ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 September 16; 8(17): 572-634

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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2014-2017

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World Journal of Gastrointestinal Endoscopy

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Monthly Volume 8 Number 17 September 16, 2016

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 17 September 16, 2016

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
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World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
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8226 Regency Drive,
Pleasanton, CA 94588, USA
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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
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World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i17.572

World J Gastrointest Endosc 2016 September 16; 8(17): 572-583
ISSN 1948-5190 (online)

REVIEW

Current role of capsule endoscopy in Crohn's disease

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Conflict-of-interest statement: The authors declare that they have no conflicts of interest (including to commercial, personal, political, intellectual or religious interests). No financial support.

Manuscript source: Invited manuscript

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Received: April 13, 2016
Peer-review started: April 16, 2016
First decision: May 19, 2016
Revised: May 25, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: September 16, 2016

Abstract

Capsule endoscopy (CE) currently plays an important role in Crohn's disease (CD). It is a noninvasive technique that has led to a breakthrough in the endoscopic diagnosis of diseases of the small intestine. Its superior diagnostic performance and excellent safety profile lead to its considerable acceptance on the part of the patient. This paper reviews current indications of CE in three stages of clinical practice: Suspected CD, unclassified colitis and its extensive role in diagnosed CD. The diagnostic and therapeutic impact of the results of CE on the monitoring of this disease is also reviewed. Knowledge of its applications, the interpretation of its results in an appropriate context and the existence of a validated endoscopic activity index could change the way in which these patients are managed. The definition of mucosal healing and postoperative recurrence by means of endoscopic scoring systems will endow CE with new applications in the management of CD in the near future.

Key words: Capsule endoscopy; Inflammatory bowel disease; Crohn's disease

Core tip: We expose current indications and practical uses of capsule endoscopy in Crohn's disease based on the most relevant published evidence. Likewise, we describe the diagnostic and therapeutic impact on this disease and an exhaustive summary of where it plays an extensive role.

Luján-Sanchis M, Sanchis-Artero L, Larrey-Ruiz L, Peño-Muñoz L, Núñez-Martínez P, Castillo-López G, González-González L, Boix Clemente C, Albert Antequera C, Durá-Ayet A, Sempere-Garcia-Argüelles J. Current role of capsule endoscopy in Crohn's disease. *World J Gastrointest Endosc* 2016; 8(17): 572-583 Available from: URL: http://www.wjgnet.com/1948-5190/full/

v8/i17/572.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.572

INTRODUCTION

Early diagnosis of inflammatory bowel disease (IBD) is crucial, as the progression of inflammatory activity leads to irreversible damage[1-4]. There is currently no test for the diagnosis of Crohn's disease (CD)[5,6]; therefore, the techniques used must be interpreted in the appropriate context[7]. Since its approval by the Food and Drug Administration (FDA) in 2001, capsule endoscopy (CE) has revolutionized the diagnostic imaging of diseases of the small bowel (SB). The endoscopic capsule is a small instrument that takes hundreds of photographs while moving naturally with intestinal movements, thus facilitating direct, noninvasive visualization of the intestinal mucosa. CE is currently the most important indicator of CD in children between 10 and 18 years age[8,9]; in adults and young children, its importance as an indicator is second only to bleeding of unknown origin[8].

This review presents the principal indications of CD based on the available evidence[10-17] in three scenarios: Suspected CD (SCD), unclassified colitis (UNC) and diagnosed CD (DCD). This is the best procedure for viewing mucosal lesions attributable to CD in the SB[11] and of identifying superficial lesions that go unnoticed by other endoscopic and radiological techniques[7,11,14,18-20].

These characteristics establish its indication as the technique of choice in the evaluation of the SB with CD in the absence of stenosis or fistulas[14,21], and particularly when it will lead to a change in patient management[6,10,14,15].

DIAGNOSTIC CRITERIA FOR CD USING CE

Lesions consistent with CD should be described according to a structured and standardized terminology called Capsule Endoscopy Structured Terminology, which was described in 2005[22]. The terminology is based on the presence of stenosis, ulcers, erosions, cankers, pseudopolyps and fistulas (Figure 1), and it enables the use of a common language to interpret lesions consistent with CD. These lesions are not specific; therefore, other diseases with the same endoscopic features (infections, ischemia, vasculitis, iatrogenesis, tumors, lymphoma and Behcet's disease, among others) need to be ruled out. Other lesions such as erythema, nodularity, denudation or petechiae are not considered to be related to inflammation of the mucous membranes. Most studies have used the diagnostic criteria for CD by means of CE, defined by Mow *et al*[23] in 2004, as the existence of more than three diffuse or multiple ulcerations when nonsteroidal anti-inflammatory drugs (NSAIDs) are not being taken. This criterion provides a sensitivity (S) of 77%, specificity (SP) of 89%, positive predictive value (PPV) of 55% and a negative predictive value (NPV) of 96% for the diagnosis of CD in relation to clinical, endoscopic, radiological and histological findings. The rate of mucosal lesions missed by CE is minimal (0.5%); therefore, CD can be excluded after two years of monitoring[24].

Other authors have described criteria used less commonly in clinical practice such as the presence of multiple aphthous or erosive lesions (> 10), whether distributed continuously or discontinuously[25], or the presence of four or more ulcers, erosions, or a region with exudate, hyperemia and edema[26].

The current guidelines of both ASGE[27] and ECCO[14] recommend the use of two endoscopic indices that quantify the inflammatory activity of the CD by means of CE. Both have been prospectively validated[28,29] and enable the objective assessment of severity of the disease. They focus more on the presence or absence of inflammatory activity than on its extent and location. The first is the Niv or Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score (Table 1), which was published by Gal *et al*[30] and defines the size of ulcers and the extent of inflammation and stenosis, dividing the SB into two segments, proximal and distal. The total score (from 0 to 36) is the sum of both segments. The CECDAI does not have a specific threshold; however, an increase in its value indicates more severe mucosal inflammation.

The second is the Lewis score described in 2008 by Gralnek *et al*[31] (Table 2). It divides the SB into three equal parts and also quantifies the edema of the villi, the ulcer and the stenosis. A score of < 135 indicates a normal mucosa or insignificant inflammation, a score of between 135 and 790 represents mild inflammation, and a score of $\geqslant$ 790 represents moderate or severe inflammation[32]. This index has been more widely used in clinical practice than the CECDAI, because there is an automatic calculation tool in a CE reading program (Rapid Reader® workstation of PillCam® capsules). It has been demonstrated that, the more lesions that are detected, the greater the endoscopic score and the more specific the diagnosis of CD by means of CE[33]. Similarly, with a Lewis score of < 135, the probability of it being a case of CD is unlikely[29,32,34]. In healthy patients (who do not take NSAIDs, have not had an intestinal resection, and do not have ankylosing spondylitis or digestive symptoms), only 9% may exhibit mucosal lesions similar to CD, and in all cases, the Lewis score would indicate mild activity (< 450)[33].

It is important to remember that the endoscopic findings themselves are not diagnostic of CD, and there is no cutoff value above which the diagnosis can be firmly established[35]. Moreover, endoscopic activity shows no correlation with the clinical evidence; consequently, in a symptomatic patient, CE detects lesions in only half of the cases[36,37] and conversely, when the patient is in clinical remission (Crohn's disease activity index < 150), CE will show signs of inflammation in 62%[38]. This means that, once the objective assessment of CD activity has been performed by means of CE, decisions can be made regarding the management of the patient.

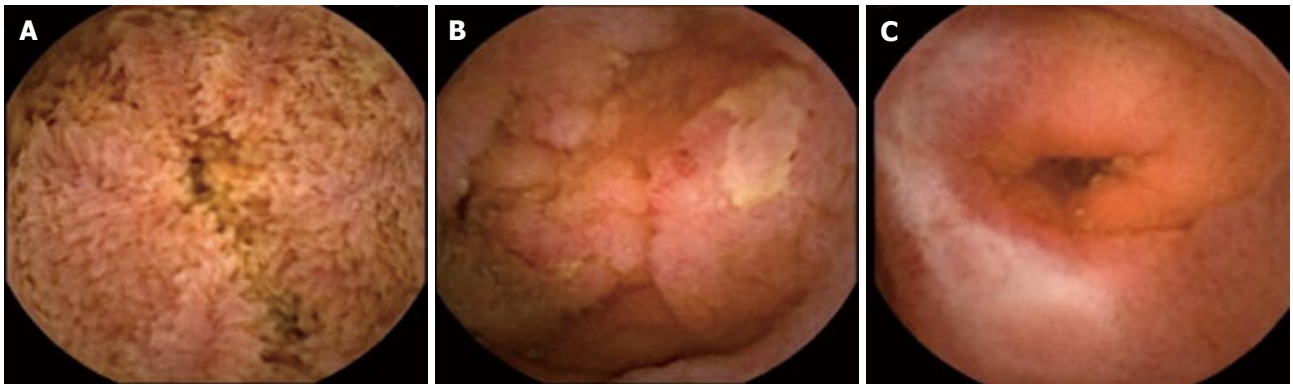

Figure 1 Lesions compatible with Crohn's disease by capsule endoscopy. A: Edema; B: Ulcers; C: Strictures.

Table 1 Capsule endoscopy Crohn's disease activity index

Inflammation score
0: None
1: Mild to moderate edema/hyperemia/denudation
2: Severe edema/hyperemia/denudation
3: Bleeding, exudate, aphtha, erosion, small ulcer (< 0.5 cm)
4: Moderate ulcer (0.5-2 cm), pseudopolyp
5: Large ulcer (> 2 cm)
Disease extension score
0: No disease - normal exploration
1: Focal disease (single segment involvement)
2: Patchy disease (2-3 segments involved)
3: Diffuse disease (> 3 segments involved)
Stricturing score
0: None
1: Single - passed
2: Multiple - passed
3: Obstructing (not passed)
Segmentary score (proximal or distal): (A × B) + C
Total score: Proximal [(A × B) + C)] + distal [(A × B) + C]

Table 2 Lewis score for mucosal inflammatory changes

Lesions in the proximal, mid, and distal small bowel thirds
Villous appearance
0: Normal
1: Edema
8: Short segment
12: Long segment; 20: The whole third
1: Single; 14: Patchy
Ulcers
0: None; 3: One; 5: Few; 10: Multiple
5: Short segment; 10: Long segment; 15: The whole third
9: 1/4; 12: 1/4-1/2; 18: > 1/2
Strictures
0: None; 14: One
2: Non ulcerated; 24: Ulcerated
7: No retention; 10: Capsule retention
Score calculation: Stricture score is added to the sum total for highest scoring villous edema and segment ulcers

INDICATIONS OF CE IN SUSPECTED CD

There is no gold standard for the diagnosis of CD; therefore, all techniques are complementary and should be interpreted with an appropriate degree of skepticism. Thus, CE and enteroscopy are useful for the early diagnosis and assessment of the extent and activity of the disease; radiology is better for studying the progression of damage and extraintestinal complications; and serological and fecal markers of inflammation are generally used to decide on the indication of radiological and endoscopic techniques. The selection of these will depend on the availability at the center, operator experience, its practical usefulness and cost[39].

The appropriate indication of CE for SCD was defined at the International Conference on CE through the selection of the following criteria: Existence of consistent symptoms, associated or not associated with extraintestinal manifestations and laboratory and/or radiological abnormalities[7]. In these cases, an ileocolonoscopy (IC) with biopsies should be performed, and regardless of the outcome, it would be advisable to assess the proximal extension of the disease into the stomach and/or intestine for its prognostic implications[5,14,15,27,40].

CE is the diagnostic technique of first resort when the IC and radiology are negative or inconclusive[14,15,27,41], because it detects subtle inflammatory changes that go unnoticed by radiological techniques or are unachievable by conventional endoscopy (Figure 2)[42,43]. Thus, two broad meta-analyses[44,45] show that its performance in cases of SCD is superior to that of IC, barium follow-through examinations (BFT) and computerized tomography (CT) at 22%, 32% and 47%, respectively. Faced with lesions consistent with CD, enteroscopy may be useful for taking biopsies, but its routine performance is not indicated according to the ASGE[27] and ECCO[14] guidelines.

The capsule's diagnostic performance with respect to CD varies as a function of how early the disease is suspected as well as the extension, activity and distribution of the disease[46,47]. The findings of CE have diagnostic value when they are interpreted with an adequate degree of skepticism. Overall performance is higher when additional data besides clinical evidence such as intestinal manifestations and/or serum or fecal markers of inflammation[7,14,26,32,48-50], are presented. Thus, when the disease is suspected based on one criterion, CE shows mild activity, and the diagnosis is confirmed in 20% of cases; however, when it is based on three criteria, activity will be more severe, and the

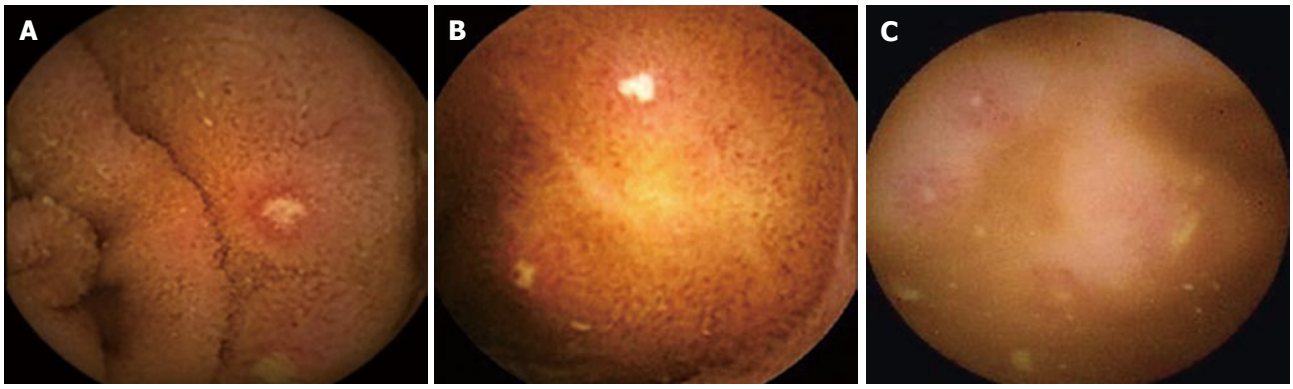

Figure 2 Aphthous erosions detected by capsule endoscopy. A: Aphtha; B: Surface erosion; C: Aphthoid erosions. The capsule may detect superficial intestinal lesions in a patient with Crohn's disease that are overlooked by radiographic techniques and inaccessible to ileocolonoscopy.

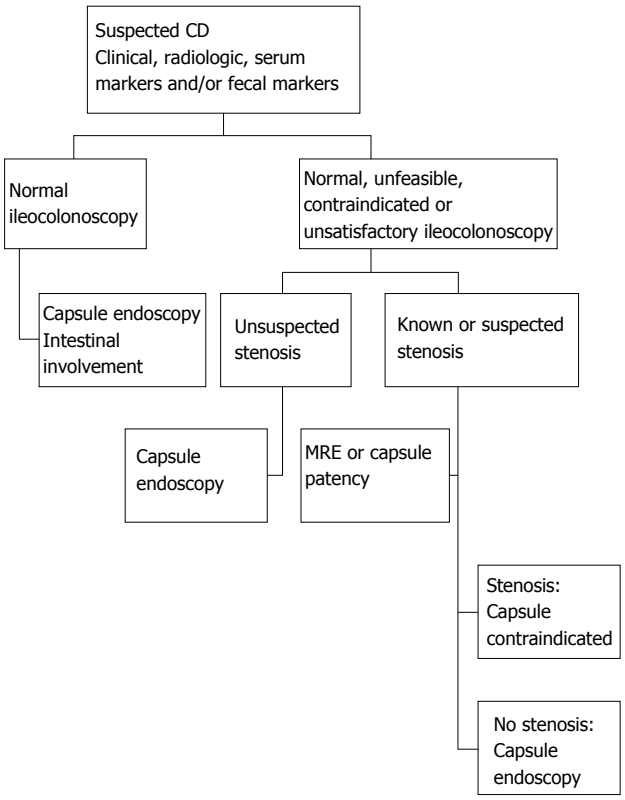

Figure 3 A diagnostic protocol for suspected Crohn's disease[127]. When CD is suspected ileocolonoscopy should be the first study to be performed, with capsule endoscopy ensuing when results are normal, unsatisfactory or not are achieved Ileoscopy. If intestinal stenosis is suspected, a test capsule should be used to confirm the feasibility of capsule endoscopy. CD: Crohn's disease; MRE: Enterography with nuclear magnetic resonance.

diagnosis is confirmed in 80%[32]. In accordance with the above, Figure 3 sets out a proposal to focus on the diagnosis of SCD.

INDICATIONS OF CE FOR DIAGNOSED CD

In the context of DCD, the indication of CE should be considered when providing for a change in the management of the disease[6,10,11,40]. It has been demonstrated that the investigation of proximal extension into the SB using CE has prognostic and therapeutic implications in disease progression[14,51]. Therefore, given its superior diagnostic performance in DCD (85.7%), its findings can influence a change in the management and clinical follow-up for 64% of these patients[52].

As with SCD, several meta-analyses[44,45] show that performance in cases of DCD is superior to that of push enteroscopy, BFT and CT at 57%, 38% and 32% respectively. The identification of mucosal lesions in the SI is better than with BFT (78% *vs* 32%) and can be better than enterotomography (ETC) (68% *vs* 38%) or enterography with nuclear magnetic resonance (MRE) (93% *vs* 79%), although the clinical significance of these differences is not defined in prospective studies. The primary role of CE in cases of DCD is when there are symptoms or signs which cannot be explained by the normal or inconclusive result of radiology and/or IC, as it can detect lesions between the duodenum and terminal ileum which are inaccessible with conventional endoscopy or imperceptible with radiology which substantiate the clinical picture[14,40,53]. The applications of CE for DCD in habitual clinical practice are set out below.

Investigation of the extent of CD

Currently, at the time of the initial diagnosis of CD, it is advisable to assess the extent throughout the entire gastrointestinal tract[14,54]. The SB is affected in 80% of patients with CD[51]. In general, in more than half of the patients with ileal CD, the proximal SB is also involved, with the most frequent distribution being in the proximal ileum (67%) followed by the proximal jejunum (53%) and/or proximal duodenum (32%)[36,55]. After the entire SB was able to be accessed with CE, it was observed that this location could coexist with the ileal and the colonic. Therefore, the Vienna classification was replaced by Montreal in 2005, adding the involvement of the upper digestive tract through to the proximal ileum (that which is called L4)[56] to the rest of the locations. The advantage of the phenotypic classification of DCD using the Montreal classification is important for predicting the progression of the disease and the selection of the best management strategy.

Flamant *et al*[51] found that jejunal (L4) involvement was 40% when the ileum (L1) was affected and 12%

when the colon (L2) was affected. Isolated jejunal involvement occurred in 17% of the cases, and this figure has been corroborated by other authors[57]; however, other authors have observed jejunal involvement in a third of patients with normal IC[58]. In the pediatric population, these figures are superimposable, with L4 involvement in 24% of patients with DCD, 30% being associated with L1, 18% with L2 and 21% if the phenotype is ileocolonic (L3)[59].

Recent findings published by Lazarev *et al*[60] have been decisive in understanding the involvement of the SB in CD. Of the 2015 patients analyzed, 14% exhibited proximal involvement, and this location is associated with younger age groups, non-smoking patients, coexistence with ileal involvement and a pattern of stenosis. Specifically, jejunal involvement is associated with patterns of stenosis which necessitate further surgery. Based on these findings, this author proposes revising the Montreal classification, as jejunal involvement should be viewed as a separate phenotype due to the prognostic implications of this location. The behavior of the proximal location is similar to that of the ileal location and most frequently develops into a pervasive, stenotic pattern in contrast with the colonic location[61].

Isolated CD in the small bowel

The diagnosis of isolated CD in the SB is a true challenge, and as it occurs with colonic involvement, it is not correlated with endoscopic activity. Population-based epidemiological studies show that more than 50% of Western patients with CD and 77%-87% of Asian patients exhibit involvement of the SB at the time of diagnosis[62-65]. The use of CE with DCD is currently considered to be complementary to other techniques, and the selection thereof will depend on the experience of each center[66].

As for radiology, ETC and MRE evaluate the progression of transmural damage and the complications (transmural extension, abscesses, fistulas, stenosis and collections); therefore, studies are preceded or completed with CE when there is interest in identifying these[10]. Its primary advantage over radiological techniques is its elevated sensitivity for the detection of superficial mucosal lesions[42], as there are few series, which provide sensitivity similar to that of MRE (75% *vs* 77.8%, respectively)[67]. The advantage of CE over MRE focuses principally on jejunal lesions, as the jejunum has a larger mucosal surface than the ileum as well as more numerous and redundant folds and a relative minor distension, which leads to false positives and negatives with MRE in this section[68]. Similarly, it has been observed that its diagnostic performance when combined with IC and CE is 97.3% *vs* 57.3% when IC and BFT[69] are performed, so the use of the BFT in this context is currently controversial in addition to its being rejected due to the radiation which it involves[70].

As regards inflammation markers, fecal calprotectin (FC) studies inflammatory activity noninvasively and indirectly but does not differentiate the location thereof in the SB or colon[71]. Some authors have observed a good correlation with the results of CE with a S of 83%, SP of 100%, PPV of 100% and NPV of 80%[37]; however, more recent studies have demonstrated that the elevation of C-reactive protein, FC, or a combination of the two are poorly correlated with significant inflammation of the SB[72]. In general, the Lewis score has demonstrated a good correlation with FC in cases of mild inflammation, so when it is < 100 μg/g, the Lewis score is normal, but it is less useful when the CBF is elevated[73]. For SCD with a normal IC, a FC of > 100 mg/g may suggest the indication of CE, and a value of approximately 200 μg/g is associated with a diagnostic performance of 65%[74].

Assessment of the activity and severity of DCD

CE enables the assessment of both the extent and the inflammatory activity in the SI. When CD is suspected based on the presence of anemia, thrombocytosis, weight loss and/or fecal inflammatory markers which are not justified by the findings of the IC or radiology, the performance of CE is indicated in order to look for activity in the SB[40,46]. In this context, the Lewis score diagnoses CD with a PPV of 82.6%, NPV of 87.9%, S of 82.6% and SP of 87.9% for the diagnosis of CD with respect to the clinical, analytical, radiological, endoscopic and/or histological evaluation[32]. Endoscopic score systems maintain a good correlation with each other, with CECDAI levels of 3.8 and 5.8 proportional to Lewis scores of 135 and 790 respectively, with the first values for mild activity and the last values for moderate to severe activity[73]. Recently, other authors have identified a higher CECDAI threshold of 23.5 for severe inflammation, which may be helpful for guiding clinical management[75]. The use of these indices in the therapeutic algorithm decision, requires prospective studies[14]; therefore, the findings should currently be seen as complementary to the rest of the panel of diagnostic tests[66].

Mucosal healing

Achieving deep remission (clinical, biological and mucosal healing) improves the prognosis for CD[3], with mucosal healing being an objective of treatment[76]. The various radiological modalities, as opposed to endoscopic modalities, cannot provide direct visualization of the mucosa of the SB; consequently, they have an inherent limitation in the objective assessment of mucosal healing.

Mucosal healing is considered the initial event in the suppression of inflammation of the deeper layers of the intestinal wall[77] and, as occurs with colonic lesions, this healing is not correlated with the clinical evidence[78]; therefore, it is necessary to evaluate it endoscopically in order to detect it. In this sense, endoscopic evaluation of the whole intestinal mucosa should be crucial for measuring the treatment response and establishing a treatment strategy.

In the few studies that have focused on mucosal healing of the SB using CE for CD (not fistulizing or pervasive), it has been observed, paradoxically, that ulcers improve one month after immunosuppressive treatment and cankers can take up to 6 mo[79]. Current

recommendations on the monitoring of mucosal healing indicate first conducting an IC in patients with involvement of the ileum and/or colon; in those with SB involvement that cannot be reached by IC, MRE would probably be the standard test. However, given the modest NPV of MRE to exclude mucosal lesions, CE should be considered if symptoms persist despite normal MRE results, or if there is suspicion of activity[80].

Currently, there is no agreed definition for mucosal healing through CE. It has been suggested that it could be the resolution of all active inflammatory lesions[37] or the absence of all visible ulcers (according to the International Organization for the Study of Inflammatory Bowel Diseases)[81]. In both cases, quantification of inflammatory activity by means of the validated Lewis score and CECDAI index is recommended[14].

Perianal disease

CE detects SB involvement in 24% of cases involving perianal disease patients with a normal IC, and these findings lead to a change in therapeutic management in all patients. In these cases, the predictors of a positive outcome from the CE are not associated with laboratory abnormalities, family history of IBD or age[82].

Association with other intestinal diseases

According to the recommendations of the ASGE[8], there are other indications of CE such as suspected intestinal tumors and malabsorption syndromes, and both can be associated during the progression of DCD.

The relative risk of intestinal tumors presented by IBD in the long term (10-25 years) is low (0.2%-2%), although this is higher than in the general population[83,84]. According to ECCO's recommendations, CE is recommended for suspected intestinal tumors. In CD with a long-term, pervasive stenotic pattern, the abrupt onset of symptoms after a prolonged remission or with refractory strictures should be suspected to medical treatment[85].

Moreover, celiac disease and its complications can be associated with DCD. CE has shown lesions consistent with CD in 6% of doubtful cases of celiac disease with negative antibodies and signs of atrophy in the duodenal biopsy[85].

INDICATIONS OF CE IN POSTSURGICAL RECURRENCE

The management of postsurgical recurrence of DCD by means of endoscopic monitoring and its management is determined by the risk factors among which is extension into the SB[86,87]. IC is currently the reference technique for evaluating postoperative recurrence, which is measured using the Rutgeerts index[86,88]. Although the clinical relevance of the findings has not been studied, CE exhibits a S of 62%-76% and a SP of 100% over ileoscopy for this indication[10]. CE is performed when endoscopy is contraindicated or unsatisfactory[40], and it is selected with anastomosis that is difficult to access or when preferred by the patient[10,15,40,89,90].

It is recommended to perform it six months to one year after surgery depending on the association with other risk factors[89] in order to identify the recurrence and the proximal lesions not attainable with ileoscopy[40,53,91]. Some authors have used the Buchmann activity index[92] to classify lesions, but the use of the Lewis score is currently recommended in the context of clinical trials[35].

However, prospective studies are lacking in this context for evaluating the prognosis and clinical significance of the results of CE for this indication. Recurrence has only been assessed in one study using CE at one month and six months after surgery, and recurrence in the SB is defined as being when the residual lesions at one month after surgery have progressed after 6 mo, with an increase of 100 points in the Lewis score[93].

INDICATIONS OF CE IN UNCLASSIFIED COLITIS

Population-based studies have shown that, for up to 10% of adult patients and 30% of children with IBD and the exclusive involvement of the colon, it is difficult to distinguish between CD and ulcerative colitis (UC). This entity is called unclassified or UNC, and in most cases, the final diagnosis is established during the first 8 years of development[94-96]. In these cases, CE can identify lesions consistent with CD in 17%-70% of the cases[96], which is better than BFT or enteroclysis. There are no comparative data for ETC or MRE. Similarly, when the CE is normal, a future diagnosis is not excluded[14], and its repetition can be recommended in the medium term[10].

Several retrospective studies have suggested that CE produces a definitive diagnosis of CD, has resulted in management changes, or has had a potential impact on prediction of the prognosis with this fact being particularly significant in young patients. In one pediatric study, 50% of UC or UNC were ultimately diagnosed as CD[97].

THERAPEUTIC IMPACT OF CE IN CD

It has been demonstrated that the extension of CD into the SB and/or its proximal location are two poor prognostic factors and determine therapeutic decisions through early indication of immunosuppression[6,51,98-100].

The management changes that CE findings prompt are related to the initiation of a new treatment, the change or suspension thereof, or the indication of surgery[52,101,102]. On a practical level, the impact on management of the disease depends on the reason why CE is indicated. This impact is particularly relevant in the pediatric age group, as CE reclassifies 50% of ulcerative colitis and UNC as CD, as it detects proximal lesions undetected by other techniques; in 78% of these cases, there is a change in the therapeutic decision[101].

In general, current publications report the diagnostic performance of CE for CD at 60%-85%[52,103], which gives rise to an overall therapeutic impact of 50% (40%-67%)[27].

In long-term studies (6 years), this will lead to changes in decision-making based on the indication: 90% of patients when CE is requested for SCD, 88% for UNC and 73% for DCD[104].

In the case of DCD, therapeutic management is modified in 64% of patients[52]. In studies involving more than 900 patients with CD[102], the decision to change the medication is made three months after the CE for 61.6%, and for 39.5%, a new treatment is initiated. Pathologic findings of CE compared with none or minimal findings, resulted in significant differences in treatment modifications (73.2% *vs* 51.1%, $P = 0.04$), the addition of drugs (58.5% *vs* 22.2%, $P < 0.01$), and the indication of surgery (21.9% *vs* 4.4%, $P = 0.01$). Treatment is intensified after CE when activity of the lesions is more severe: In 14.5%, 48% and 87% of patients with Lewis score < 135, 135-790 and ⩾ 790, respectively[72].

COMPLICATIONS

The most significant complication of CE, and almost the only one, is retention, which is still very rare with this disease, as the exploration of the entire SB is achieved in 85.4% (from 79% to 90.8%) of the cases[105]. DCD is considered a risk factor for retention with CE, although the overall figures in long series are low at 2.6% (1.6-3.9) and very similar to other indications[105]. Currently, when intestinal stenosis is suspected, the recommended approach is to assess the contraindication of CE in a test of intestinal permeability with the degradable capsule Patency (PC) (Given Imaging, Yoqneam, Israel), approved by the FDA in 2006 for this purpose, or to perform radiology depending on its local availability and the experience of the center[14,106-108]. For pediatric patients, the choice is between the PC and MRE due to the safety of both types of exploration for this age range[109].

It has been observed that, in most capsule retention cases with CE, radiology was not adequate to suspect its risk[110]; otherwise, for suspected radiation stenosis (CT or BFT) the retention rate is low (21%). Therefore, it is proposed that radiology be avoided (especially in young patients), unless the permeability test is abnormal[111]. For some authors, it is a "therapeutic" complication, because it diagnoses stenoses that have gone unnoticed by other techniques and results in a change in patient management[112]. The treatment of retention depends on the diameter and nature of the stenosis and provides for the wait-and-see approach with monitoring for the expulsion of the capsule and medical or endoscopic treatment if there is not complete obstruction, in which case surgery is indicated[113]. Most cases are resolved conservatively[114]. Medical treatment includes the administration of laxatives or corticosteroids depending on the etiology of the retention. Enteroscopy indicates whether to recover the endoscopic capsule, biopsy the stenosis and/or treat with dilation.

The risk of retention in DCD and SCD are not the same. Accordingly, the highest percentage was published in a single retrospective study of 102 patients, with the risk for DCD being 13% (5.6%-28%), whereas in cases of SCD, the figure dropped to 1.6% (0.2%-10%)[115], and that was a decade ago, when the PC did not exist. However, a multicenter Japanese study was recently published which shows no difference between retention in DCD (7.4%) and SCD (6.4%)[116].

Retention in suspected CD

In general, the retention rates with SCD are low and vary from 0% to 5%[105,112,117-119]. In 22 of the 1000 patients of the series of Li *et al*[120] CE was performed for SCD (2.2%), and of those, there were only 3 retentions.

In a retrospective study involving 78 patients with SCD, there were 3 retentions (5%)[121], and similar data were obtained in the study of Cheon, with retention rates of 5.4% (2/37)[113].

Retention in diagnosed CD

In patients with DCD, the retention rate oscillates between 1.8% and 13%[23,102,105,112,113,116,122]. The first publications, such as Cheifetz *et al*[115], estimate higher retention figures while in more recent publications, the figures have dropped considerably[116]. Cotter *et al*[99] presented a retention rate of 6% and Dussault *et al*[47] rates of 4%. However, in studies with active CD, where mucosal healing is assessed, retentions account for only 1.8%[123].

Retention with intestinal obstruction in CD

In CD, a rigorous selection of the indication of CE is required due to the risk of retention in patients with known intestinal stenosis[8,10]. It should be noted that, in the preliminary studies in which tests with the PC were not available, retention rates in this context were 21%[112]. However, in a more recent study involving 19 patients with active CD in which 43 sequential scans were performed, no retentions were recorded despite the inclusion of patients with multiple stenosis and intestinal surgery[124]. This study confirms that the PC is an excellent predictor of intestinal permeability with respect to CE for these patients[14,125]. However, the latest reports indicate that the retention rate is not affected by the selective use of the PC, as the retention rate is 2.3%, which is similar to when it is not performed (1.5%) as well as when the PC is negative (2.1%). When the PC is positive, the retention rate is 11.1%[126].

CONCLUSION

In summary, CE is a noninvasive technique, which plays a wide-ranging role in CD. Its principal advantages over other diagnostic techniques are the absence of invasiveness and irradiation and the direct study of the mucosa of the entire SB. It enables the early diagnosis of CD due to its ability to detect superficial mucosal lesions, which go unnoticed by radiology or cannot be accessed with IC. These characteristics, along with its excellent level of safety, define it as the best exploratory method for the study of inflammatory activity in the mucosa of

the SI with CD. Its only contraindication is the objective presence of intestinal stenosis.

Its primary use is well defined in the early diagnosis of SCD, the assessment of the extent of DCD and the study of unclassifiable colitis. After ruling out intestinal stenosis, CE is the technique of first resort for patients with SCD who have had negative evaluations with radiology and IC. For patients diagnosed with CD, if cross-sectional imaging tests are normal or non-diagnostic, CE is performed if the result implies a change in patient management.

The systematic use of validated indices for scoring endoscopic activity enables the interpretation of lesions and monitoring of the developmental history of each patient to be standardized. Its use in future prospective studies will enable the definition of the criteria for mucosal healing and postoperative recurrence, which may suggest guidance for treatment. As is the case with other diagnostic tests and current treatments, the involvement of all these applications of CE in changing the natural history of this disease has yet to be established.

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P- Reviewer: Actis GC, Akyuz F, Koulaouzidis A, Sipahi AM
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Li D

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i17.584

World J Gastrointest Endosc 2016 September 16; 8(17): 584-590
ISSN 1948-5190 (online)

MINIREVIEWS

Blood thinners and gastrointestinal endoscopy

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Author contributions: Ahmed M solely contributed to this work.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Manuscript source: Invited manuscript

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Received: March 25, 2016
Peer-review started: March 25, 2016
First decision: May 17, 2016
Revised: June 8, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: September 16, 2016

Abstract

As the number of diagnostic and therapeutic gastrointestinal endoscopies is increasing, and there is an increase in number of patients taking blood thinners, we are seeing more and more patients on blood thinners prior to endoscopic procedures. Gastrointestinal bleeding or thromboembolism can occur in this category of patients in the periendoscopic period. To better manage these patients, endoscopists should have a clear concept about the various blood thinners in the market. Patients' risk of thromboembolism off anticoagulation, and the risk of bleeding from endoscopic procedures should be assessed prior to endoscopy. The endoscopic procedure should be done when it is safe to do it.

Key words: Acute coronary syndrome; Gastrointestinal bleeding and endoscopy; Blood thinners; Antiplatelet agents and endoscopy; Gastrointestinal bleeding and endoscopy; Anticoagulation bridge before endoscopy; Anticoagulants and endoscopy

Core tip: While patients on blood thinners undergoing endoscopic procedures are encountered in our clinical practice frequently, endoscopists need to be familiar with the various blood thinners and have a strategy to manage these patients efficiently. This article will discuss the various blood thinners including their mechanism and duration of action, and the current guidelines of performing gastrointestinal endoscopies when the patients are on those blood thinners.

Ahmed M. Blood thinners and gastrointestinal endoscopy. *World J Gastrointest Endosc* 2016; 8(17): 584-590 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/584.htm
DOI: http://dx.doi.org/10.4253/wjge.v8.i17.584

INTRODUCTION

Blood thinners include antiplatelet agents, anticoagulants and thrombolytic agents. In the United States, more than 2 million people have been taking blood thinners every day for various cardiovascular, pulmonary and

hypercoagulable disorders[1]. Gastrointestinal tract is the most common site of significant bleeding in patients on blood thinners. Thousands of people per day and millions of people per year are having gastrointestinal endoscopies in the United States[2,3] and throughout the world. The various gastrointestinal endoscopic procedures performed are esophagogastroduodenoscopy, colonoscopy, endoscopic retrograde cholangiopancreaticography (ERCP), flexible sigmoidoscopy, pouch/stoma endoscopy, enteroscopy (push, spiral, balloon assisted, *i.e.*, single balloon or double balloon), endoscopic ultrasound (EUS - mediastinal, pancreatic, rectal), capsule endoscopy and capsule colonoscopy. All these procedures have diagnostic and therapeutic potentials except capsule endoscopy and capsule colonoscopy in which neither any diagnostic biopsy nor any intervention can be done. Blood thinners may potentiate the risk of bleeding during or after performing these procedures. In the last few years, new blood thinners have been introduced in the market. As safety is the most important concern before performing a procedure, endoscopists should be very familiar with the different blood thinners available in the market.

BLOOD THINNERS

Anti-platelet agents

These include irreversible cyclooxygenase inhibitor, adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, glycoprotein Ⅱb/Ⅲa inhibitors and protease-activated receptor-1 (PAR-1) inhibitor.

Irreversible cyclooxygenase inhibitor

Aspirin: Low dose aspirin irreversibly inhibits platelet cyclooxygenase-1, thus decreasing production of prostaglandin H2 (PGH_2) from arachidonic acid. As a result, production of thromboxane A_2 (TxA_2) derived from PGH_2 is decreased. TxA_2 is responsible for platelet aggregation and vasoconstriction. Low dose aspirin works as a weak antiplatelet agent. Aspirin is widely used in coronary artery disease, cerebrovascular disease and atrial fibrillation. Aspirin can be continued for low risk and high-risk elective procedures.

Adenosine diphosphate receptor inhibitors

They competitively inhibit ADP from binding to ADP receptors on platelets, and thus prevent ADP mediated up-regulation of glycoprotein Ⅱb/Ⅲa receptor, leading to inhibition of platelet aggregation. They include Clopidogrel (Plavix), Parasugrel (Effient), Ticagrelor (Brilinta) and Ticlopidine (Ticlid). Clopidogrel is widely used in acute coronary syndrome, post-coronary artery stenting, cerebrovascular accidents and peripheral vascular diseases. Parasugrel is used in acute coronary syndrome. It has rapid onset of action and more bleeding risk. Ticagrelor is used in acute coronary syndrome, post-myocardial infarction and post-coronary artery stenting. Ticlopidine is approved for the prevention of stroke when combined with aspirin, and also for the prevention of coronary artery thrombosis after coronary artery stenting. But because of its rare but serious side effect of neutropenia and thrombocytopenia, it is rarely used nowadays. These medications are thienopyridines which inhibit platelet aggregation by irreversibly binding to P2Y12 ADP receptors on platelets[4]. Clopidogrel, parasugrel and ticagrelor should be withheld for 5-7 d and ticlopidine for 10-14 d prior to any endoscopic procedures.

Phosphodiesterase inhibitors

Cilostazol (Pletal): It prevents platelets from sticking together to form clots and is a direct vasodilator. It reduces intermittent claudication in peripheral vascular diseases. Cilostazol should be withheld for 2 d prior to endoscopic procedures.

Dipyridamole: It inhibits phosphodiesterase and prevents adenosine reuptake into platelets, red blood cells and endothelial cells. As it prevents platelets aggregation, it is used to prevent clot formation after cardiac valve replacement, and also to prevent myocardial infarction and stroke. It should be withheld for 2 to 3 d before performing any endoscopic procedure.

Glycoprotein IIB/IIIA inhibitors

This group of medications blocks the receptor on the platelet for fibrinogen and von Willebrand factor and thus prevent cross-linking of platelets and platelet aggregation. They are intravenous drugs used in acute coronary syndrome and percutaneous coronary intervention. The 3 agents available in this group are tirofiban (Aggrastat) - a synthetic non-peptide with a plasma half-life of 1.5 to 2 h and 80% of platelet aggregation returns 4 h after stopping the medication, abciximab (ReoPro) - a murine-human chimeric antibody with a plasma half-life of 10 min and platelet function recovery over 48 h after discontinuing the medication, and Eptifibatide (Integrilin) - a synthetic peptide with a plasma half life of 2.5 h and 50% of platelet aggregation returns 4 h after stopping the medication[5]. Elective gastrointestinal procedures are not done while patients are on these medications. Urgent procedures should be on hold until recovery of platelet aggregation occurs.

PAR-1 inhibitor

Proteolytic activation of cell surface of PAR-1 by thrombin activates platelets. Selective inhibition of PAR-1 by Vorapaxar (Zontivity) leads to potent antiplatelet effect[6]. Vorapaxar has been approved as an adjunct to dual anti-platelet therapy to reduce myocardial infarction, cerebrovascular accidents, cardiovascular death and to use during revascularization procedures. It can cause moderate to severe bleeding including intracranial hemorrhage[7]. It is contraindicated in patients with transient ischemic attacks, stroke and intracerebral bleeding. Endoscopic procedures should be hold for about 2 wk as its duration of action is 5 to 13 d.

Anticoagulants

These include parenteral and oral agents. Parenteral agents include unfractionated heparin, low molecular heparin and fondaparinux. Oral agents include warfarin and novel oral anticoagulants (NOAC) which are oral direct factor Xa inhibitors and direct thrombin inhibitors.

Unfractionated heparin

Unfractionated heparin is an injectable blood thinner widely used in the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism. It is also used in atrial fibrillation, acute coronary syndrome, indwelling peripheral or central venous catheters, hemodialysis/hemofiltration and extracorporeal membrane oxygenation (ECMO) circuit for extracorporeal life support. Heparin exerts its major anticoagulant effect by activating anti-thrombin Ⅲ which inactivates thrombin and activated factor X (Factor Xa). Inactivation of thrombin inhibits formation of fibrin from fibrinogen and also inhibits thrombin-induced activation of platelets and factor Ⅴ and Ⅷ[8]. The main side effect is bleeding. Other side effects include hyperkalemia, abnormal liver function test, heparin-induced thrombocytopenia (due to formation of IgG antibody against heparin-platelet factor 4 complex in the blood), osteoporosis and alopecia. The plasma half-life varies with the dose of heparin but is approximately 90 min. In case of intravenous administration of heparin, endoscopy should be held for 4 to 6 h and in case of subcutaneous administration of heparin, endoscopy should be held for 12 to 24 h after stopping heparin. The action of heparin can be reversed by protamine (1 mg of protamine can neutralize 100 units of heparin).

Low molecular weight heparins

Low molecular weight heparins (LMWH) are derived from fractionation of standard heparin so that each fragment is about one third the size of the original compound. As the number of long chains is reduced, there is less binding to thrombin. LMWH (containing majority of short chains) mainly works by inhibiting factor Xa without inactivating thrombin. Thus partial thromboplastin time (PTT), a measure of anti-thrombin activity is not affected by LMWH. The anti-coagulation effect of LMWH is measured by anti-Xa activity. The short chains of LMWH do not bind to plasma and cellular proteins and as a result, the dose-response relationship is predictable, and the half-life becomes 2 to 4 times that of Unfractionated heparin. There is less binding of LMWH to platelets and osteoclasts leading to less heparin-induced thrombocytopenia and osteopenia respectively. Currently, the LMWH available are enoxaparin (Lovenox) and dalteparin (Fragmin). They are associated with greater efficacy and less bleeding episodes[9]. As the duration of action of LMWH is 24 h, endoscopic procedures should be done 1 d after stopping LMWH. LMWH can also be partially reversed by protamine which neutralizes 60% activity of anti-factor Xa.

Fondaparinux (Arixtra)

Fondaparinux (Arixtra) is a specific inhibitor of factor Xa without any effect on thrombin or other clotting factors but it needs antithrombin Ⅲ as a cofactor for inhibition of factor Xa. A fixed dose is given subcutaneously and does not require monitoring of PTT. It is used for the treatment of DVT with or without pulmonary embolism, and for the prevention of DVT in high-risk individuals who are immobilized or who have undergone abdominal or orthopedic surgery. As it has no affinity for PF-4 antigen, the chance of developing heparin-induced thrombocytopenia is very rare. Fondaparinux is eliminated mainly unchanged through the urine and the elimination half-life is 17 to 21 h. It should be discontinued 36 to 48 h prior to any high-risk endoscopic procedure. Fondaparinux activity can be reversed by protamine sulfate and rⅦa.

Warfarin

Warfarin is the most commonly used oral anticoagulant throughout the world. It is used in various clinical conditions like DVT, pulmonary embolism, atrial fibrillation, following cardiac valve replacement, following hip/knee surgery, to prevent stroke and myocardial infarction. It inhibits formation of vitamin K dependent clotting factors - Ⅱ, Ⅶ, Ⅸ and Ⅹ and natural anticoagulants Protein C and protein S by inhibiting C1 subunit of vitamin K epoxide reductase. The major side effect is bleeding. The duration of action of warfarin is 2 to 5 d. Endoscopy should be held for 5 d after stopping warfarin.

Oral direct factor Xa inhibitors

Oral direct factor Xa inhibitors are rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Savaysa). Factor X is activated by both extrinsic and intrinsic pathways. Unlike heparin and warfarin which inhibit multiple coagulation factors, they are specific for factor Xa. They have rapid onset of action (time to maximal effect: Rivaroxaban-2 to 4 h, Apixaban-1 to 3 h) with good oral bioavailability and they do not need any bridging therapy. Their plasma half-lives range from 8 to 15 h. They have both renal and fecal excretion. As a result they have less accumulation in the body in renal failure. Edoxaban should be stopped at least 24 h before any high-risk endoscopic procedure. Rivaroxaban and apixaban should be stopped 1 to 4 d, *i.e.,* at least 2 half-lives before high-risk endoscopic procedures depending on the creatinine clearance. These medications are approved for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF), DVT and pulmonary embolism. In ENGAGE AF-TIMI 48 Trial[10], both high dose (60 mg/d) and low dose (30 mg/d) Edoxaban were found to be non-inferior to warfarin for the prevention of recurrent symptomatic thromboembolism. The annual rate of major gastrointestinal bleeding was higher with high dose Edoxaban than with warfarin (1.51% *vs* 1.23%) but lowest with low dose Edoxaban (0.82%). Although gastrointestinal bleeding risk (GIB) is similar in patients using warfarin and NOAC in the young and middle-aged

population, in the elderly (age > 75) population, there is increased risk of GIB in patients taking NOAC[11].

Direct thrombin inhibitors

Direct thrombin inhibitors are oral Dabigatran (Pradaxa) and subcutaneous Desirudin (Iprivask). Dabigatran is an oral anticoagulant which has been approved for: (1) the treatment of patients with DVT and pulmonary embolism (PE) after 5 to 10 d of parenteral anticoagulant; (2) the prevention of DVT and PE in patients who have been treated previously; and (3) the prevention of stroke and systemic embolism in patients with NVAF. Dabigatran was found to be non-inferior to warfarin in the treatment and prevention of DVT and PE but carried increased risk of bleeding[12] particularly gastrointestinal bleeding than the placebo group (5.3% *vs* 1.8%). Its anticoagulant activity can be assessed by Ecarin Clotting Time or dilute thrombin time. Dabigatran is fixed dose, does not require monitoring by international normalized ratio (INR) and excessive bleeding can be reversed by a monoclonal antibody[13] called idarucizumab (Praxbind). Dabigatran has a half life of 12-24 h. It should be stopped 2 to 6 d (*i.e.,* at least for 4 half-lives) prior to high risk endoscopic procedures depending on the creatinine clearance. Desirudin has been approved for the prevention of DVT in patients after elective hip replacement surgery. As this medication is metabolized and excreted renally similar to Dabigatran, the dose is adjusted according to creatinine clearance. The anticoagulant activity can be monitored by aPTT. The terminal half-life is 2 h after subcutaneous administration. High-risk endoscopic procedures should be done 10 h after discontinuation of desirudin.

Thrombolytic agents

Thrombolytic agents are clot busters used in acute myocardial infarction, cerebral infarction and occasionally in massive pulmonary embolism. Thrombolytics have also been used as provocative agents to induce bleeding during endoscopic procedures, bleeding scan and angiogram to evaluate obscure gastrointestinal bleeding. The five thrombolytics currently available in the United States have different plasma half-lives: Streptokinase - 20 min, tissue plasminogen activator- 5 min, anistreplase - 2 h, reteplase - 18 min and tenecteplase - 20 min. Five percent of patients on thrombolytics can have minor bleeding, 1% serious bleeding including intracranial hemorrhage. At the present time, there is no guideline about doing endoscopic procedures on patients who received thrombolytic therapy. In patients with acute myocardial infarction and overt upper gastrointestinal bleeding, upper endoscopy prior to cardiac catheterization has been advocated as platelet inhibition and anticoagulation are needed post percutaneous coronary intervention[14].

GUIDELINES

Before doing an elective endoscopic procedure for patients on blood thinners, we must evaluate whether the patient has high-risk or low-risk condition and whether it is a high-risk or low-risk endoscopic procedure.

Low-risk conditions

Low-risk conditions have low risk of thromboembolic events after temporary interruption of blood thinners (absolute risk less than 2 per 1000 patients). These include DVT, NVAF, biologic heart valve, mechanical heart valve in the aortic position[15].

High-risk conditions

High-risk conditions have high risk of thromboembolic events after temporary interruption of blood thinners (absolute risk more than 2 per 1000 patients). These include valvular atrial fibrillation (AF) or AF associated with other risk factors (prosthetic heart valve, congestive heart failure with ejection fraction of < 35%, history of thromboembolism, diabetes mellitus, hypertension or age > 75), coronary artery stenting - bare metal less than 1 mo, drug-eluting less than 12 mo, mechanical heart valve in the mitral position, mechanical heart valve in any position with history of thromboembolism, acute coronary artery syndrome, percutaneous coronary intervention without coronary artery stenting after myocardial infarction.

Low-risk procedures

In the absence of blood thinners, the risk of clinically significant bleeding is less than 1%[16]. These include diagnostic esophagogastroduodenoscopy, colonoscopy and flexible sigmoidoscopy with or without biopsy, Argon plasma coagulation, Barrett's ablation, ERCP without sphincterotomy, EUS without FNA, push enteroscopy with or without biopsy, diagnostic balloon-assisted enteroscopy, capsule endoscopy and enteral stent placement without dilation (controversial).

High-risk procedures

The risk of clinically significant bleeding is more than 1% in the absence of blood thinners. These include polypectomy, treatment of varices, endoscopic hemostasis, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, pneumatic or bougie dilation, pneumatic balloon dilation for achalasia, endoscopic therapy of Zenker's diverticulum, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic tumor ablation by any technique (esophagus, stomach, colon and rectum), therapeutic balloon-assisted enteroscopy (other than argon plasma coagulation), endoscopic sphincterotomy, ampullary resection, EUS with FNA, cystogastrostomy, cystoenterostomy, per-oral endoscopic myotomy[17].

Risk stratification

Aspirin and non-steroidal anti-inflammatory drugs are safe in both low-risk and high-risk procedures except EMR, ESD and ampullectomy.

Table 1 Summary of recommendations for elective endoscopic procedure

	Low-risk conditions	High-risk conditions
Low-risk procedures	Continue APA, warfarin and NOAC Keep INR in therapeutic range in case of warfarin	Continue APA, warfarin and NOAC Keep INR in therapeutic range in case of warfarin
High-risk procedures	Hold thienopyridines for 5 to 7 d before the procedure. Resume theonopyridine once hemostasis is obtained In case of dual APA, hold thienopyridines for 5 to 7 d before the procedure but continue aspirin Hold warfarin 5 d before the procedure. Resume warfarin on the same day as the procedure Hold NOAC: Rivaroxaban 2 to 4 d, apixaban 2 to 4 d, edoxaban 1 d and dabigatran 2 to 6 d before the procedure depending on creatinine clearance. Resume NOAC when adequate hemostasis is obtained	Hold thienopyridines for 5 to 7 d before the procedure after discussion with the cardiologist. Resume theonopyridine once hemostasis is obtained In case of dual APA, hold thienopyridines for 5 to 7 d before the procedure but continue aspirin Delay endoscopic procedure if coronary artery stenting done and thienopyridines cannot be discontinued If the patient is on warfarin, bridge therapy with LMWH

APA: Antiplatelet agents; NOAC: Novel oral anticoagulants; LMWH: Low molecular weight heparins; INR: International normalized ratio.

Low-risk endoscopic procedures irrespective of low-risk or high-risk condition

If the patient is on antiplatelet agent or anticoagulant, it should be continued. In case of warfarin, the INR should be in therapeutic range. If the INR is supra-therapeutic, warfarin dose should be adjusted to keep the INR in therapeutic range before doing the endoscopic procedure[18]. The morning dose of NOAC should be missed on the day of the procedure.

High-risk procedure but low-risk condition

If the patient is on aspirin and clopidogrel, clopidogrel should be stopped 5 to 7 d prior to the procedure but aspirin should be continued. If the patient is on warfarin, it should be discontinued 5 d prior to the procedure. INR should be less than 1.5 prior to the procedure. Warfarin should be restarted after the procedure on the same day with the usual daily dose. Patient's INR should be rechecked one week after the procedure to make sure that the patient is getting enough anticoagulation.

NOAC should be discontinued 48 h prior to the procedure in patients with normal renal function. If the creatinine clearance is 30 to 50 mL/min, last dose of NOAC should be given 72 h prior to the procedure.

High-risk procedure and high-risk condition

If the patient is on aspirin and clopidogrel, clopidogrel should only be discontinued after discussion with the cardiologist taking care of the patient. Aspirin should be continued. As the risk of thromboembolism is always a concern, elective endoscopic procedure should be delayed. Clopidogrel should not be stopped in certain high-risk conditions such as within one month of placing of a bare metal coronary stent and within 12 mo of placing a drug-eluting coronary stent. After these periods, clopidogrel can be temporarily stopped 7 d prior to the endoscopic procedure and then can be restarted on the day after the procedure. If the patient is on warfarin, bridge therapy should be utilized. The risk of systemic thromboembolism must be taken into consideration against the risk of bleeding during bridge therapy.

Warfarin should be held 5 d prior to the procedure and LMWH should be started two days after discontinuing warfarin. On the night of the procedure, regular dose of warfarin should be started. LMWH should be started the following day and continued until therapeutic INR is achieved. NOAC are not used for high-risk conditions.

Bleeding risk

In patients with history of venous thromboembolism on warfarin, bridge therapy for invasive procedures was associated with increased risk of bleeding[19].

Thrombosis risk

There is also increased risk of thrombosis in patients receiving LMWH for mechanical heart valve (Table 1).

Emergency endoscopic procedures

Frequently we encounter acute gastrointestinal bleeding in patients: (1) who are on antiplatelet or anticoagulant therapy for various reasons; (2) who had coronary vascular stent placed recently; and (3) who have acute coronary syndrome (ACS): Unstable angina or acute myocardial infarction.

The risk of bleeding to death should be assessed against the risk of thromboembolism due to discontinuation of antiplatelet or anticoagulant therapy on an individual basis. Patients on antiplatelet therapy should be discussed with their cardiologists. In case of significant gastrointestinal bleeding, the antiplatelet agent should be stopped after discussing with the cardiologist, and platelet transfusion can be given. In case of baby aspirin induced peptic ulcer bleeding, aspirin should be continued and proton pump therapy should be started. As soon as endoscopic hemostasis is obtained, antiplatelet therapy should be resumed[20].

The risk factors for GIB in patients on anticoagulant therapy are prior history of GIB, use of aspirin and supra-therapeutic INR.

Anticoagulation therapy should be discontinued in patients with active gastrointestinal (GI) bleeding. If the patient is on warfarin and the bleeding is massive, rapid

Table 2 Summary of recommendations for emergency endoscopic procedures

	Anticoagulant	APA
Active GI bleed	Hold the anticoagulant If on warfarin, give FFP, 4-factor PCC or IV Vitamin K to improve INR Avoid vitamin K in case of mechanical heart valve Hemodialysis in case of Dabigatran Endoscopic therapy when INR is less than 2.5	Do not stop thienopyridines without discussion with the cardiologist in high risk situations like within 3 mo of ACS, within 1 mo of placing a bare metal coronary stent and within 12 mo of placing a drug eluting coronary stent

APA: Antiplatelet agents; PCC: Prothrombin complex; ACS: Acute coronary syndrome; GI: Gastrointestinal; FFP: Fresh frozen plasma; INR: International normalized ratio; IV: Intravenous injection.

reversal of INR can be done with fresh frozen plasma (FFP), 4-factor prothrombin complex (PCC) containing factors Ⅱ, Ⅶ, Ⅸ and Ⅹ, or intravenous vitamin K. In case of mechanical heart valve and massive GI bleeding, FFP or PCC can be given but vitamin K should be avoided because of the risk of hypercoagulable state[21]. Endoscopic therapy should be given in patients with active bleeding and INR < 2.5. In high-risk patients, heparin infusion should be started after endoscopic hemostasis. Hemodialysis should be done in case of dabigatran-induced massive GI bleeding.

Patients with active gastrointestinal bleeding with history of coronary artery stent placement - *i.e.,* within one month of bare metal stenting and within one year of drug eluting stenting, should be discussed with the cardiologist. Clopidogrel should not be discontinued without permission from the cardiologist as there is high risk of coronary artery thrombosis and myocardial infarction. Discontinuation of clopidogrel should not exceed 5 d because of the risk of increased stent thrombosis.

Patients with ACS and GIB are unique group of patients who require close communication between the cardiologist and the gastroenterologist. This is a serous entity as ACS and GIB are independent risk factors for ischemic complications, higher morbidity and mortality. There are two distinct settings: (1) patients develop gastrointestinal bleeding first, then develop ACS. This group of patients have primary gastrointestinal lesions which have caused GIB. As GIB is the inciting event leading to ACS, endoscopic treatment would be more beneficial for this group of patients[22]; and (2) patients develop ACS first, then develop gastrointestinal bleeding. This is the commoner entity as this group of patients receive antiplatelet and/or antithrombotic agents for their ACS, either treated conservatively or by PCI. One study showed 1.3% of patients developed GIB within 30 d of acute coronary syndrome[23]. There was significantly increased incidence of stent thrombosis in the GIB group than non-GIB group (5.8% *vs* 2.4%). Predictors of post-ACS GIB were old age, female sex, smoking status, baseline anemia, diabetes mellitus, hypertension, heart failure, ST-segment elevation ⩾ 1 mm, longer duration of blood thinner administration before angiogram[23,24]. There was 8 fold increase in mortality when ACS patients developed GIB. Another study showed that patients with ACS who had also upper GIB had 30% mortality within 30 d of their ACS[25]. Upper endoscopy can have procedural and anesthetic risk like hypotension, EKG changes, hypoxia and life threatening arrhythmia in the setting of ACS. One study done in a tertiary care center found upper endoscopy to be relatively safe in the diagnosis and management of upper GIB within 30 d of having myocardial infarction[26] (Table 2).

CONCLUSION

Because a good number of blood thinners are available in the market, sound knowledge about these blood thinners is necessary. Anti-platelet agents, heparin and warfarin have been in our clinical practice for many years. NOAC introduced over the last few years are being increasingly used as they do not need Lab test monitoring like warfarin. Their onset of action is short and the duration of action depends on creatinine clearance. So serum creatinine and half-life of these medications should be considered in the periendoscopic period. Whether it is an elective case or an emergent case, an endoscopist should always evaluate high-risk and low-risk conditions and procedures, and bleeding and thrombotic risk. The main aim is success of the procedure maintaining safety of the patient.

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P- Reviewer: Armellini E, Braden B, Zhang QS
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Li D

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i17.591

World J Gastrointest Endosc 2016 September 16; 8(17): 591-599
ISSN 1948-5190 (online)

Endoscopic management of post-bariatric surgery complications

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Author contributions: Boules M contributed to writing of the manuscript, literature review, incorporating revisions, and final review; Chang J contributed to writing of the manuscript and literature review; Haskins IN contributed to writing of the manuscript, literature review, and incorporating revisions; Sharma G contributed to literature review; Froylich D contributed to literature review and revisions; El-Hayek K contributed to writing of the manuscript, final review; Rodriguez J contributed to writing of the manuscript and revision review; Kroh M contributed to writing of the manuscript, revisions review, study concept, and final review of the manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors on this manuscript. All authors approve the final version of this manuscript.

Manuscript source: Invited manuscript

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Received: April 29, 2016
Peer-review started: May 3, 2016
First decision: June 17, 2016
Revised: July 2, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: September 16, 2016

Abstract

Understanding the technical constructs of bariatric surgery is important to the treating endoscopist to maximize effective endoluminal therapy. Post-operative complication rates vary widely based on the complication of interest, and have been reported to be as high as 68% following adjustable gastric banding. Similarly, there is a wide range of presenting symptoms for post-operative bariatric complications, including abdominal pain, nausea and vomiting, dysphagia, gastrointestinal hemorrhage, and weight regain, all of which may provoke an endoscopic assessment. Bleeding and anastomotic leak are considered to be early (< 30 d) complications, whereas strictures, marginal ulcers, band erosions, and weight loss failure or weight recidivism are typically considered late (> 30 d) complications. Treatment of complications in the immediate post-operative period may require unique considerations. Endoluminal therapies serve as adjuncts to surgical and radiographic procedures. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

Key words: Bariatric surgery; Weight loss surgery; Bariatric complications; Endoscopy; Bariatrics

Core tip: There are minimal reviews in the literature discussing therapeutic options for endoscopic management of bariatric surgery complications. Treatment of bariatric complications in the post-operative period

may require unique considerations. Endoluminal therapies serve as adjuncts to surgical and radiographic procedures. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

Boules M, Chang J, Haskins IN, Sharma G, Froylich D, El-Hayek K, Rodriguez J, Kroh M. Endoscopic management of post-bariatric surgery complications. *World J Gastrointest Endosc* 2016; 8(17): 591-599 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/591.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.591

INTRODUCTION

Obesity is an increasing health concern in the United States and worldwide. According to the World Health Organization, obesity has doubled since 1980. In 2014 alone, more than 1.9 billion adults were classified as overweight, of which 600 million were obese[1]. Durable medical therapy for morbid obesity is limited. As an alternative, many studies have demonstrated the benefits of bariatric surgery in terms of excess weight loss and improvement or resolution of weight-related co-morbid diseases[2-6]. As of 2013, the most commonly performed laparoscopic bariatric procedures worldwide are Roux-en-Y gastric bypass (RYGB) (45%), sleeve gastrectomy (SG) (37%) and adjustable gastric banding (AGB) (10%)[7].

Peri-procedural complications have been reduced by the development and widespread use of laparoscopic techniques, improved training and credentialing, and establishment of comprehensive and dedicated bariatric surgery programs[4,5,8]. Nevertheless, bariatric surgery related complications remain a clinical challenge. Traditional management of these complications has been performed using surgical and interventional radiology techniques. Recently, however, endoscopic therapies have been introduced as an alternative and minimally invasive approach to peri-procedural complications[9].

Endoluminal treatment of peri-procedural complications following bariatric surgery may help to minimize patient morbidity. In order for endoscopic therapies to be successful, the treating endoscopist must be cognizant not only of the anatomical constructs of bartiatric surgery but also of any newly constructed anastomosis or staple line[9-11]. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

EARLY COMPLICATIONS (< 30 D POST-OPERATIVELY)

Gastrointestinal bleeding

Gastrointestinal (GI) bleeding usually presents in the immediate post-operative period secondary to technical complications. Most commonly, this occurs as intra-luminal bleeding, but extra-luminal bleeding can occur. Bleeding primarily occurs from the submucosal vessels along the staple line at the gastro-jejunostomy, jejuno-jejunostomy, or along the staple lines of the gastric pouch.

Signs and symptoms of bleeding, including a drop in hemoglobin levels, hematemesis, hematochezia, or melena, should be considered an indication to undergo further evaluation. Endoscopy is often used as a first-line modality for investigation of the source of bleeding. However, when post-operative bleeding is severe and associated with hemodynamic instability, surgical re-exploration may be required.

As the incidence of RYGB increases worldwide, so too does the frequency of post-operative upper GI bleeding in this patient population[12,13]. In the immediate 48 h after LRYGB, hemorrhage is reported to occur with an incidence between 1%-4%. Thirty to sixty-three percent of these occurrences require blood transfusion but are nonetheless self-limited[11,14,15]. Endoscopy is considered in the early period when patients have proven bleeding and this is refractory to supportive therapy[11]. Literature demonstrates therapeutic endoscopy interventions range between 6%-85% in these circumstances, and the culprit is often found at the G-J anastomosis[11-14,16].

Various endoscopic treatments have been shown to be effective for the management of bleeding peptic ulcers. A meta-analysis of randomized controlled trials demonstrated efficacy with the use of several endoscopic therapies, including thermal therapies (heater probe, mono and bi-polar electrocoagulation, argon plasma coagulation, and laser therapy), injections with epinephrine and various sclerosants, clips, and fibrin or thrombin glues[17]. We believe that the approaches described in this meta-analysis will be useful for the management of early post-operative bleeding in those patients undergoing bariatric surgery as the use of epinephrine injection with thermal coagulation, sclerosants, or clips, has previously been shown to be successful in the bariatric patient population[14]. The most common endoscopic interventions performed for the management of acute bleeding in this patient population are described below.

Thermal therapy for bleeding: Electrocautery is a thermal heat therapy. It is delivered through the form of mono-, bi-, or multi-polar electrocautery. Coaptation is the process of applying mechanical pressure using the probe in combination with heat or electrical stimulation to coagulate a blood vessel. Argon plasma coagulation is considered a form of non-contact heat therapy that uses argon gas to deliver thermal energy with resultant hemostasis of superficial tissues. Laser therapy is not commonly used due to cost, need for specific training, and safety[18].

Injection therapy for bleeding: The efficacy of injection therapy occurs by volume tamponade and fibroris and vasoconstriction when used with epinephrine.

The volume of fluid injected results in mechanical tamponade of the bleeding vessel. This effect is coupled with fibrosis from an inflammatory response and vasoconstriction that is induced by an alpha-receptor mediated response to epinephrine which leads to platelet aggregation[19].

The most important factor in the immediate control of bleeding is likely mechanical compression. Dual therapy with larger volumes of fluid combined with an epinephrine component result in better rates of hemostatic control, lower rates of re-bleeding, and decreased need for transfusion in patients with bleeding foregut ulcers[19]. Several randomized trials have established the efficacy of achieving hemostasis with the use of epinephrine to treat active bleeding[17]. In a recent study, single-therapy with epinephrine was shown to be less effective in the prevention of bleeding when compared to other single-therapy treatment modalities[17,20]. These findings were also confirmed in a meta-analysis conducted by Marmo *et al*[21] who found combination therapy to be a superior approach when compared to single agent epinephrine. A decreased rate of progression of the rate of bleeding was shown when epinephrine was used in combination with a second therapy such as bipolar electrocoagulation, injectable sclerosants, or clips[17,22].

Clip therapy for bleeding: Endoscopic clips are composed of two stainless steel ribbons (with various lengths as needed), with a range of 90 to 135 degree angles. The opening distance of clips range from 6-12 mm, allowing for flexibility in securing the desired amount of tissue. Clips typically slough off after a period of 2-4 wk but have be reported to remain in place up to one year after placement[23-27]. Advantages of clip placement for hemostasis include the ability to imbricate surrounding tissues for compression, the application of direct pressure to the targeted vessel, and ease of repeat clip placement[25,28,29].

In a retrospective review of 742 patients that underwent LRYGB, post-operative bleeding was reported in 3.5% of the patients. Nineteen (2.6%) patients presented with early GI bleeding while 7 presented with late bleeding. A total of 5 patients with early GI bleeding were diagnosed by endoscopy and received a combination treatment with endoscopic clips and epinephrine injections. Similarly, a prospective study by Fernández-Esparrach *et al*[30] reported results of 381 LRYGB patients. Twenty-two (5.8%) patients were determined to have upper GI bleeding. Sixteen were managed without procedural intervention. Six patients required intervention, all of whom were managed successfully with endoscopic intervention with epinephrine injections either as a single therapy or in combination with polidocanol[30].

A retrospective study presented by Jamil *et al*[14] identified 933 patients that underwent LRYGB during a 5-year study period. Thirty patients presented with signs of upper GI bleeding, 27 of whom required endoscopic intervention. All bleeding occurred at the G-J anastomosis. Endoscopic findings revealed active oozing in 13 (48%) patients, a visible bleeding vessel in 7 (26%) patients, and an adherent clot in 7 (26%) patients. Twenty-three (85%) of these patients required endoscopic intervention, which included injection with epinephrine (n = 3, 13%), heat electrocautery (n = 4, 17%), dual therapy with epinephrine and heat electrocautery (n = 14, 61), and clips (n = 2, 9%). Hemostasis was eventually achieved in all patients but 5 (17%) patients required repeat endoscopic management for re-bleeding[14].

Anastomotic leak and fistulas

Anastomotic leaks following bariatric surgery are most commonly found along staple lines. Patients who undergo RYGB are most susceptible to anastomotic leak at the G-J anastomosis due to the single blood supply to the gastric pouch. Leak after SG is often at the EG junction and may be secondary to stenosis at the incisura. Leak after duodenal switch is typically at the duodenal-ileal staple line.

While the cause remains unclear, leaks are hypothesized to be due to technical factors including anastomotic tension, tissue ischemia, size of staple line, tissue thickness, and blood supply. Although rare, leaks are associated with significant morbidity and mortality. Overall incidence of anastomotic leak following bariatric surgery is reported to range from 1% to 6%. Specifically, LRYGB is associated with an incidence of 0.1% to 5.6% while SG is approximately 2.4%[31,32].

Bariatric surgery can be challenging for the novice surgeon. As surgeon experience in this field increases, the risk of anastomotic leak is often shown to decrease. In a study by Schauer *et al*[33], they defined the learning curve for laparoscopic bariatric surgery to be 100 cases, at which time there was a significant decrease in operative time and technical complications. In a prospective study by DeMaria *et al*[34], 281 consecutive LRYGB operations were performed, with a decrease in the rate of anastomotic leak as surgeon experience with the laparoscopic approach increased.

In the early post-operative period, extra-luminal leaks may lead to a wide array of sequelae including abscess formation, peritonitis, sepsis, multi-organ failure, and death. Clinical signs of a leak, such as tachycardia, abdominal pain, or fever warrant prompt evaluation by the surgeon in order to minimize associated morbidity[35]. The principles of managing these patients include infection control, nutritional support, and the appropriate therapeutic intervention. We recommend the use of non-surgical, endoscopic interventions for patients without hemodynamic instability in order to minimize the additional stress and risk of iatrogenic injury associated with reoperation. On the other hand, we recommend surgical re-exploration for all critically ill patients and for those patients who do not improve with endoscopic interventions. The types of endoscopic interventions for post-operative anastomotic leaks will be further discussed below.

Endoscopic stents: The use of endoscopic stents for

the management of post-operative anastomotic leaks is the most commonly used endoscopic modality in our experience. Self-expandable stents have gained popularity and can be a useful tool for management of leaks in the acute period (ref). There are several types of stents available, with fully covered and partially covered self-expanding metal stents (SEMS) being the most useful for management of bariatric complications. These stents work by means of omitting the site of leakage from esophago-gastric secretions, ultimately preventing further contamination and enhancing healing of the leak site. Patients may also resume oral liquid intake after the leak is excluded, which has been shown to lead to an improvement in the patient's nutritional status and therefore faster healing of the anastomotic or staple line leak[35,36].

Authors of a small study reported successful endoscopic treatment of leaks in three patients and concluded that endoscopic treatment may serve as a less invasive and feasible alternative when compared to surgical management[37]. A prospective study by Yimcharoen *et al*[9] from the Cleveland Clinic evaluated the use of three different stents [silicone tube (prototype salivary), fully or partially covered expandable metal stents, or a silicone-coated polyester stent] for post-bariatric surgery complications in 18 patients. The study reported success in achieving symptom improvement in 17 (89%) patients and complete resolution of the anastomotic leak in 11 (85%) patients[9]. Our group also presents results in a retrospective review of 47 patients that underwent endoscopic SEMS placement for anastomotic complication following upper GI surgery. Symptomatic improvement after stent placement was achieved in 70.9% (n = 38) of patients. Majority (68.1%, n = 32) of patients were able to initiate oral nutrition within 48 h of stent placement, with 57% of patients with anastomotic ort staple-line leak and 89% of patient with strictures and stenosis able to initiate oral nutrition[23]. A meta-analysis analyzing the use of SEMS in anastomotic leaks after bariatric surgery reports successful leak closure of 88%, with only 9% of patient's required further revisional surgical intervention for persistent anastomotic leak[38].

The use of stents for the management of bariatric complications remains under investigation and is not without associated risks. The possibility of stent migration must be considered when deciding to proceed with stent insertion. Multiple techniques have been described in an effort to decrease migration of fully covered stents by means of clipping or suturing[9,23]. Surgeons at our institute prefer the use of partially covered stents as these types of stents effectively exclude the leak while minimizing the risk of stent incorporation into the native tissues.

Clips: There is minimal data evaluating the role of endoscopic clips for management of anastomotic or staple line leaks. In a recent retrospective study by Keren *et al*[39], the over-the-scope clip (OTSC) (Ovesco Endoscopy, TEndosco, Germany) was used in 26 patients that developed leaks post-SG. The study concluded that 21 (80.7%) patients were successfully treated with the OTSC device[39]. At our institute, clips are used to compliment other management modalities, primarily stenting.

Suturing: The use of endoscopic suturing platforms has gained popularity for management of bariatric complications, including gastric pouch dilation and weight recidivism. This may be useful in both the acute and long-term setting. Current endoscopic suturing devices include the Apollo Overstitch (Apollo, Austin, TX) and the G-Prox (USGI Medical, San Capistrano, CA). Suturing *via* the Apollo Overstitch device allows for full thickness suturing for tissue approximation in the GI tract. This device has been implicated in the early use of marginal ulcers, stoma reduction after gastric bypass surgery, and closure of fistulas[40,41]. The use of endoscopic plication will be further discussed under the management of long-term complications following bariatric surgery.

Fibrin glue: Fibrin glue or sealant is described in a brief review as a two-component hemostatic and sealant with tissue adhesive capabilities. Fibrin glue is composed of fibrinogen and thrombin[42]. Once injected endoscopically at the site of leakage, the constituents promote occlusion at the site of defect, hindering the progression of the leak. Fibrin glue is rarely used a single modality but rather in combination with endoscopic stenting[43-46]. Two endoscopic techniques have been described by several authors. Bolin and colleagues applied the fibrin glue under direct vision, through a double lumen catheter, leading to coagulation and the formation of a clot which plugged the defect[47]. Victorzon *et al*[48] described the process as a promotion in swelling and consolidation of the defect after endoscopic injection leading to a plug of the defect. Several studies in the literature indicate success in closure of gastrocutaneous fistulas using endoscopic injection of fibrin glue. Papavramidis *et al*[49] reported success in two patients that received fibrin glue for high-output gastrocutaneous fistulas occurring post-vertical banded gastroplasty (VBG).

Late complications

Management of strictures: Endoscopic management of strictures continues to increase in an effort to avoid the higher morbidity of revisional procedures. The incidence of strictures varies according to the underlying bariatric operation[50]. Strictures are more common post-LRYGB, with an estimated incidence rate ranging between 3%-28%[51-53]. The cause of stricture development continues to remain unclear and is likely multifactorial. Tissue ischemia caused by the stapler, anastomotic tension, edema, and even foreign body reactions are believed to contribute to the development of anastomotic strictures[51]. The development of stenosis maybe from the aforementioned factors, but some authors would agree the rate of stenosis may also be linked to the technique used for creation of the gastric reservoir

or anastomosis. Circular staplers have been implicated to have higher stricture rates *vs* hand-sewn or linear techniques. Common symptoms that should increase the index of suspicion for stricture development include nausea, vomiting, dysphagia, malnutrition, or significant weight loss over a short period of time.

Strictures can be diagnosed by several modalities, including endoscopy. Although other modalities may suffice, the ability to have direct, visual diagnostic and therapeutic capabilities gives endoscopy the upper hand[54]. Endoscopic findings include the presence of a stenotic lumen, dilation of the gastric pouch, or non-digested food particles[55].

Although less frequent, stricture development post-SG may present a greater management challenge. Incidence in patients undergoing SG is reported to be between 0.2% to 4%[56]. Possible causes of post-SG stenosis development include the use of a small bougie. Post-SG strictures commonly occur at the proximal to mid stomach, incisura, or the gastro-esophageal junction. As in post-LRYGB, endoscopy plays a vital role in diagnosis and management of these strictures.

Endoscopic balloon dilation: Endoscopic balloon dilation has become first-line treatment and standard of care for the management of strictures post-LRYGB[51]. There are many endoscopic balloons available for use, all of which are designed from polymers that have the ability to expand to the desired diameter. These balloons are geometrically designed to advance through the working channel (2.8 mm) of an endoscope with or without a guide wire.

The first step when performing endoscopic balloon dilatation is to identify the anatomy and properly estimate the size of the stricture. If the scope is unable to advance, a standard pediatric scope should be tried. The choice of balloon should then be decided based on the ability of the endoscope to traverse the stricture.

The balloon should be positioned at the site of maximum luminal narrowing. The balloon should be expanded slowly to its maximum diameter and held under tension for one minute. A prospective study conducted by Ahmad *et al*[57], evaluating balloon dilation for strictures in patients that underwent LRYGB, concluded that balloon dilation is safe, effective and can be reproduced with minimal adverse effects. Additional studies have also shown that balloon dilation is a durable therapy for both the short- and long-term management of anastomotic strictures[58,59].

Management of strictures post-SG includes observation, endoscopic dilation with or without stenting, seromyotomy, or ultimately converting to a LRYGB. It is important to differentiate true stenosis from sleeve rotation or torsion which may mimic obstructive symptoms. This may also be managed through endoscopic dilation, myotomy or surgical revision.

Stenting: Stenting may also be used in the management of strictures. In a prospective series presented by Eubanks *et al*[36], the authors report an 83% stent success rate in managing strictures in six patients that had been refractory to repeated balloon dilations. Nevertheless, a common concern of stent application is stent migration, which is reported to occur in 58% to 66% of stents placed[9,60,61]. Controversies seem to exist regarding the rate of stent migration with the use of covered or partially covered stents. Some studies did not find a difference, while other studies reported a greater incidence of migration associated with fully covered stents. Covered stents are least likely to be incorporated by the native tissues which may lead to the higher rate of tent migration[9].

Weight loss failure or weight recidivism: Weight loss failure is a broad term with no agreed upon definition amongst bariatric surgeons. As best we can tell, the incidence of weight recidivism is estimated to be 10%-20%[62]. Technical failure may play a role in the development of initial weight loss failure post-bariatric surgery or recidivism after initial weight loss. Several other factors such as non-dietary compliance, large gastrojejunal anastomoses, dilation of the gastric pouch, and gastrogastric fistula development may contribute to weight loss failure or weight recidivism[59,63]. Endoscopic therapies for weight regain continue to advance, providing a visible assessment of the anatomy as well as therapeutic intervention.

Endoscopy allows for the reduction in the stoma size of the gastrojejunal anastomosis by means of four quadrant endoscopic injection of sodium morrhuate into the seroma, which leads to scar formation, effectively reducing the stoma size[59,63]. An alternative approach to the management of a dilated pouch is plication of the gastric pouch or stoma[64]. This is an emerging technology and data on the long-term efficacy of this approach is not currently available. Nevertheless, in an effort to reduce pouch size, utilization of endoscopic suturing devices permit a non-surgical revision of the gastrojejunal anastomoses. Further studies demonstrating the durability and feasibility in the long-term are warranted[65].

Marginal ulcer: Marginal ulcers occur at the gastrojejunal anastomosis with a reported incidence of 1% to 16% after RYGB. It typically occurs within the first several months post-operatively[66-70]. Multiple factors have been identified in the development of ulcers, which include but are not limited to, ischemia, use of non-steroidal anti-inflammatory medications, disruption along the staple line, suture or staple erosion, gastrogastric fistula, increased gastric acidity, or tobacco use[63,71]. The association of *Helicobacter pylori* (*H. pylori*) with the development of marginal ulcers remains unknown[72]. Marginal ulcer may also be a cause of late bleeding post-bariatric surgery. Morbidity and mortality may be attributed to bleeding and perforation from marginal ulcers. Most common presenting symptoms include epigastric or abdominal pain, bleeding, nausea, vomiting, iron deficiency anemia, heme-positive stools, and in certain

instances patient may be asymptomatic.

In a study evaluating the incidence of marginal ulceration one month after gastric bypass, the ulcer rate was 4.1% after open RYGB and 12.3% after LRYGB patients. The study also noted that 28% of the ulcers were asymptomatic at the time of evaluation[73]. Ulcers may be managed non-operatively by means of anti-acid, proton pump inhibitor medications and buffers such as sucralfate and discontinuation of the use of ulcer enhancing medications or lifestyles[63]. Azagury *et al*[74] reported a 68% ulcer healing rate when combining medical therapies with eradication of possible risk factors.

The role of endoscopy in dealing with marginal ulcers is primarily to aid in establishing a diagnosis. In certain cases when eroded sutures are identified at the anastomosis, the sutures can be cut with endoscopic scissors and removed. If marginal ulcers are diagnosed during endoscopy, a meticulous examination for fistulas should be performed. If ulcers are refractory to medical treatment or are severe in nature, operative management may be required in an effort to prevent complications such as recurrent bleeding, perforation, and strictures[75].

VBG: VBG was a popular procedure in the 1980s but has since been replaced by the AGB. VBG can be thought of as a combination of a SG with a non-AGB[76]. In other words, this was a restrictive procedure that created a smaller stomach pouch with a non-adjustable band at the distal aspect of the pouch that controlled the rate at which nutrients reached the rest of the GI tract. The VBG procedure was ineffective at long-term weight loss and a majority of patients suffered from band erosion, outlet stricture, and gastro-gastric fistula causing weight regain[76,77]. These complications can all be diagnosed on endoscopy but are best managed with surgical revision. Options for revision of VBG include RYGB or VBG reversal *via* gastrogastrostomy[77].

Band erosion, migration and slippage: Since VBG and AGB were once the most commonly performed bariatric procedure, there is a large population at risk of their associated complications, including band erosion, migration, and slippage. The incidence of band erosions is reported to occur in 0.1% to 7.7% of all patients[78-82]. This complication is commonly diagnosed endoscopically by the erosion of the band into the stomach lumen.

Upon discovery of erosion of a VBG, the band may be severed endoscopically just as long as the band has remained encapsulated[63,83,84]. If uncertain about the state of capsulation, a computed tomography scan should be obtained for further evaluation prior to endoscopic intervention. On the other hand, patients who have undergone AGB may have diagnosis of band erosion on endoscopy but cannot undergo endoscopic intervention due to the presence of tubing that connects the band subcutaneously for adjustment.

Band slippage is a possible complication for both VBG and AGB but is more common with AGB. This is typically diagnosed through an upper GI series but may be observed on endoscopy by visualization of a larger than expected stomach pouch with narrowing of the gastric lumen distally[63,83,84]. Band slippage is a surgical emergency as it may lead to necrosis of the stomach.

CONCLUSION

Flexible endoscopy has become an essential tool in managing bariatric surgery patients. Endoscopy offers the benefit of providing both diagnostic and therapeutic applications. Endoscopy should be performed by an experienced endoscopist familiar with bariatric anatomies and with advanced skills in their therapeutic armamentarium. Endoscopic procedures in the post-bariatric surgery patient presents unique challenges unlike other endoscopic procedures because of altered anatomy, and specifically, access to the biliopancreatic limb, remnant stomach, and jejunojejunostomy. Common complications after bariatric surgery include: Bleeding, leaks/fistulas and strictures. Increasingly, endoscopist are gaining the experience to successfully diagnose and treat post-bariatric surgery patients and their complications.

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P- Reviewer: Akere A, Koch TR, Leitman M
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i17.600

World J Gastrointest Endosc 2016 September 16; 8(17): 600-609
ISSN 1948-5190 (online)

MINIREVIEWS

Review of small-bowel cleansing scales in capsule endoscopy: A panoply of choices

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Author contributions: Ponte A designed the study, performed the research, analyzed the data and wrote the paper; Pinho R designed the study, performed the research, analyzed the data and wrote the paper; Rodrigues A performed the research and analyzed the data; Carvalho J performed the research and analyzed the data.

Conflict-of-interest statement: The authors declare no conflict of interest for this article, including commercial, personal, political, intellectual or religious interests.

Manuscript source: Invited manuscript

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Received: April 9, 2016
Peer-review started: April 10, 2016
First decision: June 6, 2016
Revised: June 17, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: September 16, 2016

Abstract

Evaluation of the quality of small-bowel cleansing is required to assess the reliability of findings in capsule endoscopy (CE). Moreover, consensus regarding the need of intestinal preparation for CE remains to be achieved. The presence of multiple grading scales for small-bowel preparation in CE, which are time-consuming and complicated, adds difficulty to the comparison of different small-bowel cleansing regimens and their application in clinical practice. Nowadays, a validated scale universally accepted for grading small-bowel cleansing is lacking. In fact, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analyzed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score. The authors performed a review which aims to systematize and summarize currently available small-bowel grading scales in CE.

Key words: Capsule endoscopy; Small-bowel; Small-bowel Cleansing Scales; Enteroscopy; Grading

Core tip: Evaluation of the quality of small-bowel cleansing is required to assess the reliability of findings in capsule endoscopy (CE). Moreover, consensus regarding the need of intestinal preparation for CE remains to be achieved. Currently, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analyzed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score. The main purpose of this review is to gather and concise all small-bowel cleansing scales in CE available, as this has not been previously performed.

Ponte A, Pinho R, Rodrigues A, Carvalho J. Review of small-bowel cleansing scales in capsule endoscopy: A panoply of choices. *World J Gastrointest Endosc* 2016; 8(17): 600-609 Available from: URL: http://www.wjgnet.com/1948-5190/full/

v8/i17/600.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.600

INTRODUCTION

Capsule endoscopy (CE) was introduced into clinical practice in 2001, and since then it has assumed an important role in the study of numerous small-bowel disorders, namely obscure gastrointestinal bleeding, Crohn's disease, small-bowel tumors, polyposis syndromes and celiac disease[1-4].

The diagnostic yield of CE and quality of mucosal visualization may be impaired by the presence of air bubbles, bile and intestinal debris. Moreover, evidence for the optimal approach for small-bowel preparation before CE is lacking. These research and clinical aspects emphasize the importance of a grading scale of small-bowel cleansing in CE, as the evaluation of the quality of small-bowel preparation is necessary to assess the accuracy of the findings in CE[5,6] and the presence of a universal grading score would contribute to standardize CE protocols and to compare the results of different methods of small-bowel preparation[6,7].

Nowadays, a validated scale universally accepted for grading small-bowel cleansing is lacking. In fact, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analysed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score.

This review aims to systematize and summarize available small-bowel grading scales in CE (Tables 1 and 2).

DISCUSSION

Computer dependent scales

In recent years, computer grading scales to evaluate small-bowel cleanliness have been developed and validated (Table 1)[6,8]. These computed scores are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Furthermore, the incorporation of these scores into the CE reading software would result in a fully automated score[6].

Van Weyenberg *et al*[6] developed a computed assessment of cleansing (CAC) score, based on objective measurements of colour intensities in red and green channels of the tissue colour bar of the Rapid Reader® in the PillCam CE® system. The authors assumed that if the tissue colour bar, which comprises the summary of all CE images, was converted to the red-green-blue mode (RGB), the relation between the mean intensity of the red and green channels could be used as a measure of small-bowel cleanliness. Therefore, areas of adequate mucosal visibility could be associated with high values of red intensity and low values of green intensity. Conversely, areas with high amount of intestinal debris could be associated with low values of red intensity and high values of green intensity. The mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar were determined using the histogram function of a photo-editing software. The final score was obtained by applying the formula [(Mean intensity of the red channel)/(Mean intensity of the green channel) - 1] × 10. The CAC score was further compared with three validated grading scales[5]. In this study, the authors concluded that the CAC score had a very good reproducibility and could be used to assess the overall and segmental quality of small-bowel cleanliness. Moreover, CAC score achieved a strong agreement with previously validated subjective scales[5].

Due to the potential advantage of a computed score of small-bowel cleansing in CE, other studies were developed to adapt the CAC score to the OMOM and MiroCam CE systems[9,10]. Ponte *et al*[10] aimed to adapt the CAC score to the MiroCam system and to evaluate its reliability with the MiroCam® CE system. The MiroCam reading software (Miroview Client®) has a function named "Map View" which displays a bar containing a representation of all images recorded by the CE. Although this bar can be zoomed, without zoom the bar is similar to the tissue colour bar of the Rapid Reader® in the PillCam® CE system. Applying the same methodology as used by Van Weyenberg *et al*[6], the mean intensities of the red and green channels of the small-bowel segment of the "Map View" bar of Miroview Client® were determined using the histogram option of two photo-editing softwares. The authors concluded that the reproducibility of the CAC score was excellent as the results of the two different photo-editing softwares were identical, resulting in an intra-test reliability of 1.0 ($P < 0.001$). CAC score achieved a moderate agreement with previously validated subjective scales[5]. The results were slightly inferior to those of Van Weyenberg *et al*[6] but still significant and reinforce the feasibility of the CAC score in the assessment of the intestinal preparation in CE systems other than the PillCam®.

More recently, Klein *et al*[8] designed and validated a computer algorithm based on the pixels in the tissue colour bar of the CE PillCam® system. To develop this algorithm, multiple points on the colour bar corresponding to a spectrum of inadequately or adequately segments were marked and defined as "adequate" or "inadequate" criteria. These criteria were defined based on the pixel color and hue derived from the pixel RGB values. A computer algorithm based on the pixels in each of the marked areas was then created, and applied to the entire tissue colour bar. Each pixel of the tissue colour bar was independently compared to the predefined criteria "adequate"/"inadequate". The computer algorithm then calculated and summarized the total number of "inadequate" pixels, their locations, the "adequate" to "inadequate" pixel ratio and the longest duration of consecutive "inadequate" pixels in the colour bar. Based on the image analysis results, the algorithm quantified

Table 1 Computer dependent scales

Ref.	Computer or human dependent	Capsule endoscopy system	Type of preparation	Qualitative/ quantitative scale	Reproducibility	Parameters evaluated	Entire video, segments of video or consecutive single frames	Time-consuming	Easy to perform[1]	Global assessment[2]
Van Weyenberg *et al*[6]	Computer dependent	PillCam	2 L of PEG	Quantitative	$r = 1.0$	Mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar	Tissue colour bar	No	ΔΔΔΔΔ	ΔΔΔΔ
Ponte *et al*[10]	Computer dependent	MiroCam	Clear liquid diet and overnight fast	Quantitative	$r = 1.0$	Mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar	Map view bar	No	ΔΔΔΔΔ	ΔΔΔΔ
Klein *et al*[8]	Computer dependent	PillCam	Clear liquid diet and overnight fast	Quantitative	Kappa = 0.9	Pixels of the small-bowel segment of the tissue colour bar	Tissue colour bar	No	ΔΔΔΔΔ	ΔΔΔΔ

[1]Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to easier scales; [2]Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to better scales. PEG: Polyethylene glycol.

the level of bowel preparation and a final result based on predetermined criteria was produced. Computer analysis restricted to adequate and inadequate cases yielded accurate classification of bowel preparation when compared to the subjective opinion of the authors with a sensitivity of 95%, specificity 82%, total accuracy 90%, and kappa 0.79.

OPERATOR DEPENDENT SCALES

The numerous operator dependent scales which have been developed are summarized in Table 2. Throughout this revision, the authors classified the scales taking into consideration the type of parameters that were used: Quantitative and/or qualitative.

Quantitative parameters

Park *et al*[11,12] developed and validated an operator dependent grading score which consists of the assessment of two parameters in the PillCam® CE, in patients who received 4 L of polyethylene glycol (PEG). The first parameter corresponds to the percentage of mucosa visualized which is classified from 0 to 3: Score 3, $\geqslant$ 75%; score 2, 50%-75%; score 1, 25%-50%; score 0, $\leqslant$ 25%. The second parameter refers to the degree of obscuration by bubbles, debris, and bile which is also classified from 0 to 3: score 3 (no obscuration), < 5%; score 2 (mild obscuration), 5%-25%; score 1 (moderate obscuration), 25%-50%; score 0 (severe obscuration), $\geqslant$ 50%. The two parameters of the Park's score were evaluated in images from the entire small bowel selected at 5-min intervals (1 frame/5 min). Mean scores of each parameter were obtained by summing the scores of all selected images and dividing them by the number of frames examined. The final score was then calculated by the overall average of the two mean scores. This scale showed an excellent inter-observer, intra-patient and intra-observer agreement. Moreover, the authors proposed a cut-off value of 2.25 for an adequate small-bowel preparation. The main limitation of this grading scale is the use of only 1 frame at 5 min intervals in the analysis of small bowel cleansing, which leaves the great majority of available frames unanalysed.

Brotz *et al*[5] developed and validated three grading systems in CE PillCam®, namely a quantitative index (QI), a qualitative evaluation (QE) and an overall adequacy assessment (OAA). As the QE and OAA are based on qualitative parameters, these scores are described in the corresponding section. In their study, patients received a clear liquid diet the day before the exam and an overnight fast. The QI was obtained by assessment of 5 elements [(1) Mucosal visualization; (2) Fluid and debris; (3) Bubbles; (4) Bile/chyme staining, and (5) Brightness], according to a 3-point scale (0 = severe impairment, 1 = moderate impairment, 2 = minimal impairment), leading to a total score ranging from 0 to 10, with higher scores corresponding to better cleansing. QI obtained a moderate interobserver agreement. As opposed to Park's score,

Table 2 Human dependent scales

Ref.	Computer or human dependent	Capsule endoscopy system	Type of preparation	Qualitative/ quantitative scale	Correlation coefficient	Parameters evaluated	Entire video, segments of video or consecutive single frames	Time-consuming	Easy to perform[1]	Global assessment[2]
Park *et al*[11]	Human dependent	PillCam	4 L of PEG	Quantitative	ICC = 0.80	Proportion of visualized mucosa and degree of obscuration by bubbles, debris, and bile	Consecutive single frames	Yes	ΔΔ	ΔΔΔ
QI - Brotz *et al*[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Quantitative	ICC = 0.47	QI based on percentage of mucosa visualized, fluid and debris, bubbles, bile/chyme staining, and brightness	Entire video	No	ΔΔΔΔ	ΔΔΔΔΔ
Spada *et al*[13]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 2 L of PEG and simethicone	Quantitative	Kappa = 0.75-0.9	Proportion of mucosa visualized	Entire video	Yes	Δ	ΔΔΔ
Oliva *et al*[14]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 25 or 50 mL/kg of PEG, and/or 20 mL of simethicone	Quantitative	Kappa = 0.89	Proportion of mucosa visualized	Consecutive single frames	Yes	ΔΔ	ΔΔΔ
van Tuyl *et al*[15]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 1 L of PEG, or 2 L of PEG	Quantitative	Kappa = 0.78	Proportion of mucosa visualized	Segments of video	No	ΔΔ	ΔΔΔ
Caddy *et al*[16]	Human dependent	-	250 mL sodium picosulphate plus 500 mL PEG with or without erythromycin	Quantitative	Kappa = 0.3	Proportion of visualized mucosa	Entire video	No	ΔΔΔΔ	ΔΔ
Viazis *et al*[19]	Human dependent	PillCam	Clear liquid diet and overnight fast or 2 L PEG	Quantitative	-	Proportion of unclean mucosa due to intestinal debris	Entire video	Yes	ΔΔΔ	ΔΔ
Kantianis *et al*[22]	Human dependent	PillCam	2 and 4 L of PEG	Quantitative	-	Proportion of mucosa visualized	Consecutive single frames	Yes	Δ	Δ
Chen *et al*[23]	Human dependent	OMOM	Clear liquid diet and overnight fast, or 250 mL mannitol with or without simethicone	Quantitative	-	Proportion of mucosa visualized	Consecutive single frames	Yes	Δ	Δ
Rosa *et al*[25]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 2 L of PEG with or without simethicone	Quantitative	-	Proportion of visualized mucosa	Entire video	Yes	ΔΔ	ΔΔ
Niv *et al*[26]	Human dependent	PillCam	Clear liquid diet and overnight fast, or NaP	Quantitative	-	Proportion of SBTT with invisible mucosa	Entire video	No	ΔΔΔ	ΔΔΔ
OAA - Brotz *et al*[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Qualitative	Kappa = 0.41	Overall assessment of small-bowel cleansing	Entire video	No	ΔΔΔΔΔ	ΔΔΔ
QE - Brotz *et al*[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Qualitative	Kappa = 0.20	QE based on percentage of mucosa visualized, fluid and debris, bubbles, bile/chyme staining, and brightness	Entire video	No	ΔΔΔΔ	ΔΔΔ
Albert *et al*[28]	Human dependent	PillCam	Overnight fast or simethicone	Qualitative	r = 0.89 (segment A)	Mucosal invisibility due to intraluminal bubbles	Segments of video	No	ΔΔΔ	ΔΔΔ

					and $r = 0.79$ (segment B)					
Pons Beltrán *et al*[29]	Human dependent	PillCam	Clear liquid diet, or 90 mL NaP, or 4 L of PEG	Qualitative	Kappa = 0.38	Amounts of enteric residues	Entire video	No	ΔΔΔΔ	ΔΔΔ
Ninomiya *et al*[30]	Human dependent	PillCam	Clear liquid diet and overnight fast, or citrate magnesium	Qualitative	-	Bubbles, food residues and intestinal juice color	Consecutive single frames	Yes	ΔΔ	ΔΔ
Esaki *et al*[31]	Human dependent	PillCam	Simethicone or magnesium citrate	Quantitative and Qualitative	r = 0.77-0.88	Fluid transparency and proportion of non-visualized mucosa	Entire video	Yes	ΔΔΔ	ΔΔΔΔ
Dai *et al*[32]	Human dependent	PillCam	4 L of PEG or overnight fast	Quantitative and qualitative	Kappa = 0.56	Proportion of visualized mucosa and overall visibility	Segments of video	Yes	ΔΔ	ΔΔΔ
Lapalus *et al*[33]	Human dependent	PillCam	Clear liquid diet and overnight fast, or NaP	Quantitative and qualitative	$r = 0.55$-0.8	Proportion of visualized mucosa and amounts of enteric liquid and bubbles	Segments of video	No	ΔΔΔ	ΔΔΔ
Hooks *et al*[34]	Human dependent	PillCam	Clear liquid diet and overnight fast, with or without lubiprostone	Quantitative and qualitative	-	Proportion of mucosa visualized and amounts of enteric debris	Entire video and segments of video	No	ΔΔΔ	ΔΔΔΔ

[1]Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to easier scales; [2]Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to better scales. PEG: Polyethylene glycol; QI: Quantitative index; QE: Qualitative evaluation; OAA: Overall adequacy assessment; ICC: Intraclass correlation coefficient.

the QI uses all available frames in the evaluation of small bowel cleansing.

Spada *et al*[13] developed an operator dependent small-bowel scale in PillCam® CE to evaluate different regimens of intestinal preparation. It consisted of a classification in "complete", "incomplete" and "insufficient" if visualization of the mucosa was equal to 100%, between 50%-100%, or less than 50%, respectively. This assessment was evaluated minute by minute and the overall small-bowel cleansing score was then calculated by determining the percentage of each classification. If different grades of cleansing level were present in each minute, the overall preparation level per minute was synthesized as follows: "complete", if the entire small-bowel wall was assessable for 35 s or more, with no more than 5 s of "insufficient" cleansing; "insufficient" if less than 50% of the small bowel wall was visible for 20 s or more; and "incomplete" in all the other cases. The authors achieved a good-to-excellent inter-observer agreement, with a kappa = 0.9 for completely clean and insufficiently clean small-bowel and a kappa = 0.75 for incompletely clean small bowel. The main limitation is that this scale is very cumbersome to perform and time-consuming.

In a study in paediatric patients using PillCam® CE, Oliva *et al*[14] applied a method of evaluation of small-bowel cleanliness similar to the score of Park *et al*[11]. The small-bowel transit time (SBTT) was divided into five equal segments and in each segment an image was picked at 5-min intervals. Every single image was evaluated according to the percentage of visualized mucosal surface area as follows: (1) < 25%; (2) 25%-49%; (3) 50%-74%; (4) 75%-89%; and (5) > 90%. Mean scores for each segment were obtained by summing the scores of all selected images and dividing the sum by the number of images. The total score for each patient was obtained by adding the five segmental scores. The authors achieved an excellent interobserver agreement (kappa 0.89) with this scale. This scale has, however, the same sampling limitations as the Park's scale.

In order to compare different small-bowel preparations for PillCam® CE, van Tuyl *et al*[15], developed a grading scale which analysed the amount of mucosa visualized. For each CE, the SBTT was divided in four quartiles and the first ten minutes of each quartile was classified according to the percentage of mucosa visualized. Moreover, the last ten minutes of the small intestine were also analysed. The visualization of the mucosa was graded into 6 categories: less than 5%, 5%-24%, 25%-49%, 50%-74%, 75%-95%, or more than 95%. Mucosal visibility was considered good if more than 75% of the mucosa was observed, otherwise it was graded as poor. Interobserver agreement for mucosal visualization was high with a kappa of 0.78. Although this scale is easier to perform than Park's and Oliva's scales, the level of cleanliness of significant portions of the CE video remain unexamined.

Caddy *et al*[16] developed a 4-graded scale which was further adopted in other studies[17,18], to analyse the effect of erythromycin in the completion rate of CE to the cecum. The scale consisted of the percentage of mucosa visualized which was graded as excellent, good, fair or poor if ⩾ 95%, 75%-94%, 50%-74%, and < 50% of the mucosa was visualized, respectively. The authors reported a poor inter-observer agreement with kappa 0.3. Nevertheless, if the parameters excellent and good were aggregated, a good level of agreement was achieved with a kappa of 0.7. Although this scale is easy and fast to implement, its low reproducibility limits its utilization.

In order to analyse the difference in small-bowel cleansing in patients receiving 2 L of a PEG and electrolyte lavage solution or ingesting a clear liquid diet during the entire day before PillCam® CE, Viazis *et al*[19] developed a classification which was subsequently adopted by other authors[20,21]. The enteric mucosa was classified as clean if less than 25% of it was covered by debris or intestinal contents. This small-bowel cleansing score consisted of recording the exact period of time during which the mucosa was considered unclean. If the total period was inferior to 10% of the SBTT the cleansing was classified was "adequate". Conversely, it was classified as "inadequate" if the period of time of unclean mucosa exceeded 10% of the SBTT. Despite the authors recognized the simplicity of use of this classification, this scale lacks validity and is cumbersome to implement.

In the study developed by Kantianis *et al*[22] to compare small-bowel cleansing using 2 L or 4 L of PEG, a 3-scale scoring system according to the visibility of the small-bowel mucosa in consecutive single frames captured every 3 min of the SBTT was adopted. Three points were given when 60%-100% of the mucosa was visible, 2 points when visibility of the mucosa ranged from 30% to 60% and 1 point if less than 30% of the mucosa was visible. The final score was obtained by dividing the sum of scores of each frame by (the total number of frames × 3), thus leading to a cleansing coefficient range between 0.33 (indicating the worst preparation) and 1.00 (indicating the ideal preparation). Although simple, the same limitations as other scales like Park's that use sampling frames remains.

In another study to evaluate different small-bowel regimens with mannitol and simethicone, Chen *et al*[23] created a method of evaluation of small-bowel cleansing using consecutive single frames of the small-bowel video selected at 3 min intervals. In each frame, the area of visible mucosa was outlined and calculated, as well as the area of the entire image. The ratio of both areas was graded as excellent (3 points), good (2 points), fair (1 point) and poor (0 point) if the ratio was 76%-100%, 51%-75%, 26%-50%, and 0%-25%, respectively. For overall assessment, small bowel cleansing for proximal and distal small bowel was separately graded, and considered adequate if the percentage of single frames assessed that was graded as good or excellent was ⩾ 85%, and inadequate otherwise. In a subsequent study[9], the same group of authors compared this scale, which they designated as assessment of cleansing score (AAC) with the CAC developed by Van Weyenberg *et al*[6]. The authors concluded that the assessment of interobserver reliability of these two scores showed a high intraclass correlation coefficient (ICC) and no significant difference between them was found using the kappa statistic. For AAC, the ICC was 0.791.

Similar to other studies[19,21,24], a 4-point scale based on the proportion of enteric mucosa visualized without any liquid, bubbles or debris was adopted by Rosa *et al*[25] in order to assess the difference in small-bowel cleansing using a liquid diet and an overnight fast or 2 L of PEG with or without simethicone. The authors recorded with the time counter of the Rapid Reader® software the exact time period during which the mucosa was not clean, due to contamination with fluid or debris. The presence of bubbles was evaluated separately. Small-bowel cleansing was graded in excellent in cases of perfect visualization in every small-bowel segments, in good where > 75% of the mucosa was in perfect conditions, with some fluid or debris remaining not interfering with the examination, in fair if 50%-75% of the mucosa was clean, with presence of enough fluid, bubbles or debris to prevent completely reliable examination and in poor if < 50% of the mucosa was clean with the presence of significant amounts of fluid or debris. The authors considered an adequate small-bowel preparation if > 75% of the mucosa was clean, corresponding to the "excellent" and "good" scores.

Niv *et al*[26] developed a cleansing scale taking into account the proportion of the SBTT which was filled with intraluminal fluid preventing visualization of the mucosa. The proportion of non-ideal visualization was determined, dividing the time duration of non-ideal visualization recorded with the time counter of the Rapid Reader® software by the SBTT. The degree of cleanliness was graded as good if this ratio is < 20%, moderate when between 21%-35% and poor if > 35%.

Qualitative parameters

As previously detailed, Brotz *et al*[5] developed and validated three grading systems in PillCam® CE system, namely a QI, a QE and an OAA. The QE was categorized in poor, fair, good and excellent according to the percentage of enteric mucosa visualized, the amounts of debris, bubbles, bile and level of brightness (Table 3). The OAA consisted of global assessment of small-bowel cleansing and rated as "adequate" or "inadequate". The authors concluded that the QI had the greatest reliability, the reliability for the OAA was in the moderate range, while the QE performed more poorly. Quantitative scales provide parameters more uniformly assessed thus reducing the subjective interpretation and providing a better evaluation of the small-bowel preparation level. These scales were adopted in other studies[27].

Albert *et al*[28] adopted a 4-grade system based on qualitative parameters do assess bowel preparation using the PillCam® CE system. Two segments of 1-h duration were selected, with the first segment (segment A) starting immediately after passage of CE through the

Table 3 Qualitative evaluation of small-bowel cleanliness developed by Brotz *et al*[5]

Qualitative evaluation
Excellent: Visualization of ⩾ 90% of mucosa; no or minimal, fluid and debris, bubbles, and bile/chyme staining; no or minimal, reduction of brightness
Good: Visualization of ⩾ 90% of mucosa; mild fluid and debris, bubbles, and bile/chyme staining; mildly reduced brightness
Fair: Visualization of < 90% of mucosa; moderate fluid and debris, bubbles, and bile/chyme staining; moderately reduced brightness
Poor: Visualization of < 80% of mucosa; excessive fluid and debris, bubbles, and bile/chyme staining; severely reduced brightness

Table 4 Grading scale of intestinal cleansing proposed by Ninomiya *et al*[30]

Residue elimination effect	
4 points	No food residue at all, clear views
3 points	Some food residue present, not interfering with observations
2 points	Quite a lot of food residue, slightly hindering observations
1 points	Large amount of food residue, hindering observations
Intestinal juice clarity	
4 points	Intestinal juice is clear, clear views
3 points	Intestinal juice is light colored and does not interfere with observations
2 points	Intestinal juice is light dark colored, slightly hindering observation
1 points	Intestinal juice is dark colored and interferes with observations
Froth reduction effect	
4 points	No froth, clear views
3 points	Froth present, not interfering with observations
2 points	Quite a lot of froth, slightly hindering observations
1 points	Large amount of froth, hindering observations

pylorus and the other segment (segment B) finishing before the passage through the ileocecal valve. In each segment, the impairment of visibility of the mucosa due to intraluminal gas bubbles was evaluated and graded as (0) if there was no intraluminal gas; (1) if only a few gas bubbles not limiting the interpretation were seen; (2) if there was an increased amount of intraluminal gas bubbles which moderately impaired visibility; and (3) if a large amount of gas bubbles which severely limited the interpretation of mucosal surface were found. Of note, the amount of food residue or small-bowel secretions was not analysed. This grading scale obtained a good interobserver agreement, with a Spearman correlation of $r = 0.89$ in segment A ($P < 0.001$) and $r = 0.79$ ($P < 0.001$) in segment B. This scale also suffers from sampling error limitations, as only two segments with 1-h duration from the entire CE video are analysed.

Pons Beltrán *et al*[29] proposed a 4-point subjective score of "poor", if there was intestinal content impending evaluation, "fair", if there was liquid or solid intestinal content allowing evaluation, "good", if there was no intestinal content or some content in the terminal ileum and/or cecum and "excellent", if there was no intestinal content in any part of the small-bowel or the cecum. Differently from QE, the enteric level of cleanliness in PillCam® CE was judged according to the amount of intestinal content throughout the small-bowel and cecum. Due to the subjectivity of the assessed parameter, the interobserver agreement was fair, with a kappa = 0.38.

In a study to assess the effect of magnesium citrate in small-bowel cleansing in PillCam® CE, Ninomiya *et al*[30] classified from 0 to 4, each of three parameters, namely food residue, intestinal juice clarity and bubbles (Table 4). After dividing the SBTT into three segments, images from each segment were recorded and classified according to the three parameters.

Quantitative and qualitative parameters

Esaki *et al*[31] developed a grading scale using the PillCam® CE system to assess the differences in small bowel preparation with magnesium citrate or simethicone. After determining the terciles of the SBTT, the authors evaluated the fluid transparency and mucosal invisibility in each segment, according to Table 5. The grade of fluid transparency was determined according to the predominant grade in each segment. The grade of mucosal invisibility was determined in each video segment by the proportion of duration in which air bubbles or food residues disturbed more than 50% of its visualization and interpretation. The overall score for each parameter corresponded to the sum of the grades obtained in each segment, ranging from 3 to 12. The authors achieved an excellent interobserver agreement in each segment analysed, with the results showing a strong correlation ($r = 0.88$, $P < 0.0001$ in the first tercile; $r = 0.77$, $P < 0.0001$ in the second tercile; $r = 0.81$, $P < 0.0001$ in the third tercile). Conversely, this grading system was applied by other authors who obtained a moderate intra-observer agreement (kappa = 0.52) and a poor interobserver agreement (kappa = 0.29 for fluid transparency and kappa = 0.42 for mucosal invisibility)[7].

Dai *et al*[32] studied the effect of bowel preparation with 4 L of PEG in small-bowel cleanliness. To assess the enteric cleanliness, the authors used an overall assessment of quality based on a 4-step scale: (1) large volume of residual ingested food or fecal material; (2) moderate volume of residual ingested food; (3) small volume of residual ingested food; and (4) clear or colored liquid. They also determined the proportion of the enteric wall visualized using 10-min video segments at 1-h intervals: (1) less than 25%; (2) 25% to 49%; (3) 50% to 75%; and (4) greater than 75%. The authors concluded that the score was subjective, as reflected by the fair interobserver agreement achieved with a kappa = 0.56.

Lapalus *et al*[33] created a small-bowel cleansing score in PillCam® to evaluate the effect of oral sodium phosphate in small-bowel preparation. The preparation was evaluated in five segments of 5 min, with the first segment starting at 5 min after passage of the CE

Table 5 Small-bowel cleansing scale of Esaki *et al*[31]

Fluid transparency	
Grade 1	Clear fluid without obscuring vision
Grade 2	Slightly dark fluid minimally obscuring vision
Grade 3	Opaque fluid partly obscuring vision
Grade 4	Turbid fluid severely obscuring vision
Mucosal invisibility[1]	
Grade 1	< 5% in duration of > 50% bubbles or residues
Grade 2	5%-15%
Grade 3	15%-25%
Grade 4	> 25%
Overall image quality[2]	
Grade A	3-5
Grade B	6-8
Grade C	9-12

[1]The percentage indicates the proportion of length of time of video image in which air bubbles or food residues disturbed more than 50% of visualization and interpretation; [2]The number indicates the sum of grades in each small intestinal segment.

through the pylorus, and the last segment corresponding to the 5 min before passage through the ileocecal valve. The remaining segments started at one fourth, one half, and three fourths of the SBTT. Each segment was graded in a 4-point scale according to the bowel cleanliness (1) no liquid and no bubbles (excellent); (2) clear liquid (good); (3) dark liquid and/or air bubbles (fair); and (4) food residue (poor) and the proportion of mucosa visualized [(1) $\geqslant$ to 75% of the mucosa visualized; (2) 50% to 74% of the mucosa visualized; (3) 25% to 49% of the mucosal visualized; and (4) $\leqslant$ to 24% of the mucosa visualized]. The interobserver agreement for the score of cleansing varied between 0.55 and 0.69 and for the score of visibility varied between 0.55 and 0.8.

Similarly to the previous grading scale, Hooks *et al*[34] developed a grading scale with quantitative and qualitative parameters using PillCam® CE to evaluate the effect of lubiprostone in the gastric and small-bowel transit time and in the enteric preparation. This last parameter was analysed with a 4-point scale considering the overall preparation in the proximal, middle and distal small bowel and the amount of mucosa visualized in 10-min segments at one-hour intervals, as described in Table 6.

In summary, various grading scales to assess the cleanliness of small-bowel in CE have been proposed, and a consensus regarding which scale is better remains to be achieved. Computer grading scales are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Current results of computer grading scales are encouraging and the future may encompass the incorporation of a fully automated cleansing score in the software of CE. Nevertheless, more research is warranted to ameliorate and achieve an optimal computed score completely independent of human action.

In human dependent grading scales, the authors consider that those which include the entire video have more advantages as the operator may score the small-bowel cleanliness during CE analysis, thus reducing the time of the procedure as the re-evaluation of single frames or segments of video is avoided. Moreover, sample bias is avoided as the overall video will be evaluated. The authors also conclude that operator dependent scales based on quantitative parameters may reduce subjective interpretation and provide a better evaluation of the small-bowel preparation level. Despite the heterogeneity of the methodology adopted by the developers of each small-bowel grading system in CE, which limit the comparison between the operator dependent grading scales, the authors suggest that the QI grading scale of Brotz *et al*[5] may aggregate the best characteristics for evaluation of small-bowel cleanliness in CE.

Table 6 Small-bowel cleansing scale of Hooks *et al*[34]

Overall preparation	
Excellent	Small bits of adherent solid material with clear or colored liquid
Good	Few liquids, small amounts of solid material, or dark fluid that did not interfere with the examination
Fair	Enough solid material or dark liquid to prevent a reliable examination
Poor	Large volume of residual food or fecal material precluding a complete examination
Proportion of mucosa visualized	
4 points	> 75%
3 points	50%-75%
2 points	25%-49%
1 point	< 25%

CONCLUSION

Numerous small-bowel grading scales to assess the cleanliness in CE have been developed, and a consensus regarding a universally accepted scale is lacking.

Computer grading scales are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Concerning human dependent grading scales, only few are validated and there is a huge heterogeneity regarding the methodology of each scale, namely the parameters and portion of the CE analysed and the objectivity of the analysis. Finally, human dependent scales which are based in quantitative assessments are more uniformly assessed thus reducing the subjective interpretation and providing a better evaluation of the small-bowel preparation.

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P- Reviewer: Christodoulou DK, Stanciu C, Sakin YS
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Li D

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i17.610

World J Gastrointest Endosc 2016 September 16; 8(17): 610-615
ISSN 1948-5190 (online)

Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges

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Author contributions: All authors contributed equally to this paper with conception and design of the study, literature review and analysis, drafting, critical revision and editing, and final approval of the final version.

Supported by Science and Technique Project of Guangdong Province, No. 2012B031800284.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

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Received: March 27, 2016
Peer-review started: March 28, 2016
First decision: May 17, 2016
Revised: June 2, 2016
Accepted: June 27, 2016

Article in press: June 29, 2016
Published online: September 16, 2016

Abstract

Primary immune thrombocytopenia (ITP) is an immune-mediated disorder affecting both adults and children, characterised by bleeding complications and low platelet counts. Corticosteroids are the first-line therapy for ITP, but only 20%-40% of cases achieve a stable response. Splenectomy is the main therapy for patients failing to respond to corticosteroids for decades, and about two-thirds of patients achieve a long-lasting response. Although some new drugs are developed to treat ITP as second-line therapies in recent years, splenectomy is still the better choice with less cost and more efficiency. Laparoscopic splenectomy (LS) for ITP proves to be a safe technique associated with lower morbidity and faster recovery and similar hematological response when compared to traditional open splenectomy. Based on the unified hematological outcome criteria by current international consensus, the response rate of splenectomy should be reassessed. So far, there are not widely accepted preoperative clinical indicators predicting favorable response to LS. Since the patients undergoing surgery take the risk of complications and poor hematological outcome, the great challenge facing the doctors is to identify a reliable biomarker for predicting long-term outcome of splenectomy which can help make the decision of operation.

Key words: Laparoscopic splenectomy; Corticosteroids; Open splenectomy; Hematological outcome; Predictor; Biomarker; Immune thrombocytopenia

Core tip: Despite the new drugs developed to treat primary immune thrombocytopenia, splenectomy is still

the main therapy for patients who fail corticosteroid treatment. Laparoscopic splenectomy proves to be a preferable technique compared to open splenectomy. The response rate to splenectomy should be reassessed based on the unified outcome criteria by current international consensus. So far, there are not widely accepted preoperative indicators predicting response to laparoscopic splenectomy. The challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

Zheng D, Huang CS, Huang SB, Zheng CX. Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges. *World J Gastrointest Endosc* 2016; 8(17): 610-615 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/610.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.610

INTRODUCTION

Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenic purpura, is an immune-mediated disease characterized by bleeding complications and low platelet counts in both children and adults[1]. ITP occurs at an annual rate of 1.9 to 6.4 per 100000 children and 3.3 per 100000 adults[2]. Bleeding symptoms are highly variable in primary ITP. According to a newly published systematic review that enrolled all prospective ITP studies with 20 or more patients, weighted proportion for intracerebral hemorrhage (ICH) was 0.4% for children and 1.4% for adults, and severe (non-ICH) bleeding rate was 20.2% for children and 9.6% for adults[3]. The term "purpura" was inappropriate because bleeding symptoms are absent or minimal in a large proportion of cases[4,5]. Therefore, an International Working Group (IWG) of recognized experts suggested to replace the original term "idiopathic thrombocytopenic purpura" or "immune thrombocytopenic purpura" with the term "immune thrombocytopenia"[1]. The new term was soonly accepted by the American Society of Hematology (ASH) and the new ASH guidelines[6].

Corticosteroids were introduced in the 1950s to treat ITP[7]. Until now, corticosteroids are still recommended as the first-line therapy in primary ITP by current international consensus[8]. However, only 20%-40% of patients can achieve a stable response with steroid treatment[9,10]. Splenectomy is recommended as the main second-line method for patients who do not respond to steroid or relapse for a long time[1]. Since the first laparoscopic splenectomy (LS) was reported by Delaitre *et al*[11] in 1991, this technique has gradually replaced traditional open splenectomy (OS) in surgical treatment of ITP. The following is our review of the current status and challenges of LS for ITP.

OVERVIEW OF PATHOPHYSIOLOGY OF ITP

Understanding of the immunopathogenesis of ITP is very important for treatment of this disease. The mechanisms which cause the accelerated platelet destruction and the inhibited platelet production are very complicated and intricate, for several abnormalities are involved in its immunopathogenesis. In terms of humoral immune dysregulation, the increased expression of B cell-activated factor and cyclophilin ligand interactor can prolong the survival and enhance the proliferation of B cells[12], and B cells can produce substantial antiplatelet autoantibodies against GP Ⅱb/Ⅲa and GP Ⅰb/Ⅸ[13]. Macrophages in the spleen and liver can destroy those autoantibody-combined platelets, causing the accelerated platelet destruction. Besides that, autoantibodies can also inhibit megakaryocyte production and maturation and platelet release, thus leading to the decreased platelet production[14]. As for cellular immune dysregulation, multiple cell types are involved in the development of ITP. $CD4^+CD25^+$ regulatory T cells (Treg cells) which can depress T cell responses are found quantitatively and functionally impaired[15]. In patients with ITP, the considerably high Th1/Th2 ratio[16], the increase of Th17 and Th22 cells[17], and the augment of $CD3^+$ cytotoxic T cells have been found[18]. Dysfunctions of macrophages and dendritic cells also take part in the immune disequilibrium of ITP patients[19].

THE STATUS OF SPLENECTOMY IN THE ERA OF NEW SECOND-LINE THERAPIES

Both intravenous anti-D immunoglobulin (IV anti-D) and intravenous immunoglobulin (IVIg) are recommended as first-line therapies for ITP in the international consensus report of IWG[1]. Either IV anti-D or IVIg produces short-term responses within 24-48 h in 60%-80% of patients. However, the responses are rarely durable beyond 4 wk[20,21]. In the past few decades, splenectomy is considered the first choice for ITP after failure treatment of corticosteroids. In recent years, some new drugs are developed to treat ITP and recommended as second-line therapies. These drugs include the monoclonal anti-CD20 antibody rituximab, recombinant human thrombopoietin molecule (rhTPO), and thrombopoietin receptor agonists (TPO-RAs). Some promising results have been reported in the treatment of ITP with these drugs. Thus whether continuing to regard splenectomy as the main second-line therapy has evoked much controversy. Rituximab has a depleting effect on B lymphocytes. However, its long-term effect is modest, for no significant differences in treatment failure rate within 78 wk between rituximab and placebo had been found [32 (58%) of 55 *vs* 37 (69%) of 54][22]. RhTPO and TPO-RAs (Eltrombopag and Romiplostim) can considerably promote the platelet production, but ITP patients should rely on these medica-

Table 1 Case series reporting 50 or more patients undergoing splenectomy for immune thrombocytopenia that contain platelet count response

Publication date	Accrual years	Ref.	Country	No. patients	Operation method	CR rate	R rate	NR rate	Relapse
2006[1]	1993-2003	Balagué *et al*[34]	Spain	103	LS	NA	NA	4.9%	6.1%
2007[2]	1988-2006	Sampath *et al*[29]	Canada	105	LS, OS	NA	NA	NA	21.6%
2007[1]	1994-2004	Kang *et al*[35]	South Korea	59	LS	47.5%	40.7%	11.9%	15.2%
2011[3]	2005-2010	Chen *et al*[36]	China	81	LS	88.9%	8.6%	2.5%	NA
2011[4]	1999-2006	Zheng *et al*[37]	China	127	LS	79.5%	9.5%	11%	9.7%
2013[3]	1982-2011	Gonzalez-Porras *et al*[38]	Spain	218	LS, OS	80.7%	8.3%	11.0%	36.1%
2014[3]	1995-2012	Montalvo *et al*[39]	Mexico	150	LS	88.7%	2.7%	8.6%	NA
2014[3]	2001-2009	Rijcken *et al*[40]	Germany	72	LS	77.8%	9.7%	12.5%	30.2%
2014[3]	2010-2012	Cai *et al*[41]	China	88	LS	77.3%	19.3%	3.4%	NA
2015[3]	1992-2013	Navez *et al*[42]	Belgium	82	LS	72.0%	24.4%	3.6%	NA

[1]Remission was defined as CR when platelet count increased to > 150 × 10^9/L, and as R when it was 50-150 × 10^9/L; [2]The criterion of ITP remission was not mentioned in the study; [3]Remission was defined as CR when platelet count increased to > 100 × 10^9/L, and as R when it was 30-100 × 10^9/L; [4]Remission was defined as CR when platelet count increased to > 100 × 10^9/L, and as R when it was 50-100 × 10^9/L. OS: Open splenectomy; LS: Laparoscopic splenectomy; CR: Complete response; R: Response; NR: No response; ITP: Immune thrombocytopenia.

tions, since these drugs only have short-term therapeutic effects[6,23]. Eltrombopag and Romiplostim were approved by the Food and Drug Administration for clinical use. While in many countries, these two drugs are unavailable. Splenectomy is also the second-line therapy for ITP patients who do not respond to first-line therapy. About 80% of ITP patients respond to splectomy and about two-thirds achieve a lasting response with no additional therapy for at least 5 years[8]. A systematic review of 23 articles and 1223 patients showed that by the resection of the site of platelet destruction and antiplatelet antibody production, laparoscopic splenectomy can cure 72% of ITP patients with long-term response[24]. Compared with expensive therapies with these drugs, splenectomy is less costly and more efficient[25]. Therefore, splenectomy is the better choice of the second-line therapy for ITP patients, especially in the developing countries.

TECHNIQUE ASPECTS OF LS

The comparison of the long-term outcomes and safety between LS and OS is always an issue. One systematic review[26] published in 2004 and some case series[27-29] in the past decade suggested that the hematologic efficacy of LS is the same as that of OS, while LS had fewer complications and mortality than OS. The systematic review[26] including 47 case series reported that mortality was 1.0% with OS and 0.2% with LS. Complication rates were 12.9% with OS and 9.6% with LS. The common complications of splenectomy include bleeding, thrombosis, pancreatic leakage, infection, prolonged hospitalization, requirement for additional intervention and readmission to the hospital; however, all the studies were retrospective. Randomized studies are needed to confirm this conclusion. LS has other advantages such as less postoperative pain, shorter hospital stays and better cosmetic outcomes[27,30]. Therefore, LS is preferred over OS for ITP by more and more surgeons.

In recent years, there are some case reports about the application of single-incision LS[31-33]. This technique emphasizes the concept of operation through one small transabdominal incision rather than the traditional multiple trocar sites, in order to show benefits of less pain and better cosmetics. However, because of the limited number of included patients in these studies, no obvious advantages of this technique could be showed when compared with traditional LS[31].

HEMATOLOGICAL OUTCOME CRITERIA

The response rate to splenectomy for ITP in different studies differs from each other. Case series[29,34-42] reporting 50 or more patients undergoing splenectomy for ITP that contain platelet count response are listed in Table 1. All these data were published in recent ten years and searched from PubMed database. One of the main reason for the discrepancies of hematological outcomes is the different definitions and clinical criteria which were used in different studies[9,43,44]. Fortunately, the standard terminology, definitions and outcome criteria for ITP have been unified[1,6]. In the new guidelines updated by ASH[6], a platelet count < 100 × 10^9/L was diagnosed as thrombocytopenia and a platelet count > 100 × 10^9/L or 30 × 10^9/L was diagnosed as complete response or partial response after splenectomy. The recommendations for using 100 × 10^9/L as an upper-threshold were based on three reasons: Over 10 years of follow-up, only 6.9% of patients with a platelet count between 100 and 150 × 10^9/L may develop a persistent platelet count < 100 × 10^9/L[45]. In some non-Western healthy individuals, platelet count values may be between 100 and 150 × 10^9/L[46-48]. Using 100 × 10^9/L as a threshold would reduce inclusion of most women with pregnancy-related thrombocytopenia[49]. The new guidelines will provide the evidence-based guidance for the diagnosis and therapy of ITP, as well as unified criteria for evaluating treatment outcome.

PREDICTORS OF SPLENECTOMY

Splenectomy is benefit for most of the patients, but there are still some patients who have a poor long-term

response. They should also take the risk of surgery, in the worst case, even death. So the choice of surgery is a deliberate decision. Many studies have attempted to determine reliable predictors of hematological response to splenectomy. Some factors including younger age[50,51], preoperative platelet count after using steroids and immunoglobulins[40,42], response to preoperative steroids[52,53], shorter disease duration (from diagnosis to splenectomy)[51], and splenic sequestration[54,55] have been reported as successful predictors of splectomy for ITP. But all the above conclusions cannot be verified in other studies. So far, there have been not widely accepted preoperative clinical indicators predicting response to splenectomy. Identifying a preoperative biological or immunological marker to predict long-term results of LS for patients with primary ITP will be the focus of future research. Our team has made preliminary progress toward this goal[56]. In our study, we showed that preoperative heptoglobin in serum may be a favourable predictor for the long-term response to splenectomy in ITP. Further studies with long-term follow-up and larger sample size are needed to confirm this finding. With the efforts of hematologists and surgeons, identifying biomarkers for favorable hematological outcome of ITP patients undergoing splenectomy and therefore avoiding invalid operation may come true in the future.

In summary, although some new drugs are developed as second-line therapies for primary ITP, splenectomy is still recommended as the first choice for patients who fail corticosteroid therapy. LS is a good alternative to OS for treatment of ITP. The great challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

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P- Reviewer: Dina I, Erginel B, Enomoto H
S- Editor: Qi Y **L- Editor**: Wang TQ **E- Editor**: Li D

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i17.616

World J Gastrointest Endosc 2016 September 16; 8(17): 616-622
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Predictors of suboptimal bowel preparation in asymptomatic patients undergoing average-risk screening colonoscopy

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Author contributions: Govani SM and Elliott EE drafted the paper; Govani SM, Elliott EE and Menees SB analyzed the data; Govani SM, Elliott EE, Menees SB, Judd SL, Saini SD, Anastassiades CP, Urganus AL and Boyce SJ performed chart review; Schoenfeld PS conceived and designed the study; all authors approved the final paper.

Institutional review board statement: The study was reviewed and approved for publication by our institutional reviewer.

Informed consent statement: Waiver of informed consent was obtained from our institutional review board.

Conflict-of-interest statement: Dr. Schoenfeld has worked as a consultant and advisory board member for Salix Pharmaceuticals, Inc, which is the manufacturer of MoviPrep®. Other authors have no conflicts of interest.

Data sharing statement: These analyses were performed using raw data that are available only within the US Department of Veterans Affairs firewall in a secure research environment, the VA Informatics and Computing Infrastructure (VINCI). In order to comply with VA privacy and data security policies and regulatory constraints, only aggregate summary statistics and results of our analyses are permitted to be removed from the data warehouse for publication. The authors have provided detailed results of the analyses in the paper. These restrictions are in place in order to maintain patient privacy and confidentiality. Access to these data can be granted to persons who are not employees of the VA; however, there is an official protocol that must be followed for doing so. Those wishing to access the raw data that were used for this analysis may contact Shail Govani (shailg@umich.edu) to discuss the details of the VA data access approval process. The authors also confirm that an interested researcher would be able to obtain a de-identified, raw dataset upon request pending ethical approval.

Manuscript source: Invited manuscript

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Received: March 20, 2016
Peer-review started: March 22, 2016
First decision: May 17, 2016
Revised: June 15, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016

Published online: September 16, 2016

Abstract

AIM

To identify risk factors for a suboptimal preparation among a population undergoing screening or surveillance colonoscopy.

METHODS

Retrospective review of the University of Michigan and Veteran's Administration (VA) Hospital records from 2009 to identify patients age 50 and older who underwent screening or surveillance procedure and had resection of polyps less than 1 cm in size and no more than 2 polyps. Patients with inflammatory bowel disease or a family history of colorectal cancer were excluded. Suboptimal procedures were defined as procedure preparations categorized as fair, poor or inadequate by the endoscopist. Multivariable logistic regression was used to identify predictors of suboptimal preparation.

RESULTS

Of 4427 colonoscopies reviewed, 2401 met our inclusion criteria and were analyzed. Of our population, 16% had a suboptimal preparation. African Americans were 70% more likely to have a suboptimal preparation (95%CI: 1.2-2.4). Univariable analysis revealed that narcotic and tricyclic antidepressants (TCA) use, diabetes, prep type, site (VA *vs* non-VA), and presence of a gastroenterology (GI) fellow were associated with suboptimal prep quality. In a multivariable model controlling for gender, age, ethnicity, procedure site and presence of a GI fellow, diabetes [odds ratio (OR) = 2.3; 95%CI: 1.6-3.2], TCA use (OR = 2.5; 95%CI: 1.3-4.9), narcotic use (OR = 1.7; 95%CI: 1.2-2.5) and Miralax-Gatorade prep *vs* 4L polyethylene glycol 3350 (OR = 0.6; 95%CI: 0.4-0.9) were associated with a suboptimal prep quality.

CONCLUSION

Diabetes, narcotics use and TCA use were identified as predictors of poor preparation in screening colonoscopies while Miralax-Gatorade preps were associated with better bowel preparation.

Key words: Preparation; Quality; Narcotics; Diabetes; Colonoscopy

Core tip: Suboptimal preparation quality affects the ability of endoscopists to identify polyps during colonoscopy, leading to repeated procedures or missed lesions. In this large retrospective review of screening and surveillance procedures, we found that suboptimal preparation affected 16% of the procedures. Diabetes, narcotics use and tricyclic antidepressants use were identified as predictors of poor preparation in multivariable analysis. More aggressive preparations should be considered with patients with these risk factors.

Govani SM, Elliott EE, Menees SB, Judd SL, Saini SD, Anastassiades CP, Urganus AL, Boyce SJ, Schoenfeld PS. Predictors of suboptimal bowel preparation in asymptomatic patients undergoing average-risk screening colonoscopy. *World J Gastrointest Endosc* 2016; 8(17): 616-622 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/616.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.616

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States, with an estimated 50830 deaths in 2013 alone[1]. Colonoscopy has been shown to be effective at detection and removal of precancerous lesions[2]. However, bowel wall mucosa that is obscured due to inadequate bowel preparation cleansing is a significant problem, affecting 17.5%-28.2% of colonoscopies[3-5]. The importance of bowel cleanliness was highlighted in a study by Froehlich *et al*[6]. While preparation quality did not affect cancer detection rates, the study demonstrated that patients with good and excellent bowel preparations were 1.7x and 1.5x, respectively, as likely to have a polyp detected and removed compared to poor bowel preparation quality.

Suboptimal bowel preparation inhibits the endoscopist's ability to visualize the mucosal lining for polyps and cancers; this lack of visualization influences recommended follow-up intervals for repeat screening or surveillance colonoscopy[7,8]. Data presented by Karasek *et al*[9] demonstrated that among all colonoscopies in a Veteran population, when the bowel preparation quality was inadequate the interval follow-up was 17.1 mo shorter than the average recommendation of 58.7 mo. Similarly in an Israeli study of seventy-eight gastroenterologists[7], they found shorter follow-up intervals when bowel preparation became increasing worse.

Regardless of indication for colonoscopy, numerous risk factors for inadequate preparation have been identified: Increasing age, male gender, diabetics, obesity, hypertension, cirrhosis, inpatient status, history of constipation, use of narcotics and tricyclic antidepressants (TCA), time of colonoscopy procedure, and patient comprehension of bowel preparation agent instructions[4,10,11].

To the best of our knowledge no previous study has identified predictors of inadequate bowel preparation within a strictly asymptomatic outpatient screening population. Thus, the aim of this study was to estimate the impact of predictors on suboptimal bowel preparation among patients undergoing average-risk screening colonoscopy in the outpatient setting.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of patient electronic medical records and colonoscopy reports from the Veterans Affairs Ann Arbor Medical Center (VA), and the University of Michigan in-hospital (Ann Arbor, MI, United States) medical procedures unit and two satellite ambulatory surgery medical procedures units (Ann Arbor, MI and Livonia, MI, United States). All colonoscopies were performed by board-certified gastroenterology staff or gastroenterology fellows under direct supervision of staff gastroenterologists.

Study population

All individuals 50 years or older undergoing average-risk screening colonoscopy in the outpatient setting between January 1st and December 31st, 2009 were reviewed for study eligibility. Subject exclusions included any listed concurrent gastrointestinal symptoms (*i.e.,* overt or occult GI bleeding, change in bowel habits, iron deficiency anemia or unexplained weight loss); family history of CRC; personal history of colon polyps, CRC, hereditary CRC syndromes (*i.e.,* hereditary non-polyposis colorectal cancer or familial adenomatous polyposis), and inflammatory bowel disease; any finding of large polyps (diameter $\geqslant$ 10 mm), or three or more polyps. Inpatient procedures or incomplete colonoscopies (determined by visualization of cecum and appendiceal orifice) resulted in study exclusion. Colonoscopy reports that lacked a preparation quality (adequate/inadequate or excellent/good/fair/poor) were also excluded.

Bowel preparation quality

The University of Michigan Healthcare System and VA Ann Arbor Medical Center use the Provation® Medical system (v5.0 and v4.2, respectively) to record endoscopic data. Physicians report bowel cleansing as "Quality" (excellent, good, fair, or poor), and/or "Adequacy" (Adequate or Inadequate/Unsatisfactory). For this analysis, bowel preparation quality was organized into a three-category variable: (1) Excellent and good and/or adequate; (2) Fair (defined as fair or fair-adequate); and (3) Poor (defined as poor and/or inadequate/unsatisfactory); and as a dichotomous variable: Optimal (excellent, good, adequate) and Suboptimal (fair, poor/inadequate).

Predictors of bowel preparation quality

Demographic and clinical factors were extracted from the patient's medical records. Demographic data included the patient's age at colonoscopy, gender, and race/ethnicity. Clinical factors included narcotic and TCA usage, diabetic status, body mass index (BMI): kg/m^2, endoscopy site, bowel preparation agent (GoLytely®, Miralax®-Gatorade®, *etc.*), number of polyps detected, and if a gastroenterology (GI) fellow was present during the procedure.

Statistical analysis

Descriptive statistics for continuous variables were calculated as means and standard errors, and categorical variables were characterized as proportions. Continuous variables (patient age and BMI) were categorized for the analysis. Logistic regression was used to estimate relative risks as odds ratios (ORs) with 95%CIs.

The primary objective was to identify predictors of fair and poor bowel preparation quality. Age was categorized into 50-59 years, 60-69 year, and $\geqslant$ 70 year; BMI was categorized into < 30 kg/m^2 and $\geqslant$ 30 kg/m^2. Bowel preparation types were categorized as 8L polyethylene glycol (PEG)-3350, 4L PEG-3350, Miralax®-Gatorade®, and other; bowel preparation effect estimates were referenced to 4L PEG-3350. All categorical variables were referenced to their lowest category, and effect estimates were adjusted for the site of colonoscopy and GI fellow presence. To measure the impact of risk factors on bowel preparation quality, a multivariable logistic regression model including all variables was fit.

All study database management and all statistical analyzes were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, United States) and $P < 0.05$ was considered statistically significant. IRB approval was obtained from the University of Michigan and Veterans Affairs Ann Arbor Medical Complex prior to commencement of the data collection.

RESULTS

We reviewed 4427 average-risk screening colonoscopies performed between 1/1/2009 and 12/31/2009; 2026 (45.8%) subjects were excluded. The most frequent exclusionary criteria was polyp diameter $\geqslant$ 10 mm and/or three or more polyps, n = 709 (15.9%). Ninety-two (2.1%) subjects were excluded due missing bowel preparation quality data. The analysis included 2401 subjects: 1507 (62.8%) from the University of Michigan satellite outpatient ambulatory surgery centers, 407 (16.9%) from the University of Michigan in-hospital endoscopy unit, and 487 (20.3%) from the Ann Arbor VA endoscopy unit.

The study population had a mean age of 56.9 (± 7.1) and mean BMI of 28.6 (± 5.9). Males made up 55.3% of the population, and a majority (78.3%) of the population was Caucasian (Table 1). Fair bowel preparation was significantly greater amongst male subjects (12.9% *vs* 9.9%, $P = 0.02$), procedures performed in the presence of a GI fellow (16.0% *vs* 10.6%, $P < 0.01$), and procedures completed at the University of Michigan in-hospital and VA endoscopy units (11.8% and 17.1% *vs* 9.7%, respectively, $P < 0.01$). African-American individuals more frequently received fair and poor preparations ratings. Narcotics and tri-cyclic antidepressant users, and diabetics more frequently received fair and poor bowel preparations. Miralax/Gatorade bowel preparation users had the lowest occurrence of fair or poor bowel quality. No trends existed in the distribution of bowel cleansing quality by increasing age or number of polyps detected.

Table 2 provides adjusted effect magnitudes of predictors of suboptimal bowel cleansing after adjust-

Table 1 Frequency distribution of subject characteristics across level of bowel preparation quality

	Bowel preparation quality[1]				
	Excellent or good	Fair		Poor or inadequate	
Characteristics	*n* (%)	*n* (%)	*P* value[2]	*n* (%)	*P* value[2]
Demographics					
Age (yr)					
50-59	1385 (84.8)	177 (10.8)	0.21	71 (4.4)	0.20
60-69	502 (82.0)	78 (12.8)		32 (5.2)	
⩾ 70	130 (83.3)	23 (14.7)		3 (1.9)	
Gender					
Female	916 (85.3)	106 (9.9)	0.02	52 (4.8)	0.46
Male	1101 (83.0)	172 (13.0)		54 (4.1)	
Race/ethnicity					
White	1596 (84.9)	210 (11.2)	0.16	73 (3.9)	< 0.01
Black	134 (75.3)	27 (15.2)		17 (9.6)	
Other[3]	150 (82.8)	21 (11.6)		10 (5.5)	
Body mass index, (kg/m^2)					
< 25	523 (85.9)	59 (9.7)	0.05	27 (4.4)	0.79
⩽ 25 to < 30	744 (85.1)	96 (11.0)		34 (3.9)	
⩽ 30 to < 35	403 (81.3)	73 (14.7)		20 (4.0)	
⩾ 35	238 (81.5)	39 (13.4)		15 (5.1)	
Clinical					
Narcotics use[4]					
Yes	159 (74.0)	37 (17.2)	< 0.01	19 (8.8)	< 0.01
No	1842 (85.0)	239 (11.0)		86 (4.0)	
TCA use[4]					
Yes	36 (69.2)	10 (19.2)	0.04	6 (11.5)	0.01
No	1965 (84.3)	266 (11.4)		99 (4.3)	
Prior diagnosis of diabetes					
Yes	204 (70.3)	61 (21.0)	< 0.01	25 (8.6)	< 0.01
No	1798 (85.9)	215 (10.3)		80 (3.8)	
GI fellow present					
Yes	344 (78.7)	70 (16.0)	< 0.01	23 (5.3)	0.22
No	1673 (85.2)	208 (10.6)		83 (4.2)	
No. of polyps[5] detected					
None	1232 (83.2)	179 (12.1)	0.57	69 (4.7)	0.65
1	537 (85.4)	68 (10.8)		24 (3.8)	
2	248 (84.9)	31 (10.6)		13 (4.5)	
Bowel prep type					
8L PEG-3350	334 (79.9)	70 (16.8)	< 0.01	14 (3.4)	0.01
4L PEG-3350	843 (81.8)	125 (12.1)		62 (6.0)	
MiraLAX®/Gatorade®	466 (90.0)	39 (7.5)		13 (2.5)	
Other[6]	306 (85.7)	35 (9.8)		16 (4.5)	
Endoscopy site					
UMich Satellite Outpatient Units[7]	1302 (86.4)	146 (9.7)	< 0.01	59 (3.9)	0.11
UMich in-Hospital Outpatient Unit	334 (82.1)	48 (11.8)		25 (6.1)	
Veterans Affairs Unit	381 (78.2)	84 (17.3)		22 (4.5)	
Total	2017 (84.0)	278 (11.6)		106 (4.4)	

[1]Values may not sum to "All Subjects" due to missing data; [2]Association relative to "Excellent or Good"; [3]Other includes Asian, Hispanic, Native American, and those self-reported bi- or multi-racial; [4]Defined as usage at time of colonoscopy procedure; [5]Defined as polyps < 10 mm in diameter, and without villous histology; [6]Includes Osmoprep®, Half-Lytely®, and MoviPrep®; [7]Includes data from two satellite endoscopy units from the academic hospital. TCA: Tricyclic antidepressants; GI: Gastroenterology; PEG: Polyethylene glycol.

ment for site of endoscopy and GI fellow presence during the procedure. Diabetic status (OR = 2.3, 95%CI: 1.7-3.1), TCA use (OR = 2.5, 95%CI: 1.4-4.6), and narcotics use (OR = 1.8, 95%CI: 1.3-2.5) were associated with suboptimal bowel preparation. Compared to Caucasians, African-Americans were 70% (95%CI: 1.2-2.4) more likely to have suboptimal bowel cleansing. Relative to the 4L PEG-3350 preparations, 8L PEG-3350 and MiraLAX®/Gatorade® bowel preparation agents were associated with decreased odds of suboptimal bowel cleansing (OR = 0.52, 95%CI: 0.30-0.91 and OR = 0.55, 95%CI: 0.39-0.76), respectively. Patients with BMI ⩾ 30 trended towards increased frequency of suboptimal bowel cleansing (relative to those with a BMI < 30).

After adjustment for all variables (Table 3), the University of Michigan in-hospital endoscopy unit patients were 10% more likely to have suboptimal bowel preparations, relative to those at the satellite ambulatory surgery centers. However, the Veteran population was at a 2.2-fold increased risk of suboptimal bowel preparation relative to the same population. All other previously noted associations remained statistically significant after fitting the saturated multivariable logistic regression model.

Table 2 Adjusted estimates [odds ratio (95%CI)] of predictors of suboptimal bowel preparation

Suboptimal bowel prep Predictors	OR (95%CI)[1]
Age (yr)	
50-59	1.0
60-69	1.1 (0.84-1.4)
⩾ 70	1.0 (0.67-1.6)
Male gender	0.99 (0.77-1.3)
Race	
White	1.0
Black	1.7 (1.2-2.4)
Other	1.2 (0.80-1.8)
Body mass index (kg/m^2)	
< 30	1.0
⩾ 30	1.3 (0.99-1.6)
Clinical	
Narcotics use	1.8 (1.3-2.5)
TCA use	2.5 (1.4-4.6)
Diagnosis of diabetes	2.3 (1.7-3.1)
GI fellow present	1.1 (0.82-1.6)
Polyps detected	0.85 (0.68-1.1)
Bowel prep type	
4L PEG 3350	1.0
8L PEG 3350	0.52 (0.30-0.91)
MiraLAX®/Gator ade®	0.55 (0.39-0.76)
Other	0.76 (0.54-1.1)
Endoscopy site	
UMich Satellite Outpatient Units	1.0
UMich in-Hospital Outpatient Unit	1.3 (0.94-1.8)
Veterans Affairs in-Hospital Unit	1.6 (1.2-2.3)

[1]Effect adjusted for endoscopy site and GI fellow presence. TCA: Tricyclic antidepressants; GI: Gastroenterology; PEG: Polyethylene glycol; OR: Odds ratio.

The distribution of bowel cleansing ratings between the University of Michigan in-hospital and VA endoscopy units varied depending on whether a GI fellow was present during the colonoscopy (Table 4). In the absence of GI fellows, endoscopists at the University of Michigan were more likely to issue bowel quality rates of poor, compared to those at the VA endoscopy unit (7.4% *vs* 3.1%, $P = 0.05$). However, when GI fellows were present during the procedure, VA endoscopists were more likely (18.9% *vs* 11.7%, $P = 0.04$) to rate bowel preparations as fair.

DISCUSSION

This retrospective study is the first to focus on identifying predictors of bowel preparation quality among patients undergoing average-risk screening colonoscopy. In addition to reduced adenoma detection rates and increased risk of procedural complications, suboptimal preparation leads to increased healthcare costs by increasing the likelihood that a patient receives a shorter interval recommendation for repeat endoscopy[7,9]. Repeat colonoscopy procedures due to suboptimal bowel preparation have significant implications on the increasing cost of medical care in the United States, especially within the average-risk screening population that accounts for approximately two million colonoscopies performed annually[12,13]. With an aging population the increased need for screening colonoscopy is greater than ever. However, predictions show no significant increase in the number of practicing gastroenterologists, thus reducing the percentage of endoscopies with suboptimal preparations is critical to utilization sustainability.

Table 3 Multivariable estimates [odds ratio (95%CI)] of predictors of suboptimal bowel preparation

Factor	Suboptimal prep, OR (95%CI)
Endoscopy site	
Academic in-Hospital Unit	1.1 (0.76-1.6)
Veterans Affairs Hospital	2.2 (1.1-4.3)
African-American	1.5 (1.0-2.2)
Diabetic	2.3 (1.6-3.2)
TCA use	2.5 (1.3-4.9)
Narcotics use	1.7 (1.2-2.5)
Bowel prep type	
8L PEG-3350	0.46 (0.24-0.87)
MiraLAX®/Gatorade®	0.61 (0.43-0.86)

TCA: Tricyclic antidepressants; OR: Odds ratio; PEG: Polyethylene glycol.

The findings of our study within an asymptomatic average-risk population are similar to those which included other indications for CRC screening. Amongst average-risk screening individuals, we identified that diabetes along with narcotics and TCA use was associated with approximately a two-fold increase in the risk of suboptimal bowel preparation. Though not statistically significant, our study showed that individuals with a BMI ⩾ 30 trended towards suboptimal bowel preparations compared those with a BMI < 30. Our study also identified that African-American patients were less likely to have optimal bowel cleansing relative to Caucasians. African-Americans have been found to have both more advanced disease at diagnosis and poorer outcomes than other groups[14]. However, unlike previous studies, we did not find that patient age or gender were predictors of suboptimal preparation quality.

Our study is novel in that it compared average-risk screening patients amongst an academic in-hospital and satellite ambulatory endoscopy centers, and a Veterans Affairs endoscopy suite. Relative to the study population at the outpatient ambulatory academic satellite surgery centers, the Veteran population was twice as likely to produce a suboptimal bowel preparation. The 2010 Veterans Health Administration Health Report[15] indicated that in the fiscal year 2009, 214955 colonoscopies were preformed for all indications; our study found that 22.2% of the screening colonoscopies amongst Veterans had suboptimal bowel preparations. This has significant implications on the already scarce availability of colonoscopy for repeat procedures especially as the VHA continues to increase the rate of colorectal screening amongst Veterans.

A number of studies have compared the results of different bowel preparation types on colonoscopy preparation quality[16,17]. The finding of the MiraLAX®-Gatorade® bowel preparation producing superior bowel preparation quality is in contrast to published literature.

Table 4 Distribution of bowel preparation quality and endoscopy site, across level of gastroenterology fellow presence during colonoscopy

	Bowel preparation quality				
	Excellent/good	Fair		Poor	
GI fellow presence	*n* (%)	*n* (%)	*P* value[1]	*n* (%)	*P* value[1]
Not present					
UMich in-Hospital Endoscopy Unit	186 (80.9)	27 (11.7)	0.34	17 (7.4)	0.05
Veterans Affairs Endoscopy Unit	185 (81.5)	35 (15.4)		7 (3.1)	
Present					
UMich in-Hospital Endoscopy Unit	148 (83.6)	21 (11.9)	0.04	8 (4.5)	0.44
Veterans Affairs Endoscopy Unit	196 (75.4)	49 (18.9)		15 (5.8)	
Total	715 (80.0)	132 (14.8)		47 (5.2)	

[1]Relative to excellent/good. GI: Gastroenterology.

Two recently published randomized controlled trials comparing MiraLAX® to Golytely® have shown Golytely® to produce superior preparation quality[18,19]. The study by Enestvedt *et al*[18] focused on screening colonoscopies, but excluded patients with a history of constipation; whereas, Hjelkrem *et al*[19] did not exclude patients with risk factors of suboptimal preparation (except prior surgery). Though our study did not directly compare GoLytely® to MiraLAX®, it did demonstrate that compared to all 4L PEG-3350 solutions, MiraLAX®-Gatorade® produced superior bowel preparation qualities. Noting the retrospective nature of the study design, our study consisted of a large population and allowed for statistical adjustment of known risk factors such as narcotics and TCA use, and diabetic status. Given these conflicting findings, further research on the efficacy of MiraLAX® as a colonoscopy preparation agent is warranted.

We are aware that our study has several limitations due to its design. The first limitation is the retrospective nature of medical records relies on patient self-report and documentation by nursing and physician personnel. Between January 1 and December 31, 2009, there were forty-eight practicing gastroenterologists. Some physicians only performed colonoscopy at a single endoscopy center, while others at performed at multiple sites; similarly not all physicians performed colonoscopy in the presence of a GI fellow. We attempted to control for this through our statistical modeling with adjustments for endoscopy site and GI fellow presence. Secondly, our measured outcome was not a standardized scale system such as the Boston Bowel Preparation Scale or the Ottawa scale, but rather subjective determination by our endoscopists using the Aronchick scale (*i.e.*, excellent, good, fair, and poor). Third, data were not collected on previously identified predictors of suboptimal prep such as patient comprehension of bowel preparation instructions, concurrent comobidities (*i.e.*, dementia, cirrhosis, and stroke), or previous gastrointestinal and/or genitourinary surgeries. The analysis of preparation types is limited by the lack of data on the amount of prep consumed. It is possible that patients may have found the MiraLAX®/Gatorade preparation more tolerable and consumed more of this than the PEG-3350 preparations. Lastly, due the tertiary nature of our hospital system, our results may not be generalizable to the community setting.

In conclusion, our study identified that average-risk patients using narcotics or TCAs prior to colonoscopy, as well as, diabetics are at increased risk for suboptimal bowel preparation quality when undergoing screening colonoscopy. Similarly, our study noted a strong disparity between bowel preparation outcomes amongst Veterans and African-Americans. Further studies aimed at improving bowel preparation outcomes of colonoscopic preparations within these populations are warranted.

COMMENTS

Background

Suboptimal bowel preparation affects approximately 20% of colonoscopies. Suboptimal preparation leads to reduced polyp detection and leads endoscopist to recommend shorter interval follow-up.

Research frontiers

Identifying predictors of suboptimal preparation may allow endoscopists to risk-stratify patients into high and low risk groups and prescribe a more aggressive preparation type for those in the high risk group.

Innovations and breakthroughs

Diabetes, narcotics and tricyclic antidepressant use predict suboptimal preparation.

Applications

Suboptimal preparation affected 1 out of every 6 colonoscopies in this population. Prescription of more aggressive preparation types for patients with diabetes or those who use narcotics or tricyclic antidepressants may reduce the incidence of suboptimal preparations.

Terminology

Suboptimal preparation occurs when the endoscopist characterizes the preparation as fair, poor or inadequate. Screening or surveillance colonoscopies are done to identify polyps and with the aim of preventing subsequent colorectal cancer.

Peer-review

The manuscript by Govani *et al* deals with clinically important question how to improve bowel cleansing before colonoscopy. Given the incidence of colon cancer, the implications of missed lesions due to suboptimal preparation and the costs of performing repeated procedures due to suboptimal preparation, this topic is of immense clinical importance.

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P- Reviewer: Tepes B **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Li D

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DOI: 10.4253/wjge.v8.i17.623

World J Gastrointest Endosc 2016 September 16; 8(17): 623-627
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Transanal endoscopic microsurgery as optimal option in treatment of rare rectal lesions: A single centre experience

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Author contributions: Ortenzi M and Ghiselli R designed the study; Ortenzi M, Cappelletti Trombettoni MM and Cardinali L contributed to acquisition of data and drafting the article; Guerrieri M approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ospedali Riuniti Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No financial support or incentive has been provided for this manuscript. All authors have no conflicts of interest or financial ties to disclose.

Data sharing statement: Technical appendix, original data, and statistical code of manuscript NO 26052 submitted to World Journal of Gastrointestinal Endoscopy are available from the corresponding author at monica.ortenzi@gmail.com. Partecipants gave informed consent for data sharing.

Manuscript source: Invited manuscript

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Received: March 28, 2016
Peer-review started: March 29, 2016
First decision: May 17, 2016
Revised: June 2, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: September 16, 2016

Abstract

AIM

To analyze the outcomes of transanal endoscopic microsurgery (TEM) in the treatment of rare rectal condition like mesenchymal tumors, condylomas, endometriosis and melanoma.

METHODS

We retrospectively reviewed a twenty-three years database. Fifty-two patients were enrolled in this study. The lesions were considered suitable for TEM if they were within 20 cm from the anus. All of them underwent an accurate preoperative workup consisting in clinical examination, total colonoscopy with biopsies, endoscopic ultrasonography, and pelvic computerized tomography or pelvic magnetic resonance imaging. Operative time, intraoperative complications, rate of conversion, tumor size, postoperative morbidity, mortality, the length of hospital stay, local and distant recurrence were analyzed.

RESULTS

Among the 1328 patients treated by TEM in our department, the 52 patients with rectal abnormalities other than adenoma or adenocarcinoma represented 4.4%. There were 30 males (57.7%) and 22 females (42.3%). Mean age was 55 years (median = 60, range = 24-78). This series included 14 (26.9%) gastrointestinal stromal tumors, 21 neuroendocrine tumors (40.4%), 1 ganglioneuroma (1.9%), 2 solitary ulcers in the rectum (3.8%), 6 cases of rectal endometriosis (11.5%), 6

cases of rectal condylomatosis (11.5%) and 2 rectal melanomas (3.8%). Mean lesion diameter was 2.7 cm (median: 4, range: 0.4-8). Mean distance from the anal verge was 9.5 cm (median: 10, range: 4-15). One patient operated for rectal melanoma developed distant metastases and died two years after the operation. We experienced 2 local recurrences (3.8%) with an overall survival equal to 97.6% (95%CI: 95%-99%) at the end of follow-up and a disease free survival of 98% (95%CI: 96%-99%).

CONCLUSION

We could conclude that TEM is an important therapeutical option for rectal rare conditions.

Key words: Transanal endoscopic microsurgery; Rare rectal conditions; Full-thickness excision; Minimally invasive surgery; Retrospective study

Core tip: This paper is about the management of rare rectal lesions by transanal endoscopic microsurgery (TEM). The rarity of these conditions and the lack of big reports about this topic make this work important. We focused our attention on operative data and post-operative long-term outcomes. Our results suggested that TEM is a safe, minimally invasive procedure that can be adopted for the treatment of these conditions with excellent results.

Ortenzi M, Ghiselli R, Cappelletti Trombettoni MM, Cardinali L, Guerrieri M. Transanal endoscopic microsurgery as optimal option in treatment of rare rectal lesions: A single centre experience. *World J Gastrointest Endosc* 2016; 8(17): 623-627 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/623.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.623

INTRODUCTION

Adenocarcinoma is the most frequent malignancy of the rectum, but the distal part of the bowel can host several other rare lesions which together represent an important part of rectal tumors[1]. This heterogeneous group comprehends mesenchymal tumors like gastrointestinal stromal tumors (GISTs), neuroendocrine tumors (NETs) and ganglioneuromas. Other abnormalities can involve the rectal wall, and surgery is the only curative option, as is also the case for condyloma, endometriosis and melanoma. The aim of this study was to analyze the results of transanal endoscopic microsurgery (TEM) in the treatment of these rare rectal conditions.

MATERIALS AND METHODS

A retrospective accurate analysis of a twenty-two-year-old database built from 1992 to 2015 identified 52 patients eligible for the study. Indications for TEM were determined on the basis of the anatomical criteria assessed by rigid preoperative rectoscopy in order to locate the lesions and to measure its distance from the anal verge.

All patients were properly informed about the operation and give their consensus to surgery. The lesions were considered suitable for TEM if they were within 20 cm from the anus. Preoperative workup included clinical examination, total colonoscopy with biopsies, endoscopic ultrasonography, and pelvic computerized tomography or pelvic magnetic resonance imaging. Patients' characteristics such as age and gender were considered. All patients received similar pre-operative management with an oral intake of an osmotic solution the day before surgery and a short term intravenous antibiotics prophylaxis to provide coverage for the normal bowel flora, aerobic and anaerobic species.

Procedures were performed by the Wolf TEM equipment (Knittlingen, Germany) consisting of a rigid 12 or 20 cm long rectoscope, an endosurgical unit steadily controlling rectal endoluminal pressure, and curved instruments. In all cases, a full-thickness excision was performed, and the rectal defect was closed by a running suture secured with silver clips at the extremities.

The operative data examined included operative time, intraoperative complications and conversion to abdominal surgery. Tumor size was measured macroscopically and reported as the maximum diameter. Pathological examination included histopathological definition, degree of differentiation, macroscopical measurement, and the examination of radial margins of excision. A urinary catheter was placed in all the patients at the time of surgery, which was removed 24 h after the operation. In the post-operative period, we analyzed postoperative morbidity, mortality and the length of hospital stay. Long-term outcomes included local and distant recurrence. We considered as local recurrence any recurrence diagnosed endoscopically and confirmed by biopsy. Follow-up included digital examination, rigid rectoscopy and endorectal ultrasound every 6 mo for the first year from the time of operation and subsequently every year.

Quantitative variables are shown as the mean value with median and range in brackets. Recurrence-free survival was considered as a continuous variable. The probability of overall survival at the end of follow-up and the probability of disease-free survival were estimated using the Kaplan-Meier method. All analyses were performed using the R statistical package.

RESULTS

Among the 1328 patients treated by TEM in our department, the 52 patients with rectal abnormalities other than adenoma or adenocarcinoma represented 4.4%. There were 30 males (57.7%) and 22 females (42.3%). Mean age was 55 years (median = 60, range = 24-78). We excised, by TEM, 14 (26.9%) GISTs, 21 NETs (40.4%), 1 ganglioneuroma (1.9%) and 2 solitary

Table 1 Population characteristics *n* (%)

Variables	
Sex	
Male	30 (67.7)
Female	22 (42.3)
Neuroendocrine tumors	21 (40.4)
Gastrointestinal stromal tumors	14 (26.9)
Ganglioneuroma	1 (1.9)
Solitary ulcers	2 (3.8)
Endometriosiosis	6 (11.5)
Condylomas	6 (11.5)
Melanomas	2 (3.8)
Diameter (cm), [mean (median, range)]	2.7 (4, 0.4-8)

ulcers in the rectum (3.8%). We used TEM to treat 6 cases of rectal endometriosis (11.5%), 6 cases of rectal condilomatosis (11.5%) and 2 rectal melanomas (3.8%).

Preoperative symptoms ranged from rectal bleeding (9/52, 17.3%), urgency (3/52, 5.8%) and alteration in bowel habit (7/52, 13.5%). Thirty-two (61.5%) patients were asymptomatic and the lesions were discovered incidentally. Mean lesion diameter was 2.7 cm (median: 4, range: 0.4-8). Mean distance from the anal verge was 9.5 cm (median: 10, range: 4-15) (Table 1).

GISTs had a mean diameter of 1.4 cm (median = 1, range = 0.4-5). Two of them received neoadjuvant Imatinib resulting in reduction in tumor size. Six GISTs were defined as medium risk GISTs and 4 as high risk.

As for NETs, the mean lesion diameter was 2.7 cm (median = 2, range = 0.5-5). Except for one, all of them were G1 well differentiated NETs. There was only one ganglioneuroma which extended circumferentially on the rectal wall and had a diameter of 10 cm. The condyloma had a mean diameter of 2.7 cm (median: 3, range: 2-3). The 2 solitary ulcers had a diameter of 3 and 4 cm respectively and were completely excised.

Complete resection with disease-free margins was achieved in all the cases except for one case in which the pathologist was unable to assess the margin due to thermal damage. Mean operative time was 41 min (median: 45, range: 20-55). There was no conversion to abdominal surgery. We observed one intraoperative minor complication (1.9%) consisting in rectal bleeding controlled by TEM.

We observed a postoperative morbidity rate of 3.8% (2/50), consisting of one case of acute urinary retention and one case of mild incontinence to gas resolved within two months from the operation by means of physiotherapy. Mean hospital stay was 3 d (median: 4, range: 2-7).

All the patients completed the follow-up protocol, including clinical and instrumental assessment. Two patients (3.8%) died from unrelated causes. One patient with rectal NET showed local recurrence within a year after operation. One patient operated for rectal melanoma developed distant metastases and died two years after the operation (Table 2). We observed an overall survival equal to 97.6% (95%CI: 95%-99%) at the end of follow-up and a disease free survival of 98% (95%CI: 96%-99%) (Figure 1).

Table 2 Operative and post-operative data *n* (%)

Variables	
Operative time-min [mean (median, range)]	41 (45, 20-55)
Intraoperative complications	1 (1.9)
Hospital stay (d) [mean (median, range)]	3 (4, 2-7)
Post-operative complications	2 (3.8)
Recurrence	1 (1.9)
Follow-up (yr) [mean (median, range)]	11 (13, 23-1)
Death at the end of follow-up	2 (3.8)

DISCUSSION

Rectal lesions different from adenomas-carcinomas represent a small but important group in terms of oncological and functional implications. Surgery is the main choice in the treatment of these conditions, but debate regarding the best method for their management exists[1-3]. Their localization in the rectum may represent a therapeutical challenge. Most authors opt for anterior resection or even abdominal perineal resection, but traditional surgery may represent an overtreatment[1,2,4].

NETs represent the largest group in our series. This kind of tumors are being diagnosed increasingly frequently, and current European Neuroendocrine Tumor Society guidelines recommend endoscopic resection for G1 rectal NET < 10 mm with a low risk of metastatic disease[5]. The current methods of endoscopic removal are polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and TEM. Since complete surgical resection for a localized lesion was demonstrated as the only effective option, several studies have proved the superiority of TEM over the other endoscopic techniques in the treatment of rectal NET. EMR and ESD achieve a complete microscopic resection in 46.3% to 65.5% and in 75% to 82.6% of cases, respectively[6-11]. TEM allows us to achieve a 100% rate of free resection margins, as observed in other reports[9,10]. We did not observe cases of incomplete resection nor recurrence in our experience. Most tumors (80%) were ⩽ 10 mm in diameter, and the risk of metastases has been estimated at less than 3% for rectal NETs within 1 cm in diameter[9]. In our series, all the lesions were G1 well-differentiated rectal NET without lymphovascular invasion except for one patient with a G3 poorly differentiated NET with lymphatic and vascular invasion, who relapsed within a year from operation and was treated by means of an abdominal perineal resection.

As for GISTs, according to Miettinen *et al*[12], the rectum is the third most common site of onset, comprising approximately 5%-10% of all GISTs. Neither radiation therapy nor chemotherapy has any proven efficacy as adjuvant therapy. Rectal GIST exhibits two specific features which may significantly affect surgical management: Metastases are extremely rare in loco-regional lymphnodes, and GISTs typically show a tendency to grow away from the intestinal lumen. These characteristics may make these tumors eligible for TEM[13-16]. In our series, all GISTs were completely resected by TEM. TEM excision is considered to be an interesting alternative

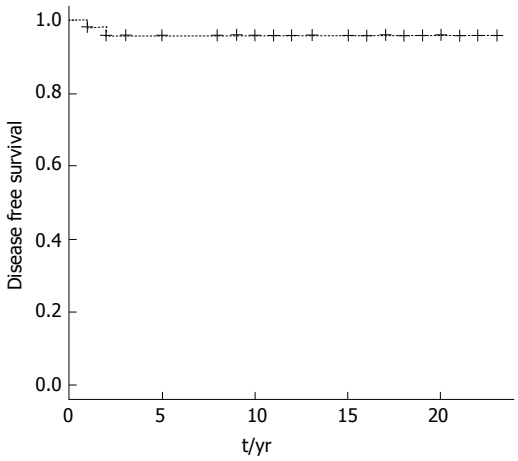

Figure 1 Disease free survival after transanal endoscopic microsurgery for rare rectal lesions.

for small GISTs located within the rectal wall, which are usually incidental findings during endoscopy. This approach, however, is considered not indicated for larger (> 5 cm) tumors growing away from the rectal lumen. In our series, only one GIST had a 5 cm diameter, but it was completely excised, and we did not observe recurrence.

Condyloma mainly affects the anorectal region, and rare reports have described condylomata involving the rectal wall which have often been incidentally discovered by endoscopy[17-19].

Standard therapy such as laser, fulguration, freezing or microwaves can be difficult to apply inside the rectum[18]. Surgical resection by TEM can offer a good local disease control, and none of the patients treated by TEM experienced recurrence.

Rectum can also be the site of extapelvic endometriosis[2,4,8,20]. Open or laparoscopic surgery is the primary mode of treatment in most of the infiltrating diseases. Surgical treatment is effective in relieving painful defecation, pelvic pain and dyspareunia[20]. We registered a positive resection margin in one patient affected by endometriosis, but no recurrence was observed in this case. Probably, the margin presented to the pathologist as elettro coagulated. Primary anorectal malignant melanoma is an extremely rare malignancy that is believed to arise from melanocytes in the mucosa around the anorectal junction. Surgery resection is the only curative option, but this malignancy is associated with poor prognosis[21,22]. We treated only two patients with rectal melanoma by TEM who were incidentally diagnosed during endoscopy. Both cases had an early stage of melanoma confirmed by the pathologist. Both patients received adjuvant chemotherapy. One of them developed local recurrence at 1 year from surgery and was treated with laparoscopic anterior resection.

TEM has demonstrated to be feasible in the treatment of different conditions different from adenomas and carcinomas which may affect the rectum. TEM allows us to reach lesions located up to 20 cm from the anal verge. The magnified tridimensional vision offered by TEM is crucial to reach the complete rate of complete resection. The possibility to perform a full thickness excision of the rectal wall makes TEM appropriate for tumors like GISTs arising from submucosal layers.

In this series, we did not experience long term morbidity. We registered only one patient with mild gas incontinence which was resolved within two months from surgery by means of physiotherapy.

We could conclude that TEM is an important therapeutic option for rectal rare diseases. Other studies with more numerous series will be necessary to understand the real role of minimally invasive transanal techniques in the treatment of these lesions.

COMMENTS

Background

The rectum can be the site of origin of different lesion far more rare than adenocarcinoma but that have surgery as the only curative option. The full thickness excision reached by transanal endoscopic microsurgery (TEM) offers the possibility to achieve a complete resection with very low morbidity.

Research frontiers

TEM has several advantages compared with traditional approach. It allows to perform a complete transanal full thickness excision of the lesions, with an accurate individuation of free margins due to a magnified stereoscopic view. The morbidity related to this approach is low compared to other surgical techniques.

Innovations and breakthroughs

The exact role of TEM in the treatment of rare rectal lesions is hard to define manly due to the lack of large series. The retrospective analysis of the authors' experience allowed them to built one of the largest series now available on this topic.

Applications

This retrospective analysis of the authors' experience suggest TEM can be considered safe and feasible in the treatment of these lesions.

Peer-review

This is a large retrospective analysis on the treatment of rare rectal lesions by TEM. The paper is overall well written. The results are well reported.

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P- Reviewer: McSorley ST, Samardzic S, Santoro GA, Sterpetti AV
S- Editor: Gong ZM **L- Editor**: A **E- Editor**: Li D

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i17.628

World J Gastrointest Endosc 2016 September 16; 8(17): 628-634
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Observational Study

Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection

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Author contributions: Arantes V and Uedo N designed the study and contributed equally to data acquisition, analysis, interpretation of the data, writing the article, critical revision and final approval of the manuscript; Pedrosa MS and Tomita Y contributed equally to the histopathological analysis and interpretation of histological findings and study results.

Institutional review board statement: The data was extracted retrospectively from the endoscopy database. Our Ethics and Research Committee does not require IRB submission for such kind of study. Patients signed a consent form for the procedure and the study was conducted according to Helsinque Declaration.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No data were created so no data are available.

Manuscript source: Invited manuscript

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Received: March 21, 2016
Peer-review started: March 23, 2016
First decision: April 20, 2016
Revised: April 26, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: September 16, 2016

Abstract

AIM

To describe a series of patients with aberrant polypoid nodule scar developed after gastric endoscopic submucosal dissection (ESD), and to discuss its pathogenesis and clinical management.

METHODS

We reviewed retrospectively the endoscopic database of two academic institutions located in Brazil and Japan and searched for all patients that underwent ESD to manage gastric neoplasms from 2003 to 2015. The criteria for admission in the study were: (1) successful *en bloc* ESD procedure with R0 and curative resection confirmed histologically; (2) postoperative endoscopic examination with identification of a polypoid nodule scar (PNS) at ESD scar; (3) biopsies of the PNS with

hyperplastic or regenerative tissue, reviewed by two independent experienced gastrointestinal pathologists, one from each Institution. Data were examined for patient demographics, *Helicobacter pylori* status, precise neoplastic lesion location in the stomach, tumor size, histopathological assessment of the ESD specimen, and postoperative information including medical management, endoscopic and histological findings, and clinical outcome.

RESULTS

A total of 14 patients (10 men/4 women) fulfilled the inclusion criteria and were enrolled in this study. One center contributed with 8 cases out of 60 patients (13.3%) from 2008 to 2015. The second center contributed with 6 cases (1.7%) out of 343 patients from 2003 to 2015. Postoperative endoscopic follow-up revealed similar findings in all patients: A protruded polypoid appearing nodule situated in the center of the ESD scar surrounded by convergence of folds. Biopsies samples were taken from PNS, and histological assessment revealed in all cases regenerative and hyperplastic tissue, without recurrent tumor or dysplasia. Primary neoplastic lesions were located in the antrum in 13 patients and in the angle in one patient. PNS did not develop in any patient after ESD undertaken for tumors located in the corpus, fundus or cardia. All patients have been followed systematically on an annual basis and no malignant recurrence in the ESD scar has been identified (mean follow-up period: 45 mo).

CONCLUSION

PNS may occur after ESD for antral lesions and endoscopically look concerning, especially for the patient or the family doctor. However, as long as curative R0 resection was successfully achieved and histology demonstrates only regenerative and hyperplastic tissue, PNS should be viewed as a benign alteration that does not require any type of intervention, other than endoscopic surveillance.

Key words: Endoscopic submucosal dissection; Early gastric cancer; Endoscopic treatment; Healing; Scar

Core tip: Endoscopic submucosal dissection is the treatment of choice for superficial gastric neoplasms. After curative endoscopic submucosal dissection (ESD), postoperative scar is expected to look consolidated and homogeneous. We describe a series of 14 patients that underwent curative gastric ESD with R0 resection and surprisingly developed an aberrant polypoid nodule at the ESD scar. We denominated this new entity as polypoid nodule scar (PNS). It is noteworthy that PNS occurred only after ESD undertaken for tumors located in the antrum. We reviewed the hypothesis and pathogenic factors that could explain the occurrence of this unusual phenomenon, and discuss propositions about patient's postoperative clinical management.

Arantes V, Uedo N, Pedrosa MS, Tomita Y. Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; 8(17): 628-634 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i17/628.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i17.628

INTRODUCTION

Endoscopic submucosal dissection (ESD) is considered by current guidelines as the treatment of choice for patients with superficial gastric neoplasms with little or no risk of lymph nodes metastasis[1-3]. It permits *en bloc* resection of tumors and reliable histological assessment of the resected specimen to determine the potential curability of the endoscopic resection. Particularly for lesions situated in the antrum, ESD is technically easier and highly effective to proportionate cure of intramucosal cancers removed with free margins. Postoperative endoscopic examination is recommended to all patients after curative ESD with two main purposes: (1) inspection of the scar to rule out residual tumor or recurrence; and (2) surveillance for metachronous neoplastic lesions.

After a curative ESD, postoperative scar usually looks consolidated and homogeneous without residual tumor, infiltration or polypoid formation. Interestingly, we have been observing that a subset of patients after curative ESD, particularly for lesions located in the antrum, may develop anomalous and bizarre postoperative scars, with relatively huge and protruded polypoid nodular neoformation, an entity that has not been described until our first report[4]. Biopsy specimens taken from these scars have demonstrated regenerative mucosa without recurrent neoplastic cells. However, in our practice, such intriguing findings can make both patients and physician concern about the reliability of the endoscopic curative resection, and may imply a request for closer follow-up or discussion about endoscopic, or even surgical, reintervention due to fear of tumor recurrence.

The objectives of this study are to describe a series of cases with aberrant polypoid nodule scar (PNS) after gastric ESD experienced in two referral centers in Latin America (Center 1) and Asia (Center 2), and to discuss the pathogenesis and propositions about the clinical management.

MATERIALS AND METHODS

The study was carried out in accordance with the Helsinki Declaration. All patients that underwent ESD provided informed consent preoperatively. Clinical information was extracted retrospectively from the endoscopy database of both institutions, which register all patients with gastric neoplasms managed by ESD.

Inclusion criteria

Eligibility for ESD was assessed preoperatively by means of white-light endoscopy, digital chromoendoscopy, magnifying observation, indigo carmine staining and

endoscopic ultrasound (in selected cases). The following criteria were utilized for patients enrollment in this study: (1) successful *en bloc* ESD procedure with confirmatory histology of R0 and curative resection; (2) postoperative endoscopic examination with identification of a polypoid nodule scar corresponding to the site where ESD was undertaken; and (3) biopsies of the PNS with histological assessment demonstrating hyperplastic or regenerative tissue. Two independent experienced gastrointestinal pathologists, one from each center, reviewed PNS biopsies. Data were examined for patient demographics, *Helicobacter pylori* (*H. pylori*) status, precise neoplastic lesion location in the stomach, tumor and specimen size, histopathological assessment of the ESD specimen, postoperative information including medical management, endoscopic and histological findings, and clinical outcome.

ESD procedure

ESD technique has been described in detail elsewhere[5,6]. Briefly, markings were placed at least 2 mm beyond the borders of the lesion after careful endoscopic assessment by chromoendoscopy and/or magnifying endoscopy with narrow band imaging (NBI) or Fuji intelligent chromoendoscopy (FICE). Viscous solutions such as 0.4% hyaluronic acid (Muco-up®, Johnsons and Johnsons, Japan) or 0.4% hydroxypropyl-methylcellulose[7] were used for submucosal (SM) injection. ESD was undertaken with 2.5 Flush-Knife Ball Tipped (Fujifilm Co., Japan) in Center 1 or ceramic-ball insulated tip knife (IT knife, Olympus Co., Japan) in Center 2. Mucosal incision was undertaken around the tumor in a circumferential or semi-circumferential manner. SM dissection was performed in the deep submucosa, just above the proper muscle layer, with identification and hemostasis of the penetrating vessels. After complete tumor resection, the ulcer site was assessed and visible vessels were coagulated with a hemostatic forceps. The specimen was stretched and fixed in a styrofoam plate, immersed in 10% formaldehyde solution and sent to the pathology department.

Histological assessment and definitions

After being embedded in 10% paraffin, the specimens were cut into 2-mm slices and stained with hematoxylin and eosin. Additional immunochemistry studies with D2-40 and CD34 were carried out for lymphatic and vascular invasion assessment, at the discretion of the pathologist. Tumor size, depth of invasion, lymphatic and vascular invasion, grade of differentiation, and resection margins were histopathologically examined[8]. *En bloc* resection was defined endoscopically as the complete removal of the tumor including the markings into one non-fragmented piece[2]. R0 resection was defined histologically as complete tumor removal with both lateral and deep margins free of neoplastic cells. Endoscopic resection was considered curative when pathology report demonstrated adenoma with low or high-grade dysplasia, well or moderately well differentiated adenocarcinoma, depth of invasion restricted to mucosa or superficial submucosal (SM1), with free vertical and radial margins and no lymphatic or vascular invasion[2,3,9]. ESD was considered non-curative according to the following criteria[2,3,5]: Undifferentiated cancer greater than 2 cm, deep submucosal tumor invasion (SM2), tumor compromise of lateral or profound borders, and lymph-vascular invasion. Patients with non-curative resection were not included in this study. PNS was defined as a protuberant polypoid appearing nodule situated exactly in the post ESD scar site, with or without converging folds and with histological assessment demonstrating only regenerative or hyperplastic tissue growth without any residual or recurrent neoplastic tissue, confirmed by two experienced gastrointestinal pathologists, one from each center.

Postoperative care

Patients remained hospitalized for postoperative observation ranging from 2 to 7 d. Intravenous proton pump inhibitors (PPI) were administered to all patients during the first postoperative days followed by an 8-wk course of oral PPI after hospital discharge. If ESD procedure was considered curative, first follow-up endoscopy was scheduled in between 3 and 6 mo, and annually thereafter. ESD scar was inspected carefully for any abnormality such as residual tumor or polypoid nodule growth and multiple forceps biopsies were performed.

RESULTS

A total of 14 patients (10 men/4 women) fulfilled the inclusion criteria and were enrolled in this series. One center contributed with 8 cases (13.3%) out of 60 patients that underwent ESD for gastric tumors from 2008 to 2015. The second center contributed with 6 cases (1.7%) out of 343 patients from 2003 to 2015. Table 1 demonstrates the total number of cases performed in each center, and the incidence of PNS according to the region of the stomach. A total of 8 patients (57%) tested positive for *H. pylori* and received eradication therapy ahead of the procedure. The remaining 6 patients were negative for *H. pylori* infection.

Postoperative endoscopic follow-up revealed similar findings in all 14 patients: A protruded polypoid appearing nodule situated in the center of the ESD scar surrounded or not by convergence of folds. Biopsies were taken from the nodular part of the scar and histological assessment showed a similar pattern in all cases characterized by hyperplastic regenerative mucosa on the fibrotic tissue in the submucosa, without any signs of residual or recurrent dysplasia or tumor. Table 2 summarizes clinical and histological information of the 14 cases. Primary neoplastic lesions were located in the antrum, except for one patient that presented a lesion situated in the angle. Specimen size ranged from 20 mm to 82 mm (mean size of 36 mm). All patients have been followed periodically on an annual basis and no malignant recurrence in the ESD scar has been identified (mean follow-up period of 45 mo; range: 6 to 144 mo). Figures 1 and 2 are illustrative of

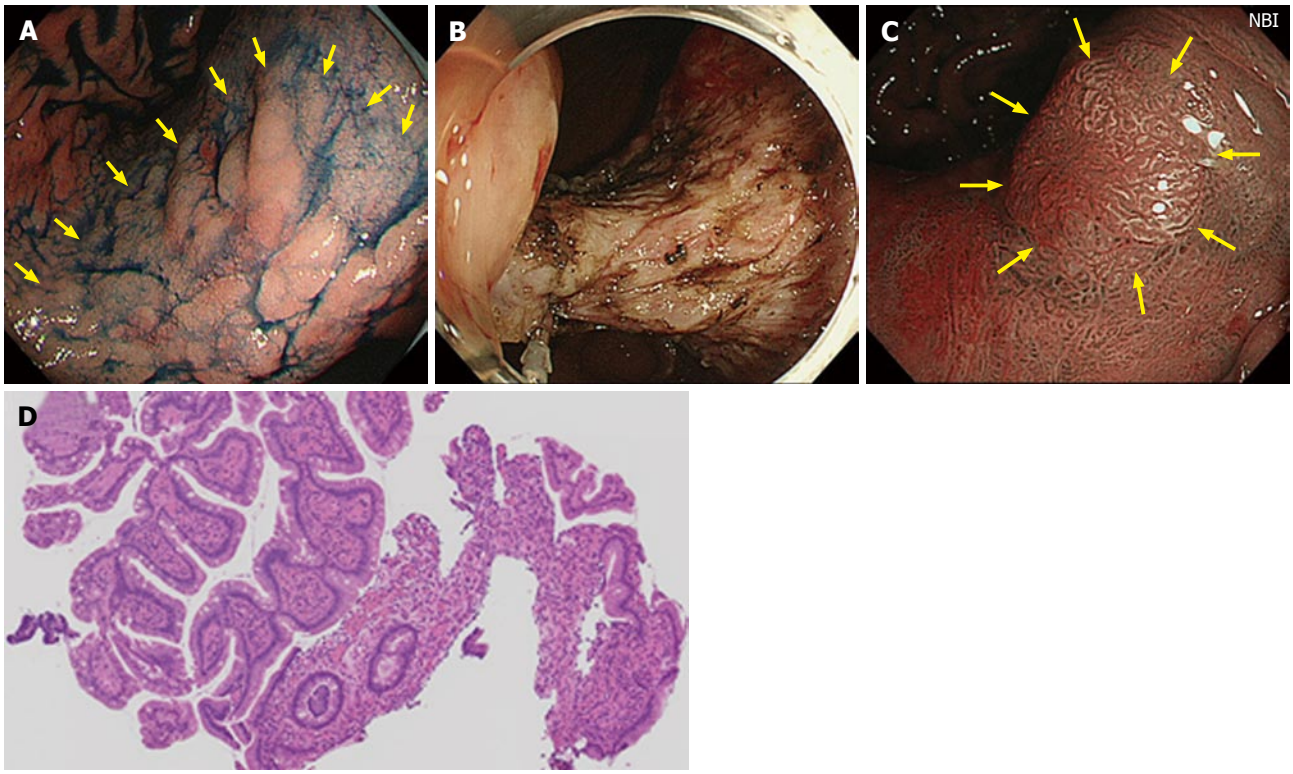

Figure 1 Case from Japan. A: A large superficial elevated lesion was found at the lesser curvature of the gastric angle (yellow arrows); B: The lesion was removed by endoscopic submucosal dissection technique. The lesion was diagnosed as well differentiated adenocarcinoma confined to the mucosa and resection margin was free from the tumor; C: One year later, a polypoid nodule was noted at the center of the scar (yellow arrows). Narrow band image suspected irregular surface structure on the surface of the nodule; D: Biopsy specimens were taken from the polypoid nodule. Histological examination showed hyperplastic change of the foveolar epithelium and increased capillaries and inflammatory cell infiltration in the lamina propria.

Table 1 Endoscopic submucosal dissection procedures distribution in Centers 1 and 2 and incidence of polypoid nodule scar according to region of the stomach *n* (%)

ESD procedures	Center 1 (Brazil)	Center 2 (Japan)
Total number of gastric ESD (*n*)	60	343
ESD in antrum	37 (62%)	158 (46%)
ESD in proximal stomach	23 (36%)	185 (54%)
Total number of PNS cases	8 (13.3%)	6 (1.7%)
Number of PNS in antrum lesions	8 (21.6%)	6 (3.8%)
Number of PNS in proximal stomach	0 (0%)	0 (0%)

ESD: Endoscopic submucosal dissection; PNS: Polypoid nodule scar.

two cases of PNS, one from Japan and the other from Brazil respectively, with the characteristic endoscopic and histologic findings.

DISCUSSION

The healing process of a post ESD ulcer is still not completely understood. In general, after a successful curative endoscopic resection, follow-up endoscopy is supposed to demonstrate a homogeneous and flat epithelized scar covered by a regular appearing mucosa with some grade of fibrosis. In the present study we originally report a series of 14 patients with gastric lesions located predominantly in the antrum, that underwent a curative ESD R0 resection confirmed by histological criteria, and that developed an aberrant polypoid nodule in the post ESD scar. Histological assessment of the tissue growth, examined independently by two experienced gastrointestinal pathologists, were all very similar among the 14 cases, and revealed regenerative and hyperplastic tissue growth, without residual or recurrent neoplasia.

Ito *et al*[10] reported that polypoid nodule at ulcer scar was observed in 12 (6%) of 200 patients with gastric ulcer. Interestingly all lesions were located in the antrum[10]. In old days, some of these patients underwent gastric resection because these alterations were suspected to be malignant[11]. For development of polypoid nodule at ulcer scar, Kato *et al*[12] investigated the gastric ulcer healing process by endoscopy and indicated that, in some patients, granulation tissue protruded in healing ulcer. This is more frequently observed in patients that received histamine-2 receptor antagonist compared to those treated with drugs other than acid suppressant (22.0% *vs* 9.7%). The protruded granulation tissue develops in 17.5%-66.6% of patents with gastric ulcer treated with PPI[13,14]. The protruded granulation tissue tends to disappear after scaring, while in some patients it may remain at the center of the scar for a long time[13,15], a finding that we also noted in our series and is illustrated in Figure 2 (images show PNS still present 3 years after ESD). Histological finding of the polypoid nodule at ulcer scar is indicated as hyperplastic regenerative mucosa on

Table 2 Characteristics of tumors and follow-up data

Case list	Gastric region	Location	Tumor size (mm)	*H. pylori* status before ESD	Specimen size (mm)	Histology	Tumor depth	Post-ESD treatment	Follow-up (yr)
1	Antrum	Anterior wall	8	Positive	30	Moderately differentiated adenocarcinoma	M	Rabeprazole	8
2	Antrum	Greater curvature	13	Positive	37	Well differentiated adenocarcinoma	M	Omeprazole	11
3	Antrum	Lesser curvature	25	Positive	50	Well differentiated adenocarcinoma	M	Rabeprazole	13
4	Antrum	Greater curvature	15	Positive	32	Well differentiated adenocarcinoma	M	Rabeprazole	5
5	Antrum	Lesser curvature	8	Negative	20	Well differentiated adenocarcinoma	M	Rabeprazole	2
6	Antrum	Greater curvature	10	Negative	20	High-grade dysplasia	M	Omeprazole	7
7	Antrum	Lesser curvature	25	Positive	40	Well differentiated adenocarcinoma	M	Omeprazole + sucralfate	4
8	Antrum	Greater curvature	20	Positive	40	High-grade dysplasia	M	Esomeprazole + sucralfate	4
9	Antrum	Anterior wall	12	Positive	22	High-grade dysplasia	M	Omeprazole + sucralfate	4
10	Antrum	Greater curvature	25	Negative	40	Inflammatory lesion indefinite for dysplasia	M	Esomeprazole + sucralfate	4
11	Antrum	Anterior wall	20	Negative	35	Inflammatory fibroid polyp	SM	Omeprazole + sucralfate	2
12	Antrum	Greater curvature	30	Positive	40	High-grade dysplasia	M	Omeprazole + sucralfate	1
13	Angle	Lesser curvature	45	Negative	82	Well differentiated adenocarcinoma	M	Rabeprazole	2
14	Antrum	Posterior wall	20	Negative	32	High-grade dysplasia	M	Omeprazole + sucralfate	1

ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*; M: Mucosa; SM: Submucosa.

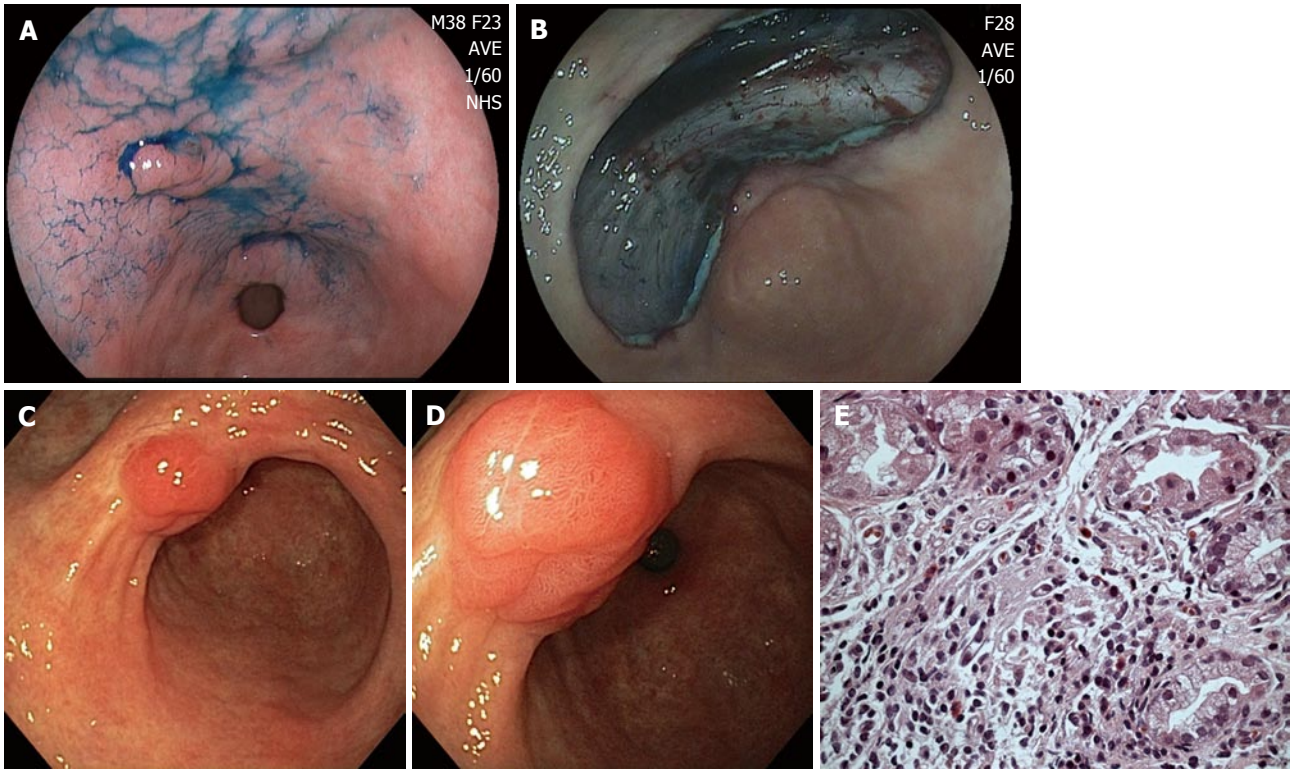

Figure 2 Case from Brazil. A: A depressed lesion (0IIc) was found at the lesser curvature of antrum; B: The lesion was removed by endoscopic submucosal dissection technique. The lesion was diagnosed as well differentiated adenocarcinoma confined to the muscularis mucosae and resection margins were free of tumor; C: Patient developed a polypoid nodule at the center of the scar. Three years later, polypoid nodule scar (PNS) with convergence of folds is still present; D: Closer view of PNS, demonstrating irregular surface and suspicious appearance on white-light image; E: Biopsy specimens were taken from the polypoid nodule. Histological examination showed similar findings to case illustrated in Figure 1: Regenerative hyperplastic tissue with inflammatory cell infiltration.

the fibrotic tissue[11].

In our series all patients received PPI in the post-operative period to speed up the healing process, a clinical management that is adopted universally in ESD referral

centers[16]. PPI accelerates ulcer healing mainly due to potent gastric acid secretion inhibition. However, PPI also increases the cyclooxigenase-2 (COX-2) expression and prostaglandin E synthases in the ulcerated mucosa[17]. COX-2 generated Prostaglandin E2 stimulates the expression of growth factors in the mucosa, such as vascular endothelial growth factor[18], hepatocyte growth factor[19], basic fibroblast growth factor[20]. This accelerated mucosal repair and angiogenesis may contribute to nodular overgrowth of the regenerative mucosa.

There still remain some questions unanswered concerning the occurrence and pathogenesis of PNS. A unique characteristic of PNS is that we noted this finding only after ESD performed in the distal stomach (antrum or incisure). In both centers, we did not notice PNS after ESD for lesions located in the gastric body, fundus or cardia. Likewise we did not observe this finding after esophageal or colorectal ESD. The reason for this phenomenon is unclear. We postulate that the frequent gastric peristalsis may enhance development of PNS in the antrum. Moreover, submucosal layer in the antrum is thicker; therefore inflammatory or regenerative reaction in the submucosa can be more obvious in the antrum than in the corpus of fundus. Another interesting question is whether PNS may also occur after EMR. Although in the present study we did not look specifically for patients that underwent EMR, data in the literature support that even peptic ulcer causes PNS, therefore it seems fair to assume that PNS may develop after EMR. The importance of *H. pylori* infection is also undetermined. Our data do not show a clear association between PNS and *H. pylori* status, as 8 patients (57%) tested positive and the other 6 (43%) were negative for *H. pylori* infection. However, more investigation in needed to draw firm conclusions about predisposing factors involved with PNS development.

Endoscopists should acknowledge the occurrence of aberrant polypoid nodules at ESD scar, particularly in antral lesions. Such occurrence, to our knowledge, has only been reported recently and we proposed to adopt the terminology PNS to describe this phenomenon[4]. It is of paramount importance to distinguish PNS from residual carcinoma or submucosal tumor recurrence. PNS is composed of granulation tissue or regenerative mucosa, and the surface structure and vasculature are as irregular as those of intramucosal carcinoma. Therefore, the first priority is to make sure that the endoscopic resection was R0 and curative by histologic criteria, ruling out a residual carcinomatous tumor. Secondly, to distinguish PNS from submucosal recurrence is not so difficult because surface structure of PNS is irregular, in contrast to submucosal recurrence that tends to present a smooth and regular surface, covered with normal gastric mucosa. Image enhanced endoscopy with magnifying endoscopy associated with indigo carmine and digital chromoendoscopy with NBI or FICE potentially are useful tools to facilitate the differential diagnosis.

The incidence of PNS post ESD is still undetermined, though expected to be rare. Apparently the size of the lesion or the size of the resected area, do not seem to be directly involved in PNS development, since we noted a wide variation in tumor size (8 mm to 82 mm), and even small lesions under 10 mm developed PNS. In this study, the incidence of PNS was significantly different between the two centers (Center 1%-13.3%; Center 2%-1.7%). This difference can be justified, at least in part, because Center 1 performed ESD more frequently for tumors located in the antrum (62%) in comparison to Center 2 (46%). Perhaps, the ESD technique could also influence the occurrence of PNS. There was a difference between the 2 centers in terms of ESD knives (Center 1 - needle type knife; Center 2 - insulated tip knife), settings of electrosurgical unit and operator's experience. Moreover, because this was a retrospective study, the incidence of PNS may be underestimated, due to cases lost for follow-up or unavailability of the endoscopic images. A prospective large-scale multicenter study enrolling multiple ESD centers is needed to assess the true incidence of PNS.

PNS endoscopically looks concerning, especially for the patient and the family doctor. Nevertheless, as long as the ESD procedure is considered curative, with R0 resection confirmed by a standardized histological evaluation, and multiple biopsies taken from the scar rule out tumor recurrence and reveals only hyperplastic changes, PNS should be viewed as a regenerative lesion with an expected benign behavior. Over time PNS may become less protruded, as we noted in some of our patients, or even disappear. Most importantly, endoscopists when facing a PNS should refrain to indicate any type of invasive measure such as endoscopic or surgical reintervention, and recommend annual endoscopic surveillance.

In summary, we report the first series of aberrant polypoid nodule scars observed after gastric ESD that corresponds to a regenerative healing process and that requires no additional treatment other than periodic endoscopic follow-up.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is considered by current guidelines as the treatment of choice for patients with superficial gastric neoplasms with little or no risk of lymph nodes metastasis. It permits *en bloc* resection of tumors and reliable histological assessment of the resected specimen to determine the potential curability of the endoscopic resection. Postoperative endoscopic examination is recommended to all patients after curative ESD with two main purposes: (1) inspection of the scar to rule out residual tumor or recurrence; and (2) surveillance for metachronous neoplastic lesions.

Research frontiers

After a curative ESD, postoperative scar is expected to look consolidated and homogeneous without residual tumor, infiltration or polypoid formation. However, there is scarce data about the healing process of post-ESD defects and ulcers.

Innovations and breakthroughs

In this study, the authors report the first series of 14 patients from two Academic Institutions from Brazil and Japan, that developed aberrant polypoid nodule scars

after curative gastric ESD, undertaken for neoplastic lesions located in the distal stomach (antrum and incisure). They denominated this new entity as polypoid nodule scar (PNS). PNS endoscopically looks concerning, especially for the patient and the family doctor. Nevertheless, as long as the ESD procedure was curative, with R0 resection confirmed by a standardized histological evaluation, and multiple biopsies taken from the scar rule out tumor recurrence and reveals only hyperplastic changes, PNS should be viewed as a regenerative lesion with an expected benign behavior, that requires no additional treatment other than periodic endoscopic follow-up.

Applications

ESD has been increasingly utilized to treat early gastric neoplasms all over the world. This study brings new concepts about the healing process of ESD defects, particularly for antral lesions. The understanding and knowledge of this new entity by endoscopists involved with ESD procedure is crucial to prevent unnecessary and aggressive reintervention to manage a benign hyperplastic tissue reaction that may be confounded with tumor recurrence.

Terminology

PNS refers to polypoid nodule scar, an aberrant and protuberant nodular scar that develops after ESD and has no histological evidence of tumor recurrence or dysplasia. PNS corresponds to a hyperplastic regenerative healing process, already know in the past to occur after the healing of gastric peptic ulcers.

Peer-review

Available papers dedicated to understand the healing process of ESD defects are scarce. The authors in this study reported a new entity named PNS that occurs after gastric ESD for lesions located mainly in the antrum. Although, the occurrence of this phenomenon is supposed to be rare, the true incidence of PNS remains to be determined. Large-scale multicenter and prospective study are needed to better investigate this newly described finding.

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P- Reviewer: Aoyagi K, Kim JJ, Morgagni P, Muguruma N, Skok P
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