only' cases. Unfortunately, the lack of separate recordings of the procedure times for the anterograde and retrograde portions of 'combined' cases means that this question cannot be answered.

There are several additional limitations to this study, most notably its retrospective design and the absence from the database of potentially relevant variables that may have affected insertion depth such as abdominal surgical history.(8, 17)

In addition, the large proportion of our patients who underwent enteroscopy to evaluate the extent or activity of Crohn's disease may make this cohort a less representative example for comparison to other centers performing DBE. That being said, when the Crohn's disease patients are removed from the analysis and the remaining cohort is assessed separately (n=192), a similar pattern of findings was observed with significantly greater retrograde insertion depths of 120 cm (95% CI 98 – 142) in the 'distal-only' group compared to 100 cm (95% CI 81 – 108) in the 'combined' group (p=0.04), and a significantly increased corresponding diagnostic yield of 45% compared to 28% (p=0.04) respectively. Thus, the large proportion of Crohn's disease patients does not appear to alter the findings of this study.

In summary, our study shows that the insertion depth of retrograde DBE is significantly greater when carried out as a separate procedure and when performed using a diagnostic DBE endoscope. This increased retrograde depth of insertion tends to be associated with an increased overall diagnostic yield. Thus, we recommend that patients who require retrograde DBE have this done as a separate procedure and not on the same

day as a prior anterograde DBE, and suggest considering the use of a diagnostic rather than therapeutic DBE endoscope, unless the likelihood of therapeutic intervention is considered to be high.

REFERENCES

1. Yamamoto H, Kita H, Sunada K, Hayashi Y, Sato H, Yano T, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clinical Gastroenterology & Hepatology 2004;2:1010-1016.
2. May A, Färber M, Aschmoneit I, Pohl J, Manner H, Lotterer E, et al. Prospective Multicenter Trial Comparing Push-and-Pull Enteroscopy With the Single- and Double-Balloon Techniques in Patients With Small-Bowel Disorders. Am J Gastroenterol 2010;105:575-81.
3. Ell C, May A, Nachbar L, Cellier C, Landi B, di Caro S, et al. Push-and-pull enteroscopy in the small bowel using the double-balloon technique: results of a prospective European multicenter study. Endoscopy 2005;37:613-6.
4. May A, Nachbar L, Schneider M, Ell C. Prospective comparison of push enteroscopy and push-and-pull enteroscopy in patients with suspected small-bowel bleeding. Am J Gastroenterol 2006; 101:2016-24.
5. Gay G, Delvaux M, Fassler I. Outcome of capsule endoscopy in determining indication and route for push-and-pull enteroscopy. Endoscopy 2006;38:49-58.
6. Li X, Chen H, Dai J, Gao Y, Ge Z. Predictive role of capsule endoscopy on the insertion route of double-balloon enteroscopy. Endoscopy 2009;41:762-6.
7. Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy 2009;41:618-37.
8. Mehdizadeh S, Han NJ, Cheng DW, Chen GC, Lo SK. Success rate of retrograde double-balloon enteroscopy. Gastrointest Endosc 2007;65:633-9.
9. May A, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. Gastrointest Endosc 2005;62:62-70.
10. Di Caro S, May A, Heine DGN, Fini L, Landi B, Petruzziello L, et al. The European experience with double-balloon enteroscopy: indications, methodology, safety, and clinical impact. Gastrointest Endosc 2005;62:545-50.
11. Heine GD, Hadithi M, Groenen MJ, Kuipers EJ, Jacobs MA, Mulder CJ. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. Endoscopy 2006;38:42-8.
12. Mehdizadeh S, Ross A, Gerson L, Leighton J, Chen A, Schembre D, et al. What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. Gastrointest Endosc 2006;64:740-50.
13. Gross SA, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. center. Gastrointest Endosc 2008;67:890-7.
14. Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy 2008;40:11-5.
15. Ramchandani M, Reddy D, Gupta R, Lakhtakia S, Tandan M, Rao G, et al. Diagnostic yield and therapeutic impact of single-balloon enteroscopy: Series of 106 cases. Journal of Gastroenterology and Hepatology 2009;24:1631-8.

16. May A, Nachbar L, Schneider M, Neumann M, Ell C. Push-and-pull enteroscopy using the double-balloon technique: method of assessing depth of insertion and training of the enteroscopy technique using the Erlangen Endo-Trainer. Endoscopy 2005;37:66-70.

17. Khashab M, Helper D, Johnson C, Chiorean M. Predictors of Depth of Maximal Insertion at Double-Balloon Enteroscopy. Dig Dis Sci 2009;23:739-44.

18. Pasha SF, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2008;6:671-6.

19. Fry LC, Bellutti M, Neumann H, Malfertheiner P, Mönkemüller K. Incidence of bleeding lesions within reach of conventional upper and lower endoscopes in patients undergoing double-balloon enteroscopy for obscure gastrointestinal bleeding. Aliment Pharmacol Ther 2009;29: 342-9.

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Hyperamylasemia and pancreatitis after spiral enteroscopy

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ABSTRACT

Aims: To determine the incidence of pancreatitis and hyperamylasemia with spiral enteroscopy.

Background: Acute pancreatitis is a significant potential complication with double balloon enteroscopy (DBE). Hyperamylasemia is frequently observed after both DBE and single balloon enteroscopy (SBE) but often without associated pancreatitis. Whether the same phenomenon occurs with spiral enteroscopy is currently unknown.

Study methods: A prospective cohort study of consecutive patients undergoing proximal spiral enteroscopy was conducted. Serum amylase levels were measured immediately before and following the procedure, combined with observation for clinical signs of pancreatitis.

Results: 32 patients underwent proximal spiral enteroscopy with a mean total procedure time of 51 minutes (range 30 – 100) and depth of insertion of 240 cm (range 50 – 350). The diagnostic yield was 50%, with 31% of all procedures being therapeutic. While no patients exhibited signs that raised suspicion of pancreatitis, hyperamylasemia was common (20%). Hyperamylasemia was not significantly associated with procedure duration or depth of insertion but was linked to patients with Peutz-Jeghers syndrome and with the use of propofol sedation, suggesting that it may be more common in difficult cases.

Conclusions: Postprocedural hyperamylasemia occurs frequently with proximal spiral enteroscopy, while no associated pancreatitis was observed. This frequent finding suggests that hyperamylasemia may not necessarily reflect pancreatic injury nor portend a risk of pancreatitis.

INTRODUCTION

Spiral enteroscopy[1, 2] is the latest form of small bowel endoscopy to join the techniques of single balloon enteroscopy (SBE)[3] and double balloon enteroscopy (DBE)[4, 5] for the investigation of small intestinal diseases. Large series have been performed with DBE demonstrating that the most common, significant adverse events with the procedure are bleeding (0.2-0.8%), perforation (0.3-0.4%) and pancreatitis (0.2-0.3%).[6, 7] While considerable attention has focused on the occurrence of post-DBE pancreatitis, asymptomatic hyperamylasemia remains quite common.[8] In the first study reporting complications with SBE, there were no cases of pancreatitis but again hyperamylasemia was frequently encountered.[9] Currently, there are no published studies on complications with spiral enteroscopy, and the risks of pancreatitis and hyperamylasemia remain unknown. Thus, the aim of this study was to determine the incidence of pancreatitis and hyperamylasemia after proximal spiral enteroscopy.

MATERIALS AND METHODS

Study design

Consecutive patients undergoing proximal spiral enteroscopy at Erasmus MC University Medical Center, a tertiary referral university hospital in Rotterdam, The Netherlands, were prospectively included in the study after providing written informed consent. Demographic and clinical data were noted and the insertion depth, duration, sedation requirements, diagnostic and therapeutic outcomes, and adverse events were recorded. Blood samples were collected immediately prior and 2 – 4 hours following the proximal spiral enteroscopy procedure for measurement of serum amylase and C-reactive protein (CRP). All patients were clinically evaluated 2 – 5 hours after the procedure to assess for abdominal complaints that could be suggestive of pancreatitis. Any need for overnight hospital stay or readmission was noted. All patients were contacted the following day for evaluation of complaints. Referring physicians and/or general physician were asked to report adverse outcomes within 30 days of the procedure. The study was approved by the institutional review board of Erasmus MC University Medical Center.

Spiral enteroscopy procedure

Spiral enteroscopy was performed using the Discovery SB spiral overtube (Spirus Medical Inc.; Stoughton, Mass) in combination with either the Olympus SIF-Q160Y SBE endoscope (Olympus Optical Co., Tokyo, Japan) or the Fujinon EN-450P5 or EN-450T5 DBE endoscopes (Fujinon Inc., Saitama, Japan) without attached balloons. The spiral

overtube has raised helices at its distal end, a locking device to fix the overtube to the endoscope, and two foam handles at its proximal end to facilitate overtube rotation. Clockwise rotation of the spiral overtube acts in a similar manner to that of a screw, advancing the endoscope while pleating the bowel onto its surface.[1] The procedure was performed by two physicians: an endoscopist with considerable small bowel enteroscopy experience (P.M.) together with an advanced endoscopy fellow (C.T. or H.A). The endoscope was inserted into the proximal esophagus in the usual fashion, after which further advancement was achieved by rotation of the overtube by twisting of the foam handles. While the first operator rotated the overtube, the second operator steered the endoscope tip. Withdraw of the endoscope was achieved by counter-clockwise overtube rotation. The depth of insertion was estimated during endoscope withdrawal according to the previously described and accepted spiral enteroscopy method.[1, 2]

All patients had bowel preparation with 4 L of a polyethylene glycol solution and an overnight fast, which is the standard practice for small bowel enteroscopy at our institution due to our belief that improved mucosal views are obtained once deep insertion reaches the ileum. Most procedures were performed under conscious sedation (midazolam and fentanyl) while selected cases were done using anesthesia-administered propofol. Propofol was selected for cases expected to be prolonged or more difficult (e.g. multiple polypectomies in Peutz-Jeghers patients), as well as for cases performed during live endoscopy courses. With few exceptions, spiral enteroscopy was performed without prior capsule endoscopy, which is not performed at our center, and was chosen in favor of DBE or SBE according to the endoscopist's discretion. All procedures were performed on an outpatient basis.

Definition of hyperamylasemia and pancreatitis

Hyperamylasemia was defined as a twofold or greater increase in serum amylase (ratio of post-procedure to pre-procedure amylase ≥ 2) to a level exceeding the upper limit of normal (> 99 U/L). Clinical pancreatitis was defined according to the revised 2008 version of the Atlanta Classification of acute pancreatitis, which consists of typical abdominal pain strongly suggestive of acute pancreatitis, serum amylase at least three times greater than the upper limit of normal and/or characteristic findings of acute pancreatitis on contrast-enhanced CT scan.[10] Radiological imaging was not routinely performed in all patients but instead was reserved for cases when pancreatitis was suspected based on clinical grounds (abdominal pain with abnormal amylase between 100-299 U/L that was less than 3 times the upper limit of normal). An abnormal pre-procedure serum amylase of ≥ 100 U/L in combination with the absence of postprocedural abdominal pain was considered sufficient to exclude pancreatitis and suggest macroamylasemia. The normal values for serum amylase and CRP were 0 – 99 U/L and < 9 mg/L, respectively.

Statistical analysis

The statistical software Stata 10.1 (Stata Corp, College Station, Texas) was used to analyze the data. Means and ranges were used to summarize data for continuous variables and percentages were used to summarize data for categorical variables. Continuous data were compared using Student's t-test (with Welch's approximation to correct for unequal variances) while categorical data were assessed with the Chi-squared test. A two-sided p-value of < 0.05 was considered statistically significant. Univariate and multivariable logistic regression were planned but not performed because the number of positive outcomes was too low to draw reliable conclusions from that analysis.

RESULTS

Patient characteristics

Between November 2008 and March 2010, 32 patients underwent proximal spiral enteroscopy, with a mean age of 64 (range 32 – 86) years; 19 (59%) were females. The most common indications for small bowel enteroscopy were anemia (81%) and Peutz-Jeghers

Table 1. Clinical and endoscopic data

	Entire cohort (n=32)
Patient characteristics	
Age, years (range)	64 (32 – 86)
Female sex	19 (59%)
Indication for enteroscopy	
- *anemia*	26 (81%)
- *Peutz-Jeghers*	4 (13%)
- *other*[a]	2 (6%)
Enteroscopy data	
Conscious sedation	20 (63%)
Propofol sedation	12 (37%)
Insertion depth, cm (range)	240 (50-350)
Procedure time, min (range)	51 (30 – 100)
Diagnostic yield	16 (50%)
- *angiodysplasia*	7 (22%)
- *polyp(s)*	4 (13%)
- *tumor*	3 (9%)
- *ulcer(s)*	2 (6%)
Therapeutics[b]	10 (31%)

[a] Abdominal pain with abnormal imaging (n=2)

[b] Polypectomy (n=4; removed 24 polyps), argon plasma coagulation (n=6)

syndrome (13%); see Table 1. Two patients with anemia had undergone prior video capsule endoscopy, whereas two of the Peutz-Jeghers patients previously had DBE. None of the included patients had a medical history of acute or chronic pancreatitis. While 6 (19%) patients consumed ≥ 2 units of alcohol per week, no patient consumed more than 5 units.

Spiral enteroscopy procedure

The mean depth of insertion beyond the ligament of Treitz was 240 cm (range 50 - 350) with an average total procedure time of 51 (range 30 - 100) minutes. Conscious sedation was used for 20 (62%) while anesthesia-administered propofol was used in 12 (38%) patients. All Peutz-Jeghers syndrome patients received propofol, compared to 29% of the remaining cohort. The majority of patients (91%) underwent just the proximal procedure, with only 3 (9%) having both a proximal and a distal spiral enteroscopy. Among those 3 patients, total enteroscopy with complete visualization of the small bowel was not achieved. The proximal spiral enteroscopy was diagnostic in 50% of cases, identifying angiodysplasia in 7 (22%), polyps in 4 (13%), a tumor in 3 (9%), and ulcerations in 2 (6%) procedures. Spiral enteroscopy was therapeutic in 10 (31%) patients, with argon plasma coagulation used to treat angiodysplasia in 6 (19%) (performed when angiodysplasias were considered clinically significant, defined as "large" lesions or ones that bled when probed by a catheter) and polypectomy performed in 4 (13%) cases, removing a total of 24 polyps.

Hyperamylasemia and pancreatitis

Serum samples were taken at a mean of 175 (range 130 – 270) minutes after the spiral enteroscopy procedure. Two patients had an elevated amylase prior to the procedure, 101 and 112 U/L respectively, without any signs or symptoms suggestive of pancreatitis. Neither of these patients developed an elevation in serum amylase after the procedure greater than two times the baseline value, rising to 112 and 167 U/L respectively. Both were considered to have macroamylasemia and were excluded from subsequent analysis.

Six (19%) patients developed hyperamylasemia with a mean ratio of post- to pre-procedure amylase of 2.9 and a mean post-procedure amylase level of 210 (range 104 – 510) U/L, reflecting an average increase in amylase of 139 (range 56 – 403) U/L. These changes significantly exceeded those among the 24 (80%) patients without hyperamylasemia, who had a mean post-procedure amylase of 73 U/L ($p < 0.01$) and an average increase of only 21 U/L ($p < 0.01$). The mean CRP levels did not increase after the spiral procedures and did not differ significantly between patients with normal amylase and those with hyperamylasemia. Comparing the patient group with post-procedural hyperamylasemia

Table 2. Comparison of normal amylase and hyperamylasemia groups

	Normal amylase (n=24)	Hyperamylasemia (n=6)	p-value
Patient characteristics			
Age, years (range)	65 (32 – 86)	60 (34 – 83)	0.59
Female sex	15 (63%)	3 (50%)	0.58
Indication (anemia)	22 (92%)	3 (50%)	**0.01**
Enteroscopy data			
Conscious sedation	18 (75%)	1 (17%)	**0.01**
Propofol sedation	6 (25%)	5 (83%)	**0.01**
Insertion depth, cm (range)	233 (50 – 350)	250 (200 – 300)	0.43
Procedure time, min (range)	50 (30 – 100)	62 (30 – 80)	0.26
Diagnostic yield	11 (46%)	4 (67%)	0.36
Therapeutic yield	7 (29%)	3 (50%)	0.17
Serum measurements			
Amylase (U/L) (all range)			
Pre-procedure amylase	52 (28 – 98)	71 (27 – 113)	0.08
Post-procedure amylase	73 (28 – 130)	210 (104 – 510)	**<0.01**
Absolute Δ (Post – Pre)	21 (-3 – 44)	139 (56 – 403)	**<0.01**
Ratio Post-amylase/pre-amylase	1.4 (0.9 – 2.3)	2.9 (2.0 – 4.8)	**<0.01**
CRP (mg/L) (all range)			
- pre-procedure	17 (1 – 190)	5 (1 – 16)	0.17
- post-procedure	17 (1 – 206)	6 (1 – 20)	0.23
Clinical pancreatitis[a]	0	0	-

Data presented with percentages unless otherwise stated.
[a] Defined according to the revised (2008) Atlanta Classification for acute pancreatitis.

with the normal amylase group, the only significant differences were the indication for the procedure (p=0.01) and the type of sedation used (p=0.01) (hyperamylasemia was more likely with Peutz Jeghers patients and propofol sedation; normal amylase levels were more likely with anemia as the indication and conscious sedation). There were no significant differences in terms of demographic features or endoscopic outcomes, including both depth of insertion and procedure time (see Table 2). In addition, there was no significant linear relationship between the duration of the enteroscopy procedure and the subsequent change in serum amylase level (p=0.34).

There were no cases of acute pancreatitis. In fact, none of the patients experienced post-procedural abdominal pain that raised suspicion for possible pancreatitis and so no imaging studies were performed. Furthermore, no adverse events were recorded at follow-up.

DISCUSSION

Acute pancreatitis is a concerning potential complication with DBE. Large, multicenter, retrospective studies suggested the risk of pancreatitis after diagnostic DBE procedures was 0.2-0.3%.[6, 7, 11] Two prospective studies demonstrated a much higher frequency of hyperamylasemia (up to 50%) after DBE than the observed rate of pancreatitis (nearly 5%).[12, 13] This has been interpreted as evidence of a causative link between oral DBE, hyperamylasemia and pancreatic injury. However, multiple theories have been put forth speculating about the mechanism by which DBE leads to pancreatitis with no clear consensus.[14] Recently, we performed two prospective studies with DBE[8] and SBE[9] demonstrating that after modifying the insertion technique to delay balloon inflation until beyond the ligament of Treitz, the incidence of pancreatitis was very low; 0.7% and 0% for DBE and SBE respectively. However, hyperamylasemia remained relatively common, 17% and 16% for DBE and SBE respectively, although much less so compared to earlier reports.[12, 13] It is unclear if this persistent hyperamylasemia results from injury to the pancreas or if it is caused by other factors, such as local strain or mucosal injury to the small bowel itself.

In this current study, 20% of patients developed hyperamylasemia after proximal spiral enteroscopy, with no patients developing suggestive abdominal pain symptoms and no cases of pancreatitis. Interestingly, the development of hyperamylasemia was not associated with the duration of the procedure as has been suggested by previous DBE studies.[8, 13]. However, the development of hyperamylasemia was significantly associated with Peutz-Jeghers syndrome and with propofol sedation. Since propofol was specifically selected for cases anticipated to be more technically challenging and since Peutz-Jeghers patients each underwent multiple polypectomies (mean 6 polyps per patient), it is interesting to speculate that the development of hyperamylasemia may be more closely linked to *difficult* procedures, which may not necessarily be longer than other cases but may involve more strain on the pancreas or on the small bowel itself.

The present study has several limitations, chief among them its small sample size. We observed a high frequency of hyperamylasemia without associated pancreatitis, but the sample was insufficient to capture these events.

Indeed, only multicenter registry data are likely capable of identifying complications as infrequent as pancreatitis. In fact, a large, multicenter registry exists that has reported in abstract form the early experience with spiral enteroscopy, and found no cases of pancreatitis after 1750 spiral procedures.[15] While amylase levels were not reported, the absence of pancreatitis after such a considerable number of procedures implies that the

risk is low with spiral enteroscopy, and suggests that the hyperamylasemia observed in our study is not necessarily a harbinger of pancreatitis. A second notable limitation is our lack of measurement of serum lipase or fractionation of pancreatic and salivary amylase isoenzymes, which may have been useful for differentiating the origin of the elevated amylase. Even though other series examining DBE and hyperamylasemia have shown a strong correlation between serum amylase and lipase measurements,[12, 13] it is regrettable that these were not measured in our study to provide more definitive evidence regarding the source of hyperamylasemia.

Nevertheless, the findings of this study begin to shed more light on the etiology of hyperamylasemia observed after deep enteroscopy. Since the spiral method does not involve the inflation of balloons nor the same degree of stretching of the small bowel with repetitive insertion and shortening of the endoscope and overtube, a number of previously considered causative theories seem less likely given the persistent observation of hyperamylasemia after spiral enteroscopy. In particular, duodenal hypertension from balloon inflation,[16] mechanical strain on the pancreas from repetitive stretching of the endoscope and overtube,[17-19] irritation of the pancreatic sphincter from the inflation of the overtube balloon or compression of the sphincter from the back-and-forth movements of the overtube[20] seem much less likely. However, the suggestion of mechanical strain on the pancreas from the profound straightening of the duodenum at the ligament of Treitz,[11] as well as the ischemic vascular injury theory due to compression or stretching of the peri-pancreatic vessels[18, 20] remain. In addition, it is still possible that overtube-induced strain on the small bowel itself is responsible for the hyperamylasemia.[21]

In summary, this study is the first to report the incidence of hyperamylasemia after proximal spiral enteroscopy, being a frequent finding occurring after one-in-five procedures despite no cases of pancreatitis. Thus, we hypothesize that while DBE can clearly cause pancreatitis, patients who develop elevated amylase levels after deep enteroscopy do not necessarily have injury to the pancreas or elevated risk for pancreatitis. In fact, patients with significant abdominal pain after enteroscopy, even in the context of an elevated amylase, should first be evaluated for other, possibly more serious complications such as intestinal perforation before considering pancreatitis, particularly in light of reports of perforations resulting from spiral enteroscopy,[15, 22] and the growing realization that pancreatitis is an unlikely event for which hyperamylasemia may be a non-specific finding.

REFERENCES

1. Akerman PA, Agrawal D, Cantero D, et al. Spiral enteroscopy with the new DSB overtube: a novel technique for deep peroral small-bowel intubation. Endoscopy 2008;40:974-978.
2. Akerman PA, Agrawal D, Chen W, et al. Spiral enteroscopy: a novel method of enteroscopy by using the Endo-Ease Discovery SB overtube and a pediatric colonoscope. Gastrointest Endosc 2009;69:327-332.
3. Tsujikawa T, Saitoh Y, Andoh A, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy 2008;40:11-15.
4. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001;53:216-220.
5. Yamamoto H, Kita H, Sunada K, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clin Gastroenterol Hepatol 2004;2:1010-1016.
6. Mensink PBF, Haringsma J, Kucharzik T, et al. Complications of double balloon enteroscopy: a multicenter survey. Endoscopy 2007;39:613-615.
7. Gerson LB, Tokar J, Chiorean M, et al. Complications associated with double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol 2009;7:1177-1182.
8. Aktas H, Mensink PBF, Haringsma J, et al. Low incidence of hyperamylasemia after proximal double-balloon enteroscopy: has the insertion technique improved? Endoscopy 2009;41:670-673.
9. Aktas H, de Ridder L, Haringsma J, et al. Complications of single-balloon enteroscopy: a prospective evaluation of 166 procedures. Endoscopy 2010;42:365-368.
10. Acute Pancreatitis Classification Working Group. Revision of the Atlanta classification of acute pancreatitis (3rd revision) [Pancreas Club website]. April 9, 2008. Available at: www.pancreasclub.com/resources/AtlantaClassification.pdf. Accessed May 1, 2010.
11. Möschler O, May A, Müller MK, et al. Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. Endoscopy 2011;43:484-489.
12. Honda K, Itaba S, Mizutani T, et al. An increase in the serum amylase level in patients after peroral double-balloon enteroscopy: an association with the development of pancreatitis. Endoscopy 2006;38:1040-1043.
13. Kopácová M, Rejchrt S, Tachecí I, et al. Hyperamylasemia of uncertain significance associated with oral double-balloon enteroscopy. Gastrointest Endosc 2007;66:1133-1138.
14. Kopacova M, Tacheci I, Rejchrt S, et al. Double balloon enteroscopy and acute pancreatitis. World J Gastroenterol 2010;16:2331-2340.
15. Akerman PA, Cantero D. Severe complications of spiral enteroscopy in the first 1750 patients. Gastrointest Endosc 2009;69:AB127[abstract].
16. Groenen MJ, Moreels TG, Orlent H, et al. Acute pancreatitis after double-balloon enteroscopy: an old pathogenetic theory revisited as a result of using a new endoscopic tool. Endoscopy 2006;38:82-85.
17. Heine GD, Hadithi M, Groenen MJ, et al. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. Endoscopy 2006;38:42-48.

18. Matsushita M, Shimatani M, Uchida K, et al. Mechanism of acute pancreatitis after peroral double-balloon enteroscopy. Endoscopy 2007;39:480; author reply 481.

19. Jarbandhan SVA, Van Weyenberg SJB, van der Veer WM, et al. Double balloon endoscopy associated pancreatitis: a description of six cases. World J Gastroenterol 2008;14:720-724.

20. Lo SK, Simpson PW. Pancreatitis associated with double-balloon enteroscopy: how common is it? Gastrointest Endosc 2007;66:1139-1141.

21. Monkemuller K, Fry L, Malfertheiner P. Double-balloon enteroscopy: beyond feasibility, what do we do now? Endoscopy 2007;39:229-231.

22. Li X-B, Gu L-Y, Song Y, et al. Small-bowel perforation in a patient with Roux-en-Y anatomy for Peutz-Jeghers polyps after spiral enteroscopic investigation. Endoscopy 2011;43:E85.

7

General Discussion and Conclusions

The development of new techniques and technologies are necessary in order to continually advance the capabilities and performance of GI endoscopy. This is important because it may improve the medical care of patients with gastrointestinal ailments. To ensure that patient care benefits from innovations in endoscopy committed research efforts and ongoing, critical evaluations of current practices are required. In this thesis these issues were addressed with respect to colonoscopy and to small bowel endoscopy.

Magnetic imaging-assisted colonoscopy (MIC) is an innovative technology that utilizes electromagnetic coils embedded within the endoscope that are detected by an external receiver dish, resulting in the production of a three dimensional image of the shape of the endoscope while inside the patient's body, which is then projected onto a display monitor. This enables the endoscopist to directly identify the position of the endoscope tip as well as to visualize any loop formation that may hinder the advancement of the colonoscope. The hope was that a newly redesigned, second generation MIC would result in faster and more successful colonoscopy on the part of the endoscopist and a more comfortable and safe procedure for patients. In a prospective clinical trial (Chapter 2) in which patients were randomized to undergo MIC or conventional colonoscopy, no significant differences were observed in terms of procedural outcomes such as cecal intubation rate, time-to-cecum, endoscope insertion distance, or polyp detection rate, and no differences were seen with respect to patient comfort and sedation requirements, or with safety. Only amongst a subgroup of procedures self-rated by the endoscopist as difficult did any significant differences emerge, specifically with faster times-to-cecum for the MIC group. Nevertheless, the *a priori* hypothesis in this study was that MIC would improve technical performance and patient comfort for routine colonoscopy procedures in general, which is not supported by the findings. In fact, based on this study there appears to be little evidence to support the widespread, routine use of MIC, and certainly no justification to support the additional costs of adopting the technology. While there may exist an important role for using MIC for challenging or previously failed colonoscopy cases, this remains an hypothesis derived from subgroup analysis and requires further study on its own. In addition, while there are many theoretical benefits for using MIC to facilitate colonoscopy training for GI residents and fellows,[1] this question was not addressed by this study and so no conclusions can be drawn in this regard.

Despite various improvements in colonoscopy technology and technique, a proportion of procedures will invariably be incomplete, failing to successfully reach the cecum. This is a concerning problem, particularly in the context of colon cancer screening and polyp surveillance where complete colon examination is essential.[2] In recent years, double balloon endoscopy (DBE) and single balloon endoscopy (SBE) emerged as effective new technologies for enteroscopy deep into the small bowel.[3,4] In order to perform retro-

grade balloon-assisted enteroscopy up from the distal ileum, the DBE or SBE endoscope must first be completely advanced through the colon. This led to the idea that DBE could be used as a salvage method to enable the completion of colonoscopy in cases that had previously failed by conventional means, a concept that has been successfully demonstrated.[5] In this paper, SBE has now been shown (Chapter 3) to also be a feasible and safe technique for patients with previously failed colonoscopy, achieving outcomes similar to those in earlier studies regarding DBE colonoscopy. Complete colonoscopy to the cecum was achieved in 96% of cases using SBE, similar to completion rates of 88% - 100% seen with DBE.[6-8] However, it must be noted that balloon-assisted colonoscopy, whether with SBE or with DBE, is a more time consuming and laborious procedure compared to standard colonoscopy, with median procedure times of 30 minutes in our study. Thus, while most patients who have an incomplete colonoscopy can be safely "rescued" by using SBE or DBE, it takes longer to complete these cases with balloon assistance, although without need for deep sedation, unlike when DBE or SBE are performed for enteroscopy deep into the small bowel.

In the next section of this thesis, attention shifted from colonoscopy to the new techniques of small bowel endoscopy, which predominantly consist of capsule endoscopy (CE) and DBE, but also include the newer methods of SBE and spiral enteroscopy. The most frequent indication for small bowel endoscopy is for the investigation of obscure GI bleeding (OGIB) after negative esophagogastroduodenoscopy (EGD) and colonoscopy indicate that a GI bleeding source may be located within the small bowel.[9] In this paper, a meta-analysis was performed (Chapter 4) to determine whether a higher diagnostic yield is achieved by performing CE or DBE in these OGIB patients. The meta-analysis only included studies that had directly compared CE and DBE specifically for the evaluation of OGIB, and in this way differed from previous systematic comparisons of CE and DBE.[10,11] The data showed that CE and DBE have similar diagnostic yields for OGIB, 62% and 56% respectively, with a non-statistically significant higher odds ratio for CE compared to DBE of 1.39 (95% CI 0.88-2.20; p=0.16). Thus, both CE and DBE are equally likely to identify a bleeding source in patients with OGIB. However, two other important findings emerged from this study. The first was that the yield for DBE performed after a previously positive CE (75%) was substantially higher than that for DBE performed in all OGIB patients (p=0.02), and that the yield for DBE after a negative CE (28%) is much lower. While this makes intuitive sense, it provides further rationale for the argument that in most patients, small bowel investigations for OGIB should begin with CE, since doing so optimizes the performance of the highly invasive and time consuming DBE procedure by selecting the patients most likely to benefit.

The second point was that DBE performed after a normal CE identified a bleeding source in more than one-fourth of patients. This means that when clinical suspicion remains

high or if bleeding reoccurs, further small bowel investigations should be considered even after a negative CE.

Optimizing the performance of retrograde DBE was the subject of the next section of this paper (Chapter 5). In particular, the technical performance of retrograde DBE was compared between combined bi-directional cases, in which the retrograde procedure immediately followed anterograde DBE, and uni-directional cases, in which retrograde DBE was performed solely on its own. The study demonstrated that significantly increased endoscope insertion depth above the ileocecal valve was achieved when retrograde DBE was performed in isolation rather than as part of a combined procedure, with a trend toward a corresponding increase in diagnostic yield. Furthermore, regression analysis suggested that greater distal insertion was achieved when using the narrower caliber diagnostic rather than larger therapeutic endoscope. The results from this study provide useful information that may lead to more effective and efficient performance of distal DBE, suggesting that in most circumstances, retrograde DBE should be performed by itself as an isolated, uni-directional procedure rather than as part of a bi-directional procedure that follows anterograde DBE. Furthermore, when maximal insertion depth into the distal small bowel is desired and therapeutic interventions are considered unlikely, a diagnostic rather than a therapeutic enteroscope should be considered.

There is a relative paucity of data available for spiral enteroscopy, the newest version of overtube-assisted small bowel endoscopy. In fact, only a small number of studies have been published, contributing to a relatively limited understanding of endoscopic procedural outcomes, long-term clinical outcomes, and safety using this new endoscopic device. Thus, while many studies have characterized the adverse event profile associated with DBE,[12-14] none have done the same for spiral enteroscopy. In particular, the risk of acute pancreatitis is well documented following DBE, as well as the much higher incidence of significant elevation of serum amylase.[15,16] The final study included in this paper examined the risk of acute pancreatitis and hyperamylasemia following anterograde spiral enteroscopy (Chapter 6). While no cases of acute pancreatitis were observed, the incidence of hyperamylasemia remained high at 20%. This mirrors the increasingly common observation that significant elevations of serum amylase occur with many forms of overtube-assisted small bowel endoscopy without associated pancreatitis,[17] raising the possibility that hyperamylasemia in the context of small bowel endoscopy may not necessarily represent pancreatic injury nor portend risk for acute pancreatitis.

On other hand, it is equally possible that hyperamylasemia reflects subclinical pancreatitis, and so ongoing vigilance remains necessary regarding the possibility of this serious complication. While no case of acute pancreatitis following spiral enteroscopy

has been reported to date by this or by other studies, this may simply be a function of insufficient sample size. Only time will tell whether the different mechanism of insertion with spiral enteroscopy (rotation of raised helices on the overtube leading to progressive movement) compared to that with DBE and SBE (push-and-pull cycles associated with successive inflation and deflation of balloons) is somehow protective against acute pancreatitis. This question is particularly difficult to answer since the mechanism of acute pancreatitis in DBE has never been clearly determined.[18,19]

GENERAL CONCLUSION

This thesis examined innovation and best practices in endoscopy, first with respect to colonoscopy, and second in regards to small bowel endoscopy. The findings from the included studies provide useful information that may help improve the practice of endoscopy. The thesis makes clear that critical evaluation of existing practices and scrutiny of new technologies is essential on a widespread scale and on an ongoing basis, in order to maximize the capabilities and performance of GI endoscopy. I hope that I may continue to contribute to these efforts throughout my career in Gastroenterology.

REFERENCES

1. Kaltenbach T, Leung C, Wu K, Yan K, Friedland S, Soetikno R. Use of the colonoscope training model with the colonoscope 3D imaging probe improved trainee colonoscopy performance: a pilot study. Dig Dis Sci. 2011 May;56(5):1496–502.
2. Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2002. pp. 1296–308.
3. Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc. 2001 Jan 31;53(2):216–20.
4. Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy. 2008;40(1):11–5.
5. Delvaux M, Gay G. Novel applications of balloon endoscopy. Gastrointestinal endoscopy clinics of North America. 2009 Jun 30;19(3):509–18.
6. Pasha S, Harrison M, Das A, Corrado C, Arnell K, Leighton J. Utility of double-balloon colonoscopy for completion of colon examination after incomplete colonoscopy with conventional colonoscope. Gastrointest Endosc. 2007 Apr 30;65(6):848–53.
7. Gay G, Delvaux M. Double-balloon colonoscopy after failed conventional colonoscopy: a pilot series with a new instrument. Endoscopy. 2007 Aug 31;39(9):788–92.
8. Moreels T, Macken E, Roth B, Van Outryve M, Pelckmans P. Cecal intubation rate with the double-balloon endoscope after incomplete conventional colonoscopy: A study in 45 patients. J Gastroenterol Hepatol. 2010;25(1):80–3.
9. Raju GS, Gerson L, Das A, Lewis B, American Gastroenterological Association. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. Gastroenterology. 2007 Oct 31;133(5):1697–717.
10. Chen X, Ran Z-H, Tong J-L. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. World J Gastroenterol. 2007 Aug 27;13(32):4372–8.
11. Pasha SF, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol. 2008 May 31;6(6):671–6.
12. Mensink PBF, Haringsma J, Kucharzik T, Cellier C, Pérez-Cuadrado E, Mönkemüller K, et al. Complications of double balloon enteroscopy: a multicenter survey. Endoscopy. 2007 Jun 30;39(7):613–5.
13. Gerson LB, Tokar J, Chiorean M, Lo S, Decker GA, Cave D, et al. Complications associated with double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol. 2009 Oct 31;7(11):1177–82, 1182.e1–3.
14. Möschler O, May A, Müller MK, Ell C, German DBE Study Group. Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. Endoscopy. 2011 Jun;43(6):484–9.

15. Honda K, Itaba S, Mizutani T, Sumida Y, Kanayama K, Higuchi N, et al. An increase in the serum amylase level in patients after peroral double-balloon enteroscopy: an association with the development of pancreatitis. Endoscopy. 2006 Sep 30;38(10):1040–3.

16. Kopacova M, Rejchrt S, Tacheci I, Bures J. Hyperamylasemia of uncertain significance associated with oral double-balloon enteroscopy. Gastrointest Endosc. 2007 Nov 30;66(6):1133–8.

17. Aktas H, de Ridder L, Haringsma J, Kuipers EJ, Mensink PB. Complications of single-balloon enteroscopy: a prospective evaluation of 166 procedures. Endoscopy. 2010 Apr 30;42(5):365–8.

18. Matsushita M, Shimatani M, Uchida K, Okazaki K. Mechanism of acute pancreatitis after peroral double-balloon enteroscopy. Endoscopy. 2007;39(5):480.

19. Shibuya T, Osada T, Nomura O, Fukuo Y, Watanabe S. The Origin of Hyperamylasemia Associated With Peroral Double-Balloon Endoscopy. J Clin Gastroenterol. 2012;46(10):888–9.

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Curriculum Vitae

Christopher Teshima was born on February 22, 1977 in Calgary, Canada. He attended the University of Calgary from 1995 to 1999 and was awarded a Bachelor of Science in Biological Sciences. He then went to medical school at the University of Toronto and received a Doctor of Medicine in 2003. From 2003 to 2006, he remained at the University of Toronto and undertook residency training in Internal Medicine at Toronto General Hospital, Mt. Sinai Hospital and St. Michael's Hospital. Then from 2006 to 2008, he received subspecialty residency training in Gastroenterology at the University of Alberta. He completed his Royal College of Physicians of Canada qualifying exams for Internal Medicine in 2007 and for Gastroenterology in 2008. In 2008 he was awarded a Canadian Institute of Health Research/Canadian Association of Gastroenterology research fellowship and began work on a Masters of Science in Clinical Epidemiology that he was ultimately awarded several years later in 2012. In the meantime, he came to Erasmus MC University Medical Center in 2009 - 2010 and undertook a fellowship in advanced endoscopy under the mentorship of Professor Ernst Kuipers, receiving endoscopy training under the supervision of Drs. Marco Bruno, Jan-Werner Poley, Jelle Haringsma and Peter Mensink. While in Rotterdam, he developed an interest in endoscopy research and began work eventually leading to this thesis. After completing his endoscopy training at Erasmus MC, he returned to Edmonton, Canada in September 2010 and for the past 3 years has been appointed as an Assistant Professor in the Division of Gastroenterology at the University of Alberta Hospital.

PhD Portfolio

Oral Presentations

Erasmus live endoscopy conference
Erasmus MC live endoscopy, Rotterdam, the Netherlands – 2010

Advances in therapeutic endoscopy
Gastroenterology rounds, University of Alberta Hospital, Edmonton, Canada – 2010

Small bowel imaging
Canadian Digestive Diseases Week, Vancouver, Canada – 2011

Endoscopic RCT's that will change practice
DDW Review Course, Lake Louise, Canada – 2011

Introduction to endoscopic ultrasound
Canadian Society of Gastrointestinal Nurses & Associates meeting, Edmonton, Canada – 2012

Imaging of the small and large bowel: when to consider radiology vs. endoscopy
GI Update Course, Edmonton, Canada – 2012

Endoscopic options for mid-gut Crohn's disease
General Surgery and Gastroenterology combined rounds, Edmonton, Canada – 2012

Advances in therapeutic endoscopy
University of Alberta telehealth rounds, Edmonton, Canada – 2012

Asymptomatic first-degree relatives of Crohn's patients display endoscopic small intestinal lesions independent of their gut permeability status
Digestive Diseases Week, San Diego, California, U.S.A. – 2012

GI endoscopy emergencies
Canadian Digestive Diseases Week, Victoria, Canada – 2013

Diagnosis and management of obscure GI bleeding
Canadian Digestive Diseases Week, Victoria, Canada – 2013

Poster Presentations

Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis.
Digestive Diseases Week, New Orleans, Louisiana, U.S.A. – 2010

Single-balloon assisted colonoscopy in patients with previously failed colonoscopy.
Digestive Diseases Week, New Orleans, Louisiana, U.S.A. – 2010

Hyperamylasemia and pancreatitis after spiral enteroscopy.
Canadian Digestive Diseases Week, Vancouver, Canada – 2011

Prospective assessment of the Rosemont classification criteria for the diagnosis of chronic pancreatitis by endoscopic ultrasound.
Digestive Diseases Week, Chicago, Illinois, U.S.A. – 2011

Scopeguide-assisted colonoscopy vs. conventional colonoscopy for improved endoscopic performance and enhanced patient experience.
Canadian Digestive Diseases Week, Montreal, Canada – 2012

Early experience using a new core EUS biopsy needle for the diagnosis of solid mass lesions.
Canadian Digestive Diseases Week, Montreal, Canada – 2012

Crohn's disease genotype is similar between patients who sustain a long-term remission and those who rapidly relapse after discontinuing infliximab.
Canadian Digestive Diseases Week, Montreal, Canada – 2012

Increased intestinal permeability among first-degree relatives of Crohn's patients is not associated with increased mucosal ulcerations on small bowel video capsule endoscopy.
United European Gastroenterology Week, Amsterdam, Netherlands – 2012

Magnetically guided colonoscopy vs. conventional colonoscopy for improved endoscopic performance and enhanced patient experience.
United European Gastroenterology Week, Amsterdam, Netherlands – 2012

EUS-guided biopsy of solid mass lesions using a 25-gauge core biopsy needle.
Canadian Digestive Diseases Week, Victoria, Canada – 2013

Memberships

2008 – Canadian Association of Gastroenterology
2009 – American College of Gastroenterology
2009 – American Gastroenterological Association
2009 – American Society of Gastrointestinal Endoscopy
2010 – Alberta Society of Gastroenterology
2010 – Gastroenterology residency admissions committee
2012 – Small bowel endoscopy program lead - University of Alberta Hospital
2013 – Endoscopy research lead - University of Alberta Hospital
2013 – Director, Therapeutic endoscopy training program - University of Alberta

Supervision of trainee projects

Ali Kohansal, therapeutic endoscopy fellow, University of Alberta
Large colorectal polyp removal by endoscopic mucosal resection: an outcome analysis.

Samson Haimanot, therapeutic endoscopy fellow, University of Alberta
Clinical outcomes of palliative stenting for malignant biliary obstruction.

Penny D'Souza, GI subspecialty resident, University of Alberta
ProCore needle biopsy vs. conventional FNA for EUS-guided tissue acquisition of solid lesions.

List of Publications

1. Teshima C, Fedorak RN. Are there differences in type, dosage and method of administration for the systemic steroids in IBD treatment? Inflammatory Bowel Diseases 2008;14(Suppl 2):S216-218.

2. Teshima CW, Meddings JB. The measurement and clinical significance of intestinal permeability. Current Gastroenterology Reports 2008;10:443-449.

3. Teshima CW, Thompson A, Dhanoa L, Dieleman L, Fedorak RN. Long-term response rates to infliximab therapy for Crohn's disease in an outpatient cohort. Canadian Journal of Gastroenterology 2009;23:348-352.

4. Teshima CW, Aktas H, Haringsma J, Kuipers EJ, Mensink PB. Single-balloon assisted colonoscopy in patients with previously failed colonoscopy. Gastrointestinal Endoscopy 2010;71:1319-23.

5. Waugh AW, Garg S, Matic K, Gramlich L, Wong C, Sadowski DC, Millan M, Bailey R, Todoruk D, Cherry R, Teshima CW, Dieleman L, Fedorak RN. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. Alimentary Pharmacology & Therapeutics 2010;32:1129-34.

6. Teshima CW, Poley JW. Endoscopic ultrasonography. Endoscopy 2010;42:944-49.

7. Loomes DE, Teshima C, Jacobs P, Fedorak R. Health care resource use and costs for Crohn's disease before and after infliximab therapy. Canadian Journal of Gastroenterology 2011;25:497-502.

8. Teshima CW, Aktas H, van Buuren H, Kuipers EJ, Mensink PB. Retrograde double balloon enteroscopy: comparing performance of solely retrograde versus combined same-day anterograde and retrograde procedure. Scandinavian Journal of Gastroenterology 2011;46:220-26.

9. Teshima CW, Kuipers EJ, Veldhuyzen van Zanten S, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. Journal of Gastroenterology and Hepatology 2011;26:796-801.

10. Teshima CW, Mensink PB. Small bowel endoscopy. Endoscopy 2011;43:38-41.

11. Lu C, Waugh A, Bailey RJ, Cherry R, Dieleman LA, Gramlich L, Matic K, Millan M, Kroeker KI, Sadowski D, Teshima CW, Todoruk D, Wong C, Wong K, Fedorak RN. Crohn's disease

genotypes of patients in remission vs relapses after infliximab discontinuation. World J Gastroenterol 2012;18:5058-5064.

12. Teshima CW, May G. Small bowel enteroscopy. Canadian Journal of Gastroenterology 2012;26:269-275.

13. Teshima CW, Bridges RJ, Fedorak RN. Canadian Digestive Health Foundation Public Impact Series 5: Pancreatitis in Canada. Incidence, prevalence, and direct and indirect economic impact. Canadian Journal of Gastroenterology 2012;26:544-545.

14. Teshima CW, Aktas H, Kuipers EJ, Mensink PB. Hyperamylasemia and pancreatitis after spiral enteroscopy. Canadian Journal of Gastroenterology 2012;26:603-606.

15. Teshima CW, Dieleman LA, Meddings JB. Abnormal intestinal permeability in Crohn's disease pathogenesis. Annals of the New York Academy of Sciences 2012;1258:159-165.

16. Teshima CW. Small bowel endoscopy for obscure GI bleeding. Best Practice & Research Clinical Gastroenterology 2012;26:247-261.

17. D'Souza P, Girgis S, Teshima CW. Challenges in the diagnosis of Enteropathy Associated T-Cell Lymphoma. Canadian Journal of Gastroenterology 2013;27:255-256.

18. D'Souza P, Sandha G, Teshima CW. Refractory bleeding from a malignant duodenal ulcer treated with placement of a fully-covered gastroduodenal stent. Dig Dis Sci 2013 [available early online].